Diseases of the Liver and Biliary System

SHEILA SHERLOCK
DBE, FRS
MD (Edin.), Hon. DSc (Edin., New York, Yale),
Hon. MD (Cambridge, Dublin, Leuven, Lisbon,
Mainz, Oslo, Padua, Toronto), Hon. LLD (Aberd.),
FRCP, FRCPE, FRACP, Hon. FRCCP,
Hon. FRCPI, Hon. FACP

Professor of Medicine,
Royal Free and University College Medical School
University College London,
London

JAMES DOOLEY
BSc, MD, FRCP

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ELEVENTH EDITION

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Science

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Preface to the Eleventh Edition

The eleventh edition welcomes the new Millenium. Progress in basic and clinical hepatology remains exponential. Since 1997, the advances have been wide-ranging, with those in molecular and cellular biology, and in diagnosis and treatment, leading the way. In a world in which information technology gives all too ready access to individual publications, the eleventh edition sets the new within established knowledge and practice.

Viral hepatitis remains the worldwide hepatological challenge. This is reflected in a change in format with separate chapters on hepatitis B and C. Molecular virology continues to expose the inner workings of all the viruses. New therapeutic approaches are proving more effective against hepatitis C. Molecular and cellular biologists are showing us the importance of apoptosis and the intricate regulation of fibrosis. Mutation analysis for diagnosis of genetic haemochromatosis is routine, while the identification of the haemochromatosis gene has led to a surge of exploration in iron metabolism. Canalicular transporters have been cloned and linked to cholestatic syndromes, giving a new perspective to the bile plug seen under the microscope. Advances in imaging, particularly magnetic resonance, continue to reduce the need for invasive techniques. Patients needing transplantation benefit from improvements in immunosuppression and surgical techniques, while there is steady progress in the management of complications of cirrhosis.

This edition contains more than 1000 new references and 100 new figures. Developments in publishing allow a more colourful format, but care has been taken to preserve clarity. Experience has shown that students, interns, postgraduate trainees as well as generalists and specialist clinicians have found previous editions useful. The goal of the book remains unchanged: a textbook of manageable size, critical and current.

We are indebted to many colleagues for their generous contributions to this edition including in particular Professor Peter Scheuer, Professor Amar Dhillon and Dr Susan Davies for histological material, and Dr Robert Dick, Dr Tony Watkinson and Dr Jon Tibballs for radiological images. We would also like to express our great thanks to Dr Leslie Berger, Dr Andrew Burroughs, Dr John Buscombe, Dr Martyn Caplin, Professor Geoffrey Dusheiko, Dr David Harry, Dr Andrew Hilson, Professor Humphrey Hodgson, Professor Neil McIntyre, Dr Kevin Moore, Dr Marsha Morgan, Dr Chris Kibbler and Dr David Patch for their help in the preparation of this edition.

Miss Aileen Duggan and Miss Karma Raines have assisted tirelessly with their meticulous secretarial support. The clarity and style of figures preserved from previous editions owes much to the artistry of Miss Janice Cox over many years.

We are grateful to Blackwell Publishing and, in particular, Rebecca Huxley for her tireless help with both manuscript and proofs, and for responding without a murmur to demands within a tight schedule. We also thank Jane Fallows who has reformatted and coloured all the previous line drawings as well as creating the many new and visually inviting figures for the eleventh edition.

The preface to the first edition which was published in 1955 refers to daughters Amanda and Auriole. Amanda is now an ordained Minister in the Baptist Church, and Auriole is working with Kent Police. Grandchildren have arrived, including Alice aged 9 and Emily aged 6.

On the 13th July 2001, the senior author was elected a Fellow of the Royal Society in its 341st year, a Society founded to improve natural knowledge. This honour was achieved because of the support of all the clinicians and scientists who have contributed to the Liver Unit and its associated departments at The Royal Free. The new Millenium is indeed an exciting time for all those working to solve the puzzles within hepato-biliary disease.

SHEILA SHERLOCK
JAMES DOOLEY
November 2001

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 reticulo-endothelial 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 section 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

Chapter 1
Anatomy and Function

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 (figs 1.1–1.3). 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

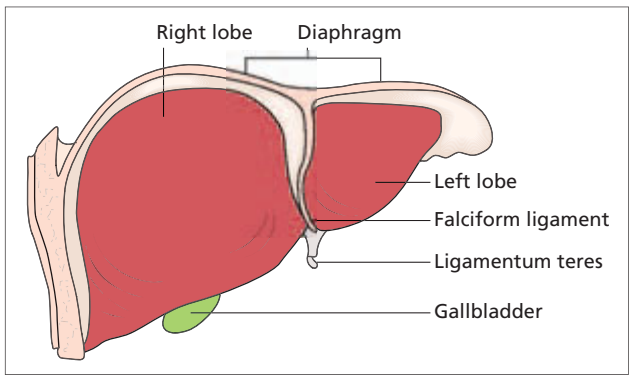


Fig. 1.1. Anterior view of the liver.

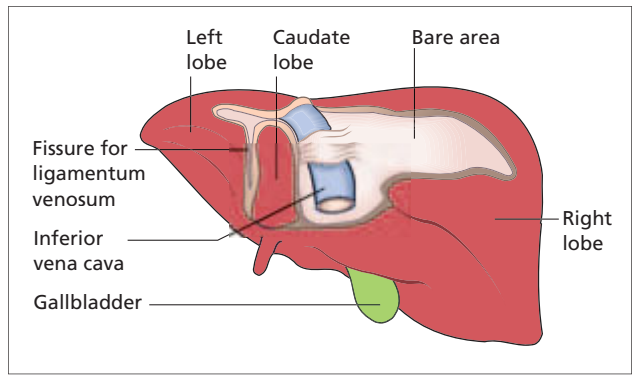


Fig. 1.2. Posterior view of the liver.

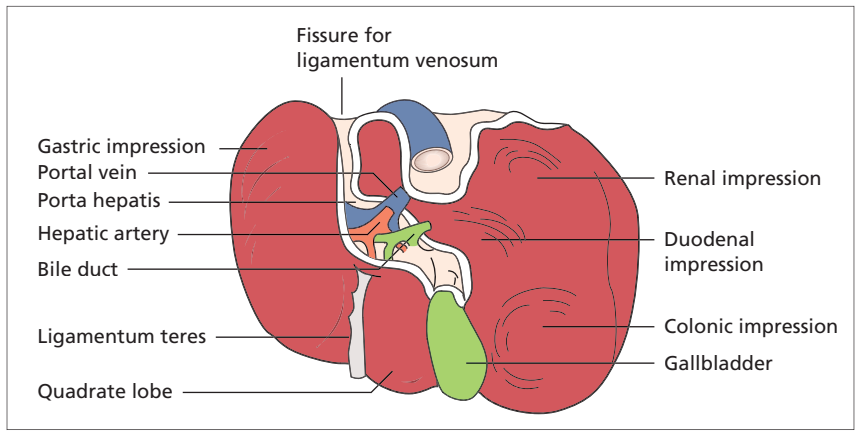


Fig. 1.3. Inferior view of the liver.

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 mid-line.

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 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 anatomy: sectors and segments

Based on the external appearances described above, 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 studies of vascular and biliary casts made by injecting vinyl into the vessels and bile ducts. This classification correlates with that seen by 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 plains 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, segments II and III. There is no vascular anastomosis between the macroscopic vessels of the segments but communications exist at 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

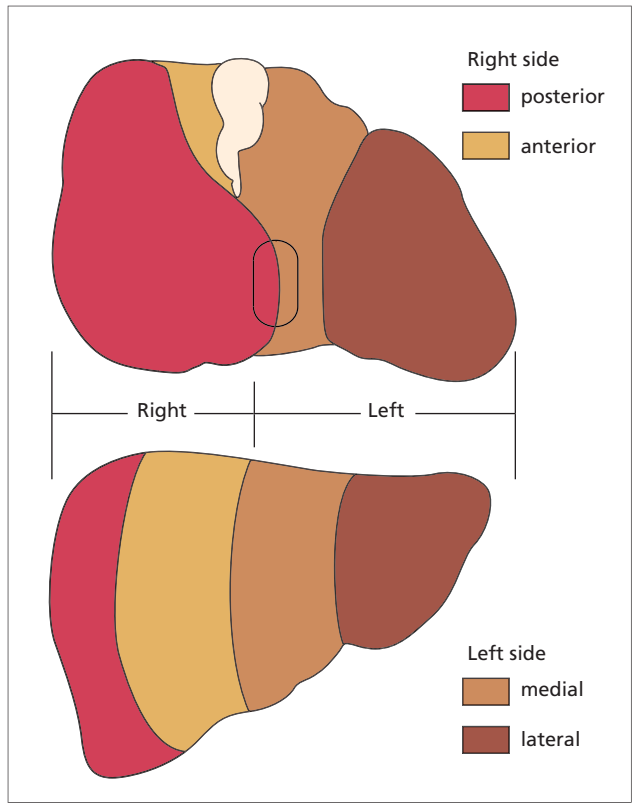


Fig. 1.4. The sectors of the human liver.

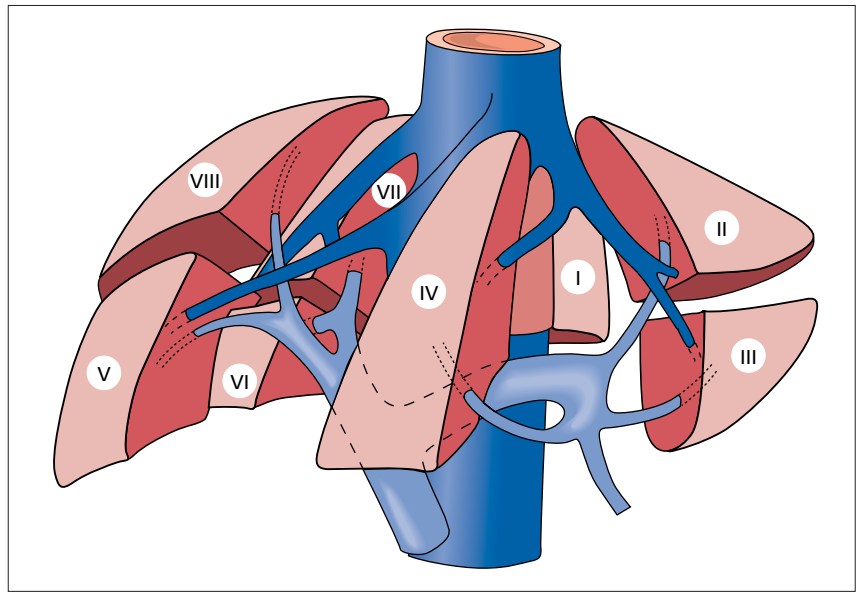


Fig. 1.5. Schematic representation of the functional anatomy of the liver. Three main hepatic veins (dark blue) divide the liver into four sectors, each of them receiving a portal pedicle; hepatic veins and portal veins are intertwined as the fingers of two hands [5].

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 [41].

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 postero-medial wall, usually joining the main pancreatic duct to form the *ampulla of Vater* (1720). The ampulla makes the 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* (1887).

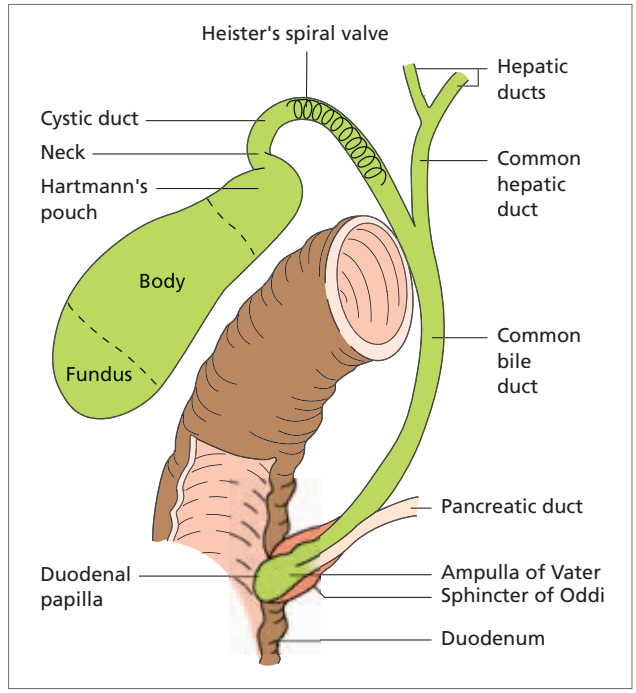


Fig. 1.6. Gallbladder and biliary tract.

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.

Any decrease in concentrating power is accompanied by reduced distensibility. 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 wall consists of a musculo-elastic network without definite layers, the muscle being particularly well developed in the neck and fundus. The mucous membrane is in delicate closely woven folds; instead of glands there are deep indentations of mucosa, the *crypts of Luschka*, which penetrate into the muscular layer. There is no submucosa or muscularis mucosae.

The *Rokitansky–Aschoff sinuses* are branching evaginations from the gallbladder lumen lined by mucosa reaching into the muscularis of the gallbladder. They play an important part in acute cholecystitis and gangrene of the gallbladder wall.

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.

The arterial blood supply to the supra-duodenal bile duct is generally by two main (axial) vessels which run beside the bile duct. These are supplied predominantly by the retro-duodenal 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 [24].

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.

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 (ductal plates). Differentiation is accompanied by changes in cytokeratin type within the cell [40]. 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 extra-hepatic bile ducts. Bile begins to flow at about the 12th week. Haemopoietic cells, Kupffer cells and connective tissue cells are derived from the mesoderm of the septum transversum. The fetal liver has a major haemopoietic function which subsides during the last 2 months of intra-uterine life so that only a few haemopoietic cells remain at birth.

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 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 under surface of the liver so that they are not detected clinically but are noted incidentally at scanning, operation or necropsy. Rarely they are intrathoracic. 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.

Riedel's lobe is fairly common and is a downward tongue-like projection of the right lobe of the liver. 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. Scanning may be used to identify Riedel's lobe and other anatomical abnormalities.

Cough furrows on the liver are parallel grooves on the convexity of the right lobe. They are one to six in number and run antero-posteriorly, being deeper posteriorly. They are said to be associated with a chronic cough.

Corset liver. This is a fibrotic furrow or pedicle on the anterior surface of both lobes of the liver just below the costal margin. 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.

Obstruction to the right or left hepatic bile duct by benign stricture or cholangiocarcinoma is now the most common cause of lobar atrophy [16]. 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 [27]. This rare lesion may be an incidental finding associated, probably coincidentally, with biliary tract disease and also with other congenital abnormalities. It can cause pre-sinusoidal portal hypertension. The other liver segments undergo compensatory hypertrophy. It must be distinguished from lobar atrophy due to cirrhosis or hilar cholangiocarcinoma.

Anatomical abnormalities of the gallbladder and biliary tract are discussed in Chapter 33.

Surface marking (figs 1.7, 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 mid-clavicular 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 mid-clavicular 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 mid-line about mid-way 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.

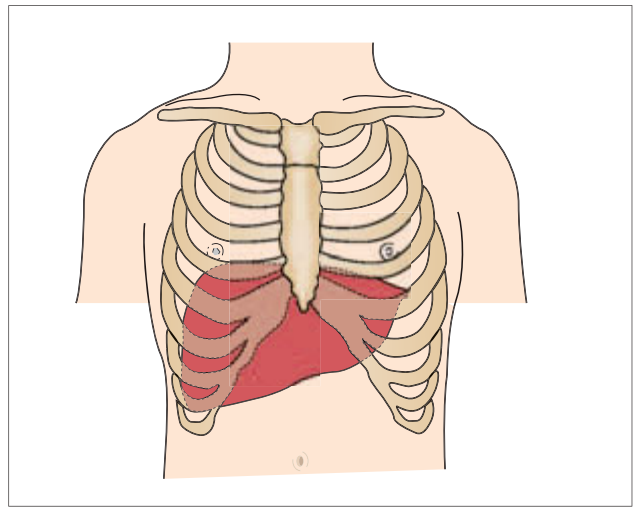


Fig. 1.7. The surface marking of the liver.

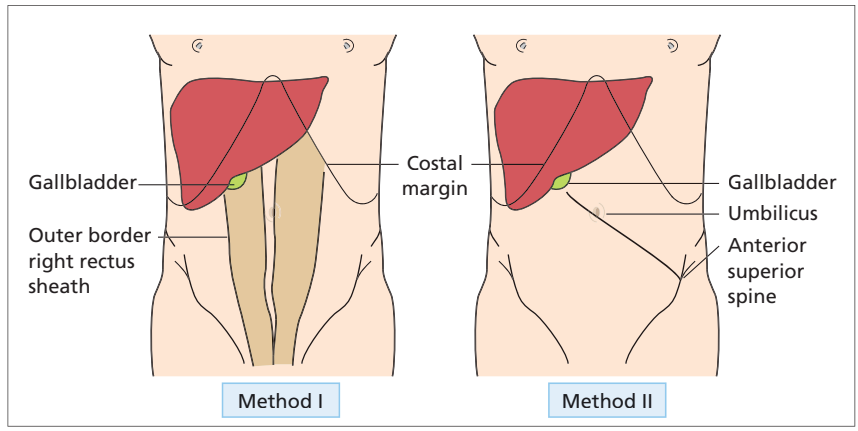


Fig. 1.8. Surface markings of the gallbladder. Method I: the gallbladder is found where the outer border of the right rectus abdominis muscle intersects the 9th costal cartilage. Method II: a line drawn from the left anterior superior iliac spine through the umbilicus intersects the costal margin at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

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's 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 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 [33].

Friction may be palpable and audible, usually due to recent biopsy, tumour or peri-hepatitis. 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.

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 also be used to study liver size, shape and content.

Hepatic morphology

Kiernan (1833) introduced the concept of hepatic lobules as the basic architecture. He described circumscribed pyramidal lobules consisting of a central tributary of the hepatic vein and at the periphery a portal tract containing the bile duct, portal vein radicle and hepatic artery branch. Columns of liver cells and blood-containing sinusoids extend between these two systems.

Stereoscopic reconstructions and scanning electron microscopy have shown the human liver as columns of liver cells radiating from a central vein, and interlaced in orderly fashion by sinusoids (fig. 1.9).

The liver tissue is pervaded by two systems of tunnels, the portal tracts and the hepatic central canals which dovetail in such a way that they never touch each other; the terminal tunnels of the two systems are separated by about 0.5 mm (fig. 1.10). As far as possible the two systems of tunnels run in planes perpendicular to each other. The sinusoids are irregularly disposed, normally in a direction perpendicular to the lines connecting the central veins. 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.

The *central hepatic canals* contain radicles of the hepatic vein and their adventitia. They are surrounded by a limiting plate of liver cells.

The *portal triads* (syn. portal tracts, Glisson's capsule) contain the portal vein radicle, the hepatic arteriole and bile duct with a few round cells and a little connective tissue (fig. 1.11). They are surrounded by a limiting plate of liver cells. Portal dyads are as frequent as triads, with the portal vein being the most frequently absent element. Within each linear centimetre of liver tissue obtained at

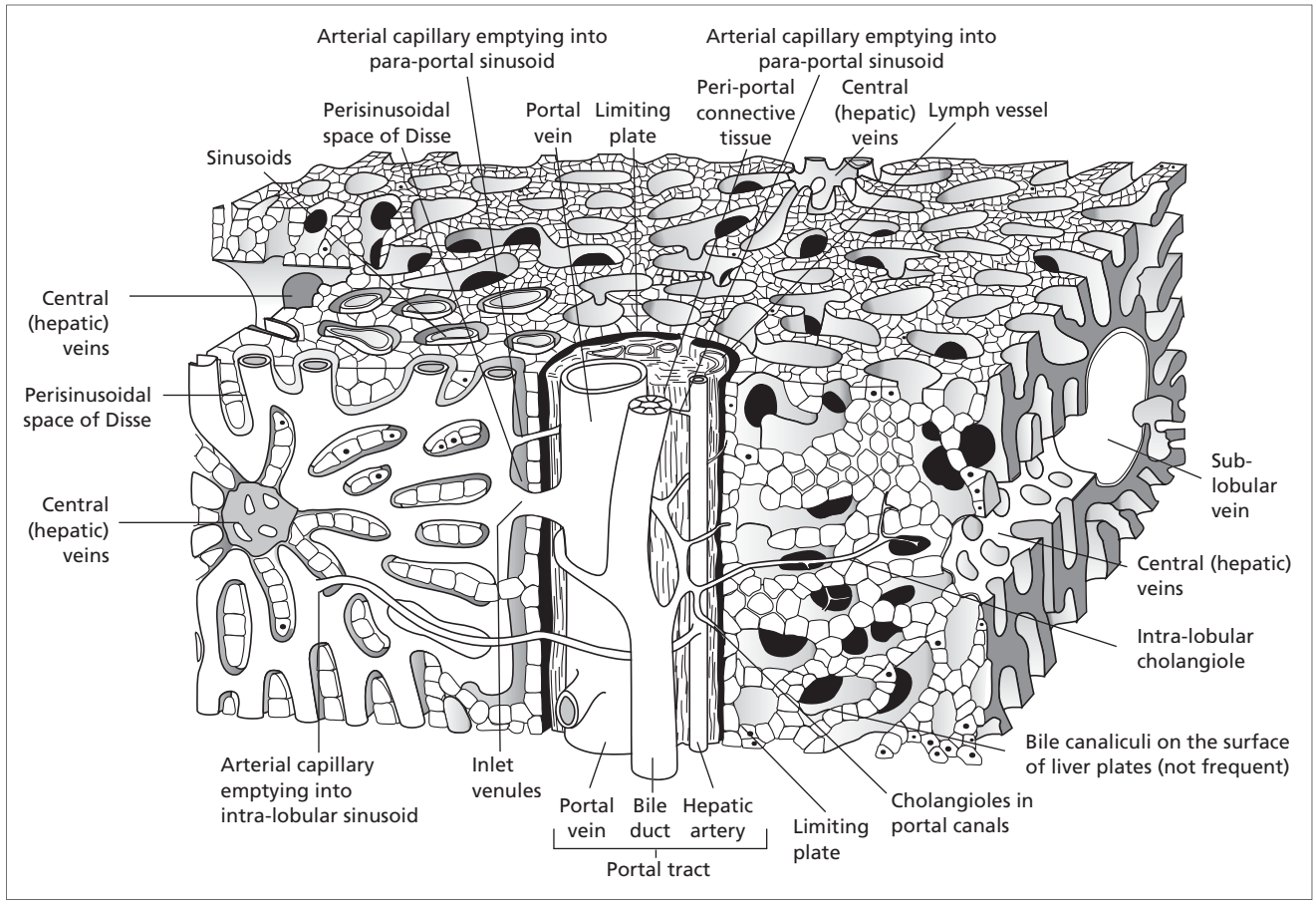


Fig. 1.9. The structure of the normal human liver.

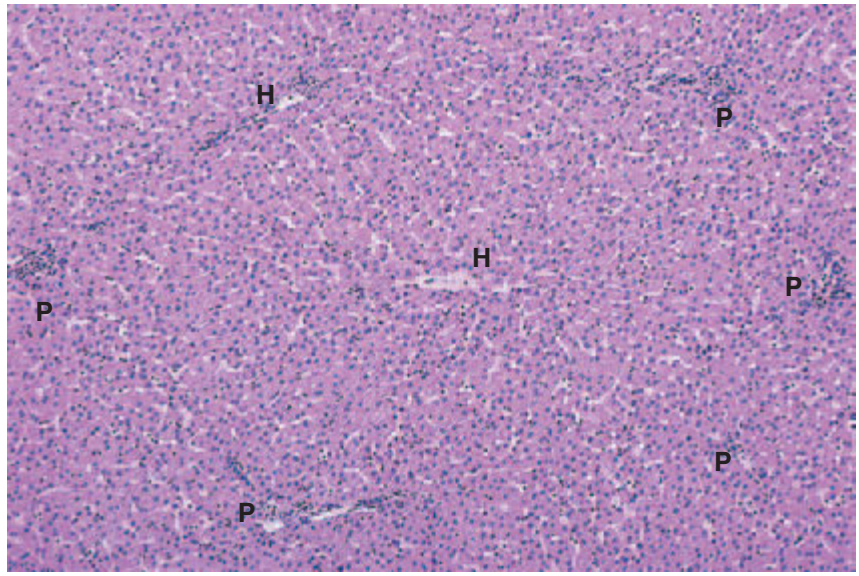


Fig. 1.10. Normal hepatic histology. H, terminal hepatic vein; P, portal tract. (H & E, ×60.)

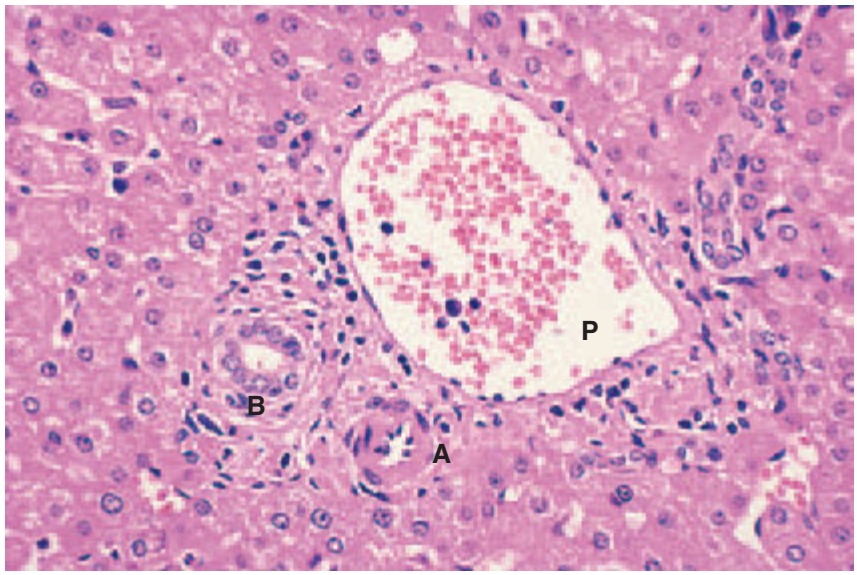


Fig. 1.11. Normal portal tract. A, hepatic artery; B, bile duct; P, portal vein. (H & E.)

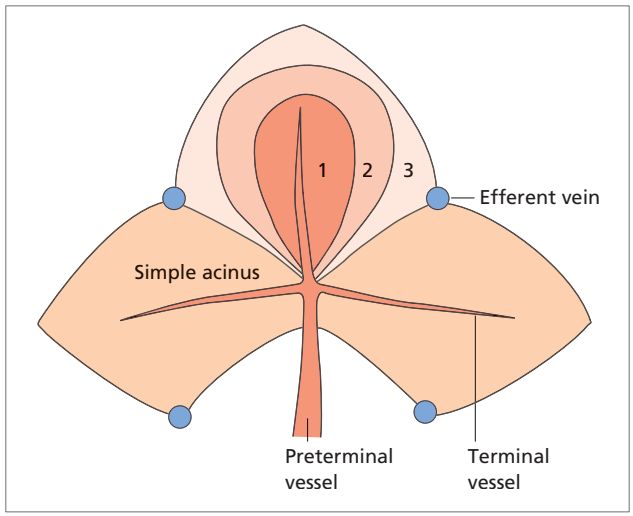


Fig. 1.12. The complex acinus according to Rappaport. Zone 1 is adjacent to the entry (portal venous) system. Zone 3 is adjacent to the exit (hepatic venous) system.

biopsy there are usually two interlobular bile ducts, two hepatic arteries and one portal vein per portal tract, with six full portal triads [8].

The liver has to be divided *functionally*. Traditionally, the unit is based on a central hepatic vein and its surrounding liver cells. However, Rappaport [28] envisages a series of functional acini, each centred on the portal triad with its terminal branch of portal vein, hepatic artery and bile duct (zone 1) (figs 1.12, 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 is located in this area. 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 [28].

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. Associated with the sinusoids are the phagocytic cells of the reticulo-endothelial system (Kupffer cells), and the hepatic stellate cells, which have also been called fat-storing cells, Ito cells and lipocytes.

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* is a tissue space between hepatocytes and sinusoidal endothelial cells. The *hepatic lymphatics* are found in the peri-portal connective tissue and are lined throughout by endothelium. Tissue fluid seeps through the endothelium into the lymph vessels.

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*

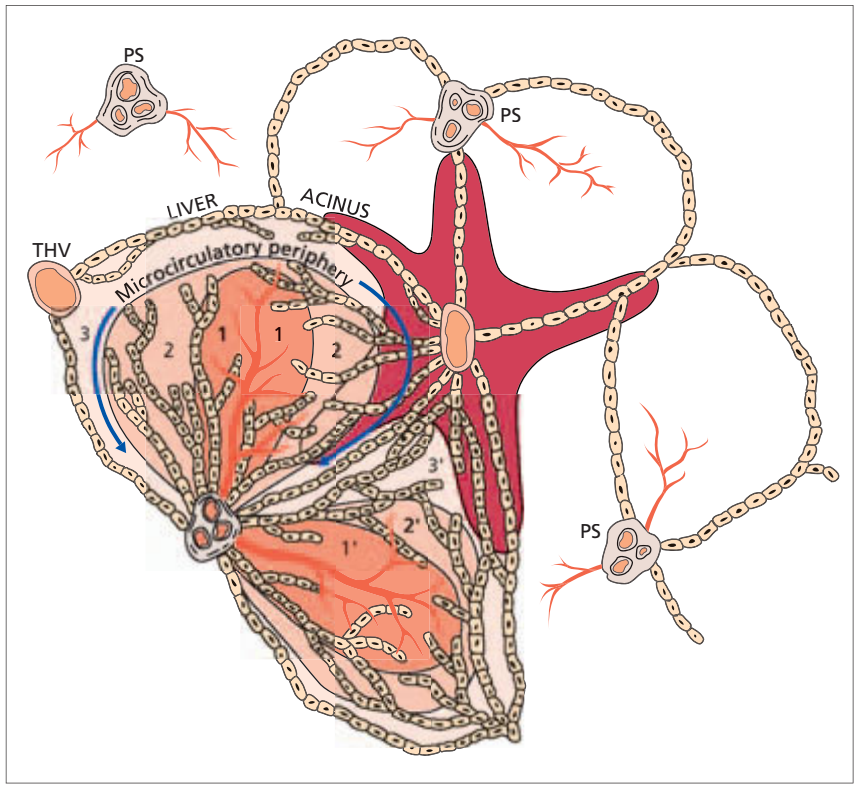


Fig. 1.13. Blood supply of the simple liver acinus, zonal arrangements of cells and the microcirculatory periphery. The acinus occupies adjacent sectors of the neighbouring hexagonal fields. Zones 1, 2 and 3, respectively, represent areas supplied with blood of first, second and third quality with regard 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 *peri-venular* 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 [28].

canaliculi (see figs 13.2, 13.3). These have no walls but are simply grooves on the contact surfaces of liver cells (see fig. 13.1). Their surfaces are covered by microvilli. The plasma membrane is reinforced by micro-filaments forming a supportive cytoskeleton (see fig. 13.2). 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 thin-walled terminal bile ducts or ductules (cholangioles, canals of Hering) lined with cuboidal epithelium. These terminate in larger (interlobular) bile ducts in the portal canals. They are classified into small (less than 100 µm in diameter), medium (about 100 µm) and large (more than 100 µm).

Electron microscopy and hepato-cellular function (figs 1.14, 1.15)

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 peri-sinusoidal 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

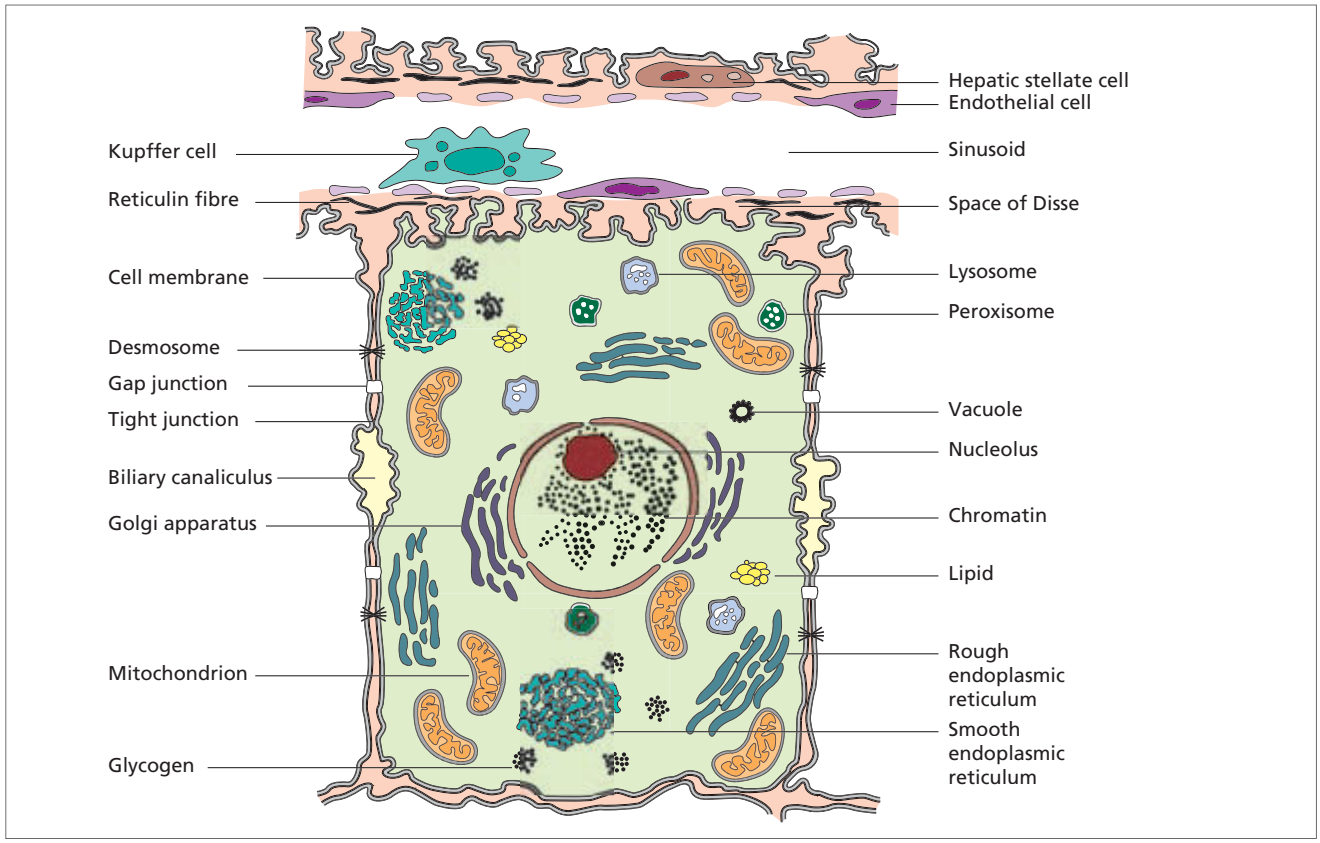


Fig. 1.14. The organelles of the liver cell.

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 used in blood coagulation and enzymes. They may adopt a helix arrangement, as polysomes, for co-ordination 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 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 [14]. Endotoxin severely damages peroxisomes [7].

The *lysosomes* are dense bodies adjacent to the bile canaliculi. They contain many hydrolytic enzymes which, if released, could destroy the cell. They are probably intra-cellular scavengers which destroy organelles with shortened lifespans. They are the site of deposition of ferritin, lipofuscin, bile pigment and copper. Pinocytic vacuoles may be observed in them. Some pericanalicular dense bodies are termed *microbodies.*

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 which 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 fine fibrils.

The *cytoskeleton* supporting the hepatocyte consists

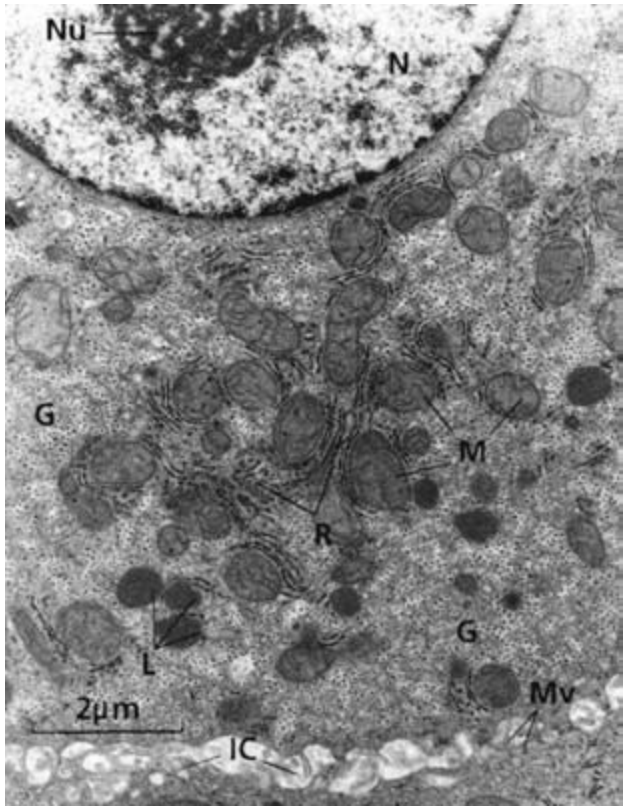


Fig. 1.15. Electron microscopic appearances of part of a normal human liver cell. G, glycogen granules; IC, intercellular space; L, lysosomes; M, mitochondria; Mv, microvilli in the intra-cellular space; N, nucleus; Nu, nucleolus; R, rough endoplasmic reticulum. (Courtesy of Ms J. Lewin.)

of microtubules, micro-filaments and intermediate filaments [12]. Microtubules contain tubulin and control subcellular mobility, vesicle movement and plasma protein secretion. Micro-filaments 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 [40]. They extend from the plasma membrane to the peri-nuclear area and are fundamental for the stability and spatial organization of the hepatocyte.

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 [34].

Endothelial cells line the sinusoids and have fenestrae which provide a graded barrier between the sinusoid and space of Disse (fig. 1.16). The Kupffer cells are attached to the endothelium.

The hepatic stellate cells lie in the space of Disse between the hepatocytes and the endothelial cells (fig. 1.17). *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 else-

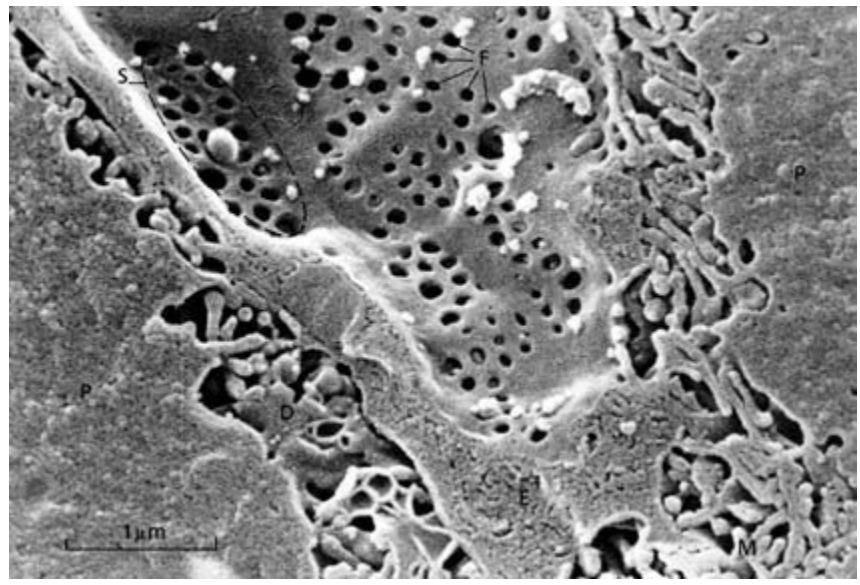


Fig. 1.16. Scanning electron micrograph of sinusoid showing fenestrae (F) grouped into sieve plates (S). D, space of Disse; E, endothelial cell; M, microvilli; P, parenchymal cell. (Courtesy of Professor E. Wisse.)

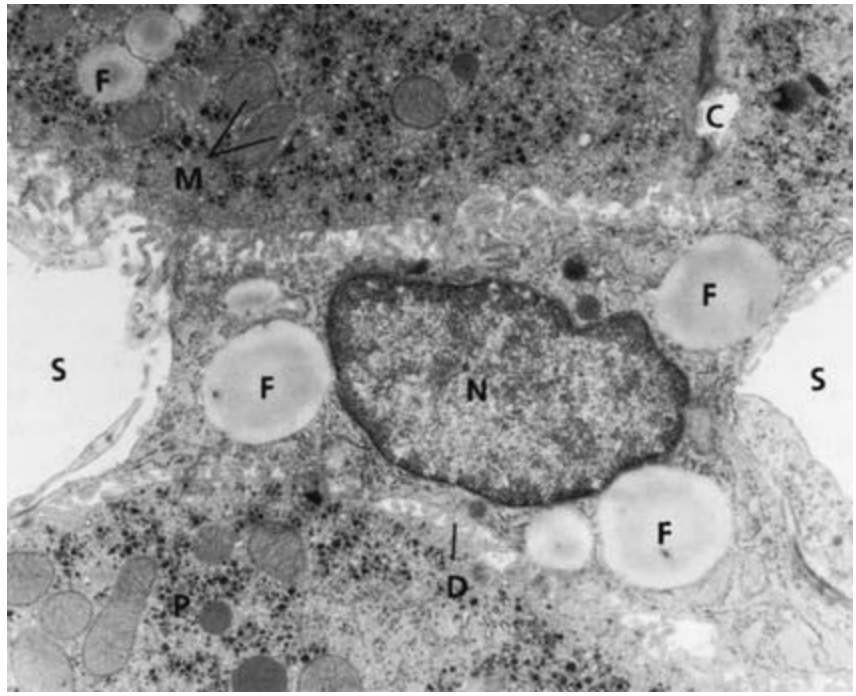


Fig. 1.17. Transmission electron micrograph of a hepatic stellate cell. Note the characteristic fat droplets (F). C, bile canaliculus; D, space of Disse; M, mitochondria; N, nucleus; P, parenchymal cell; S, lumen of sinusoid. (×12 000.) (Courtesy of Professor E. Wisse.)

where in not having a regular basal lamina. 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. 1.16). These make up 6–8% of the total endothelial cell surface, and there are more in the centrilobular zone of the sinusoid than the peri-portal area. Extra-cellular matrix affects their function.

Fenestrae are clustered into sieve plates, and act as a biofilter between sinusoidal blood and the plasma within the space of Disse. They have a dynamic cytoskeleton [6]. This maintains and regulates their size, which can be changed by many influences including alcohol, nicotine, serotonin, endotoxin and partial hepatectomy. The fenestrae filter macro-molecules of differing size. Particles >0.2 μm diameter, which includes large triglyceride-rich parent chylomicrons, will not pass. Smaller triglyceride-depleted, cholesterol-rich and retinol-rich remnants can enter the space of Disse [15]. In this way the fenestrae have an important role in chylomicron and lipoprotein metabolism.

Endothelial cells have a high capacity for endocytosis (accounting for 45% of all pinocytotic vesicles in the liver) and are active in clearing macro-molecules and small particles from the circulation [35]. 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 [17].

Kupffer cells. These are highly mobile macrophages attached to the endothelial lining of the sinusoid, particularly in the peri-portal area. They stain with peroxidase. They have microvilli and intra-cytoplasmic-coated vesicles and dense bodies which make up the lysosomal apparatus. They proliferate locally but under certain circumstances macrophages can immigrate from an extra-hepatic 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) mechanisms [39]. Several processes aid this, including cell surface Fc and complement receptors. Coating of the particle with plasma fibronectin or opsonin also facilitates phagocytosis, since Kupffer cells have specific binding sites for fibronectin on the cell surface. These cells also take up and process oxidized LDL (thought to be atherogenic), and remove fibrin in disseminated intravascular coagulation. Alcohol reduces the phagocytic capacity.

Kupffer cells are activated by a wide range of agents, including endotoxin, sepsis, shock, interferon-γ, arachi-

donic acid and tumour necrosis factor (TNF). The result of activation is the production of an equally wide range of products: cytokines, hydrogen peroxide, nitric oxide, TNF, interleukin (IL) 1, IL6 and IL10, interferon-α and -β, transforming growth factor (TGF-β) and various prostanoids [34]. This whole array acts alone or in combination to stimulate other events in the cytokine cascade, but also increases discomfort and sickness. The Kupffer cell products may be toxic to parenchymal cells and endothelial cells. Kupffer cell-conditioned medium inhibits albumin synthesis in parenchymal cells, as do IL1, IL6 and TNF-α. The toxicity of endotoxin is caused by the secretory products of Kupffer cells since endotoxin itself is not directly toxic.

Hepatic stellate cells (fat-storing cells, lipocytes, Ito cells). These cells lie within the sub-endothelial space of Disse. They have long cytoplasmic extensions, some giving close contact with parenchymal cells, and others reaching several sinusoids, where they may regulate blood flow and hence influence portal hypertension [29]. In normal liver they are the major storage site of retinoids, giving the morphological characteristic of cytoplasmic lipid droplets. When empty of these droplets, they resemble fibroblasts. They contain actin and myosin and contract in response to endothelin-1 and substance P [30]. With hepatocyte injury, hepatic stellate cells lose their lipid droplets, proliferate, migrate to zone 3 of the acinus, change to a myofibroblast-like phenotype, and produce collagen type I, III and IV and laminin. Stellate cells also release matrix proteinases and inhibitory molecules of matrix proteinases (tissue inhibitor of metalloproteinases, TIMP) (Chapter 21) [3]. Collagenization of the space of Disse results in decreased access of protein-bound substrates to the hepatocyte.

Pit cells. These are highly mobile liver-specific natural killer lymphocytes attached to the sinusoidal surface of the endothelium [42]. They are short-lived cells and are renewed from circulating large granular lymphocytes which differentiate within the sinusoids. They have characteristic granules and rod-cored vesicles. Pit cells show spontaneous cytotoxicity against tumour- and virus-infected hepatocytes.

Sinusoidal cell interactions

There are complex interactions between Kupffer and endothelial cells, as well as sinusoidal cells and hepatocytes [31]. Kupffer cell activation by lipopolysaccharide suppresses hyaluronan uptake by endothelial cells, an effect probably mediated by leukotrienes [10]. Cytokines produced by sinusoidal cells can both stimulate and inhibit hepatocyte proliferation [22].

Hepatocyte death and regeneration

(fig. 1.18)

Normal liver structure and function depends upon a balance between cell death and regeneration [11, 20].

Cell death. Hepatocytes die as a result of either necrosis or apoptosis. The characteristic of *necrosis* is loss of plasma membrane integrity with release of the cellular contents locally which elicit an inflammatory response. This may potentiate the disease process and lead to further cell death.

Apoptosis is the mechanism by which cells, damaged, senescent or excess to requirement, self-destruct with the least production of inflammatory products [13, 26]. There is DNA fragmentation; organelles remain viable. Thus in comparison with necrotic cells, there is minimal release of injurious products, although there may still be a fibrotic reaction. Equilibrium within normal tissue depends upon the mitotic rate equalling the rate of apoptosis.

Pathological processes can alter the cellular mechanisms involved in apoptosis, leading to disease [25]. Increased apoptosis affecting cholangiocytes may lead to ductopenia. Experimentally, maximal stimulation of

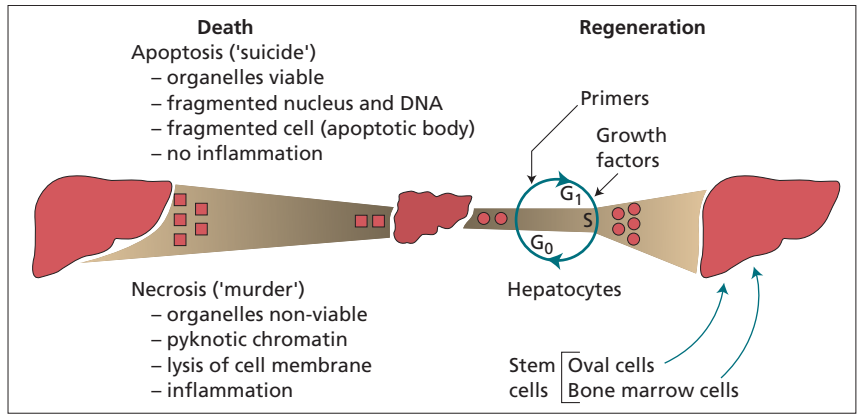


Fig. 1.18. Liver cell death and regeneration. Hepatocytes are lost either through apoptosis or necrosis. The liver normally regenerates through cellular replication. Priming is necessary for hepatocytes to respond to growth factors. If hepatocyte loss is massive or the toxic attack persists, cellular replication may not be possible. Liver cells may then be derived from stem cells either from within the liver (oval cells) or from the bone marrow.

hepato-cellular apoptosis leads to fulminant liver failure. Apoptosis is increased in alcoholic hepatitis [23]. If cells containing a mutation predisposing to malignant change do not undergo apoptosis, malignant transformation is enhanced.

The pathway to apoptopic cellular destruction is complex, and can be described in morphological and biochemical terms. Once the process is initiated a cascade of changes occurs, which may be irreversible after a particular stage is reached. There is great interest in the development of agents that interfere with the apoptotic process, since these may have a therapeutic place in diseases where apoptosis is increased or decreased.

Regeneration. When there is a need for additional hepatocytes, quiescent cells are stimulated by mediators (primers), including cytokines, to move into a primed state ($G_0 \rightarrow G_1$), when growth factors can stimulate DNA synthesis and cellular replication (fig. 1.18). Priming activates transcription factors including NFλB and STAT 3. Regeneration may be rapid, as seen after partial hepatectomy.

If hepatocytes are damaged so that this response is impaired, hepatocytes may be derived from cells associated with bile ductules, so-called oval cells. It is thought that these cells are derived from the cells of small bile ducts or canals of Hering and are related to embryonic ductal plate hepatocytes [32, 38].

Hepatocytes may also be derived from extra-hepatic stem cells, probably of bone marrow origin [9, 36]. Thus Y chromosome positive (male) hepatocytes and cholangiocytes are found in female livers transplanted into male recipients, and in the livers of female patients who have had a bone marrow transplant from a male donor [2, 37].

Extra-cellular matrix

This is obvious when there is liver disease, but also exists in a subtle form even in normal liver. In or around the space of Disse, all major constituents of a basement membrane can be found including type IV collagen, laminin, heparan sulphate, protoglycan and fibronectin. All cells impinging on the sinusoid can contribute to this matrix. The matrix within Disse's space influences hepato-cellular function [31], affecting expression of tissue-specific genes such as albumin as well as the number and porosity of sinusoidal fenestrations [21]. It may be important in liver regeneration.

Altered hepatic microcirculation and disease

In liver disease, particularly in the alcoholic, the liver microcirculation may be altered by collagenization of the space of Disse—formation of a basal lamina beneath the endothelium and modification of the endothelial fenestrations [17]. All these processes are maximal in zone 3. They contribute to deprivation of nutrients intended for the hepatocyte and to the development of portal hypertension.

Adhesion molecules

In hepatic inflammation lymphocytes are often the cells infiltrating the liver. There is an interaction between the receptor on the leucocyte surface, lymphocyte function-associated antigen (LFA-1) and an inter-cellular adhesion molecule (ICAM-1 or -2). ICAM-1 is expressed strongly on sinusoidal lining cells and weakly on portal and hepatic endothelium in normal liver. Induction of ICAM-1 on biliary epithelium, vascular endothelium and peri-venular hepatocytes is found in post-transplant rejection. Expression of this adhesion molecule on bile ducts has been found in primary biliary cirrhosis and primary sclerosing cholangitis [1].

Functional heterogeneity [18]

The relative functions of cells in the circulatory periphery of acini (zone 3) adjacent to terminal hepatic veins are different from those in the circulatory area adjacent to terminal hepatic arteries and portal veins (zone 1) (see figs 1.12, 1.13, table 1.1).

Krebs' cycle enzymes (urea synthesis and glutaminase) are found in the highest concentration in zone 1, whereas glutamine synthetase is peri-venous.

Oxygen supply is an obvious difference [18]; cells in zone 3 receive their oxygen supply last and are particularly prone to anoxic liver injury.

The drug-metabolizing P450 enzymes are present in greater amounts in zone 3. This is particularly so after enzyme induction, for instance with phenobarbital. Hepatocytes in zone 3 receive a higher concentration of any toxic product of drug metabolism. They also have a reduced glutathione concentration. This makes them particularly susceptible to hepatic drug reactions.

Hepatocytes in zone 1 receive blood with a high bile salt concentration and, therefore, are particularly important in bile-salt-dependent bile formation. Hepatocytes in zone 3 are important in non-bile-salt-dependent bile formation. There are also zonal differences in the hepatic transport rate of substances from the sinusoid to canaliculus.

The cause of the metabolic difference between the zones varies. For some functions (gluconeogenesis, glycolysis, ketogenesis) it appears to be dependent upon the direction of blood flow along the sinusoid. For others (cytochrome P450) the gene transcription rate differs between peri-venous and peri-portal hepatocytes. The

Table 1.1. Metabolism related to the zonal location of the hepatocyte whether acinar zone 1 ('peri-portal') or zone 3 ('central')

	Zone 1	Zone 3
Carbohydrates	Gluconeogenesis	Glycolysis
Proteins	Albumin } synthesis	Albumin } synthesis
	Fibrinogen }	Fibrinogen }
Cytochrome P450	+	++
after phenobarbital	+	++++++++
Glutathione	++	–
Oxygen supply	+++	+
Bile formation		
bile-salt-dependent	++	–
non-bile-salt-dependent	–	++
Sinusoids	Small	Straight
	Highly anastomotic	Radial

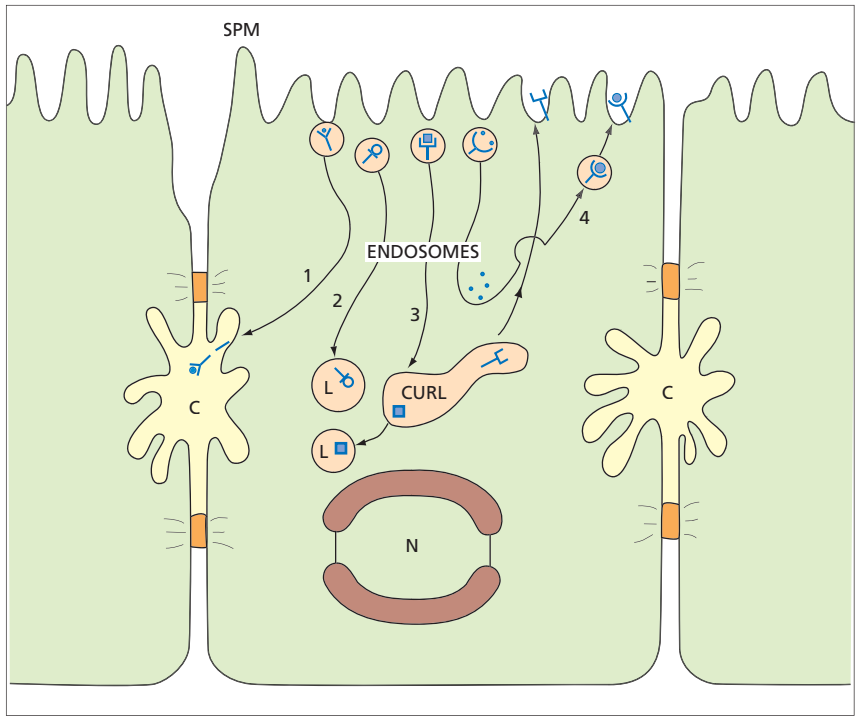


Fig. 1.19. Pathways of endocytosis from the sinusoidal plasma membrane (SPM). Receptors bound to ligand group together in a coated pit. There is endocytosis resulting in a coated vesicle which then loses its clatharin coat and fuses with other vesicles to form early endosomes (the site of sorting). Subsequent pathways include:
1 vesicular transport to the bile canaliculus (C) where the ligand and receptor are released (transcytosis) (e.g. polymeric IgA);
2 transfer of the ligand and receptor to a lysosome (L) where they are degraded;
3 the receptor and ligand are transferred to a compartment of uncoupling of receptor and ligand (CURL). The receptor and ligand separate. The receptor returns to sinusoidal plasma membrane and the ligand enters a lysosome and is degraded (e.g. LDL, asialoglycoprotein, insulin);
4 the ligand and receptor return to the plasma membrane (e.g. transferrin and its receptor after release of iron).
N, nucleus.

differential expression of glutamine synthetase across the acinus is already established in fetal liver.

Sinusoidal membrane traffic

The sinusoidal plasma membrane is a receptor-rich and metabolically dynamic domain which is separated from the bile canaliculus by a lateral domain which participates in cell–cell interactions (see fig. 1.14). Receptor-mediated endocytosis is responsible for the transfer of large molecules such as glycoproteins, growth factors and carrier proteins (transferrin). These ligands bind to receptors on the sinusoidal membrane, the occupied receptors cluster into a coated (clatharin) pit and endocytosis proceeds. The fate of the ligand within the cell varies according to the molecule involved, and the pathways are complex (fig. 1.19). Many ligands terminate in lysosomes where they are broken down while the receptor returns to the sinusoidal plasma membrane to perform again. Some ligands pass by vesicular transport across the cell to be discharged into the bile canaliculus.

Bile duct epithelial cells

Bile duct epithelial cells (cholangiocytes) [19] line the extra-hepatic and intra-hepatic bile ducts, and modify the bile derived from the canaliculi of the hepatocytes (Chapter 13). Cholangiocytes have both secretory (bicarbonate) and re-absorptive processes, which are under the control of hormones (e.g. secretin), peptides (endothelin-1) and cholinergic innervation. Cholangiocytes derived from different levels of the bile duct have different properties—as is true for hepatocytes from different areas of the acinus. This heterogeneity may explain in part the distribution of different diseases across specific areas of the biliary tree.

References

1 Adams DH, Hubscher SG, Shaw J *et al*. Increased expression of intercellular adhesion molecule 1 on bile ducts in primary biliary cirrhosis and primary sclerosing cholangitis. *Hepatology* 1991; **14**: 426.

2 Alison MR, Poulsom R, Jeffery R *et al*. Hepatocytes from non-hepatic adult stem cells. *Nature* 2000; 406: 257.

3 Arthur MJP, Mann DA, Iredale JP. Tissue inhibitors of metalloproteinases, hepatic stellate cells and liver fibrosis. *J. Gastroenterol. Hepatol.* 1998; **13**: S33.

4 Bioulac-Sage P, Lafon ME, Saric J *et al*. Nerves and perisinusoidal cells in human liver. *J. Hepatol*. 1990; **10**: 105.

5 Bismuth H. Surgical anatomy and anatomical surgery of the liver. *World J. Surg*. 1982; **6**: 3.

6 Braet F, De Zanger R, Baekeland M *et al*. Structure and dynamics of the fenestrae-associated cytoskeleton of rat liver sinusoidal endothelial cells. *Hepatology* 1995; **21**: 180.

7 Contreras MA, Khan M, Smith BT *et al*. Endotoxin induces structure–function alterations of rat liver peroxisomes: Kupffer cells released factors as possible modulators. *Hepatology* 2000; **31**: 446.

8 Crawford AR, Lin X-Z, Crawford JM. The normal adult human liver biopsy: a quantitative reference standard. *Hepatology* 1998; **28**: 323.

9 Crosbie OM, Reynolds M, McEntee G *et al*. *In vitro* evidence for the presence of haematopoietic stem cells in the adult human liver. *Hepatology* 1999; **29**: 1193.

10 Deaciuc IV, Bagby GJ, Niesman MR *et al*. Modulation of hepatic sinusoidal endothelial cell function by Kupffer cells: an example of intercellular communication in the liver. *Hepatology* 1994; **19**: 464.

11 Fausto N. Liver regeneration. *J. Hepatol.* 2000; **32** (suppl. 1): 19.

12 Feldmann G. The cytoskeleton of the hepatocyte. *J. Hepatol*. 1989; **8**: 380.

13 Feldmann G. Liver apoptosis. *J. Hepatol*. 1997; **26** (suppl. 2): 1.

14 FitzPatrick DR. Zellweger syndrome and associated phenotypes. *J. Med. Genet*. 1996; **33**: 863.

15 Fraser R, Dobbs BR, Rogers GWT. Lipoproteins and the liver sieve: the role of the fenestrated sinusoidal endothelium in lipoprotein metabolism, atherosclerosis, and cirrhosis. *Hepatology* 1995; **21**: 863.

16 Hadjis NS, Blumgart LH. Clinical aspects of liver atrophy. *J. Clin. Gastroenterol*. 1989; **11**: 3.

17 Horn T, Christoffersen P, Henriksen JH. Alcoholic liver injury: defenestration in noncirrhotic livers. A scanning microscopic study. *Hepatology* 1987; **7**: 77.

18 Jungermann K, Kietzmann T. Oxygen: modulator of metabolic zonation and disease of the liver. *Hepatology* 2000; **31**: 255.

19 Kanno N, LeSage G, Glaser S *et al*. Functional heterogeneity of the intrahepatic biliary epithelium. *Hepatology* 2000; **31**: 555.

20 Kaplowitz N. Mechanisms of liver cell injury. *J. Hepatol.* 2000; **32** (suppl. 1): 39.

21 McGuire RF, Bissell DM, Boyles J *et al*. Role of extracellular matrix in regulating fenestrations of sinusoidal endothelial cells isolated from normal rat liver. *Hepatology* 1992; **15**: 989.

22 Maher JJ, Friedman SL. Parenchymal and nonparenchymal cell interactions in the liver. *Semin. Liver Dis.* 1993; **13**: 13.

23 Natori S, Rust C, Stadheim LM *et al*. Hepatocyte apoptosis is a pathologic feature of human alcoholic hepatitis. *J. Hepatol*. 2001; 34: 248.

24 Northover JMA, Terblanche J. A new look at the arterial supply of the bile duct in man and its surgical implications. *Br. J. Surg*. 1979; **66**: 379.

25 Patel T, Roberts LR, Jones BA *et al*. Dysregulation of apoptosis as a mechanism of liver disease: an overview. *Semin. Liver Dis.* 1998; **18**: 105.

26 Patel T, Steer CJ, Gores GJ. Apoptosis and the liver: a mechanism of disease, growth regulation and carcinogenesis. *Hepatology* 1999; **30**: 811.

27 Radin DR, Colletti PM, Ralls PW *et al*. Agenesis of the right lobe of the liver. *Radiology* 1987; **164**: 639.

28 Rappaport AM. The microcirculatory acinar concept of normal and pathological hepatic structure. *Beitr. Path.* 1976; **157**: 215.

29 Rockey DC, Weisiger RA. Endothelin induced contractility of stellate cells from normal and cirrhotic rat liver: implica-

tions for regulation of portal pressure and resistance. *Hepatology* 1996; **24**: 233.
30 Sakamoto M, Ueno T, Kin M *et al*. Ito cell contraction in response to endothelin-1 and substance P. *Hepatology* 1993; **18**: 978.
31 Selden C, Khalil M, Hodgson HJF *et al*. What keeps hepatocytes on the straight and narrow? Maintaining differentiated function in the liver. *Gut* 1999; **44**: 443.
32 Sell S. Heterogeneity and plasticity of hepatocyte lineage cells. *Hepatology* 2001; 33: 738.
33 Skrainka B, Stahlhut J, Fullbeck CL *et al*. Measuring liver span. Bedside examination vs. ultrasound and scintiscan. *J. Clin. Gastroenterol*. 1986; **8**: 267.
34 Smedsrod B, De Bleser PJ, Braet F *et al*. Cell biology of liver endothelial and Kupffer cells. *Gut* 1994; **35**: 1509.
35 Smedsrod B, Pertoft H, Gustafson S *et al*. Scavenger functions of the liver endothelial cell. *Biochem. J*. 1990; **266**: 313.
36 Theise ND, Badve S, Saxena R *et al*. Derivation of hepatocytes from bone marrow cells in mice after radiation-induced myeloablation. *Hepatology* 2000; **31**: 235.
37 Theise ND, Nimmakayalu M, Gardner R *et al*. Liver from bone marrow in humans. *Hepatology* 2000; 32: 11.
38 Theise ND, Saxena R, Portmann BC *et al*. The canals of Hering and hepatic stem cells in humans. *Hepatology* 1999; **30**: 1425.
39 Toth CA, Thomas P. Liver endocytosis and Kupffer cells. *Hepatology* 1992; **16**: 255.
40 van Eyken P, Desmet VJ. Cytokeratins and the liver. *Liver* 1993; **13**: 113.
41 van Leeuwen MS, Noordzij J, Fernandez MA *et al*. Portal venous and segmental anatomy of the right hemiliver: observations based on three-dimensional spiral CT renderings. *Am. J. Roentgenol.* 1994; **163**: 1395.
42 Wisse E, Luo D, Vermijlen D *et al*. On the function of pit cells, the liver-specific natural killer cells. *Semin. Liver Dis.* 1997; **17**: 265.

Chapter 2
Assessment of Liver Function

Selection of biochemical tests

Tests are needed to detect disease, direct the diagnostic work-up, estimate severity, assess prognosis and evaluate therapy (table 2.1). There is no 'magic' test and it is unnecessary to use a large number of methods. The more investigations are multiplied, the greater chance there is of a biochemical deficiency being demonstrated. This type of 'shotgun' investigation adds to the confusion. A few simple tests of established value should be used.

If an abnormality is found it may need to be confirmed by a repeat estimation to show that it is real and not a laboratory error.

The tests most useful in the *diagnostic work-up of jaundice* (Chapter 12) are the serum alkaline phosphatase level and serum transaminase values. An isolated rise in serum unconjugated bilirubin suggests Gilbert's syndrome or haemolysis.

The *severity of liver cell damage* is assessed by serial measurement of serum total bilirubin, albumin, transaminase and prothrombin time after vitamin K.

The diagnosis of *minimal hepato-cellular damage* may be suspected by noting minimally elevated serum transaminase values and sometimes serum bilirubin. Causes will include alcoholic liver damage, where serum γ-glutamyl transpeptidase (γ-GT) is of particular value, and well-compensated cirrhosis—although similar changes may be seen in heart failure and fever.

Hepatic infiltrations such as primary or secondary cancer, amyloid disease or the reticuloses are suggested by an elevated serum alkaline phosphatase value without jaundice.

Fibrosis may be assessed by serum markers, including procollagen type III peptide (Chapter 21).

The pattern of *conventional tests* (bilirubin, enzymes) indicate which more specialist tests are likely to be valuable. These more specific methods include viral hepatitis markers and immunological tests such as the mitochondrial antibody for primary biliary cirrhosis. Imaging by ultrasonography, CT and MRI are important links in the diagnostic pathway, as is liver biopsy.

The liver is central to the metabolism of protein, carbohydrate and fat (fig. 2.1) as well as being important in drug metabolism. Quantitative methods of assessment of liver function using substrates for a specific hepatic pathway, including galactose, caffeine and lignocaine, give a better measure of hepatic *function* rather than *damage* (p. 23). Quantification of the asialoglycoprotein receptor also provides a measure of the 'functional mass' of the liver.

Table 2.1. Essential serum methods in hepato-biliary disease

Test	Normal range	Value
Bilirubin		
total	5–17 μmol/l*	Diagnosis of jaundice; assess severity
conjugated	<5 μmol/l	Gilbert's disease, haemolysis
Alkaline phosphatase	35–130 iu/l	Diagnosis of cholestasis, hepatic infiltrations
Aspartate transaminase (AST/SGOT)	5–40 iu/l	Early diagnosis of hepato-cellular disease; follow progress
Alanine transaminase (ALT/SGPT)	5–35 iu/l	ALT relatively lower than AST in alcoholism
γ-glutamyl transpeptidase (γ-GT)	10–48 iu/l	Diagnosis of alcohol abuse, marker biliary cholestasis
Albumin	35–50 g/l	Assess severity
γ-globulin	5–15 g/l	Diagnosis chronic hepatitis and cirrhosis; follow course
Prothrombin time (PT) (after vitamin K)	12–16 s	Assess severity

*0.3–1.0 mg/dl.

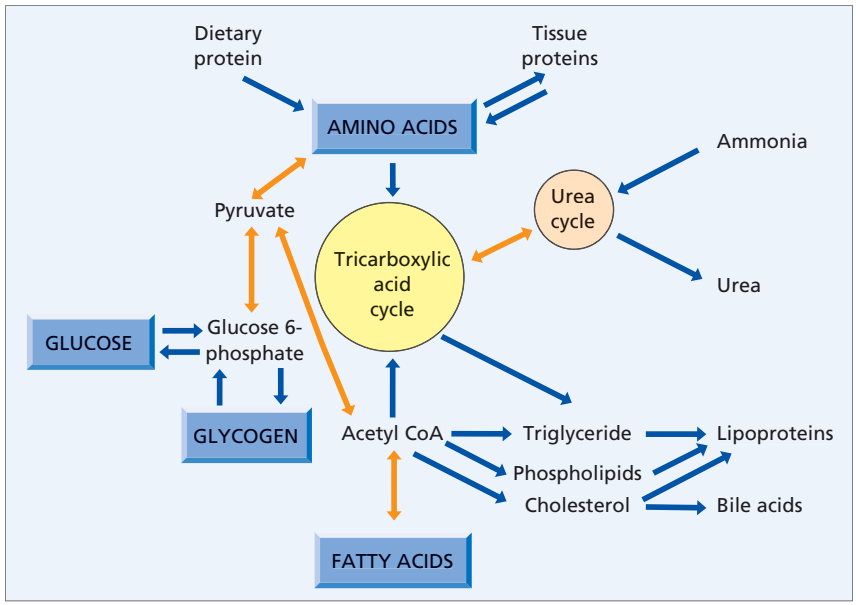


Fig. 2.1. The important metabolic pathways of protein, carbohydrate and fat in the liver.

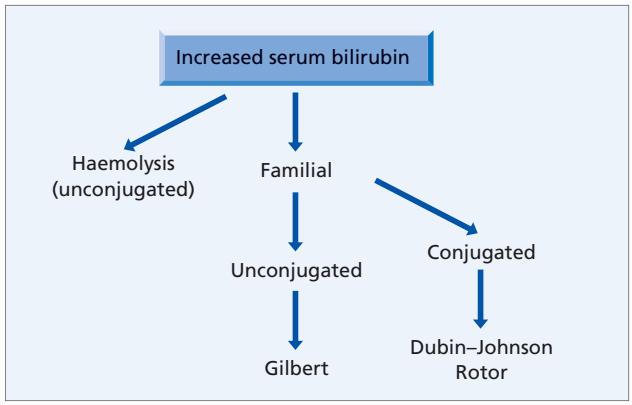


Fig. 2.2. Algorithm for managing a patient with an isolated increase in serum total bilirubin.

Bile pigments

Bilirubin

Bilirubin metabolism is described in detail in Chapter 12.

The serum bilirubin may be increased in both cholestatic and hepato-cellular disease with an associated rise in liver enzymes. In these cases the bilirubin is predominantly conjugated. An isolated rise in serum bilirubin (without enzyme elevation) may be familial or due to haemolysis (fig. 2.2).

Serum bilirubin estimations are based on the van den Bergh diazo reaction. A direct reaction at 10 min gives an estimate of the conjugated bilirubin present. The total bilirubin is determined in the presence of an accelerator such as caffeine benzoate or methanol. An approximate value for the unconjugated (indirect) bilirubin is obtained by subtracting the value for conjugated bilirubin from that for the total bilirubin.

These diazo reactions are subject to error and diagnosis should not be based solely upon them. Other more accurate methods for estimation, such as thin layer chromatography, high performance gas liquid chromatography and alkaline methanolysis, are available but are too elaborate to be clinically useful [2].

Inspection of *faeces* is an important investigation in jaundice. Clay-coloured stools indicate cholestatic jaundice but may also occur in hepato-cellular jaundice. The colour will be normal in haemolytic jaundice. Rarely, pale stools occur in very severe bilirubin glucuronyl-transferase deficiency (Chapter 12).

Bilirubin cannot be detected in the *urine* of normal subjects or in patients with unconjugated hyperbilirubinaemia. In cholestatic patients, a small fraction of the conjugated bilirubin in plasma is dialysable and filtered by the glomerulus, some is reabsorbed by the tubules, and the remainder gives the dark colour to the urine.

'Dipsticks' are commercially available, easy to use and give satisfactory results for the detection of conjugated bilirubin in urine.

Uses. In acute viral hepatitis, bilirubin appears in the urine before urobilinogen or before jaundice. In an undiagnosed febrile illness, bilirubinuria favours the diagnosis of hepatitis.

As a screening test urinary bilirubin has some value in general practice in detecting the pre-icteric patient. It is, however, an insensitive test for patients with enzyme elevation alone [1].

Urobilinogen

Bacterial action converts bilirubin in the colon to a series

of colourless tetrapyrroles collectively called urobilinogen. Approximately 20% is absorbed and undergoes an enteric circulation with re-excretion into bile by the liver. A small proportion is excreted in the urine. Urinary urobilinogen has been used in the evaluation of liver problems. In complete bile duct obstruction where no bilirubin enters the intestine, urinary urobilinogen may be absent. However, measurement of this substance in the urine has been superseded by more sensitive serum tests as well as by imaging, which give a more direct path to diagnosis. As with urinary bilirubin measurements, spot urinary urobilinogen is a poor predictor of hepatic disease with a high proportion of false negative results [1].

Bromsulphalein

The dye bromsulphalein (BSP) is rapidly removed by the liver and excreted in the bile. The intravenous test was used to assess liver dysfunction in the absence of jaundice. However, in view of the cost, the occasional side-effects (which may be fatal) and the inconvenience, it is rarely performed nowadays.

In patients suspected of Dubin–Johnson hyperbilirubinaemia a blood sample is taken not only at 45 min after injection but also at 2 h. A higher level of BSP at 2 h than at 45 min is diagnostic and reflects the release of conjugated BSP back into the blood stream after a normal initial uptake [3].

References

1 Binder L, Smith D, Kupka T *et al*. Failure of prediction of liver function test abnormalities with the urine urobilinogen and urine bilirubin assays. *Arch. Pathol. Lab. Med.* 1989; **113**: 73.

2 Fevery J, Blanckaert N. What can we learn from analysis of the serum bilirubin? *J. Hepatol.* 1986; **2**: 113.

3 Mandema E, DeFraiture WH, Nieweg HO *et al*. Familial chronic idiopathic jaundice (Dubin–Sprinz disease) with a note on bromsulphalein metabolism in this disease. *Am. J. Med.* 1960; **28**: 42.

Serum enzyme tests

These tests will usually indicate the type of liver injury, whether hepato-cellular or cholestatic, but cannot be expected to differentiate one form of hepatitis from another or to determine whether cholestasis is intra- or extra-hepatic. They are valuable in directing the choice of specific serological tests, imaging or liver biopsy to reach the diagnosis. Only a few tests are necessary and the combination of a serum aspartate transaminase (AST formerly SGOT) and alkaline phosphatase, with occasionally serum alanine transaminase (ALT formerly SGPT) is adequate. Ideally, normal ALT values should be adjusted for body mass index and gender [5]. During pregnancy, serum ALT, AST and γ-GT levels, as well as serum bile acid and bilirubin concentrations, remain within the normal range [1].

Alkaline phosphatase

The level of alkaline phosphatase rises in cholestasis and to a lesser extent when liver cells are damaged (fig. 2.3). The mechanisms of the increase are complex. Synthesis of alkaline phosphatase by the hepatocyte is increased and this depends on intact protein and RNA synthesis. Secretion into the serum may arise through leakage from the canaliculus into the sinusoid because of leaky tight junctions. Increased release of alkaline phosphatase into sinusoids from the hepatocyte plasma membranes may contribute.

Serum hepatic alkaline phosphatase may be distinguished from bony phosphatase by fractionation into

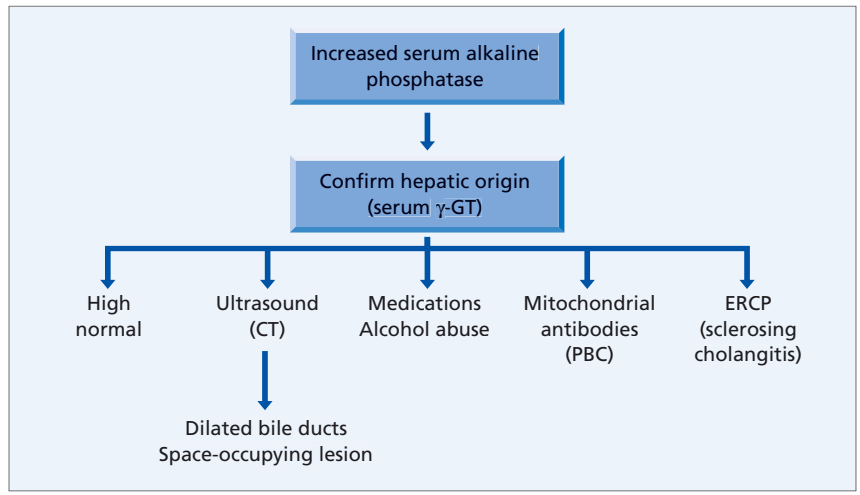


Fig. 2.3. Algorithm for managing a patient with an isolated increase in serum alkaline phosphatase or serum γ-glutamyl transpeptidase (γ-GT). CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; PBC, primary biliary cirrhosis.

isoenzymes, but this is not routinely carried out. An isolated rise in alkaline phosphatase may be of intestinal origin [6]. A rise in γ-GT confirms the likely source of alkaline phosphatase as being hepato-biliary. Raised levels are sometimes observed with primary or secondary hepatic tumours, even without jaundice or involvement of bone. Increased values without a rise in serum bilirubin are also found with other space-occupying lesions or infiltration, such as amyloid, abscess, leukaemia or granulomas. Non-specific mild elevations are seen in a variety of conditions including Hodgkin's disease and heart failure. The cause is presumably focal, intra-hepatic bile duct obstruction caused by these lesions.

Gamma glutamyl transpeptidase

Serum values are increased in cholestasis and hepatocellular disease. Levels parallel serum alkaline phosphatase in cholestasis and may be used to confirm that a raised serum phosphatase is of hepato-biliary origin (see above). Levels are increased with hepatic metastases, not consistently but more so than for alkaline phosphatase.

An isolated rise in serum γ-GT is seen in patients with alcohol abuse, even without liver disease, perhaps because of microsomal enzyme induction. More often there is steatosis. In fibrosis, cirrhosis and hepatitis due to alcohol, other liver enzymes are elevated in conjunction with γ-GT [4].

Unfortunately many factors influence the level so that increases are non-disease-specific. Disorders include hepato-biliary disease, alcoholism and concomitant drug administration, for instance with barbiturates or phenytoin. Screening with serum γ-GT may have led to more alcohol abusers being identified, although in a third of such individuals the serum γ-GT does not rise. The finding of an increased level, however, often leads to over-investigation in an innocent person who has never taken alcohol or a social drinker who has never abused alcohol.

Aminotransferases

Aspartate transaminase (AST; serum glutamic oxaloacetic transaminase or SGOT) is a mitochondrial enzyme present in large quantities in heart, liver, skeletal muscle and kidney, and the serum level increases whenever these tissues are acutely destroyed, presumably due to release from damaged cells.

Alanine transaminase (ALT; serum glutamic pyruvic transaminase or SGPT) is a cytosolic enzyme also present in liver. Although the absolute amount is less than SGOT, a greater proportion is present in liver compared with heart and skeletal muscles. A serum increase is therefore more specific for liver damage than SGOT.

Transaminase determinations are useful in the early diagnosis of viral hepatitis. Measurements must be made early, for normal values may be reached within a week of the onset. The patient may develop fatal acute hepatic necrosis in spite of falling transaminase values. Serial estimations are essential.

The commonest causes for an AST being greater than 10 times the upper limit of normal in a general hospital are hepatic hypoxia and calculous bile duct obstruction. Viral and drug hepatitis are rare [8].

Routine screening may show unexpectedly raised aminotransferase levels. These are often due to obesity, diabetes mellitus, alcohol abuse, hepatic drug reaction or circulatory failure (fig. 2.4). Chronic viral and autoimmune hepatitis must be considered, as must haemochromatosis. Rarer causes include α_1-antitrypsin deficiency, coeliac disease [2] and hyperthyroidism [3]. Liver biopsy is usually necessary to make the diagnosis. However, this should be delayed if the patient is asymptomatic and the increase in transaminase is modest. The value should be monitored.

Results vary in cirrhosis, and are particularly high in chronic hepatitis with active inflammation. Very high levels are unusual in alcoholic liver disease. A high ratio of SGOT to SGPT (greater than two) may be useful in diagnosing alcoholic hepatitis and cirrhosis. This is due

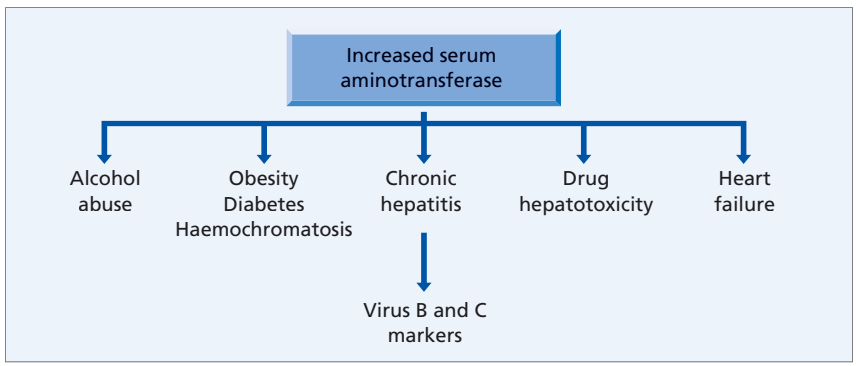


Fig. 2.4. Algorithm for managing a patient with an isolated increase in serum aminotransferase on routine screening.

not only to hepatocyte damage but to pyridoxal 5-phosphate (vitamin B_6) deficiency.

Other serum enzymes

Lactic dehydrogenase (LDH) is a relatively insensitive index of hepato-cellular injury and is not routinely used. Marked increases are found in patients with neoplasms, especially with hepatic involvement.

Glutathione-*S*-transferase α-isoenzyme (GST-α) is a potential alternative to the transaminases for assessing hepato-cellular damage. While AST is concentrated in peri-portal hepatocytes, GST-α has a more even distribution across the liver acinus. This enzyme also has a short half-life of 90 min and may therefore be a sensitive rapidly responding marker of liver injury [7].

References

1 Bacq Y, Zarka O, Bréchot J-F *et al*. Liver function tests in normal pregnancy: a prospective study of 103 pregnant women and 103 matched controls. *Hepatology* 1996; **23**: 1030.

2 Bardella MT, Vecchi M, Conte D *et al*. Chronic unexplained hypertransaminasemia may be caused by occult celiac disease. *Hepatology* 1999; **29**: 654.

3 Gurlek A, Cobankara V, Bayraktar M. Liver tests in hyperthyroidism: effect of antithyroid therapy. *J. Clin. Gastroenterol*. 1997; **24**: 180.

4 Ireland A, Hartley L, Ryley N *et al*. Raised γ-glutamyltransferase activity and the need for liver biopsy. *Br. Med. J.* 1991; **302**: 388.

5 Piton A, Poynard T, Imbert-Bismut I *et al*. Factors associated with serum alanine transaminase activity in healthy subjects: consequences for the definition of normal values, for selection of blood donors, and for patients with chronic hepatitis C. *Hepatology* 1998; **27**: 1213.

6 Rosalki SB, Foo AY, Dooley JS. Benign familial hyperphosphatasaemia as a cause of unexplained increase in plasma alkaline phosphatase activity. *J. Clin. Pathol.* 1993; **46**: 738.

7 Tredger JM, Sherwood RA. The liver: new functional, prognostic and diagnostic tests. *Ann. Clin. Biochem.* 1997; **34**: 121.

8 Whitehead MW, Hawkes ND, Hainsworth I *et al*. A prospective study of the causes of notably raised aspartate aminotransferase of liver origin. *Gut* 1999; **45**: 129.

Quantitative assessment of hepatic function (table 2.2) [13]

Chronic liver diseases pass through a long period of minimum non-specific symptoms ('compensated') until the final stage of ascites, jaundice, encephalopathy and pre-coma ('decompensated'). Serum albumin and prothrombin time give some indication of the synthetic function of the liver, but this is usually maintained until late disease. Serial estimates of *quantitative liver function* in the early stages would be helpful both in monitoring treatment and in prognosis but are of no value in diagnosis.

Table 2.2. Quantitative hepatic function tests

Site	Substrate	Function
Cytosol	Galactose*	Galactokinase (phosphorylation)
Microsome (cytochrome P450 system)	Aminopyrine	*N*-demethylation
	Caffeine	*N*-demethylation
	Lignocaine	*N*-deethylation
	Antipyrine	Hydroxylation/ demethylation
Sinusoidal receptor membrane	Galactose-terminated glycoprotein	Asialoglycoprotein receptor

*Low dose assesses hepatic perfusion.

In the rat model of biliary cirrhosis, serial breath tests allow prediction of the time of death from cirrhosis. In 78 patients with cirrhosis, galactose elimination capacity, aminopyrine breath test and indocyanine green clearance predicted survival (fig. 2.5) but were not significantly better than the Child (Pugh) score [6]. In 190 alcoholic cirrhotics, the aminopyrine breath test had added prognostic value in Child grade A and B, but not grade C patients [14].

Such tests suffer from the drawback of their complexity (multiple blood samples or measurement of isotopes). The lack of a major impact above routine laboratory tests and Child grading is reflected in their present role in clinical research rather than the routine management of patients.

Galactose elimination capacity

Galactose is pharmacologically safe and can be injected intravenously in a dose sufficient to saturate the enzyme system responsible for its elimination. The rate-limiting step is the initial phosphorylation by galactokinase. Account must be taken of the substantial fraction of the dose eliminated extra-hepatically. This test seems to reflect hepato-cellular function fairly accurately (fig. 2.5) but requires multiple determinations over a 2-h period.

Breath tests

Aminopyrine is metabolized (*N*-demethylated) by the cytochrome P450 (microsomal) system to carbon dioxide. It has many of the characteristics of an ideal breath test substance for the measurement of hepatic function. The aminopyrine is labelled with ^{14}C and given by mouth. Samples of breath are collected at intervals

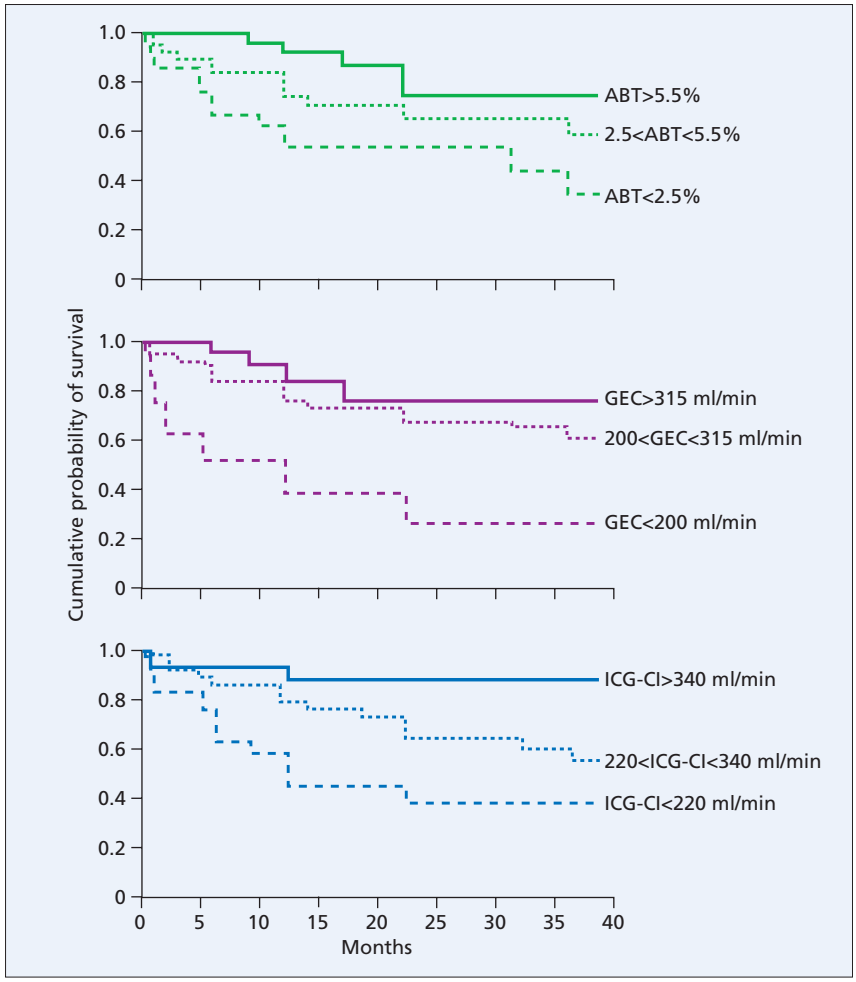


Fig. 2.5. Kaplan–Meier survival curves in 78 patients with cirrhosis stratified according to the results of an aminopyrine breath test (ABT), galactose elimination capacity (GEC) and indocyanine green clearance (ICG-Cl) [6].

over 2h for analysis. The expired $^{14}CO_2$ correlates with the rate of disappearance of radio-activity from the plasma. The test reflects the residual functional microsomal mass and viable hepatic tissue, but is affected by basal metabolic rate and administered drugs. Results in cirrhotic rats suggest that reduced *N*-demethylation is due to loss of liver cell volume. The function per hepatocyte remains constant. It is of value in prognosis [6] and to assess therapy rather than for screening or diagnosis. It may be useful to assess the effect of drugs on hepatic microsomal enzyme function.

The ^{13}C-methacetin breath test discriminates well between cirrhotic and non-cirrhotic patients but its prognostic value has not been established [4].

^{14}C-caffeine and phenacetin have been used as breath test substances. The ^{14}C-galactose breath test measures cytosolic function; stable isotopes (^{13}C) have also been used [1]. All breath tests are complex and costly. They are unlikely to achieve general popularity.

Salivary caffeine clearance

Caffeine (1,3,7-trimethylxanthine) is metabolized almost exclusively by *N*-demethylation in the hepatic microsomal enzyme system (cytochrome P448). The methylxanthines are excreted in the urine. Serum and salivary caffeine levels can be assayed simply using an enzyme multiplied immuno-assay technique. Overnight caffeine clearance in saliva correlates well with serum clearance and also with the aminopyrine breath test [16]. Salivary caffeine clearance is a simple method to measure hepatic functional impairment. Although caffeine clearance in normal volunteers may vary four-fold [9], it has been found to predict survival in cirrhotic patients [3]. There is, however, reduced caffeine clearance with increasing age, induction of metabolism by cigarette smoking and interference with metabolism by certain drugs such as cimetidine and oral contraceptives. Serial caffeine clearance testing in the same patient should be done with a

standardized dose of caffeine since clearance is dose dependent. Caffeine intake and the number of cigarettes smoked must be kept constant.

Lignocaine metabolite formation

Lignocaine is metabolized by oxidative *N*-deethylation by the cytochrome P450 system. Monoethylglycinexylidide (MEGX) is formed and correlates with the rate of lignocaine clearance. Serum MEGX concentration after intravenous injection of lignocaine gives a quantitative assessment of liver function. The MEGX formation test using a lower dose of lignocaine gives almost identical results to the standard test with fewer side-effects [11]. MEGX concentrations vary widely both in patients without liver disease as well as in those with only mild abnormalities [7]. They are significantly lower in cirrhotics and correlate with a worse prognosis [2]. Galactose elimination and aminopyrine breath test may discriminate mild disease from cirrhosis better than MEGX formation [7].

Arterial blood ketone body ratio

The ratio of acetoacetate to 3-hydroxybutyrate in arterial blood has been used as an indicator of hepatic mitochondrial function and hepatic redox state. It has been used prognostically in patients undergoing hepatic surgery and in those with fulminant hepatic failure, but experience is limited. Extra-hepatic metabolism may limit its value as a liver function test [5].

Antipyrine

Antipyrine has a long half-life, which in patients with severe liver disease may increase to 30 h or more. Sampling of blood or saliva has to be over an extended period which limits the practicability of this agent.

Indocyanine green

This dye is removed from the circulation by the liver and excreted into bile. Its clearance has been used to assess hepato-cellular function. There is no extra-hepatic removal but clearance does depend in part on liver blood flow, which may be reduced in chronic liver disease due to shunting. Thus it can be used for liver blood flow studies. It discriminates disease severity in cirrhotic patients [12].

Asialoglycoprotein receptor

Hepatocytes clear asialoglycoproteins (galactose-terminated) from the circulation by a specific receptor on the sinusoidal plasma membrane. The number of receptors falls with hepato-cellular damage. Receptor number is quantified by computer analysis of the hepatic uptake of ^{99m}Tc-labelled galactosyl-neoglycalbumin (an asialoglycoprotein analogue) using a standard scintillation camera and a single blood test. Results correlate with severity of liver disease (Child score), aminopyrine breath test and indocyanine green clearance. Mean receptor concentration in end-stage cirrhosis ($0.35 \pm 0.07\,\mu mol/l$) compares with $0.83 \pm 0.06\,\mu mol/l$ in controls [10]. There are similar results with ^{99m}Tc-diethylanetriamine-penta-acetic acid–galactosyl human serum albumin which is useful for predicting the post-operative hepatic reserve before performing partial hepatectomy [8]. Receptor number is reduced in acute hepatitis, increasing with recovery [15]. Despite promising results, application of this functional test remains experimental.

Excretory capacity (BSP)

The old intravenous BSP disappearance technique allowed an estimate of the storage capacity of the hepatocyte and its excretory function. It was abandoned because of its complexity, its cost and the untoward reactions to BSP.

References

1 Becker M. ^{13}C breath tests for measurement of liver function. *Gut* 1998; **43** (suppl. 3): S25.

2 Fabris L, Jemmolo RM, Toffolo G *et al*. The monoethylglycinexylidide test for grading of liver cirrhosis. *Alim. Pharmacol. Ther.* 1999; **13**: 67.

3 Jover R, Carnicer F, Sanchez-Paya J *et al*. Salivary caffeine clearance predicts survival in patients with liver cirrhosis. *Am. J. Gastroenterol.* 1997; **92**: 1905.

4 Klatt S, Taut C, Mayer D *et al*. Evaluation of the ^{13}C-methacetin breath test for quantitative liver function testing. *Z. Gastroenterol.* 1997; **35**: 609.

5 Matsushita K, Kawasaki S, Makuuchi M. Arterial ketone body ratio in liver surgery. *Hepatology* 1994; **20**: 331.

6 Merkel C, Gatta A, Zoli M *et al*. Prognostic value of galactose elimination capacity, aminopyrine breath test, and ICG clearance in patients with cirrhosis: comparison with the Pugh score. *Dig. Dis. Sci.* 1991; **36**: 1197.

7 Meyer-Wyss B, Renner E, Luo H *et al*. Assessment of lidocaine metabolite formation in comparison with other quantitative liver function tests. *J. Hepatol.* 1993; **19**: 133.

8 Mitsumori A, Nagaya I, Kimoto S *et al*. Preoperative evaluation of hepatic functional reserve following hepatectomy by technetium-99m galactosyl human serum albumin liver scintigraphy and computed tomography. *Eur. J. Nucl. Med.* 1998; **25**: 1377.

9 Nagel RA, Hayllar KM, Tredger JM *et al*. Caffeine clearance and galactose elimination capacity as prognostic indicators in fulminant hepatic failure. *Eur. J. Gastroenterol. Hepatol.* 1991; **3**: 907.

10 Pimstone NR, Stadalnik RC, Vera DR *et al*. Evaluation of hepatocellular function by way of receptor-mediated uptake of a technetium-99m labelled asialoglycoprotein analogue. *Hepatology* 1994; **20**: 917.
11 Reichel C, Nacke A, Sudhop T *et al*. The low-dose monoethylglycinexylidide test: assessment of liver function with fewer side-effects. *Hepatology* 1997; **25**: 1323.
12 Stremmel W, Wojdat R, Groteguth R *et al*. Liver function tests in a clinical comparison. *Gastroenterology* 1992; **30**: 784.
13 Tredger JM, Sherwood RA. The liver: new functional, prognostic and diagnostic tests. *Ann. Clin. Biochem.* 1997; **34**: 121.
14 Urbain D, Muls V, Thys O *et al*. Aminopyrine breath test improves long-term prognostic evaluation in patients with alcoholic cirrhosis in Child classes A and B. *J. Hepatol.* 1995; **22**: 179.
15 Virgolini I, Müller C, Höbart J *et al*. Liver function in acute viral hepatitis as determined by a hepatocyte-specific ligand: ^{99m}Tc-galactosyl-neoglycoalbumin. *Hepatology* 1992; **15**: 593.
16 Wahllander A, Mohr S, Paumgartner G. Assessment of hepatic function: comparison of caffeine clearance in serum and saliva during the day and at night. *J. Hepatol.* 1990; **10**: 129.

Lipid and lipoprotein metabolism

Lipids

The liver is central to lipid (cholesterol, phospholipid, triglyceride) and lipoprotein metabolism. Lipids are insoluble in water. Lipoproteins, hydrophobic within and hydrophilic on the outside, allow their transport in the plasma.

Cholesterol is found in cell membranes and is a precursor of bile acids and steroid hormones. It is synthesized in the liver, small intestine and in other tissues. Some is derived from intestinal absorption, reaching the liver in chylomicron remnants.

Cholesterol synthesis takes place mainly from acetyl coenzyme A (CoA) in the microsomal fraction and in cytosol (fig. 2.6). Hepatic synthesis is inhibited by cholesterol feeding and by fasting, and is increased by a biliary fistula or bile duct ligation and also by an intestinal lymph fistula. The rate-limiting step is the conversion of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) to mevalonate by the enzyme HMG-CoA reductase. The mechanism controlling this process is uncertain. Cholesterol in membranes and in bile is present almost exclusively as free cholesterol. Bile provides the only significant route for cholesterol excretion. In plasma and in certain tissues such as liver, adrenal and skin, cholesterol esters (cholesterol esterified with long-chain fatty acids) are also found. Cholesterol esters are more nonpolar than free cholesterol and therefore are even less soluble in water. Esterification is carried out in plasma by the enzyme lecithin cholesterol acyl transferase (LCAT) which is synthesized in the liver.

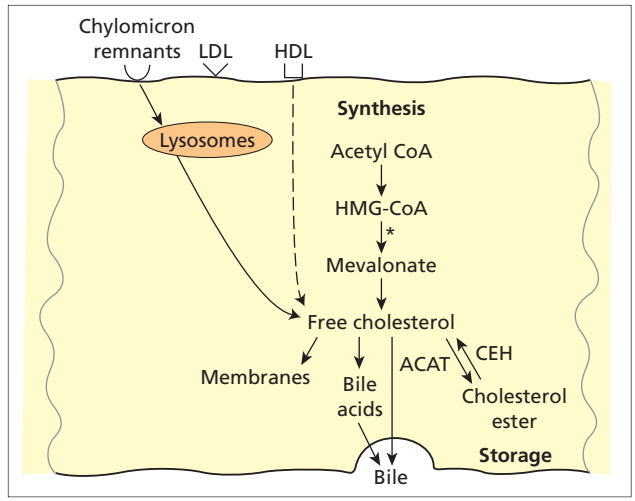


Fig. 2.6. Hepatic cholesterol balance. Free cholesterol is derived from intra-cellular synthesis, and from the uptake of chylomicron remnants and lipoproteins from the circulation. Storage is as cholesterol ester: ACAT (acyl CoA-cholesterol ester transferase, which esterifies free cholesterol to fatty acids) and CEH (cholesteryl ester hydrolase, which hydrolyses the ester linkage). Bile acids are synthesized from free cholesterol, and both are secreted into bile. 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is the rate-limiting step. HDL, high density lipoprotein; LDL, low density lipoprotein.

Phospholipids are a heterogeneous group of compounds. They contain one or more phosphoric acid groups and another polar group. This may be a heterogeneous base such as choline or ethanolamine. In addition there are one or more long-chain fatty acid residues. The phospholipids are much more complex in terms of chemical reactivity than cholesterol and cholesterol esters. They are important constituents of cell membranes and take part in a large number of chemical reactions. The most abundant phospholipid in plasma and most cellular membranes is phosphatidyl choline (lecithin).

Triglycerides are simpler compounds than the phospholipids. They have a backbone of glycerol, the hydroxy groups of which have been esterified with fatty acids. Naturally occurring triglycerides contain a variety of fatty acids; they act as a store of energy and also a method of transport of energy from the gut and liver to peripheral tissues.

Lipoproteins

These are essential for the circulation and metabolism of lipids. They are particles and are separated by their differing density on ultracentrifugation. This explains their nomenclature. Their surface comprises apolipoprotein, of several different types (table 2.3), free cholesterol and phospholipids. Inside there is cholesterol ester, triglycerides and fat-soluble vitamins.

Table 2.3. Properties of lipoproteins

Lipoproteins	Apolipoprotein	Source	Carries
Chylomicrons	B48, AI, C-II, E	Intestine	Dietary fat
VLDL	B100, C-II, E	Liver	Hepatic triglyceride and cholesterol
LDL	B100	From VLDL	Cholesterol
HDL	A-I, A-II	Peripheral tissue	Cholesterol ester

HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein.

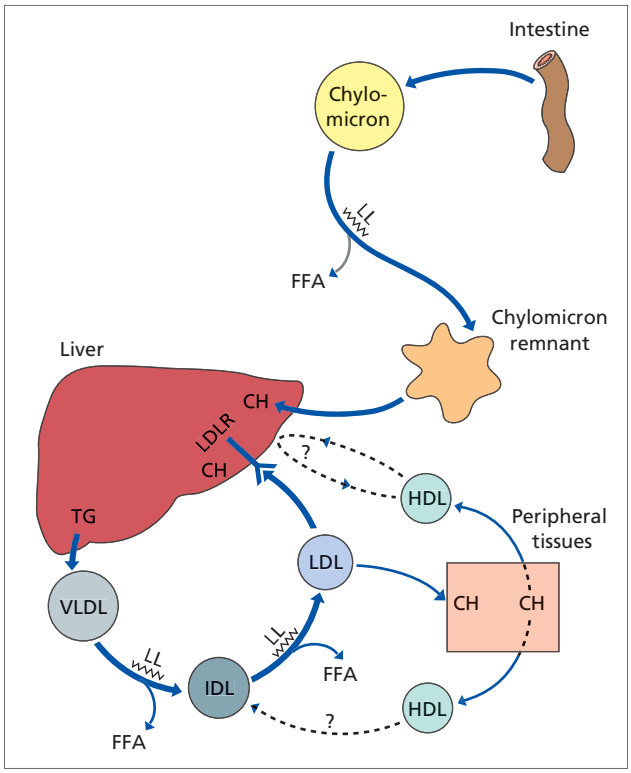


Fig. 2.7. The role of the liver in lipoprotein metabolism. CH, cholesterol; FFA, free fatty acid; LDLR, LDL receptor; LL, lipoprotein lipase; TG, triglyceride. (For lipoproteins see table 2.3.)

There are several metabolic cycles for lipoprotein, of which two are prominent: one is involved in fat absorbed from the intestine, and the other is responsible for the handling of endogenously synthesized lipid (fig. 2.7). There is overlap between the two.

Dietary fat is absorbed from the small intestine, and incorporated into chylomicrons. These enter the circulation (via the thoracic duct) where the triglyceride is removed by the action of lipoprotein lipases. The triglyceride is utilized or stored in tissue. The chylomicron remnant is taken up by the liver by the LDL receptor-related protein. The cholesterol enters metabolic pathways or plasma membranes, or is excreted in bile.

In the endogenous pathway, cholesterol and triglyceride leave the liver in VLDL. In the circulation the triglyceride is removed by the action of lipoprotein lipases. As a result VLDL particles become smaller, forming intermediate density lipoprotein (IDL), and then LDL, the major carrier for cholesterol. The predominant route for removal of LDL is by LDL receptors on the liver surface, but there are receptors on other cells which become important in the formation of atheromatous plaques.

HDL is the particle facilitating cholesterol removal from peripheral tissues. Cholesterol is transported out of the cell by the cholesterol-efflux regulatory protein, expressed from the adenosine triphosphate (ATP) binding cassette transporter 1 gene (ABC1) [2]. The HDL cholesterol is either taken up by the liver, or is incorporated into IDL resulting in the mature LDL. This removal of peripheral cholesterol is an important pathway, as reflected in the protective effect of a high HDL–cholesterol level against coronary artery disease. The metabolism of the HDL particle is still unclear.

Most apolipoproteins are made by the liver, some by the intestines. Apart from being components of lipoproteins, some have other functions: Apo A-1 activates plasma LCAT; C-11 activates lipoprotein lipase.

Changes in liver disease [1]

Cholestasis. Total and free cholesterol are increased. This is not due simply to the retention of cholesterol normally excreted in the bile. The mechanism is uncertain. Four factors have been implicated: regurgitation of biliary cholesterol into the circulation; increased hepatic synthesis of cholesterol; reduced plasma LCAT activity; and regurgitation of biliary lecithin, which produces a shift of cholesterol from pre-existing tissue cholesterol into the plasma. Whereas slight increases to 1.5–2 times normal are sometimes seen in acute cholestasis, very high values are found in chronic conditions, especially post-operative stricture and primary biliary cirrhosis. Values of over five times the upper limit of normal are associated with skin xanthomas. Malnutrition lowers the serum cholesterol so that values may be normal in carcinomatous biliary obstruction.

The level of cholesterol ester is decreased due to LCAT deficiency. Triglycerides tend to be increased. An abnormal lipoprotein, lipoprotein X, very rich in free cholesterol and lecithin is found which appears on electron microscopy as bilamellar discs. The red cell changes in cholestasis are related to abnormalities in cholesterol and lipoprotein.

Parenchymal injury. Triglyerides tend to be increased relating to an accumulation of triglyceride-rich LDL. Cholesterol ester is reduced due to a low LCAT. In cirrhosis total serum cholesterol values are usually normal.

Low results indicate malnutrition or decompensation. In the fatty liver due to alcohol, VLDL is increased, together with triglycerides. With drug toxicity, failure of apolipoprotein synthesis leads to difficulty in export of triglycerides as VLDL, and hence fatty liver.

Serum cholesterol esters, lipoproteins, LCAT and lipoprotein X are not estimated routinely. They are not of any established value in the diagnosis or assessment of liver function.

References

1 Harry DS, McIntyre N. Plasma lipids and lipoproteins. In Bircher J, Benhamou J-P, McIntyre N, Rizzetto M, Rodés J, eds. *Oxford Textbook of Clinical Hepatology*, 2nd edn. Oxford University Press, Oxford, 1999, p. 287.

2 Owen J. Role of ABC1 gene in cholesterol efflux and atheroprotection. *Lancet* 1999; **354**: 1402.

Bile acids

Bile acids [5] are synthesized in the liver and other tissues, 250–500 mg being produced and lost in the faeces daily. Synthesis is under negative feedback control. The primary bile acids, cholic acid and chenodeoxycholic acid, are formed from cholesterol (fig. 2.8). There are two different metabolic pathways for bile acid synthesis. The well-established pathway is 7α-hydroxylation of cholesterol in the liver. A more recently described alternate pathway begins with 27α-hydroxylation of cholesterol in various tissues. Both enzymes belong to the cytochrome P450 group but differ in their substrate specificity [12], subcellular localization and tissue distribution. The C-7α-hydroxylase is found in the endoplasmic reticulum while the C-27α-hydroxylating enzyme is

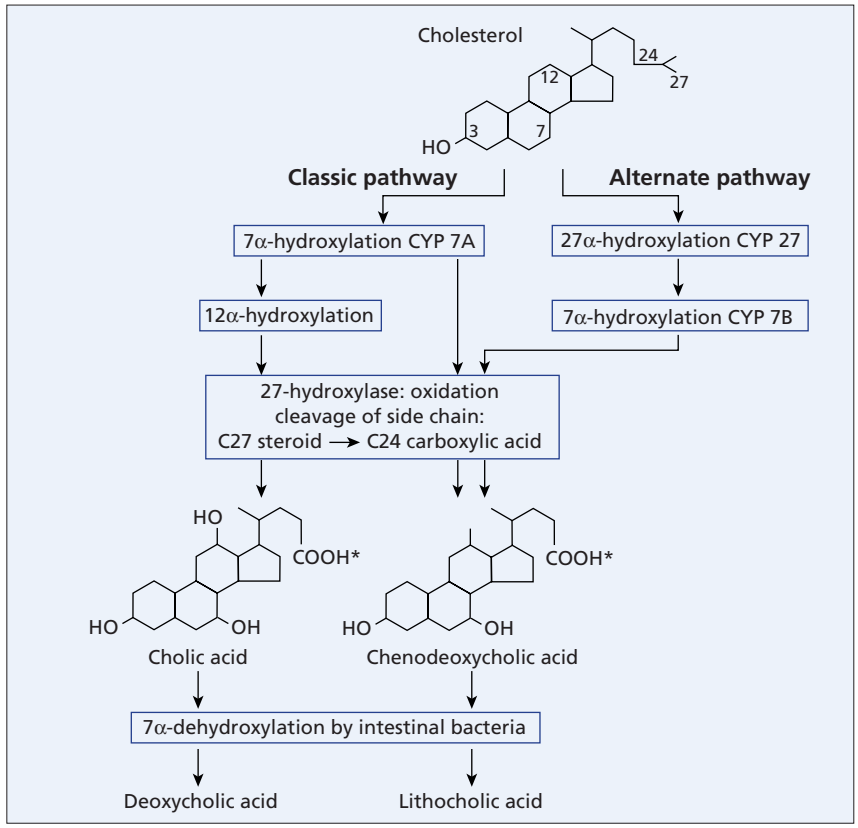


Fig. 2.8. Bile salt synthesis. There are two pathways: classic (neutral) and alternate (acidic).

Classic pathway: 7α-hydroxylation is the initial, rate-limiting step, converting cholesterol to 7α-hydroxycholesterol. The cytochrome P450 enzyme responsible (CYP 7A) is restricted to hepatic microsomes. After further modifications, including 12α-hydroxylation for precursors of cholic acid, the mitochondrial enzyme sterol 27-hydroxylase cleaves the side chain, with the formation of chenodeoxycholate or cholate. The asterisks (*) indicate the site of conjugation with glycine and taurine.

Alternate pathway: cholesterol is transported to mitochondria. CYP 27 catalyses 27-hydroxylation. This reaction can occur in many tissues. 7α-hydroxylation follows—by an oxysterol 7α-hydroxylase distinct from CYP 7A in the classic pathway. The alternate pathway leads to the predominant formation of chenodeoxycholic acid.

found in mitochondria. The interplay between these two synthetic pathways in maintaining bile salt pool size and cellular cholesterol levels is under study [2].

Hepatic synthesis is controlled by the amount of bile acid returning to the liver in the entero-hepatic circulation. When exposed to colonic bacteria the primary bile acids undergo 7α-dehydroxylation with the production of the secondary bile acids, deoxycholic and a very little lithocholic acid. Tertiary bile acids, largely ursodeoxycholic acid, are formed in the liver by epimerization of secondary bile acids. In human bile the amount of the trihydroxy acid (cholic acid) roughly equals the sum of the two dihydroxy acids (chenodeoxycholic and deoxycholic).

The bile acids are conjugated in the liver with the amino acids glycine or taurine. This prevents absorption in the biliary tree and small intestine but permits conservation by absorption in the terminal ileum. Sulphation and glucuronidation (as a detoxifying mechanism) may be increased with cirrhosis or cholestasis when these conjugates are found in excess in the urine and also in bile [9]. Bacteria can hydrolyse bile salts to bile acid and glycine or taurine.

Bile salts are excreted into the biliary canaliculus against an enormous concentration gradient between liver and bile. This depends in part on the intra-cellular negative potential of approximately –35 mV, which provides potential-dependent facilitated diffusion, and also ATP-stimulated transporters (the major one being the canalicular bile salt export pump). The bile salts enter into micellar and vesicular association with cholesterol and phospholipids. In the upper small intestine the bile salt micelles are too large and too polar (hydrophilic) to be absorbed. They are intimately concerned with the digestion and absorption of lipids. When the terminal ileum and proximal colon are reached, absorption of bile acid takes place by an active transport process found only in the ileum. Non-ionic passive diffusion occurs throughout the whole intestine and is most efficient for unconjugated, dihydroxy bile acid. Oral administration of ursodeoxycholic acid interferes with the small intestinal absorption of both chenodeoxycholic and cholic acid [8].

The absorbed bile salts enter the portal venous system and reach the liver where they are taken up with great avidity by the hepatocytes. This depends upon a sodium-coupled co-transport system using the sodium gradient across the sinusoidal membrane as a driving force. Chloride ions may also be involved. The most hydrophobic bile acids (unconjugated mono- and dihydroxy bile acids) probably enter the hepatocyte by simple diffusion ('flip-flop') across the lipid membrane. The mechanism of bile acid passage across the liver cell from sinusoid to bile canaliculus is controversial. Cytosolic bile acid-binding proteins, for example 3α-hydroxysteroid dehydrogenase, are involved [10]. The role of microtubules is uncertain. Vesicles seem to play a role but only at higher bile acid concentrations [3]. The bile acids are reconjugated and re-excreted into bile. Lithocholic acid is not re-excreted.

This entero-hepatic circulation of bile salts takes place 2–15 times daily (fig. 2.9). Because absorption efficiency varies among the individual bile acids they have different synthesis and fractional turnover rates.

In cholestasis bile acids are excreted in the urine by active transport and passive diffusion. They tend to be sulphated and these conjugates are actively secreted by the renal tubule [11].

Changes in disease

Bile salts increase the biliary excretion of water, lecithin, cholesterol and conjugated bilirubin. Ursodeoxycholic acid produces a much greater choleresis than chenodeoxycholic or cholic acid [6].

Altered biliary excretion of bile salts with defective biliary micelle formation is important in the pathogenesis of gallstones (Chapter 34). It also leads to the steatorrhoea of cholestasis.

Bile salts form a micellar solution with cholesterol and phospholipid, and in this way help to emulsify dietary fat and also play a part in the mucosal phase of absorption. Diminished secretion leads to steatorrhoea (fig. 2.10). They assist pancreatic lipolysis and release gastrointestinal hormones.

Disordered intra-hepatic metabolism of bile salts may be important in the pathogenesis of cholestasis (Chapter 13). They used to be thought to have a role in the pruritus of cholestasis but data now suggest that other substances are responsible (Chapter 13).

Bile salts may be responsible for target cells in the peripheral blood of jaundiced patients (Chapter 4) and for the secretion of conjugated bilirubin in urine. If bile acids are deconjugated by small intestinal bacteria, the resulting free bile acids are absorbed. Micelle formation and absorption of fat are then impaired. This may partly explain the malabsorption complicating diseases with bacterial overgrowth in the small intestine.

Removal of the terminal ileum interrupts the entero-hepatic circulation and allows large amounts of primary bile acids to reach the colon and to be dehydroxylated by bacteria, thus reducing the body's bile salt pool. The altered bile salts in the colon excite a profound electrolyte and water loss with diarrhoea.

Lithocholic acid is mostly excreted in the faeces and only slightly absorbed. It is cirrhotogenic to experimental animals and can be used to produce experimental gallstones. Taurolithocholic acid can also cause intra-

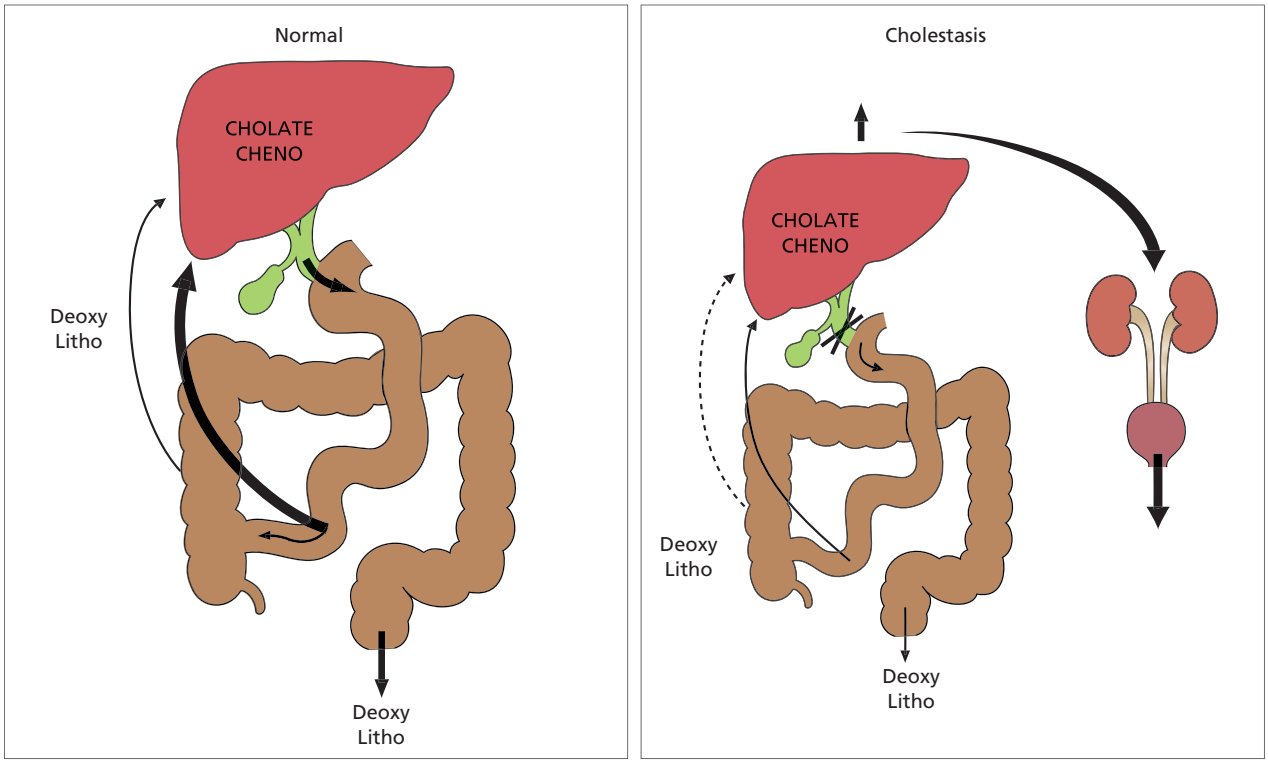


Fig. 2.9. The entero-hepatic circulation of bile acids in normal subjects and in cholestasis.

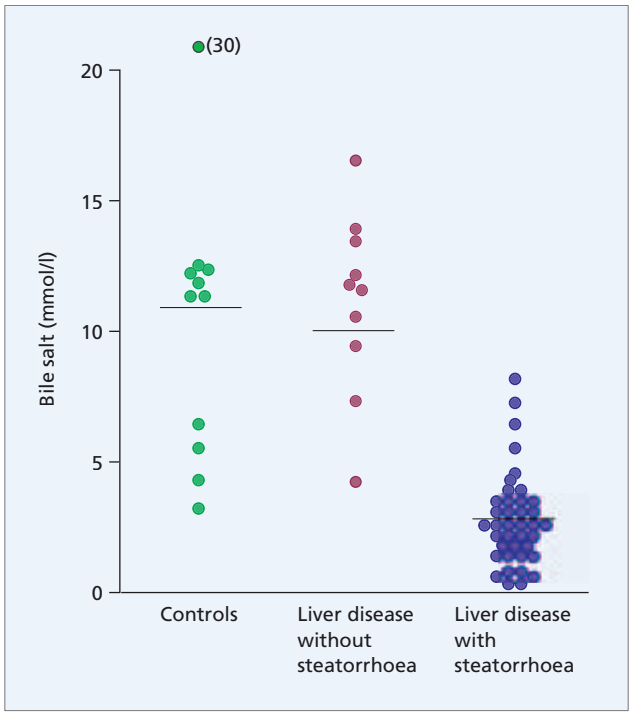


Fig. 2.10. Patients with chronic, non-alcoholic liver disease and steatorrhoea show a reduced bile salt concentration in their aspirated intestinal contents compared with control subjects and patients with chronic liver disease without steatorrhoea.

hepatic cholestasis, perhaps by interfering with the bile-salt-independent fraction of bile flow.

Serum bile acids

Gas–liquid chromatography allows individual bile acids to be distinguished, but the method is time consuming and the equipment expensive.

Enzymatic assays are based on the use of bacterial 3-hydroxysteroid dehydrogenase. The use of a bioluminescence assay has improved the sensitivity of this enzymatic technique up to that of radio-immunoassay. The method is simple and inexpensive if the equipment is available. Radio-immunoassay techniques can also measure individual bile acids.

The serum concentration of total bile acids reflects the extent to which bile acids reabsorbed from the intestine have escaped extraction on their first passage through the liver. The value reflects the instantaneous balance between intestinal absorption and hepatic uptake. Intestinal load is more important than hepatic extraction in regulating peripheral serum bile acid levels.

Raised levels of serum bile acids are specific for hepato-biliary disease. The sensitivity of serum bile acid estimations is less than originally thought for detecting hepato-cellular damage in viral hepatitis or chronic liver disease. The addition to the fasting serum bile acid value

of a 2-h post-prandial level adds little in sensitivity [4]. The dual cholate clearance test (simultaneous ^{2}H-cholate orally and ^{13}C-cholate intravenously) has been used to measure intrinsic hepatic clearance as a reflection of liver function and the severity of liver disease [7].

Estimations of individual bile acids are not diagnostic. In cholestasis the ratio of serum trihydroxy to dihydroxy acid increases. Patients with hepato-cellular failure usually have a low ratio, the main bile acid being chenodeoxycholic acid. This is due to a reduction in the activity of the 12α-hydroxylase enzyme in the hepatocyte.

Amino acid conjugation is preserved even with severe hepato-cellular damage [1].

References

1 Arisaka M, Arisaka O, Nittono H *et al*. Conjugating ability of bile acids in hepatic failure. *Acta Paediatr. Scand.* 1986; **75**: 875.

2 Cooper AD. Bile salt biosynthesis: an alternate synthetic pathway joins the mainstream. *Gastroenterology* 1997; **113**: 2005.

3 Crawford JM, Gollan JL. Transcellular transport of organic anions in hepatocytes: still a long way to go. *Hepatology* 1991; **14**: 192.

4 Greenfield SM, Soloway RD, Carithers RL Jr *et al*. Evaluation of postprandial serum bile acid response as a test of hepatic function. *Dig. Dis. Sci.* 1986; **31**: 785.

5 Hofmann AF. The continuing importance of bile acids in liver and intestinal disease. *Arch. Intern. Med.* 1999; **159**: 2647.

6 Loria P, Carulli N, Medici G *et al*. Determinants of bile secretion: effect of bile salt structure on bile flow and biliary cation secretion. *Gastroenterology* 1989; **96**: 1142.

7 Shrestha R, McKinley C, Showalter R *et al*. Quantitative liver function tests define the functional severity of liver disease in early stage cirrhosis. *Liver Transplant Surg*. 1997; **3**: 166.

8 Stiehl A, Raedsch R, Rudolph G. Acute effects of ursodeoxycholic and chenodeoxycholic acid on the small intestinal absorption of bile acids. *Gastroenterology* 1990; **98**: 424.

9 Stiehl A, Raedsch R, Rudolph G *et al*. Biliary and urinary excretion of sulphated, glucuronidated and tetrahydroxylated bile acids in cirrhotic patients. *Hepatology* 1985; **5**: 492.

10 Stolz A, Takikawa H, Ookhtens M *et al*. The role of cytoplasmic proteins in hepatic bile acid transport. *Ann. Rev. Physiol.* 1989; **51**: 161.

11 Summerfield JA, Cullen J, Barnes S *et al*. Evidence for renal control of urinary excretion of bile acids and bile acid sulphates in the cholestatic syndrome. *Clin. Sci. Mol. Med.* 1977; **52**: 51.

12 Vlahcevic ZR, Pandak WM, Stravitz RT. Regulation of bile acid biosynthesis. *Gastroenterol. Clin. N. Am.* 1999; **28**: 1.

Amino acid metabolism

Amino acids derived from the diet and from tissue breakdown reach the liver for metabolism. Specific Na^{+}-independent and Na^{+}-dependent systems mediate the transport of free amino acids across the sinusoidal membrane of the hepatocyte [7]. Some are transaminated or deaminated to keto acids which are then metabolized by many pathways including the tricarboxylic acid cycle (Krebs–citric acid cycle). Others are metabolized to ammonia and urea (Krebs–Henseleit urea cycle).

The maximal rate of urea synthesis in chronic liver disease is markedly reduced. However, experimentally, at least 85% of liver must be removed before this mechanism fails significantly and before blood and urinary amino acid levels increase. A low blood urea concentration is an occasional feature of fulminant liver failure. A rise in blood ammonia level also represents a failure of the Krebs urea cycle and this increase has been related to hepatic encephalopathy.

Clinical significance

A generalized or selective amino aciduria is a feature of hepato-cellular disease. In patients with severe liver disease the usual picture is an increase in the plasma concentration of one or both of the aromatic amino acids, tyrosine and phenylalanine, together with methionine, and a reduction in the branched-chain amino acids valine, leucine and isoleucine (fig. 2.11) [6]. The changes are explained by impaired hepatic function, porto-systemic shunting of blood, hyperinsulinaemia and hyperglucagonaemia. Patients with minimal liver disease also show changes, particularly a reduction in plasma proline, perhaps reflecting increased collagen

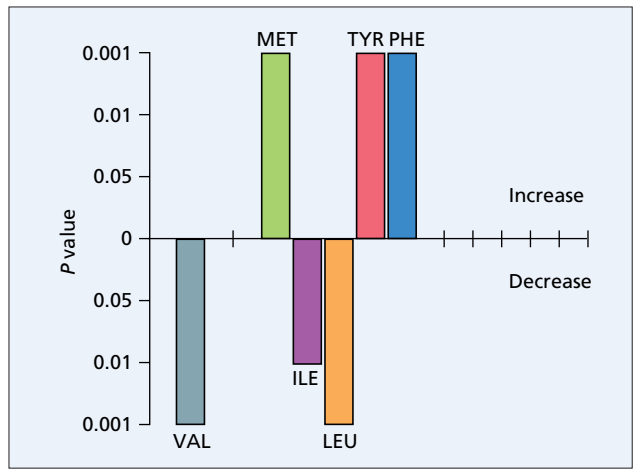


Fig. 2.11. The plasma amino acid pattern in cryptogenic cirrhosis (mean of 11 patients) compared with normal individuals. The aromatic amino acids and methionine are increased while the branched-chain amino acids are decreased. ILE, isoleucine; LEU, leucine; MET, methionine; PHE, phenylalanine; TYR, tyrosine; VAL, valine [6].

production. There is no difference in the ratio between branched-chain and aromatic amino acids whether or not the patients show hepatic encephalopathy.

In fulminant hepatitis there is marked generalized aminoaciduria involving particularly cystine and tyrosine and this carries a bad prognosis.

Plasma proteins

The plasma proteins produced by the hepatocyte are synthesized on polyribosomes bound to the rough endoplasmic reticulum, from which they are discharged into the plasma [9]. Falls in concentration usually reflect decreased hepatic synthesis although changes in plasma volume and losses, for instance into gut or urine, may contribute.

The hepatocyte makes albumin, fibrinogen, α_1-antitrypsin, haptoglobin, caeruloplasmin, transferrin and prothrombin (table 2.4). Some liver-produced proteins are acute phase reactors and rise in response to tissue injury such as inflammation (table 2.4). These include fibrinogen, haptoglobin, α_1-antitrypsin, C_3 component of complement and caeruloplasmin. An acute phase response may contribute to well-maintained or increased serum concentrations of these proteins, even with hepato-cellular disease.

The mechanism is complex but cytokines (interleukin (IL) 1, IL6, TNF-α) play a role [1, 8]. IL6 binds to the cell-surface receptor and this stimulates a message from the hepatocyte membrane to the nucleus where there is induction of specific nuclear factors which interact with promoter elements at the 5′ end of several acute phase plasma protein genes. There are also post-transcriptional as well as transcriptional mechanisms. Cytokines not only stimulate production of acute phase proteins but also inhibit the synthesis of albumin, transferrin and a range of other proteins.

Table 2.4. Serum (plasma) proteins synthesized by the liver

	Normal concentration
Albumin	40–50 g/l
α_1-antitrypsin*	2–4 g/l
α-fetoprotein	<10 KU/l
α_2-macroglobulin	2.2–3.8 g/l
Caeruloplasmin*	0.2–0.4 g/l
Complement components (C_3, C_6 and C_1)	
Fibrinogen*	2–6 g/l
Haemopexin	0.8–1.0 g/l
Prothrombin (factor II)†	
Transferrin	2–3 g/l

* Acute phase proteins.
† Vitamin K dependent; also factors VII and X.

The *immunoglobulins* IgG, IgM and IgA are synthesized by the B cells of the lymphoid system.

Some 10 g of *albumin* is synthesized by the normal liver daily (figs 2.12, 2.13), whereas those with cirrhosis can only synthesize about 4 g (35 mg/kg/day in Child C cirrhosis) [2, 3]. The fractional synthetic rate of albumin is approximately 6% per day compared with 25% for total liver protein [3]. In liver disease, the fall in serum albumin concentration is slow, for the half-life of albumin is about 22 days. Thus a patient with fulminant liver failure may die with a virtually normal serum albumin value. A patient with decompensated cirrhosis would be expected to have a low level.

α_1-Antitrypsin deficiency is inherited (Chapter 25).

Haptoglobin is a glycoprotein composed of two types of polypeptide chains, α and β, which are covalently associated by disulphide bonds. Haptoglobin is largely synthesized by hepatocytes. Hereditary deficiencies are frequent in American black people. Low values are found in severe, chronic hepato-cellular disease and in haemolytic crises.

Caeruloplasmin is the major copper-containing protein in plasma and is responsible for the oxidase activity. A low concentration is found in 95% of those who are homozygous and about 10% of those heterozygous for Wilson's disease (Chapter 24). Caeruloplasmin increases to normal if a patient with Wilson's disease has a hepatic transplant. One must estimate caeruloplasmin in all patients with chronic hepatitis so that Wilson's disease, with its mandatory copper chelation therapy, may be diagnosed. However, low values are also found in very severe, decompensated cirrhosis which is not due to Wilson's disease. High values are found in preg-

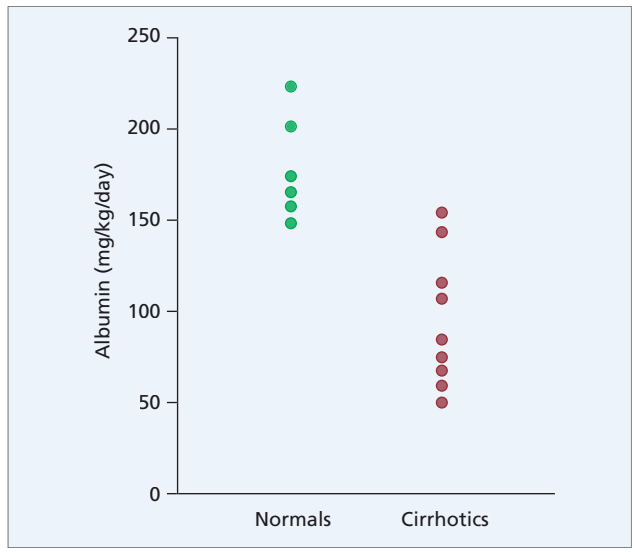


Fig. 2.12. The absolute synthesis of serum albumin (^{14}C carbonate method) in cirrhosis is reduced [10].

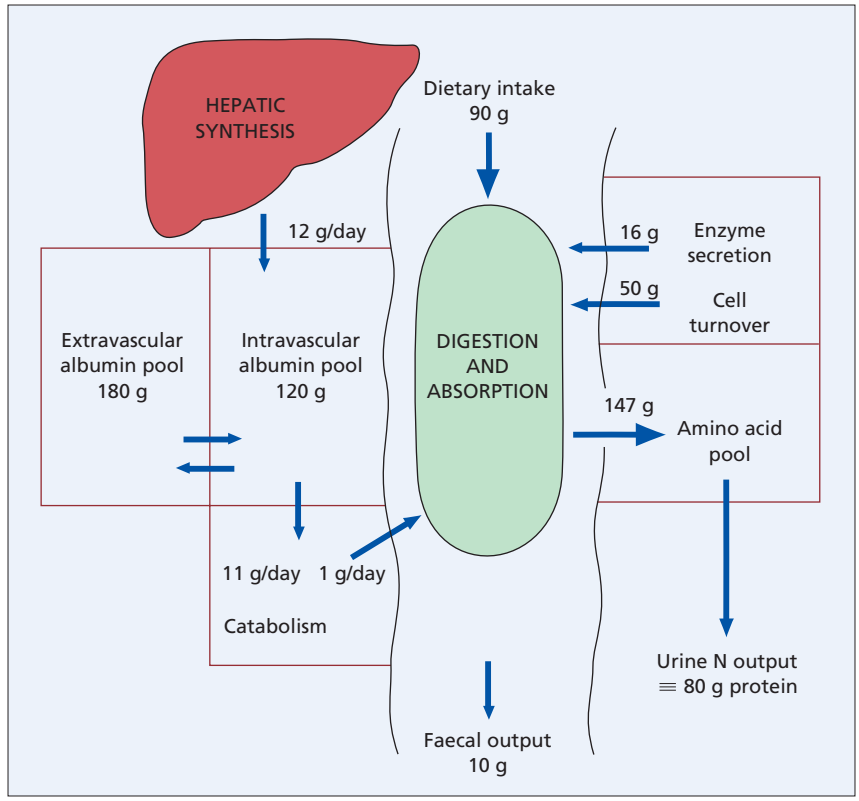


Fig. 2.13. The turnover of plasma albumin in a 70-kg adult seen in the context of the daily protein economy of the gastrointestinal tract and overall nitrogen balance. The total exchangeable albumin pool of about 300 g is distributed between the intravascular and extravascular compartments in a ratio of approximately 2:3. In this simplified schema the balance sheet is expressed in terms of grams of protein (6.25×grams of nitrogen). Losses do not include relatively minor routes, e.g. 2 g/day from the skin [9].

nancy, following oestrogen therapy and with large bile duct obstruction.

Transferrin is the iron transport protein. The plasma transferrin is more than 90% saturated with iron in patients with untreated idiopathic haemochromatosis. Reduced values may be found with cirrhosis.

The C_3 *component of complement* tends to be reduced in cirrhosis, normal in chronic hepatitis and increased in compensated primary biliary cirrhosis. Low values in fulminant hepatic failure and alcoholic cirrhosis with or without hepatitis reflect reduced hepatic synthesis and there is a correlation with prolonged prothrombin time and depression of serum albumin concentration [4]. There is also a contribution from increased consumption due to activation of the complement system. Transient reductions are found in the early 'immune complex' stage of acute hepatitis B.

Alpha-fetoprotein is a normal component of plasma protein in human fetuses older than 6 weeks, and reaches maximum concentration at between 12 and 16 weeks of fetal life. A few weeks after birth it disappears from the circulation but reappears in the blood of patients with primary liver cancer and can be shown in the tumour by indirect immunofluorescence. Raised values are also found with embryonic tumours of the ovary and testis and in embryonic hepatoblastoma. It may also be present with carcinomas of the gastrointestinal tract with hepatic secondaries. Raised values are also found in active chronic hepatitis and during acute viral hepatitis, where they may indicate hepato-cellular regeneration. However, very high values are virtually confined to primary liver cancer. In a hepatitis B or C positive patient, rising values are of particular significance as an indicator of the development of hepato-cellular carcinoma (Chapter 31).

Electrophoretic pattern of serum proteins

Electrophoresis is used to determine the proportions of the various serum proteins. In cirrhosis, albumin is reduced.

The α_1-globulins contain glycoproteins and hormone-binding globulins. They tend to be low in hepato-cellular disease, falling in parallel with the serum albumin. An increase accompanies acute febrile illnesses and malignant disease. Ninety per cent of α_1-globulin consists of α_1-antitrypsin and an absent α_1-globulin may indicate α_1-antitrypsin deficiency.

The α_2- and β-globulins include lipoproteins. In cholestasis the increase in α_2- and β-globulin components correlates with the height of serum lipids.

The γ-globulins rise in hepatic cirrhosis due to increased production. The increased numbers of plasma cells in marrow, and even in the liver itself, may be the

source. The γ-globulin peak in hepato-cellular disease shows a wide base (*polyclonal gammopathy*). *Monoclonal gammopathy* is rare and may be age-related rather than related to chronic liver disease. The dip between β- and γ-globulins tends to be bridged.

Immunoglobulins. IgG is markedly increased in chronic hepatitis and cryptogenic cirrhosis. In autoimmune hepatitis the raised level of IgG falls during treatment with corticosteroids. There is a slow and sustained increase in viral hepatitis and it is also increased in alcoholic cirrhosis.

IgM is markedly increased in primary biliary cirrhosis and to a lesser extent in viral hepatitis and cirrhosis.

IgA is markedly increased in cirrhosis of the alcoholic but also in primary biliary and cryptogenic cirrhosis.

The increase in serum secretory IgA, the predominant immunoglobulin in bile, may be related to communication of the bile canaliculus with the space of Disse and/or through the bile duct into the portal blood vessels [5].

In chronic hepatitis with active inflammation and cryptogenic cirrhosis the pattern is surprisingly similar, with increases in IgG, IgM and to a lesser extent IgA.

About 10% of patients with chronic cholestasis due to large bile duct obstruction show increases in all three main immunoglobulins.

Patterns are not diagnostic of any one disease but together with other data add support to considering a particular diagnosis.

References

1 Andus T, Bauer J, Gerok W. Effects of cytokines on the liver. *Hepatology* 1991; **13**: 364.
2 Ballmer PE, Reichen J, McNurlan MA *et al*. Albumin but not fibrinogen synthesis correlates with galactose elimination capacity in patients with cirrhosis of the liver. *Hepatology* 1996; **24**: 53.
3 Barle H, Nyberg B, Essen P *et al*. The synthesis rates of total liver protein and plasma albumin determined simultaneously *in vivo* in humans. *Hepatology* 1997; **25**: 154.
4 Ellison RT, Horsburgh CR Jr, Curd J. Complement levels in patients with hepatic dysfunction. *Dig. Dis. Sci.* 1990; **35**: 231.
5 Fukuda Y, Nagura H, Asai J *et al*. Possible mechanisms of elevation of serum secretory immunoglobulin A in liver disease. *Am. J. Gastroenterol.* 1986; **81**: 315.
6 Morgan MY, Marshall AW, Milsom JP *et al*. Plasma amino-acid patterns in liver disease. *Gut* 1982; **23**: 362.
7 Moseley RH. Hepatic amino acid transport. *Semin. Liver Dis.* 1996; **16**: 137.
8 Sehgal PB. Interleukin-6: a regulator of plasma protein gene expression in hepatic and nonhepatic tissues. *Mol. Biol. Med.* 1990; **7**: 117.
9 Tavill AS. The synthesis and degradation of liver-produced proteins. *Gut* 1972; **13**: 225.
10 Tavill AS, Craigie A, Rosenoer VM. The measurement of the synthetic rate of albumin in man. *Clin. Sci.* 1968; **34**: 1.

Carbohydrate metabolism

The liver occupies a key position in carbohydrate metabolism (see fig. 2.1) [2]. The changes in cirrhosis are complex and not fully understood.

In fulminant acute hepatic necrosis the blood glucose level may be low. This is rare in chronic liver disease.

In fasted patients with cirrhosis the contribution of carbohydrates to energy production is reduced (2 vs. 38% in normal controls) with the contribution from fat increasing (86 vs. 45%) [3]. This may be caused by impaired release of hepatic glucose or a reduced reserve of glycogen in the liver. After eating a meal, however, cirrhotics, like control subjects, make immediate use of dietary carbohydrate, indeed perhaps to a greater degree, because of a reduced ability to store and then mobilize energy as triglyceride [1].

The oral and intravenous glucose tolerance tests may show impairment in cirrhosis and there is relative insulin resistance (Chapter 25).

Galactose tolerance is also impaired in hepato-cellular disease and oral and intravenous tests have been devised. Results are independent of insulin secretion. Galactose removal by the liver has been used to measure hepatic blood flow.

References

1 Avgerinos A, Harry D, Bousboulas S *et al*. The effect of an eucaloric high carbohydrate diet on circulating levels of glucose, fructose and nonesterified fatty acids in patients with cirrhosis. *J. Hepatol.* 1992; **14**: 78.
2 Kruszynska YT. Carbohydrate metabolism. In Bircher J, Benhamou J-P, McIntyre N, Rizzetto M, Rodes J, eds. *Oxford Textbook of Clinical Hepatology*, 2nd edn. Oxford University Press, Oxford, 1999, p. 257.
3 Schneeweiss B, Graninger W, Ferenci P *et al*. Energy metabolism in patients with acute and chronic liver disease. *Hepatology* 1990; **11**: 387.

Effects of ageing on the liver [6]

Although there are many studies of hepatic function and ageing, results have been conflicting or unsubstantiated. Differences could be due to the study protocols used.

However, liver weight and volume decrease with age, and liver blood flow is reduced [8]. There is compensatory hypertrophy of hepatocytes.

In animals the rate of hepatic regeneration declines with increasing age but whether this is related to lower circulating levels of hepato-trophic factors is not clear. Somatic mutations, including gene rearrangements, increase with age and are more frequent in the liver than the brain in experimental models [1].

Structural changes in the hepatocyte include an

increase in secondary lysosomes and residual bodies, with a concomitant accumulation of lipofuscin. There are conflicting data on structural changes in mitochondria. However impaired mitochondrial enzyme activity and defects in the respiratory chain are reported [4, 5]. No consistent mitochondrial DNA mutations are seen.

In animals, protein synthesis by the liver falls with age. Since the total protein content of cells remains relatively constant it is thought that protein turnover is also reduced [6]. Hepatic nitrogen clearance (conversion of α-amino nitrogen into urea nitrogen) is impaired with advancing age [2].

First-pass metabolism of drugs is reduced and this may be due to reduced liver mass and hepatic blood flow rather than to alterations in the relevant enzyme systems. It has been suggested that increased hepatocyte volume extends the path length for oxygen diffusion (the 'oxygen diffusion barrier' hypothesis) which might affect cell function [3]. Hepatic microsomal monooxygenase enzyme activity does not appear to decline with age [7].

Fatal reactions to halothane and drugs such as benoxyprofen are more frequent in the elderly, but the overall increase in adverse reactions observed may be related to the multiplicity of drugs that these patients receive.

Cholesterol saturation of bile increases with age due to enhanced hepatic secretion of cholesterol and decreased bile acid synthesis. This may explain age as a risk factor for cholesterol gallstones.

References

1 Dolle ME, Giese H, Hopkins CL *et al*. Rapid accumulation of genome rearrangements in liver but not in brain of old mice. *Nature Genet.* 1997; **17**: 431.

2 Fabbri A, Marchesini G, Bianchi G *et al*. Kinetics of hepatic amino-nitrogen conversion in ageing man. *Liver* 1994; **14**: 288.

3 LeCouter DG, McLean AJ. The ageing liver. Drug clearance and an oxygen diffusion barrier hypothesis. *Clin. Pharmacokinet*. 1998; **34**: 359.

4 Muller-Hocker J, Aust D, Rohrbach H *et al*. Defects of the respiratory chain in the normal human liver and in cirrhosis during ageing. *Hepatology* 1997; **26**: 709.

5 Sastre J, Pallardó FV, Plá R *et al*. Ageing of the liver: age-associated mitochondrial damage in intact hepatocytes. *Hepatology* 1996; **24**: 1199.

6 Schmucker DL. Ageing and the liver: an update. *J. Gerontol.* 1998; **53A**: B315.

7 Ward W, Richardson A. Effect of age on liver protein synthesis and degradation. *Hepatology* 1991; **14**: 935.

8 Wynne HA, Cope LH, Mutch E *et al*. The effect of age upon liver volume and apparent liver blood flow in healthy man. *Hepatology* 1989; **9**: 297.

Chapter 3
Biopsy of the Liver

A needle biopsy of the liver was said to have been first performed by Paul Ehrlich in 1883 (table 3.1) [13] in a study of the glycogen content of the diabetic liver, and later in 1895 by Lucatello in Italy, for the diagnosis of tropical liver abscess. The first published series was by Schüpfer (1907) [38] in France, where the technique was used for the diagnosis of cirrhosis and hepatic tumours. The method, however, never achieved early popularity until the 1930s when it was used for general purposes by Huard and co-workers [20] in France, and by Baron [3] in the USA. The Second World War saw a rapid increase in the use of liver biopsy, largely to investigate the many cases of non-fatal viral hepatitis which were affecting the armed forces of both sides [2, 21, 39].

The indications and techniques have changed, the complications are better recognized and the risks have decreased. Interpretation of the biopsy is an important part of a histopathologist's training.

Selection and preparation of the patient

The patient is usually admitted to hospital. Outpatients selected must not be jaundiced or show any sign of decompensation such as ascites or encephalopathy. Outpatient biopsy should be avoided in cirrhotic patients or in those with tumours [34]. Outpatient biopsies are usually indicated because of patient preference and reduction of cost. The American Gastroenterological Association recommends that clinicians should decide whether the biopsy is done as an inpatient or outpatient, and this should not be dictated by insurance coverage [22].

The one-stage prothrombin time should not be more than 3 s prolonged over control values after 10 mg vitamin K is given intramuscularly. The platelet count should exceed 50 000.

In thrombocytopenic patients the risk of haemorrhage depends on the function of the platelets rather than on their numbers. A patient with 'hypersplenism' and a platelet count of less than 50 000 is much less likely to bleed than one with leukaemia who has a similar platelet count. This distinction particularly arises in patients with haematological problems or after organ transplants where the effects on the liver of cytotoxic therapy, viruses and other infective agents and of the graft-versus-host reaction have to be resolved. In such patients, if the platelet count can be raised to greater than 60 000 by platelet infusion, biopsy seems to be safe. Care should also be taken in recently imbibing alcoholic patients who may have reduced platelet counts and platelet dysfunction, especially if acetyl salicylic acid has been consumed. In such patients the platelet count may be 100 000 and the prothrombin time only 3 s prolonged over control values, yet the bleeding time may be 25 min.

The patient's blood group should be known and facilities for blood transfusion must always be available.

Clinically significant haemorrhage complicated 12.5% of 155 liver biopsies in haemophiliacs [1]. Liver biopsy should not be performed in haemophilia A unless there are very definite indications when the factor VIII level should be raised, and maintained, to about 50% for at least 48 h.

Techniques

The Menghini needle obtains a specimen by aspiration (fig. 3.1) [30]. The sheathed 'Trucut' is a cutting technique of particular value in cirrhotic patients [8]. Fragmentation of the biopsy is greater with the Menghini method, but the procedure is quicker, easier and has less complications [34]. The cost of the needle is less.

Menghini 'one second' needle biopsy (fig. 3.1). The 1.4-mm diameter needle is used routinely. A short needle is available for paediatric use. The tip of the needle is

Table 3.1. History of liver biopsies [40]

Author	Date	Country	Purpose
Ehrlich	1883	Germany	Glycogen
Lucatello	1895	Italy	Tropical
Schüpfer	1907	France	Cirrhosis
Huard *et al.*	1935	France	General
Baron	1939	USA	General
Iversen & Roholm	1939	Denmark	Hepatitis
Axenfeld & Brass	1942	Germany	Hepatitis
Dible *et al.*	1943	UK	Hepatitis

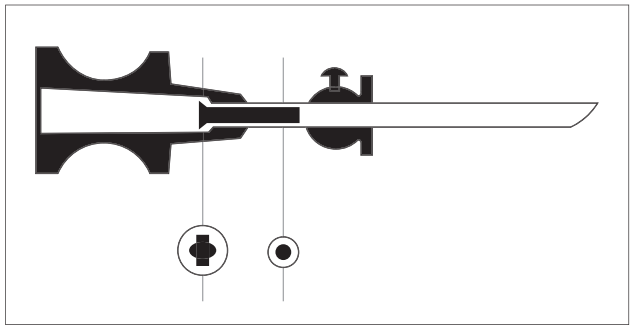


Fig. 3.1. Longitudinal section of the Menghini liver biopsy needle. Note the nail in the shaft of the needle [30].

oblique and slightly convex towards the outside. The needle is fitted within its shaft with a blunt nail. This internal block prevents the biopsy from being fragmented or distorted by violent aspiration into the syringe.

Sterile solution (3 ml) is drawn into the syringe which is inserted through the anaesthetized track down to but not through the intercostal space. Two millilitres of solution are injected to clear the needle of any skin fragments. Aspiration is now commenced and maintained. This is the slow part of the procedure. With the patient holding his breath in expiration, the needle is rapidly introduced perpendicularly to the skin into the liver substance and extracted. This is the quick part of the procedure. The tip of the needle is now placed on sterile paper and some of the remaining saline flushed through the needle to deposit the biopsy gently onto the paper. The tissue is transferred into fixative.

Sedation is not given routinely before biopsy as it may interfere with the patient's co-operation. However, analgesia is sometimes needed after the procedure.

The *intercostal technique* is the most frequently used method [40]. It rarely fails, provided care is taken to assess liver size carefully by light percussion. A preliminary ultrasound or CT scan is useful. A small fibrotic liver is a contraindication. After adequate local anaesthesia, the needle is inserted in the 8th or 9th intercostal space in the mid-axillary line at the end of expiration with the patient breathing quietly. The direction is slightly posterior and cranial which helps to avoid the gallbladder. If an epigastric mass is present or imaging indicates left lobe disease, an anterior approach is made.

Transjugular (*transvenous liver biopsy*) [25]. A special Trucut needle is inserted through a catheter placed in the hepatic vein via the jugular vein. The needle is then introduced into the liver tissue by transfixing the hepatic venous wall (fig. 3.2). The correct position is confirmed by injecting contrast medium into the needle.

The technique is used in those who have a coagulation disorder, massive ascites, a small liver or who are uncooperative. It is useful in acute liver failure to determine prognosis and the need for liver transplantation [11]. In patients with advanced liver disease, it has the advantage of measuring wedged and free hepatic venous pressure and of opacifying the hepatic vein (table 3.2).

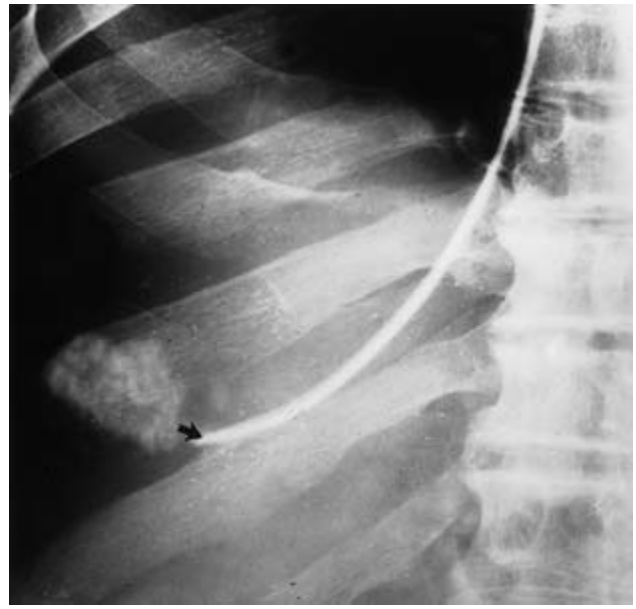


Fig. 3.2. Transvenous liver biopsy. The catheter is in the hepatic vein and contrast has been injected to show the wedged position. The Trucut needle is taking the liver biopsy (arrow).

Table 3.2. Indications for transjugular liver biopsy

Coagulation defects
Acute liver failure pre-transplant
Massive ascites
Small liver
Measurement of wedged hepatic venous pressure
Unco-operative patient

Biopsies are smaller than with the intercostal technique, but are adequate in two-thirds of patients with cirrhosis and extensive fibrosis, and in 99% of those without fibrosis and with normal architecture. Complications are between 0 and 20%. Mortality is very low, but perforation of the liver capsule can be fatal [26]. The disadvantage is the greater complexity. The cost is 10 times that of trans-capsular biopsy.

Directed (*guided biopsy*). The lesion is recognized under imaging, which is usually ultrasound, but may be CT. The Trucut biopsy needle is advanced into it (fig. 3.3). In patients with poor coagulation, a gel foam plug may be injected through the outer cannula of the Trucut needle after the inner cutting needle, with its contained speci-

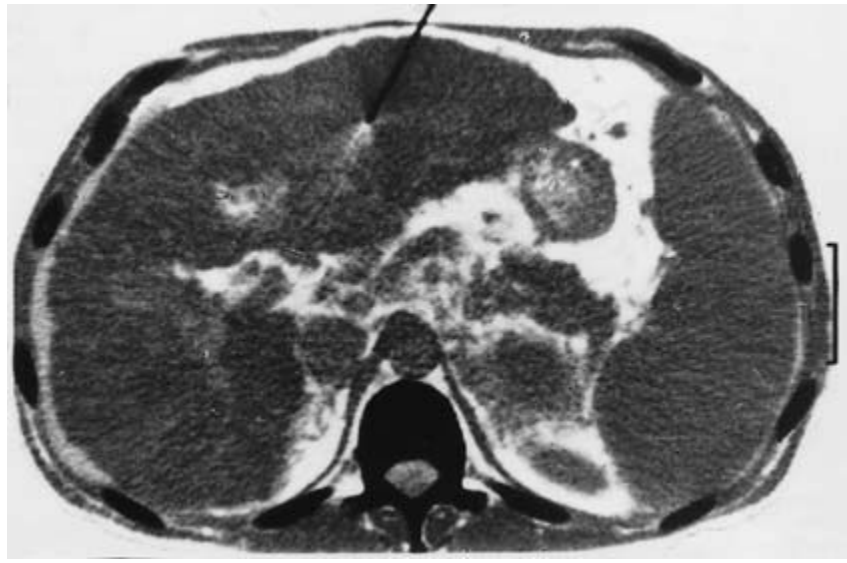


Fig. 3.3. CT scan of a 45-year-old male with hepatitis B positive cirrhosis. An irregular liver outline and splenomegaly are clearly seen. A directed biopsy of a suspected neoplasm of the left lobe of liver diagnosed hepato-cellular carcinoma.

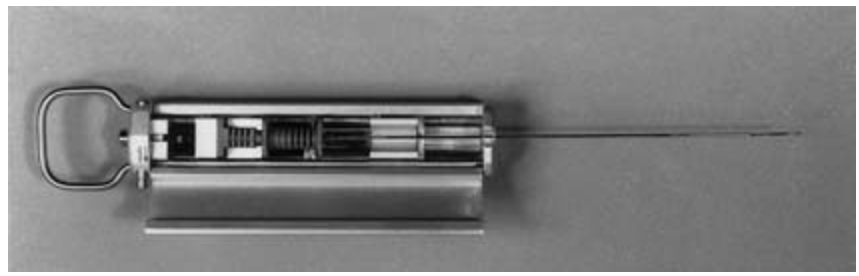


Fig. 3.4. The Biopty gun (Biopter).

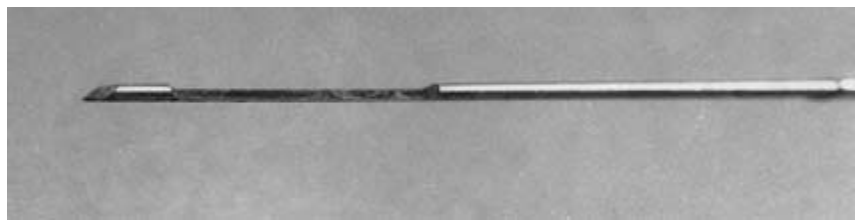


Fig. 3.5. The Trucut needle tip has an outer cannula and inner cutting needle. The inner needle is advanced and a liver biopsy is cored out.

men, has been removed [45]. This is effective in preventing major bleeding. Preliminary ultrasound may be used to assess liver size, the position of the gallbladder and any anatomical abnormality or focal lesion. The ultrasound may be performed in relation to the biopsy, preferably by the operator, and a portable ultrasound machine may be used. In diffuse disease, ultrasound decreases the incidence of major and minor complications such as pain, hypotension and bleeding [44].

Directed liver biopsy gives a higher percentage of positives than the trans-capsular technique. In chronic liver disease, the blind technique is approximately 81% accurate, but this can be raised to 95% if a directed form of liver biopsy is used [33]. Ultrasound-guided liver biopsy increases the cost but new generation, portable ultrasound may be less expensive and reduction of major and minor complications is similarly cost-effective [27, 35].

The *Biopty gun* uses a modified 18- or 14-gauge Trucut needle and is operated with one hand (figs 3.4, 3.5). It is fired by a fast and powerful spring mechanism. It allows precise positioning of the needle and is less painful than the manual procedure. It is particularly useful for focal lesions [43].

Fine-needle-guided biopsy. Using a 22 swg (0.7 mm) needle adds to the safety. It is particularly useful for the diagnosis of focal lesions although diagnostic accuracy is variable [6]. Because of the size, fine-needle biopsy is not

so useful in generalized disease such as chronic hepatitis or cirrhosis.

Cytological examination of the aspirate is useful for tumour typing [15].

After-care. Bleeding is most likely within the first 3–4 h [23]. Pulse rate and blood pressure are charted every 15 min for the first hour and every 30 min for the next 2 h.

Inpatients continue to have their pulse rates charted for 24 h and routine visits are paid 4 and 8 h post-biopsy. A very careful watch must be kept on the patient. Rest in bed is essential for 24 h.

During the puncture the patient may complain of a drawing feeling across the epigastrium. Afterwards some patients have a slight ache in the right side for about 24 h and some complain of pain referred from the diaphragm to the right shoulder.

Outpatients are admitted to a supervised day ward at 9.00 a.m. The biopsy is never done later than 11.00 a.m. Pulse and blood pressure are monitored as for inpatients. The patient remains recumbent until 4.00 p.m., is seen at 4.30 p.m. by the physician and is allowed to go home at 5.00 p.m., accompanied and being driven. The patient should stay less than a 30-min drive from the hospital. The patient should not be alone and must have a telephone available. The transvenous biopsy technique is unsuitable for outpatients because of premedication and usually more severe liver disease and a higher rate of complications. The usual indication for outpatient biopsy is the diagnosis and management of chronic hepatitis, cirrhosis or alcoholic liver disease.

Difficulties

Failures arise in patients with cirrhosis, especially with ascites, for the tough liver is difficult to pierce and a few liver cells may be extracted, leaving the fibrous framework behind. Another difficulty may be pulmonary emphysema; the liver is then pushed downwards by the low diaphragm so that the trocar passes above it.

Failure is often due to the needle not being sharp enough to penetrate the capsule. Disposable needles are an advantage for they are sharp.

The percentage of successes increases with the diameter of the needle used, but so does the complication rate, and one must be weighed against the other. The 1-mm Menghini needle, for instance, which is extremely safe, often fails to procure adequate hepatic tissue for diagnosis. The Trucut needle causes more haemorrhages.

Liver biopsy in paediatrics

The Menghini technique may be employed. In infants a local anaesthetic, with 15–60 mg pentobarbital 30 min before the biopsy, is adequate. The child is restrained by adhesive strapping across the upper thighs and chest and the subcostal approach used. If the liver is small then the intercostal route is employed, the assistant compressing the chest at the end of expiration to arrest respiration.

Complications (4.5%) are more frequent in children than in adults and bleeding is particularly likely in those with cancer or having bone marrow transplants [7]. In older children, general anaesthesia is usually preferred, depending on the co-operation of the child.

Transjugular biopsy can be used in children [14].

Risks and complications

The mortality from various large combined series is about 0.01% (table 3.3). Complications are reported in 0.06–0.32% of patients [41].

In 17 years, some 8000 needle biopsies of the liver have been performed at the Royal Free Hospital with only two deaths, one in a haemophiliac and one in a patient with acute viral hepatitis [40]. In spite of the low mortality and complication rate, liver biopsy must only be performed when the patient can be expected to benefit from the information and where it cannot be obtained by less invasive means.

Pleurisy and peri-hepatitis

A friction rub caused by fibrinous peri-hepatitis or pleurisy may be heard on the next day. It is of little consequence and pain subsides with analgesics. A chest X-ray may show a small pneumothorax.

Haemorrhage

In a series of 9212 biopsies, there were 10 (0.11%) fatal

Table 3.3. Fatalities from needle liver biopsy

Source	Date	Reference	Biopsies	Mortality (%)
USA	1953	[1,2]	20016	0.17
Europe combined	1964	[3]	23382	0.01
Germany	1967	[4]	80000	0.015
Italy	1986	[5]	68276	0.009
USA	1990	[6]	9212	0.11

1 Zamcheck. *N. Engl. J. Med.* 1953; **249**: 1020.
2 Zamcheck. *N. Engl. J. Med.* 1953; **249**: 1062.
3 Thaler. *Wien. Klin. Wchschr.* 1964; **29**: 533.
4 Lindner. *Dtsch. Med. Wschr.* 1967; **92**: 1751.
5 Piccinino. *J. Hepatol.* 1986; **2**: 165 [34].
6 McGill. *Gastroenterology* 1990; **99**: 1396 [28].

and 22 (0.24%) non-fatal haemorrhages [28]. Malignancy, age, female sex and number of passes were the only predictable factors for bleeding. The complication rate is higher when referrals are from a haematology department than when predominantly hepatological problems are being investigated. Haemorrhage usually develops when least expected and when, at the time of biopsy, the risk seemed small. It might be related to factors other than peripheral clotting, for instance the concentration of clotting factors in hepatic parenchyma and the failure of mechanical compression of the needle tract by elastic tissue [12].

Bleeding from the puncture wound usually consists of a thin trickle lasting 10–60 s and the total blood loss is only 5–10 ml. Serious haemorrhage is usually intraperitoneal but may be intrathoracic from an intercostal artery. The bleeding results from perforation of distended portal or hepatic veins or aberrant arteries. The occasional laceration of a major intra-hepatic vessel cannot be avoided. In some cases, a tear of the liver follows deep breathing during the intercostal procedure.

Perforation of the capsule with intra-peritoneal haemorrhage may follow transvenous biopsy.

Spontaneous recovery may ensue, otherwise angiography followed by transcatheter embolization is usually successful (figs 3.6, 3.7).

Severe haemothorax usually responds to blood transfusion and chest aspiration.

Haemorrhage is rare in the non-jaundiced.

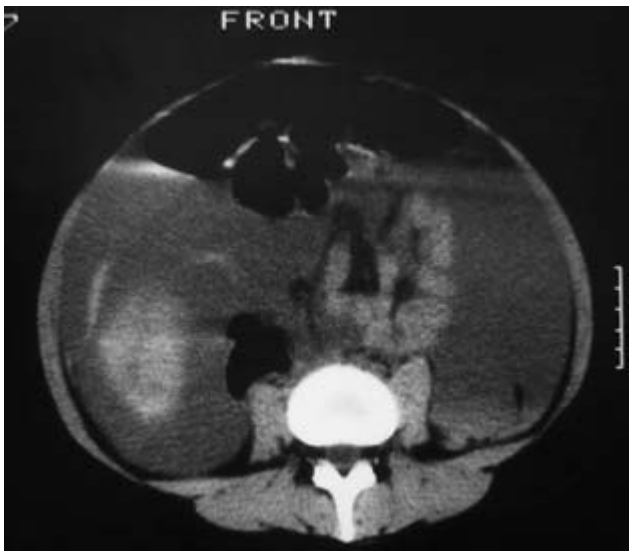


Fig. 3.6. CT scan taken 4 h post-biopsy in a patient with hepatic metastases and jaundice showing haemorrhage around and into the liver.

Intra-hepatic haematomas

At 2–4 h post-biopsy, intra-hepatic haematomas are detected by ultrasound in only about 2% [18]. This is probably an underestimate as the haematomas remain isoechoic for the first 24–48 h and are not detected by ultrasound. The day after biopsy, haematomas, usually asymptomatic, are detected in 23% [31]. They can cause fever, rises in serum transaminases, a fall in haematocrit and, if large, right upper quadrant tenderness and an enlarging liver. They may be seen in the arterial phase of a dynamic CT scan as triangular hyper-dense segments. Sometimes a distal portal vein branch may be noted during the arterial phase. Occasionally, haematomas are followed by delayed haemorrhage.

Haemobilia

Haemobilia follows bleeding from a damaged hepatic vessel, artery or vein, into the bile duct (fig. 3.8). It is marked by biliary colic with enlargement and tenderness of the liver and sometimes the gallbladder. The diagnosis is confirmed by ultrasound, magnetic resonance (MR) cholangiography or endoscopic retrograde cholangiopancreatography (ERCP). It may be treated by hepatic arterial embolization; however, spontaneous recovery is usual.

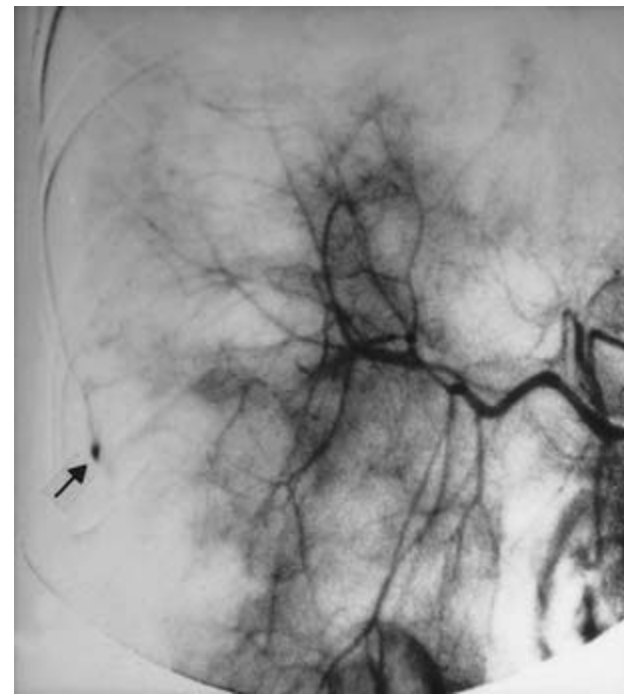


Fig. 3.7. Same patient as in fig. 3.6. Hepatic arteriography (DSA technique) shows blood beside the liver (arrow). The bleeding point was later successfully embolized via the hepatic artery.

Arteriovenous fistula

An arteriovenous fistula is shown by hepatic arteriography (figs 3.9, 3.10).

Histology shows marked phlebosclerosis of the portal vein tributaries [16]. The fistula may close spontaneously, otherwise it can be treated by direct hepatic arterial catheterization and embolization of the feeding artery.

Biliary peritonitis

This is the second commonest complication after haemorrhage. It was seen 49 times in 123 000 biopsies with 12 deaths. The bile usually comes from the gallbladder, which may be in an unusual position, or from dilated bile ducts. Biliary scintigraphy demonstrates the leak [42]. Surgical management is usually necessary although conservative measures with intravenous fluids, antibiotics and intensive care monitoring may be successful.

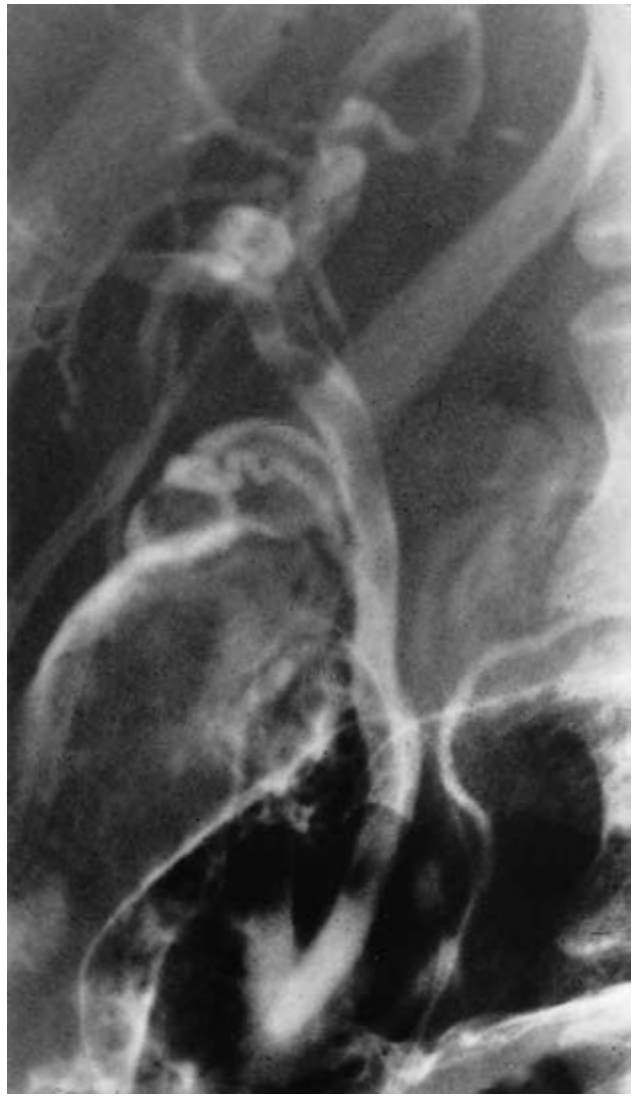


Fig. 3.8. Haemobilia following needle liver biopsy. ERCP shows linear filling defects in the common bile duct.

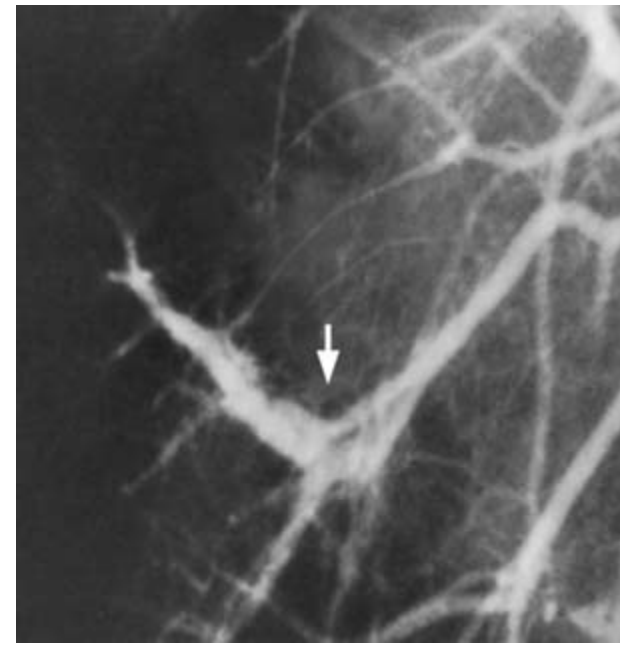


Fig. 3.9. Hepatic arteriography taken post liver biopsy shows an arteriovenous fistula (arrow).

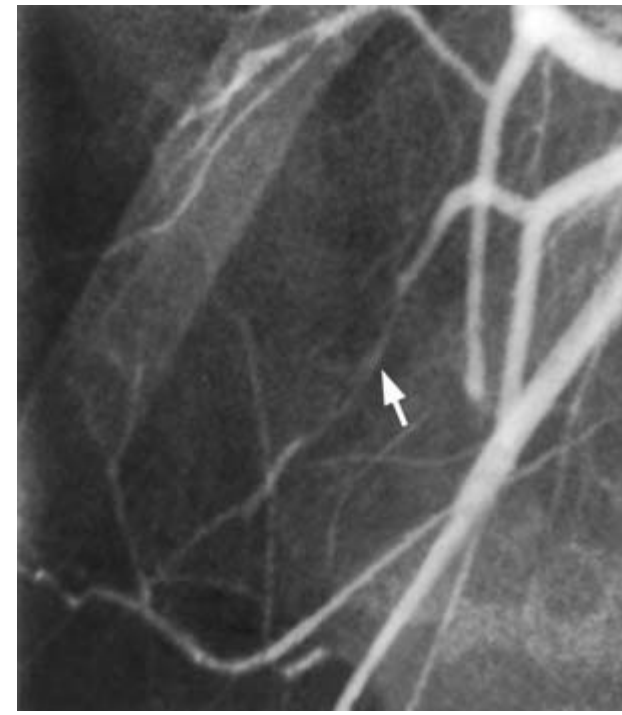


Fig. 3.10 Same patient as in fig. 3.9. The arteriovenous fistula has been successfully embolized (arrow).

Puncture of other organs

Puncture of organs such as the kidney or colon is rarely clinically significant.

Infection

Transient bacteraemia is relatively common, particularly in patients with cholangitis. Septicaemia is rarer; blood cultures are usually positive for *Escherichia coli*.

Carcinoid crisis

This can follow percutaneous biopsy [4].

Sampling variability

It is surprising that such a small biopsy should so often be representative of changes in the whole liver. Cholestasis, steatosis, viral hepatitis and the reticuloses are fortunately diffuse. This is also true of most cirrhoses, although in macronodular cirrhosis it is possible to aspirate a large nodule and find normal architecture. There is sampling variability in the diagnosis of cirrhosis in the presence of acute hepatitis or chronic hepatitis. The focal granulomatous diseases such as sarcoidosis, tumour deposits and abscesses may be missed; this is infrequent if serial sections are cut.

Misdiagnosis is often due to smallness of the sample, especially failure to obtain portal zones, the focal nature of the disease process and particularly the inexperience of the interpreter.

The diagnostic yield may be improved if three consecutive samples are obtained by redirecting the biopsy needle through a single entry site [29].

Fibrous tissue is increased under the capsule in operative biopsies and this may give a false impression of the liver as a whole.

Operative biopsies may show artefactual changes such as patchy loss of glycogen, haemorrhages, polymorph infiltration and even focal necrosis. These are presumably related to the effects of trauma, circulatory changes and hypoxia.

Naked eye appearances

A satisfactory biopsy is 1–4 cm long and weighs 10–50 mg.

The cirrhotic liver tends to crumble into fragments of irregular contour. The fatty liver has a pale greasy look and floats in the formol–saline fixative. The liver containing malignant deposits is dull white in colour. The liver from a patient with Dubin–Johnson hyperbilirubinaemia is diffusely chocolate coloured (see fig. 12.12).

In cholestatic jaundice, the greenish central areas contrast with the less green periphery. The vascular centres of lobules in hepatic congestion may be obvious.

Preparation of the specimen

The biopsy is usually fixed in 10% formol–saline. The time taken to fix such a small piece is less than for a larger specimen. Routine stains include haematoxylin and eosin and a good stain for connective tissue. All specimens are stained for iron and by the diastase/PAS (periodic acid–schiff) method. Orcein staining is also useful. This shows hepatitis B surface antigen in the hepatocyte as a uniform, finely granular, brown material. It also stains copper-associated protein in lysosomes as black–brown granules, usually in the peri-portal area (zone 1). This is a useful indicator of cholestasis and is also sometimes found in Wilson's disease.

Adequate biopsies (3 mm in length) excised from paraffin blocks can be analysed retrospectively for iron and copper by atomic absorption spectrophotometry [32]. If iron overload is suspected, the specimen must not be fixed in saline as this leads to rapid loss of iron.

Frozen sections are needed to demonstrate lipids. These are stained with oil red O to show microvesicular fat.

Specimens for electron microscopy are fixed within seconds in glutaraldehyde and preserved at 4°C until processed. Electron microscopy is particularly valuable for diagnosis of tumours of uncertain origin and storage disorders, including Wilson's disease, Niemann–Pick disease and Dubin–Johnson syndrome.

Serial sections are important for the diagnosis of lesions such as granulomas which may be scattered through the liver.

Cytological preparations are made by smearing the aspirated tissue core on a slide.

Interpretation

The specimen should preferably be at least 2 cm in length with four portal zones if a reliable opinion is to be given. In the normal liver, zone 1 (portal) bears a regular relation to zone 3 (central). This orientation is an essential first step. Each portal zone consists of one or two bile ductules, a branch of the hepatic artery and of the portal vein, a few mononuclears and an occasional fibroblast. Using the 1.6-mm Menghini technique, a liver biopsy from a normal adult contains six full portal triads per linear centimetre of tissue [9]. Portal triads contain at least one of portal vein, hepatic artery and interlobular bile duct. Portal triads which do not contain one of these profiles (usually the portal vein) are almost as common as portal triads in normal liver.

The liver cell plates are one cell thick and contain abundant glycogen. Mitoses are not seen in the liver cells which are usually mononucleate and of regular size. The sinusoids are lined by Kupffer cells and can be seen converging upon zone 3.

Isolated sinusoidal dilatation prompts a search for a tumour or a disease associated with granulomas.

Liver biopsy appearances are described in individual chapters, and detailed histology can be found in the monographs of Klatskin and Conn [24] and Scheuer and Lefkowitch [37].

Indications (table 3.4) [40]

Numbers of liver biopsies are falling due to increasing use of cholangiography, imaging, virological and immunological diagnostic tools. Thus liver biopsies are rarely performed in patients with typical acute jaundice. Biopsy of patients with malignant tumours has to be related to the possibility of tumour seeding [8]. Focal lesions such as haemangioma or focal nodular hyperplasia are better diagnosed by imaging. Patients with typical primary biliary cirrhosis and positive serum mitochondrial antibodies, or those with fatty liver secondary to obesity, do not need a biopsy for diagnosis. Numbers are maintained by biopsies performed for the management of patients with chronic hepatitis or following hepatic transplantation.

Drug-related liver disease can be difficult to identify and the history is essential. Sometimes the distinction from acute viral hepatitis is impossible.

Chronic hepatitis remains a most important indication. Biopsy is needed for diagnosis and to follow the progress and the effects of treatment. A semiquantitative assessment can be made of inflammation (grading) and fibrosis (progression) (Knodell score) (Chapter 19) [10].

The diagnosis of *cirrhosis* demands connective tissue stains, particularly for reticulin.

Alcohol-related disease liver biopsy is used for diagnosis and prognosis but also as a deterrent to further consumption.

Table 3.4. Indications for liver biopsy

Drug-related hepatitis
Chronic hepatitis
Cirrhosis
Liver disease in the alcoholic
Intra-hepatic (ductopenic) cholestasis
Infective conditions
Storage diseases
Post-hepatic transplantation
Complications of renal transplantation
Space-occupying lesions
Unexplained hepatomegaly or enzyme elevations

Extra-hepatic cholestasis can usually be diagnosed by cholangiography with imaging and without the need for liver biopsy, but this is particularly useful in small duct disease (ductopenia) (Chapter 13).

Infections. These include tuberculosis, brucellosis, syphilis, histoplasmosis, coccidioidomycosis, pyogenic infection, leptospirosis, amoebiasis and opportunistic infections such as herpes, cytomegalovirus and cryptosporidosis. When indicated, the appropriate stains for the causative organism should be applied and a portion of the biopsy cultured.

Liver biopsy is useful in elucidating the cause of *fever* of unknown origin [19].

Storage diseases. These include amyloidosis and glycogen disease (Chapter 25). Haemochromatosis and Wilson's disease can be diagnosed and the effect of therapy is assessed by serial biopsies.

Orthotopic liver transplant. Liver biopsy is useful in the pre-transplant work-up. Post-transplant pathology includes rejection, infection and bile leaks. Liver biopsy is essential to unravel these complications. The protocol 5-day biopsy is particularly useful in diagnosing episodes of rejection [5].

Renal transplants. Liver biopsy is useful in evaluating the chronic liver disease in kidney recipients [36].

Space-occupying lesions are diagnosed by direct biopsy under imaging.

Other indications include obscure hepatomegaly or splenomegaly, and abnormal biochemical tests of uncertain cause, particularly where fatty liver is suspected.

Special methods [37]

Bile canaliculi may be shown by staining for adenosine triphosphatase (ATPase) and glucose-6-phosphatase. Electron microscopy may be combined with histochemistry. ATPase is localized to the microvilli of the canaliculi and 5-nucleotidase to the microvilli of the sinusoidal border. Acid phosphatase is found in Kupffer cells, degenerating foci and regenerating nodules; alkaline phosphatase defines cholangioles.

Immunohistochemical stains may be used to demonstrate antigens of viral hepatitis A, B, C, D and E, also herpes and adenovirus. Immunohistochemistry is also used to diagnose amyloid disease and α_1-antitrypsin deficiency.

Markers for bile duct epithelial cells such as cytokeratin 7 are useful in cholestatic disorders and especially for ductular reactions and ductopenia. Immunostaining for specific tumour markers may be useful in detecting the origin of tumour metastases and diagnosing hepatocellular carcinoma from cholangiocarcinoma. Studies on the expression of oncogenic products have not yet reached clinical application.

Factor VIII-related antigen is used to diagnose angiosarcoma and epithelioid haemangio-endothelioma.

In situ hybridization techniques, using complementary DNA or RNA sequences, are being increasingly used to assess viral replication, for instance cytomegalovirus, herpes and hepatitis B or C viruses (HBV or HCV).

Polymerase chain reaction (PCR) is useful in human immunodeficiency virus (HIV), HBV and HCV infections, but the whole biopsy is required for the analysis.

Mononuclear cells derived from liver biopsies may be studied by histochemistry using monoclonal antibodies specific for various surface antigens [17]. Flow cytometry is used to immunotype lymphocytes from fresh liver tissue.

Polarized light is useful for showing malarial and schistosomal pigment, crystals or amyloid after Congo red staining.

Ultraviolet light may help to identify porphyrins in fresh frozen sections from patients with porphyria cutanea tarda.

Quantitative analysis of liver biopsy specimens is plagued by sampling difficulties and by failure to find a suitable standard of reference. In the liver with normal structure, results are reasonably reliable. Difficulties arise particularly in biopsies from cirrhotic livers where the proportion of fibrous tissue is uncertain. DNA, which is confined to the nucleus, is probably the best reference base although this may be valueless where the proportion of cells of different types is variable. Alternatively, the substance being investigated may be referred to dry weight or to total nitrogen content of the biopsy.

References

1 Aledort LM, Levine PH, Hilgartner M *et al*. A study of liver biopsies and liver disease among haemophiliacs. *Blood* 1985; **66**: 367.

2 Axenfeld H, Brass K. Klinische und bioptische Untersuchungen über den sogenannten Icterus catarrhalis. *Frankfurt Z. Pathol.* 1942; **57**: 147.

3 Baron E. Aspiration for removal of biopsy material from the liver. *Arch. Intern. Med.* 1939; **63**: 276.

4 Bissonnette RT, Gibney RG, Berry BR *et al*. Fatal carcinoid crisis after percutaneous fine-needle biopsy of hepatic metastasis: case report and literature review. *Radiology* 1990; **174**: 751.

5 Brunt EM, Peters MG, Flye MW *et al*. Day-5 protocol liver allograft biopsies document early rejection episodes and are predictive of recurrent rejection. *Surgery* 1992; **111**: 511.

6 Buscarini L, Fornari F, Bolondi L *et al*. Ultrasound-guided fine-needle biopsy of focal liver lesions: techniques, diagnostic accuracy and complications. *J. Hepatol.* 1990; **11**: 344.

7 Cohen MB, A-Kader HH, Lambers D *et al*. Complications of percutaneous liver biopsy in children. *Gastroenterology* 1992; **102**: 629.

8 Colombo M, del Ninno E, de Franchis R *et al*. Ultrasound assisted percutaneous liver biopsy: superiority of the Trucut over the Menghini needle for diagnosis of cirrhosis. *Gastroenterology* 1988; **95**: 487.

9 Crawford AR, Lin X-Z, Crawford JM. The normal adult human liver biopsy: a quantitative reference standard. *Hepatology* 1998; **28**: 323.

10 Desmet VJ, Gerber M, Hoofnagle JH *et al*. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* 1994; **19**: 1513.

11 Donaldson BW, Gopinath R, Wanless IR *et al*. The role of transjugular liver biopsy in fulminant liver failure: relation to other prognostic indicators. *Hepatology* 1993; **18**: 1370.

12 Ewe K. Bleeding after liver biopsy does not correlate with indices of peripheral coagulation. *Dig. Dis. Sci.* 1981; **26**: 388.

13 Frerichs FT von. *Über den Diabetes*. Hirschwald, Berlin, 1884.

14 Furuya KN, Burrows PE, Phillips MJ *et al*. Transjugular liver biopsy in children. *Hepatology* 1992; **15**: 1036.

15 Glenthoj A, Sehested M, Torp-Pedersen S. Diagnostic reliability of histological and cytological fine needle biopsies from focal liver lesions. *Histopathology* 1989; **15**: 375.

16 Hashimoto E, Ludwig J, MacCarty RL *et al*. Hepatoportal arteriovenous fistula: morphologic features studied after orthotopic liver transplantation. *Hum. Pathol.* 1989; **20**: 707.

17 Hata K, Van Thiel DH, Herberman RB *et al*. Phenotypic and functional characteristics of lymphocytes isolated from liver biopsy specimens from patients with active liver disease. *Hepatology* 1992; **15**: 816.

18 Hederstrom E, Forsberg L, Floren C-H *et al*. Liver biopsy complications monitored by ultrasound. *J. Hepatol.* 1989; **8**: 94.

19 Holtz T, Moseley RH, Scheiman JM. Liver biopsy in fever of unknown origin: a reappraisal. *J. Clin. Gastroenterol.* 1993; **17**: 29.

20 Huard P, May JM, Joyeux B. La ponction biopsie du foie et son utilté dans le diagnostique des affections hépatiques. *Ann. Anat. Path. Anat. Norm. Méd-chir.* 1935; **12**: 1118.

21 Iversen P, Roholm K. On aspiration biopsy of the liver, with remarks on its diagnostic significance. *Acta. Med. Scand.* 1939; **102**: 1.

22 Jacobs WH, Goldberg SB and the Patient Care Committee of the American Gastroenterological Association. Statement on outpatient percutaneous liver biopsy. *Dig. Dis. Sci.* 1989; **34**: 322.

23 Janes CH, Lindor KD. Outcome of patients hospitalized for complications after outpatient liver biopsy. *Ann. Intern. Med.* 1993; **118**: 96.

24 Klatskin G, Conn HO. *Histopathology of the Liver*, vols 1 and 2. Oxford University Press, New York, 1993.

25 Lebrec D. Various approaches to obtaining liver tissue: choosing the biopsy technique. *J. Hepatol.* 1996; **25** (suppl. 1): 20.

26 Lebrec D, Goldfarb G, Degott C *et al*. Transvenous liver biopsy—an experience based on 1000 hepatic tissue samplings with this procedure. *Gastroenterology* 1982; **82**: 338.

27 Lindor KD, Bru C, Jorgensen RA *et al*. The role of ultrasonography and automatic-needle biopsy in outpatient percutaneous liver biopsy. *Hepatology* 1996; **23**: 1079.

28 McGill DB, Rakela J, Zinsmeister AR *et al*. A 21-year experience with major haemorrhage after percutaneous liver biopsy. *Gastroenterology* 1990; **99**: 1396.

29 Maharaj B, Maharaj RJ, Leary WP *et al*. Sampling variability and its influence on the diagnostic yield of percutaneous needle biopsy of the liver. *Lancet* 1986; **i**: 523.
30 Menghini G. One-second needle biopsy of the liver. *Gastroenterology* 1958; **35**: 190.
31 Minuk GY, Sutherland LR, Wiseman DA *et al*. Prospective study of the incidence of ultrasound-detected intrahepatic and subcapsular haematomas in patients randomized to 6 or 24 h of bed rest after percutaneous liver biopsy. *Gastroenterology* 1987; **92**: 290.
32 Olynyk JK, O'Neill R, Britton RS *et al*. Determination of hepatic iron concentration in fresh and paraffin-embedded tissue: diagnostic implications. *Gastroenterology* 1994; **106**: 674.
33 Pagliaro L, Rinaldi F, Craxi A *et al*. Percutaneous blind biopsy vs. laparoscopy with guided biopsy in diagnosis of cirrhosis: a prospective, randomised trial. *Dig. Dis. Sci.* 1983; **28**: 39.
34 Piccinino F, Sagnelli E, Pasquale G *et al*. Complications following percutaneous liver biopsy. A multicentre retrospective study on 68 276 biopsies. *J. Hepatol.* 1986; **2**: 165.
35 Pisha T, Gabriel S, Therneau T *et al*. Cost-effectiveness of ultrasound-guided liver biopsy. *Hepatology* 1998; **27**: 1220.
36 Rao KV, Anderson WR, Kasiske BL *et al*. Value of liver biopsy in the evaluation and management of chronic liver disease in renal transplant recipients. *Am. J. Med.* 1993; **94**: 241.
37 Scheuer PJ, Lefkowitch JH. *Liver Biopsy Interpretation*, 6th edn. WB Saunders, Philadelphia, 2000.
38 Schüpfer F. De la possibilité de faire 'intra vitam' un diagnostic histo-pathologique précis des maladies du foie et de la rate. *Sem. Méd*. 1907; **27**: 229.
39 Sherlock S. Aspiration liver biopsy, technique and diagnostic application. *Lancet* 1945; **ii**: 397.
40 Sherlock S, Dick R, van Leeuwen DJ. Liver biopsy today. The Royal Free Hospital experience. *J. Hepatol.* 1984; **1**: 75.
41 Tobkes AI, Nord HJ. Liver biopsy: review of methodology and complications. *Digestion* 1995; **13**: 267.
42 Veneri RJ, Gordon SC, Fink-Bennett D. Scintigraphic and culdoscopic diagnosis of bile peritonitis complicating liver biopsy. *J. Clin. Gastroenterol.* 1989; **11**: 571.
43 Whitmire LF, Galambos JT, Phillips VM *et al*. Imaging guided percutaneous hepatic biopsy: diagnostic accuracy and safety. *J. Clin. Gastroenterol*. 1985; **7**: 511.
44 Younossi ZM, Teran JC, Ganiats TG. Ultrasound-guided liver biopsy for parenchymal liver disease: an economic analysis. *Dig. Dis. Sci.* 1998; **43**: 46.
45 Zins M, Vilgrain V, Gayno S *et al*. US-guided percutaneous liver biopsy with plugging of the needle track: a prospective study in 72 high-risk patients. *Radiology* 1992; **184**: 841.

Chapter 4
The Haematology of Liver Disease

General features

Hepato-cellular failure, portal hypertension and jaundice may affect the blood picture. Chronic liver disease is usually accompanied by 'hypersplenism'. Diminished erythrocyte survival is frequent. In addition both parenchymal hepatic disease and cholestatic jaundice may produce blood coagulation defects. Dietary deficiencies, alcoholism, bleeding and difficulties in hepatic synthesis of proteins used in blood formation or coagulation add to the complexity of the problem.

Spontaneous bleeding, bruising and purpura, together with a history of bleeding after minimal trauma such as venepuncture, are more important indications of a bleeding tendency in patients with liver disease than laboratory tests.

Blood volume

Plasma volume is frequently increased in patients with cirrhosis, especially with ascites and also with long-standing obstructive jaundice or with hepatitis. This hypervolaemia may partially, and sometimes totally, account for a low peripheral haemoglobin or erythrocyte level. Total circulating haemoglobin is reduced in only about half the patients.

Erythrocyte changes

The red cells may be *hypochromic*. This is often due to gastrointestinal bleeding leading to iron deficiency. In portal hypertension anaemia follows gastro-oesophageal bleeding and is enhanced by thrombocytopenia and disturbed blood coagulation. In cholestasis or cirrhosis of the alcoholic, haemorrhage may be from an ulcer or gastritis. Epistaxis, bruising and bleeding gums add to the anaemia.

The erythrocytes are usually *normocytic*. This is a combination of the microcytosis of chronic blood loss and the macrocytosis inherent in patients with liver disease. Thus the red cell membrane cholesterol and phospholipid content and/or ratio is changed and this results in various morphological abnormalities including thin macrocytes and target cells.

Thin macrocytes are frequent and are associated with a macronormoblastic marrow. These resolve when liver function improves.

Target cells are also thin macrocytes. They are found in both hepato-cellular and cholestatic jaundice. They are flat, macrocytic and have an increased surface area and increased resistance to osmotic lysis. They are particularly prominent in cholestasis where a rise in bile acids may contribute by inhibiting lecithin cholesterol acyl transferase (LCAT) activity [12]. The red cell membrane LCAT is decreased, resulting in loading of the membrane with both cholesterol and lecithin. Membrane fluidity is unchanged.

Spur cells are cells with unusual thorny projections. They are also termed *acanthocytes* (fig. 4.1). They are associated with far advanced liver disease, usually in alcoholics. Severe anaemia and haemolysis are also found. Their appearance is a bad prognostic sign. They disappear after liver transplantation [11]. The mechanism of their formation is unclear but they may be derived from *echinocytes*, which are also called burr cells [28]. These spiculated cells are not usually seen on dry blood films but are present on wet films or scanning electron microscopy in many patients with liver disease. They form because of an interaction with the abnormal HDL found in liver disease [28]. There is excess accumulation of unesterified cholesterol compared with phospholipid, with resultant reduced membrane fluidity and the formation of thorny projections. Reticulo-endothelial cells in the spleen modify these rigid cells with removal of membrane.

Alcoholics show genuine *thick macrocytes* which are probably related to the toxic effect of alcohol on the bone marrow. Folic acid and B_{12} deficiency may contribute.

Bone marrow of chronic hepato-cellular failure is hyperplastic and macronormoblastic. In spite of this, erythrocyte volume is depressed and the marrow therefore does not seem able to compensate completely for the anaemia (*relative marrow failure*).

Folate and B_{12} metabolism

The liver stores folate and converts it to its active storage form, tetrahydrofolate. Folate deficiency may accom-

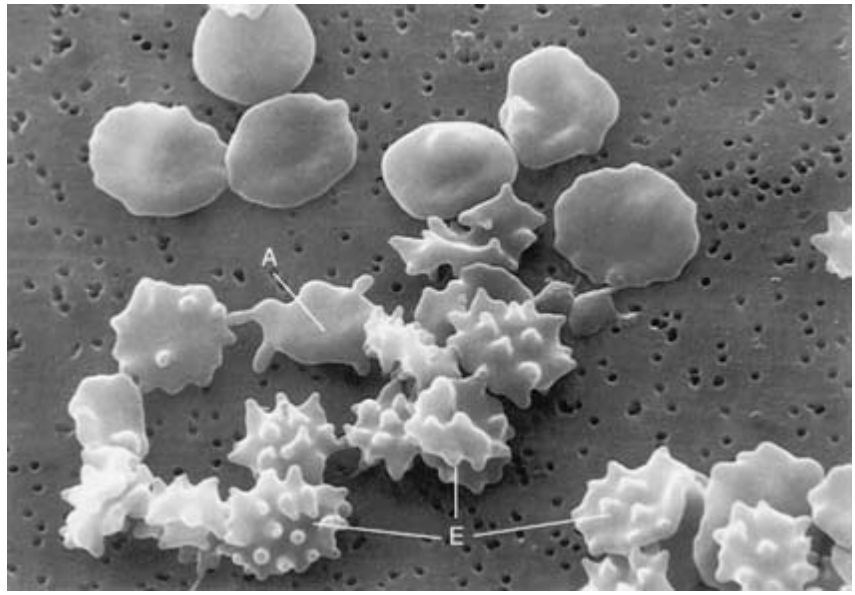


Fig. 4.1. Scanning electron micrograph of abnormal red cells from a patient with alcoholic hepatitis, showing echinocytes (E) at various stages of development, and an acanthocyte (A). (Courtesy of Dr J. Owen and Ms J. Lewin.)

pany chronic liver disease, usually in the alcoholic. This is largely due to dietary deficiency. Serum folate levels are low. Folate therapy is useful. The liver also stores vitamin B_{12} [27]. Hepatic levels are reduced in liver disease. When hepatocytes become necrotic the vitamin is released into the blood and high serum B_{12} levels are recorded. This is shown in hepatitis, active cirrhosis and with primary liver cancer. Values in cholestatic jaundice are normal.

Megaloblastic anaemia is rare with chronic liver disease and vitamin B_{12} therapy is rarely needed.

Erythrocyte survival and haemolytic anaemia

Increased red cell destruction is almost constant in hepato-cellular failure and jaundice of all types [35]. This is reflected in erythrocyte polychromasia and reticulocytosis.

The mechanism is extremely complex. The major factor is hypersplenism with destruction of red blood cells in the spleen. Also, spur cells have membrane defects, particularly decreased fluidity, and this, with the altered architecture, exacerbates splenic destruction. In some instances, however, the spleen is not the site of erythrocyte destruction. Splenectomy or corticosteroid therapy have little effect [35].

Haemolysis may occur in Wilson's disease (Chapter 24), and this diagnosis is likely in the young patient presenting with haemolysis and liver dysfunction.

Haemolysis may be acute in patients with alcoholic hepatitis who also have hypercholesterolaemia (*Zieve's syndrome*) [43].

Rarely, an autoimmune haemolytic anaemia with a positive Coombs' test is seen in chronic hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis. Haemolytic anaemia may also follow liver transplantation due to 'passenger lymphocytes' in a mismatch donor organ [14] or a delayed transfusion reaction. A syndrome of haemolysis, elevated liver enzymes and a low platelet count (the HELLP syndrome) is a rare complication of the third trimester of pregnancy (Chapter 27) [34]. Haemolysis is a complication of ribavirin therapy due to oxidative damage to the red cell membrane with binding of specific IgG [13].

Aplastic anaemia is a rare complication of acute viral hepatitis, usually type non-A, non-B, non-C. It may be fatal but response to intensive immunosuppressive treatment is reported [7]. It may follow liver transplantation [16].

Changes in the leucocytes and platelets

Leucopenia and thrombocytopenia are commonly found in patients with cirrhosis, usually with a mild anaemia ('*hypersplenism*').

Leucocytes

The leucopenia is of the order of $1.5–3.0\times10^9$/l, with the depression mainly affecting polymorphs. Occasionally it may be more severe.

Leucocytosis accompanies cholangitis, fulminant hepatitis, alcoholic hepatitis, hepatic abscess and malignant disease. Atypical lymphocytes are found in the peripheral blood in viral infections such as infectious mononucleosis and viral hepatitis.

Platelets

Abnormalities in platelet count and function are common in patients with all forms of liver disease.

Platelet count. In patients with chronic liver disease and portal hypertension, a low platelet count is due in part to increased splenic sequestration and to low thrombopoietin levels. Thus, although platelet counts rise after the insertion of a transjugular intra-hepatic portosystemic shunt, they do not return to normal [18]. Plasma concentrations of thrombopoietin, the key regulator of platelet function produced mainly by the liver, are reduced in patients with cirrhosis, correlate with platelet count, and rise after liver transplantation [17, 32, 38].

In chronic liver disease increased destruction of platelets is minimal and their half-life is normal, calling into question whether there is any biological effect of the IgG and IgM antibodies detected in patients with chronic hepatitis [20, 26]. Decreased production of platelets from the bone marrow follows alcohol excess, folic acid deficiency and viral hepatitis.

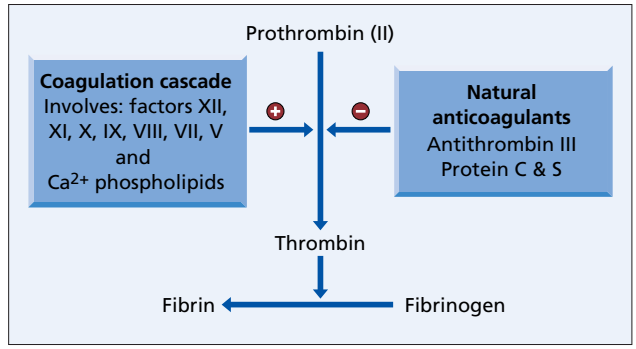
Platelet function, in particular aggregation, is impaired in patients with cirrhosis, particularly Child's grade C, due to an intrinsic defect and circulating serum factors [42]. There is reduced availability of arachidonic acid for prostaglandin production, and also a reduction in platelet adenosine triphosphate and 5-hydroxytryptamine [21]. Abnormal platelet aggregation due to disseminated intravascular coagulation may be an additional important factor in severe liver failure.

The thrombocytopenia of chronic liver disease (usually 60–90$\times 10^9$/l) is extremely frequent and is largely due to hypersplenism. It is very rarely of clinical significance. Unless the patient is actually suffering from the leucopenia or thrombocytopenia the spleen should not be removed; mere demonstration of a low platelet or leucocyte count is not sufficient. The circulating platelets and leucocytes, although in short supply, are functioning well, in contrast to those of leukaemia. Splenectomy is contraindicated. The mortality in patients with liver disease is high and the operation is liable to be followed by splenic and portal vein thrombosis which preclude later operations on the portal vein and may make hepatic transplantation more difficult.

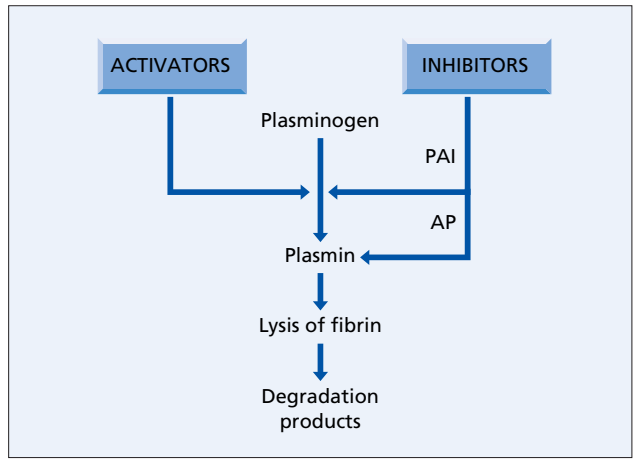
The liver and blood coagulation [9, 24, 31]

Disturbed blood coagulation in patients with hepatobiliary disease is particularly complex. This is due to the many changes in pathways which lead to fibrin production occurring at the same time as changes in the fibrinolytic process (fig. 4.2, table 4.1). Changes in platelet number and function are discussed in the previous section. Despite the complexity of the changes, the end result is reduced coagulation, which needs therapeutic intervention if there is bleeding or if a procedure is planned that risks haemorrhage.

The hepatocyte is the principal site of *synthesis* of all the *coagulation proteins* with the exception of von Wille-



(a)



(b)

Fig. 4.2. Normal pathways of (a) coagulation and (b) fibrinolysis. Liver disease effects virtually all components. PAI, plasminogen activator inhibitor; AP, antiplasmin.

Table 4.1. Effect of liver disease on haemostasis

Reduced synthesis of clotting factors
hepatic dysfunction *per se*
vitamin K deficiency/malabsorption
Reduced synthesis of inhibitors of coagulation
Production of abnormal/dysfunctional proteins
Enhanced fibrolytic activity
reduced clearance of activators of fibrinolysis
reduced production of inhibitors of fibrinolysis
Reduced hepatic clearance of activated clotting factors
Disseminated intravascular coagulation
multifactorial including endotoxaemia
Platelet abnormalities
number
function

brand factor and factor VIIIC. The proteins include the vitamin K-dependent factors II, VII, IX and X, also labile factor V, factor VIII, contact factors XI and XII, fibrinogen and fibrin-stabilizing factor XIII. The half-life of all these clotting proteins is very short and hence reductions can rapidly follow acute hepato-cellular necrosis. Factor VII is particularly affected with a half-life of 100–300 min.

Vitamin K is a fat-soluble vitamin produced by intestinal bacteria. Deficiency occurs most commonly due to cholestasis, intra- and extra-hepatic, but may also follow treatment with bile acid chelators (cholestyramine) or oral antibiotics. The vitamin K-dependent proteins are made in the rough endoplasmic reticulum. They all have a number of glutamic acid residues in their aminoterminal region that must be converted, post-ribosomally, to γ-carboxyglutamic acid by a carboxylase that requires vitamin K [15]. The function of these blood-clotting proteins depends on this conversion since γ-carboxyglutamic acid is responsible for calcium binding, interaction with membrane phospholipids and protease activity. In cholestasis parenteral replacement of vitamin K corrects the prothrombin time (PT) rapidly to normal (24–48 h) and is useful diagnostically. If the coagulopathy is due to hepatic disease the PT may improve but not to normal.

Inhibitors which modulate the coagulation cascade are also synthesized by the liver. These include antithrombin III (ATIII), protein C and S, and heparin co-factor II. Protein C and S are vitamin K dependent. In fulminant hepatic failure [22] and cirrhosis [3] these inhibitors are reduced but their deficiency is not associated with thrombotic events, probably because of the other changes in coagulation. Homozygous protein C deficiency has been cured by hepatic transplantation [8].

In liver disease, structurally and functionally *inadequate clotting factors and proteins* may be produced. *Dysfibrinogenaemia* is particularly frequent in cirrhosis, chronic hepatitis and acute liver failure. The fibrinogen may contain an excessive number of sialic acid residues. These are thought to lead to abnormal polymerization of fibrin monomers. There may also be a low molecular weight fibrinogen. Abnormalities of fibrinogen account for the prolongation of thrombin time in many patients with liver disease. This should be suspected if the partial thromboplastin time (PTT) is increased but fibrinogen levels are normal and fibrinogen degradation products not increased.

There is evidence for *enhanced fibrinolytic activity* in patients with liver disease (fig. 4.2b). Goodpasture first described the accelerated lysis of incubated clotted blood taken from cirrhotic patients in 1914. The synthesis of tissue plasminogen activator by vascular endothelial cells is stimulated *in vitro* by plasma from patients with decompensated cirrhosis [19]. Hepatocytes synthesize plasmin inhibitors such as α_2-antiplasmin, as well as tissue plasminogen activator inhibitor (PAI). In patients with cirrhosis, PAI antigen is reduced even without features of clotting activation (increased fibrin/fibrinogen degradation products; D-dimer) [41]. The resulting increased tissue plasminogen activator activity relative to PAI activity and α_2-antiplasmin is thought to lead to increased fibrinolysis [23]. Patients with severe liver disease and markers of hyperfibrinolysis are at higher risk of bleeding [40].

Whether there is background *disseminated intravascular coagulation* (DIC) in patients with cirrhosis, chronic hepatitis and acute hepatitis has been debated for some time. The complex changes found in coagulation proteins, inhibitors and protein fragments usually associated with DIC could have been due to liver disease. Studies of thrombin–antithrombin (TAT) complexes, soluble fibrin, fibrin and fibrinogen degradation products (D-dimer, D-monomer) suggest that low-grade DIC is a component of the coagulopathy in some patients with severe liver disease [1]. The mechanisms stimulating this are thought to include impaired clearance of activated clotting factors, and endotoxaemia [39].

Whatever the background state, cirrhotic patients are, however, at greater risk of overt DIC than patients with normal liver function, particularly in the presence of sepsis and hypotension.

Ascitic fluid contains fibrin monomers, fibrin degradation products and low levels of fibrinogen. This indicates active intra-peritoneal coagulation. Fibrinolysis, induced by infusion of plasminogen activators, accounts for the coagulopathy which complicates intravenous infusion of ascitic fluid as in the LeVeen shunt.

Thrombotic complications can occur in cirrhotic patients. The relationship between antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies) reported in cirrhotics [37], the reduction in physiological anticoagulants (ATIII, protein C and S) and thrombotic events remains to be established.

Tests of coagulation

The PT before and after 10 mg vitamin K given intravenously is the most satisfactory test for a coagulation defect in patients with hepato-biliary disease. It is also a most sensitive indication of hepato-cellular necrosis and/or prognosis. The PTT is sometimes performed and is slightly more sensitive than the PT. Prolongation indicates not only deficiency of the prothrombin complex but also factors XI and XII.

Estimation of individual clotting factors is rarely necessary although in patients with fulminant hepatic failure the level of factor V is related to outcome. Thus, in patients with paracetamol-induced hepatic failure a factor V concentration of <10% on admission predicts a poor outcome [33]. The ratio of factor VIII (increased in liver disease) to factor V on admission is also valuable.

The platelet count is done. Measurement of the bleeding time assesses the contribution of platelet number and function to haemostasis.

Fibrinolysis and DIC are diagnosed by marked prolongation of the PT, fibrinogen levels below 1.0 g/l, fibrin degradation products greater than 100 µg/l and thrombocytopenia less than 100×10^9/l.

Thromboelastography (TEG) is a measure of the net outcome of many factors in haemostasis and results are abnormal in cirrhotic patients particularly when associated with sepsis [30]. Hypocoagulability as measured by TEG may relate to variceal haemorrhage [10].

Management of coagulation defect

Vitamin K_1 should be given to all patients with a prolonged PT. The usual course is 10 mg vitamin K_1 by intravenous injection for 3 days. This is effective in about 3 h and will correct hypoprothrombinaemia related to malabsorption of vitamin K secondary to bile salt deficiency. Defects predominantly due to hepato-cellular disease will not be restored by the vitamin K_1 treatment. Nevertheless, even in patients with predominantly hepato-cellular jaundice there may be a component of bile salt secretory failure and the PT often improves by a few seconds.

A prolongation of the PT of more than 3 s (INR 1.2) after intravenous vitamin K_1 contraindicates such procedures as liver biopsy, splenic venography, percutaneous cholangiography or laparotomy. If such procedures are essential, the clotting defect may be improved by fresh frozen plasma which is effective for a few hours (table 4.2). However, even patients with PTs and platelet counts regarded as acceptable for invasive procedures (PT < 17 s; platelets $>80\times10^9$/l) may have a prolonged bleeding time [5]. Multiple linear regression analysis shows bleeding time to correlate independently with serum bilirubin concentration and platelet count.

In general, apart from vitamin K_1 therapy, it is not necessary to restore blood coagulation to normal in patients with liver disease unless there is active bleeding. Stored blood transfusion will supply prothrombin and factors VII, VIII and X. Fresh blood also supplies factor V and platelets. Fresh frozen plasma is a good source of clotting factors, especially factor V. If an invasive procedure such as liver biopsy or percutaneous ethanol injection of a tumour is required, administration of recombinant factor VIIa corrects the PT in cirrhotic patients [4, 29].

Desmopressin (DDAVP), a vasopressin analogue, causes transient shortening of the bleeding time and PTT (but not PT) with increases in factor VIII and von Willebrand factor. Infusions may be helpful for the control of bleeding in patients with chronic liver disease.

DIC is treated by control of trigger factors such as infection, shock and dehydration. Fresh blood is most useful but, if unavailable, fresh frozen plasma and packed red blood cells may be used. DIC is never severe enough to merit heparin therapy.

Platelet-rich plasma concentrates are used if thrombocytopenia is a problem and may be given to cover a procedure such as transjugular liver biopsy in a severely thrombocytopenic patient.

Table 4.2. Routine before invasive techniques (including surgery)

Measure	Prothrombin time Partial thromboplastin time Platelet count
Routine	Abstain from alcohol for 1 week Vitamin K_1 10 mg intramuscularly
If necessary	Fresh frozen plasma Platelet infusion

Hepatic transplantation

The bleeding problems associated with liver transplantation are mainly due to hyperfibrinolysis during the anhepatic phase superimposed on the coagulopathy due to the underlying end-stage liver disease. Operative blood loss often leads to replacement with about 20 units of red blood cells and 15 units of platelets. Surgical skill and experience are important factors in reducing blood loss [2]. Prognosis is related to the volume of blood and blood products given [25].

During surgery, coagulation and fibrinolysis are activated. Activation of the fibrinolytic system occurs particularly during the anhepatic and post-reperfusion stages. Plasma concentrations of tissue-type plasminogen activator increase and there are high concentrations of fibrin degradation products.

Aprotinin, a low molecular weight serine–protease inhibitor with potent anti-fibrinolytic activity, reduces blood transfusion requirements during liver transplantation by 50–60% [36]. There is no increased complication rate from thrombus formation. Another anti-fibrinolytic agent, tranexamic acid, has also been shown to reduce blood loss during liver transplantation [6].

References

1 Bakker CM, Knot EAR, Stibbe J *et al*. Disseminated intravascular coagulation in liver cirrhosis. *J. Hepatol*. 1992; **15**: 330.

2 Bechstein WO, Neuhaus P. A surgeon's perspective on the management of coagulation disorders before liver transplantation. *Liver Transplant Surg*. 1997; **3**: 653.

3 Bell H, Odegaard OR, Andersson T *et al*. Protein C in patients with alcoholic cirrhosis and other liver diseases. *J. Hepatol*. 1992; **14**: 163.
4 Bernstein DE, Jeffers L, Erhardtsen E *et al*. Recombinant factor VIIa corrects prothrombin time in cirrhotic patients: a preliminary study. *Gastroenterology* 1997; **113**: 1930.
5 Blake JC, Sprengers D, Grech P *et al*. Bleeding time in patients with hepatic cirrhosis. *Br. Med. J*. 1990; **301**: 12.
6 Boylan JF, Klinck JR, Sandler AN *et al*. Tranexamic acid reduces blood transfusion requirements and coagulation factor use in primary orthotopic liver transplantation. *Anaesthesiology* 1996; **85**: 1043
7 Brown KE, Tisdale J, Barrett AJ *et al*. Hepatitis-associated aplastic anaemia. *N. Engl. J. Med*. 1997; **336**: 1059.
8 Casella JF, Lewis JH, Bontempo FA *et al*. Successful treatment of homozygous protein C deficiency by hepatic transplantation. *Lancet* 1988; **i**: 435.
9 Castelino DJ, Salem HH. Natural anticoagulants and the liver. *J. Gastroenterol. Hepatol*. 1997; **12**: 77.
10 Chau TN, Chan YW, Patch D *et al*. Thrombelastographic changes and early rebleeding in cirrhotic patients with variceal bleeding. *Gut* 1998; **43**: 267.
11 Chitale AA, Sterling RK, Post AB *et al*. Resolution of spur cell anaemia with liver transplantation—a case report and review of the literature. *Transplantation* 1998; **65**: 993.
12 Cooper RA, Arner EC, Wiley JS *et al*. Modification of red cell membrane structure by cholesterol-rich lipid dispersions: a model for the primary spur cell defect. *J. Clin. Invest*. 1975; **55**: 115.
13 De Francheschi L, Fattovich G, Turrini F *et al*. Hemolytic anaemia induced by ribavarin therapy in patients with chronic hepatitis C virus infection: role of membrane oxidative damage. *Hepatology* 2000; **31**: 997.
14 Dzik WH, Jenkins RL. Renal failure from ABO haemolysis due to anti-A of graft origin following liver transplantation. *Transfusion* 1987; **27**: 550.
15 Furie B, Furie BC. Molecular basis of vitamin K-dependent γ-carboxylation. *Blood* 1990; **75**: 1753.
16 Goss JA, Schiller GJ, Martin P *et al*. Aplastic anaemia complicating orthotopic liver transplantation. *Hepatology* 1997; **26**: 865.
17 Goulis J, Chau TN, Jordan S *et al*. Thrombopoietin concentrations are low in patients with cirrhosis and thrombocytopenia and are restored after orthotopic liver transplantation. *Gut* 1999; **44**: 754.
18 Gschwantler M, Vavrik J, Gebauer A *et al*. Course of platelet counts in cirrhotic patients after implantation of a transjugular intrahepatic portosystemic shunt—a prospective controlled study. *J. Hepatol*. 1999; **30**: 254.
19 Hayashi T, Kamogawa A, Ro S *et al*. Plasma from patients with cirrhosis increases tissue plasminogen activator release from vascular endothelial cells *in vitro*. *Liver* 1998; **18**: 186.
20 Kosugi S, Imai Y, Kurata Y *et al*. Platelet-associated IgM elevated in patients with chronic hepatitis C contains no antiplatelet autoantibodies. *Liver* 1997; **17**: 230.
21 Laffi G, Marra F, Gresele P *et al*. Evidence for a storage pool defect in platelets from cirrhotic patients with defective aggregation. *Gastroenterology* 1992; **103**: 641.
22 Langley PG, Williams R. Physiological inhibitors of coagulation in fulminant hepatic failure. *Blood Coag. Fibrinol*. 1992; **3**: 243.
23 Leebeek FWG, Kluft C, Knot EAR *et al*. A shift in balance between profibrinolytic and antifibrinolytic factors causes enhanced fibrinolysis in cirrhosis. *Gastroenterology* 1991; **101**: 1382.
24 Mammen EF. Coagulation defects in liver disease. *Med. Clin. North Am*. 1994; **78**: 545.
25 Mor E, Jennings L, Gonwa TA *et al*. The impact of operative bleeding on outcome in transplantation of the liver. *Surg. Gynecol. Obstet*. 1993; **176**: 219.
26 Nagamine T, Ohtuka T, Takenhara K *et al*. Thrombocytopenia associated with hepatitis C viral infection. *J. Hepatol*. 1996; **24**: 135.
27 Okuda K. Discovery of vitamin B_{12} in the liver and its absorption factor in the stomach: a historical review. *J. Gastroenterol. Hepatol*. 1999; **14**: 301.
28 Owen JS, Brown DJC, Harry DS *et al*. Erythrocyte echinocytosis in liver disease. Role of abnormal plasma high density lipoproteins. *J. Clin. Invest*. 1985; **76**: 2275.
29 Papatheodoridis GV, Chung S, Keshav S *et al*. Correction of both prothrombin time and primary haemostasis by recombinant factor VII during therapeutic alcohol injection of hepatocellular cancer in liver cirrhosis. *J. Hepatol*. 1999; **31**: 747.
30 Papatheodoridis GV, Patch D, Webster GJM *et al*. Infection and haemostasis in decompensated cirrhosis: a prospective study using thrombelastography. *Hepatology* 1999; **29**: 1085.
31 Paramo JA, Rocha E. Hemostasis in advanced liver disease. *Semin. Thromb. Hemost*. 1993; **19**: 184.
32 Peck-Radosavljevic M, Zacherl J, Wichlas M *et al*. Thrombopoietic cytokines and reversal of thrombocytopenia after liver transplantation. *Eur. J. Gastroenterol. Hepatol*. 1999; **11**: 151.
33 Pereira LMMB, Langley PG, Hayllar KM *et al*. Coagulation factor V and VIII/V ratio as predictors of outcome in paracetamol induced fulminant hepatic failure: relation to other prognostic indicators. *Gut* 1992; **33**: 98.
34 Pereira SP, O'Donohue J, Wendon J *et al*. Maternal and perinatal outcome in severe pregnancy-related liver disease. *Hepatology* 1997; **26**: 1258.
35 Pitcher CS, Williams R. Reduced red cell survival in jaundice and its relation to abnormal glutathione metabolism. *Clin. Sci*. 1963; **24**: 239.
36 Porte RJ, Molenaar IQ, Begliomini B *et al*. Aprotinin and transfusion requirements in orthotopic liver transplantation: a multicentre randomized double-blind study. *Lancet* 2000; **355**: 1303.
37 Quintarelli C, Ferro D, Valesini G *et al*. Prevalence of lupus anticoagulant in patients with cirrhosis: relationship with beta-2-glycoprotein 1 plasma levels. *J. Hepatol*. 1994; **21**: 1086.
38 Stiegler G, Stohlawetz P, Peck-Radosavljevic M *et al*. Direct evidence for an increase in thrombopoiesis after liver transplantation. *Eur. J. Clin. Invest*. 1998; **28**: 755.
39 Violi F, Ferro D, Basili S *et al*. Association between low-grade disseminated intravascular coagulation and endotoxaemia in patients with liver cirrhosis. *Gastroenterology* 1995; **109**: 531.
40 Violi F, Ferro D, Basili S *et al*. Hyperfibrinolysis increases the risk of gastrointestinal haemorrhage in patients with advanced cirrhosis. *Hepatology* 1992; **15**: 672.
41 Violi F, Ferro D, Basili S *et al*. Hyperfibrinolysis resulting from clotting activation in patients with different degrees of cirrhosis. *Hepatology* 1993; **17**: 78.
42 Younger HM, Hadoke PWF, Dillon JF *et al*. Platelet function

in cirrhosis and the role of humoral factors. *Eur. J. Gastroenterol. Hepatol.* 1997; **9**: 989.
43 Zieve L. Hemolytic anaemia in liver disease. *Medicine (Baltimore)* 1966; **45**: 497.

Haemolytic jaundice

Haemoglobin is released in excessive amounts, increasing from the normal of 6.25 g to as much as 45 g daily. Consequently there is an increase in the serum bilirubin, 85% of which is unconjugated. The rise in conjugated bilirubin is probably due to reflux from hepatocytes.

Even if bilirubin production reaches its maximum of 1500 mg daily (six times normal), serum bilirubin rises only to about 2–3 mg/100 ml (35–50 µmol/l). This is because of the great capacity of the liver to handle bilirubin. If patients with haemolytic jaundice show serum bilirubin values greater than 70–85 µmol/l there is probably the additional factor of Gilbert's syndrome, hepatocellular dysfunction or kidney failure. Anaemia itself will, of course, depress liver function.

Unconjugated bilirubin is not water soluble and does not pass into the urine. A little bilirubin may be detected in the urine by sensitive tests if the conjugated level in the blood rises to values that are unusually high for haemolysis.

Bile pigment excretion is greatly increased and large quantities of stercobilinogen are found in the stools. Each milligram of stercobilinogen corresponds to the breakdown of 24 mg haemoglobin. This estimate can only be approximate, for a significant proportion of the faecal haem pigment is derived from sources other than haemoglobin of mature erythrocytes.

Pathological changes

The breakdown of haemoglobin yields iron. *Tissue siderosis* is a feature of most types of haemolytic anaemia.

The *liver* is normal sized and is reddish-brown due to increased amounts of iron. Histology shows iron in the Kupffer cells, large macrophages of the portal tracts and, to a lesser extent, in hepatic parenchyma (fig. 4.3). In the severely anaemic, there is centrizonal sinusoidal distension with fatty change. The Kupffer cells are generally swollen and hyperplastic foci of erythropoiesis are uncommon. The *gallbladder* and *bile passages* contain dark viscid bile. Calcium bilirubinate pigment calculi are found in one-half to two-thirds of patients.

The *spleen* is enlarged, fleshy and packed with erythrocytes. The *red bone marrow* is hyperplastic.

Clinical features

The picture varies with the cause, but certain symptoms and signs are common to all forms of haemolysis.

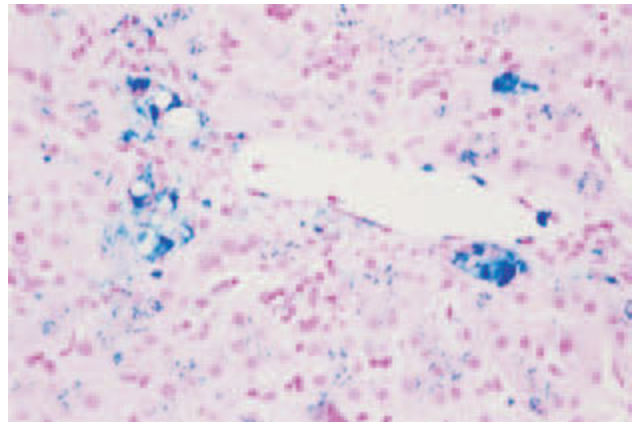


Fig. 4.3. Hepatic siderosis due to haematological disease. Increased amounts of iron (stained blue) are seen in the larger Kupffer cells and portal macrophages and, to a lesser extent, as granular staining in hepatocytes. (Perls' stain.)

Anaemia depends on the rate of destruction compared with regeneration of red blood cells. The haemoglobin falls rapidly with crises where the patient becomes ill with aching pains in the abdomen and limbs, fever, headache and sometimes even a fall in blood pressure and collapse.

Jaundice is usually mild and lemon yellow. It increases rapidly with haemolytic crises or if there is a coincidental difficulty in biliary excretion such as viral hepatitis or choledocholithiasis or if the kidney fails.

Bilirubin pigment *gallstones* may be associated with the features of chronic cholecystitis. Stones in the common bile duct may cause obstructive jaundice, and the coexistence of two types of jaundice provides a confusing clinical picture. Gallstones in children always suggest a haemolytic aetiology.

Splenomegaly is present in the chronic forms.

Ulcers or pigmentation from healed ulcers, usually over the internal or external malleoli, occur in some types.

Haematological changes

Anaemia is variable and the peripheral blood shows a reticulocytosis. Leucocytes are usually increased.

The bone marrow is hyperplastic and the proportion of erythroid to leucopoietic cells rises.

The survival of labelled erythrocytes is reduced and increased uptake can be shown in the spleen.

In some hereditary anaemias iron overload may occur without transfusion. This is particularly when there is a high degree of ineffective erythropoiesis, for example in congenital dyserythropoietic anaemias, congenital sideroblastic anaemia and thalassaemia intermedia. It may also occur in pyruvate kinase deficiency [12]. Muta-

tions in the haemochromatosis gene do not appear to be a prerequisite for the iron deposition (Chapter 23).

Faeces and urine

The faeces are dark and stercobilinogen is increased. Urobilinogen is increased in the urine. Bilirubin is detected in the urine only rarely, when jaundice is deep. When red cell destruction is rapid, free haemoglobin may be found in the urine and microscopy reveals pigmented casts.

Serum biochemistry

Serum unconjugated bilirubin levels are raised but conjugated bilirubin is only slightly increased.

The serum alkaline phosphatase, albumin and globulin concentrations are normal. Serum haptoglobins are diminished. The serum cholesterol level is low.

If haemolysis is particularly acute, methaemalbumin can be detected in the serum. Serum ferritin is increased. Free haemoglobin may be detected.

Differential diagnosis

The diagnosis of haemolytic from other forms of jaundice is usually easy. The absence of pain, pruritus, the dark colour of the stools and normal alkaline phosphatase are points of difference from cholestatic jaundice. The absence of stigmas of hepato-cellular disease, the normal serum alanine transaminase and protein values distinguish it from viral hepatitis and cirrhosis.

Distinction from the congenital unconjugated hyperbilirubinaemias may be difficult, particularly as many patients with Gilbert's disease show a decreased erythrocyte survival.

The liver in haemolytic anaemias

Hereditary spherocytosis [5]

The main signs are jaundice, anaemia, splenomegaly and gallstones, but the spectrum of disease is wide, from no clinical expression to death *in utero*. Inheritance is dominant or recessive. In 70% of cases the molecular defect is a mutation in ankyrin, one of the components of the red cell skeleton.

Jaundice is rarely noticed before school age or adolescence. The mean serum bilirubin level is 35 µmol/l (2 mg/dl) (range 10–100 µmol/l). Deep jaundice is rare. This may develop in the neonatal period and be associated with incipient kernicterus.

Gallstones are related to age and are rare at less than 10 years of age. They are symptomatic in about half of the patients. The stones are usually removed at the time of splenectomy.

Hereditary elliptocytosis, another genetic defect due to a mutation in a protein within the red cell membrane skeleton, is usually a harmless trait, the haemolysis being compensated. It may occasionally develop into active decompensated haemolytic anaemia.

Various enzyme defects

Many of the hereditary non-spherocytic anaemias are now known to be due to various defects in the metabolism of the red cells. They include deficiency of pyruvate kinase or triose phosphate isomerase, or deficiency in the pentose phosphate pathway such as glucose-6-phosphate dehydrogenase (G6PD). These conditions may be of particular importance in the aetiology of neonatal jaundice. The gene responsible for G6PD deficiency has now been cloned and a wide range of mutations recognized. These are beginning to explain the wide spectrum of clinical pictures seen in this condition ranging from haemolysis during the neonatal period, after infection or after the ingestion of certain drugs, to chronic anaemia irrespective of any of these factors. Variants of the gene are now recognized where there is no significant reduction in enzyme activity in red cells [2].

Viral hepatitis can precipitate destruction of G6PD-deficient cells and so cause acute haemolytic anaemia and very high serum bilirubin concentrations.

Sickle cell disease [1]

The abnormal haemoglobin crystallizes in the erythrocytes when the oxygen tension is reduced. There are crises of blood destruction with acute attacks of pain. The liver may be affected acutely by sickling crises. There is right upper quadrant pain, fever and increased jaundice, associated with systemic and haematological features of sickling. This should help to differentiate the clinical picture from a common bile duct stone. Fulminant liver failure is rare [11]. A distinct clinical picture of intra-hepatic cholestasis is also recognized but is unusual [7]. Histologically there is intra-canalicular cholestasis, sinusoidal dilatation, Kupffer cell hyperplasia and erythrophagocytosis.

There may be chronic elevation of transaminases and/or alkaline phosphatase with hepatic scarring. Several factors have been implicated including microvascular stasis, with recurrent ischaemic episodes, and transfusion-related disease (haemosiderosis and viral hepatitis).

Jaundice accompanying sickle cell disease is always particularly deep, the high serum bilirubin levels being related to the combination of haemolysis and impaired hepato-cellular function. Depth of jaundice *per se* should

not be regarded as an indication of severity. Concomitant viral hepatitis or obstructed bile ducts lead to exceptionally high serum bilirubin values.

Gallstones are found in 25% of children and 50–70% of adults with homozygous sickle cell disease. They are usually in the gallbladder; duct calculi are rare. In two-thirds of adults the stones are asymptomatic. The high frequency of gallbladder stones may be due in part to changes in gallbladder volume and motility. Elective cholecystectomy may be hazardous and precipitate a sickle crisis [1].

Hepatic histology

Active and healed areas of necrosis may have followed anoxia due to vascular obstruction by impacted sickle cells or by Kupffer cells swollen with phagocytosed erythrocytes following intra-hepatic sickling. The widened sinusoids show a foam-like fibrin reticulum within their lumen. This intra-sinusoidal fibrin may later result in fibre deposition in the space of Disse and narrowed sinusoids. Bile plugs are prominent. Fatty change is related to anaemia. Multiple transfusions lead to hepatic siderosis which is not accurately reflected by the serum ferritin [8].

The classic findings are of intra-sinusoidal sickling, Kupffer cell erythrophagocytosis and ischaemic necrosis. It is difficult to explain the severe liver dysfunction on these histological findings, which have been reported largely on autopsy specimens. In biopsies, the histological picture is more likely to be that of a complicating disease such as septicaemia or viral hepatitis [9].

Electron microscopy

The changes are those of hypoxia. There are sinusoidal aggregates of sickled erythrocytes, fibrin and platelets, with increased collagen and occasional basement membranes in the space of Disse.

Clinical features

Asymptomatic patients commonly have raised serum transaminases and hepatomegaly. Hepatitis B and C, and iron overload may have complicated transfusions.

In about 10%, the crisis selectively affects the liver. It lasts 2–3 weeks. It is marked by abdominal pain, fever, jaundice, an enlarged tender liver and a rise in serum transaminases. In some patients the crisis is precipitated by *Salmonella* infection or by folic acid deficiency.

Acute liver failure, usually with cholestasis, is rare. Jaundice is very deep with a markedly increased PT and encephalopathy but with only modestly increased serum transaminases. Liver biopsy shows the changes of sickle cell disease with marked zone 2 necrosis and cholestasis. The diagnosis of hepatic sickle crisis from viral hepatitis is difficult. In general, in viral hepatitis pain is less, jaundice deeper and transaminase elevations more prolonged. Liver biopsy and hepatitis viral markers usually help to make the distinction. Exchange transfusion has been successful [11]. Liver transplantation has been attempted unsuccessfully with graft loss and death of the patient due to vascular problems [3].

Prolonged intra-hepatic cholestasis associated with sickle cell anaemia has also responded to exchange transfusion [7].

Acute cholecystitis and choledocholithiasis may simulate hepatic crisis or viral hepatitis. Endoscopic or percutaneous cholangiography are important investigations in excluding biliary obstruction. Complications after cholecystectomy are common, and this is indicated only if there is great difficulty in making a distinction from abdominal crisis or where symptoms are clearly related to gallbladder disease. Pre-operative exchange transfusion may lessen later complications.

General features include leg ulcers, which are frequent. The upper jaw is protuberant and hypertrophied. The fingers are clubbed. Bone deformities seen radiologically include rarefaction and narrowing of the cortex of the long bones and a 'hair-on-end' appearance in the skull.

Thalassaemia

Crises of red cell destruction and fever and the reactionary changes in bone are similar to those seen in sickle cell disease. The liver shows siderosis and sometimes fibrosis. The haemosiderosis may progress to an actual haemochromatosis and indicate treatment by continuous desferrioxamine therapy (Chapter 23). The stainable iron in the liver cells may be greater in those who have lost the spleen as a storage organ for iron.

Transfusion-acquired hepatitis B and C may lead to chronic liver disease.

Episodes of intra-hepatic cholestasis of uncertain nature can also develop. Gallstones may be a complication.

Previously the commonest cause of death in thalassaemia major was heart failure but the clinical course of the disease is changing with improved therapy including, in particular, iron chelation.

Treatment

This may include folic acid, blood transfusion, iron chelation therapy, antiviral treatment and occasionally splenectomy with pneumococcal vaccination. Bone marrow transplantation may be considered but the survival is worse in those with liver disease [6].

Paroxysmal nocturnal haemoglobinuria [10]

In this rare acquired disease, there is intravascular, complement-mediated haemolysis. The defect is due to mutation of the PIG-A gene on chromosome X which results in deficient biosynthesis of the glycosylphosphatidylinositol (GPI) anchor. This leads to an absence of certain proteins on the red cell surface. The cells are sensitive to lysis when the pH of the blood becomes more acid during sleep. During an episode of haemolysis the urine passed in the morning may be brown or reddish-brown due to haemoglobinuria.

Acutely, the patients show a dusky, reddish jaundice and the liver enlarges. Aspartate transaminase may be increased (due to haemolysis) and serum studies show iron deficiency (due to urinary loss of haemoglobin). Liver histology shows some centrizonal necrosis and siderosis.

Hepatic vein thrombosis may be a complication. Bile duct changes similar to primary sclerosing cholangitis, perhaps due to ischaemia, have been reported [4].

Acquired haemolytic anaemia

The haemolysis is due to extra-corpuscular causes. Spherocytosis is slight and osmotic fragility only mildly impaired.

The patient is moderately jaundiced. The increased bilirubin is unconjugated, but in severe cases conjugated bilirubin increases and appears in the urine. This may be related to bilirubin overload in the presence of liver damage. Blood transfusion accentuates the jaundice, for transfused cells survive poorly.

The haemolysis may be *idiopathic*. The increased haemolysis is then due to autoimmunization. The Coombs' test is positive.

The *acquired* type may complicate other diseases, especially those involving the reticulo-endothelial system. These include Hodgkin's disease, the leukaemias, reticulosarcoma, carcinomatosis and uraemia. The anaemia of hepato-cellular jaundice is also partially haemolytic. The Coombs' test is usually negative.

Autoimmune haemolytic anaemia is a rare complication of autoimmune chronic hepatitis and primary biliary cirrhosis.

Wilson's disease may present as a haemolytic crisis (Chapter 24).

Haemolytic disease of the newborn

See Chapter 26.

Incompatible blood transfusion

Chills, fever and backache are followed by jaundice. Urobilinogen is present in the urine. Liver function tests give normal results. In severe cases free haemoglobin is detected in blood and urine. Diagnostic difficulties arise when a patient suffering from a disease that may be complicated by hepato-cellular failure or biliary obstruction becomes jaundiced soon after a blood transfusion.

References

1 Banerjee S, Owen C, Chopra S. Sickle cell hepatopathy. *Hepatology* 2001; **33**: 1021.
2 Beutler E. G6PD: population genetics and clinical manifestations. *Blood Rev.* 1996; **10**: 45.
3 Emre S, Kitibayashi K, Schwartz M *et al*. Liver transplantation in a patient with acute liver failure due to sickle cell intrahepatic cholestasis. *Transplantation* 2000; **69**: 675.
4 Huong DLT, Valla D, Franco D *et al*. Cholangitis associated with paroxysmal nocturnal haemoglobinuria: another instance of ischemic cholangiopathy? *Gastroenterology* 1995; **109**: 1338.
5 Iolascon A, Miraglia del Giudice E, Perrotta S *et al*. Hereditary spherocytosis: from clinical to molecular defects. *Haematologica* 1998; **83**: 240.
6 Lucarelli G, Galimberti M, Polchi P *et al*. Marrow transplantation in patients with thalassemia responsive to iron chelation therapy. *N. Engl. J. Med*. 1993; **329**: 840.
7 O'Callaghan A, O'Brien SG, Ninkovic M *et al*. Chronic intrahepatic cholestasis in sickle cell disease requiring exchange transfusion. *Gut* 1995; **37**: 144.
8 Olivieri NF. Progression of iron overload in sickle cell disease. *Semin. Haematol*. 2001; **38** (Suppl. 1): 57.
9 Omata M, Johnson CS, Tong M *et al*. Pathological spectrum of liver diseases in sickle cell disease. *Dig. Dis. Sci*. 1986; **31**: 247.
10 Rosse WF. Paroxysmal nocturnal haemoglobinuria as a molecular disease. *Medicine* 1997; **76**: 63.
11 Stephan JL, Merpit-Gonon E, Richard O *et al*. Fulminant liver failure in a 12-year-old girl with sickle cell anaemia: favourable outcome after exchange transfusion. *Eur. J. Paediatr*. 1995; **154**: 469.
12 Zanella A, Berzuini A, Colombo MB *et al*. Iron status in red cell pyruvate kinase deficiency: study of Italian cases. *Br. J. Haematol*. 1993; **83**: 485.

The liver in myelo- and lymphoproliferative disease [37]

The liver contains multipotential cells that can differentiate into reticulo-endothelial, myeloid and lymphoid cells. These can be affected by malignant disease (leukaemia, lymphoma), usually in association with systemic disease, but rarely occur as a primary hepatic disease. Reduced haemopoietic activity in the marrow is followed by extra-medullary haemopoiesis in the liver. Reticulo-endothelial storage diseases affect the liver as well as other organs. This section outlines the involvement of the liver in this broad group of diseases.

The liver is involved to a variable extent, usually with no functional effect, but with mildly abnormal liver

function tests. However, liver biopsies are helpful for diagnosis. Staining of sections with monoclonal antibodies may be necessary to define the cell type or disease. Involvement may be focal, so that serial sections should be cut. If scanning shows a focal lesion, guided biopsy is worthwhile.

Rarely, fulminant liver failure complicates the primary disease, due to replacement of hepatocytes with malignant cells. This is reported in acute lymphoblastic leukaemia [33] and non-Hodgkin's lymphoma [40]. It is important to differentiate these from liver failure due to viral or drug hepatitis, since liver transplantation is contraindicated when there is underlying haematological malignancy [40].

Acute and chronic abnormalities of liver function tests may be due to treatment. Drugs given should be reviewed. More aggressive chemotherapy has increased hepato-toxic drug reactions. Multiple blood transfusions are a frequent cause of viral hepatitis, particularly hepatitis C and non-A, non-B, non-C, and to a lesser extent type B. This is usually mild in the immunocompromised host. Hepatitis B may be reactivated during cytotoxic or immunosuppressive therapy, and there may be a fulminant hepatitis-like episode following withdrawal of treatment. This is thought to be due to a rebound effect with the return of immunity, and clearance of a large number of hepatocytes containing the virus [2, 17].

Gastrointestinal haemorrhage may complicate myeloproliferative diseases, leukaemia or lymphoma. In some this is caused by peptic ulceration or erosions. There may be portal hypertension due to hepatic, portal or splenic vein thrombosis related to a hypercoagulable state. Evidence for a myeloproliferative disorder was found in 14 of 33 patients with non-tumour-related portal vein thrombosis [35].

Occasionally the portal hypertension is pre-sinusoidal and seems to be secondary to infiltrative lesions in the portal zones and sinusoids. In others, increased blood flow due to splenomegaly may be important. Portal and central zone fibrosis can be related to cytotoxic therapy.

Leukaemia

Myeloid [37]

The enlarged liver is smooth and firm, and the cut section shows small, pale nodules.

Microscopically both portal tracts and sinusoids are infiltrated with immature and mature cells of the myeloid series. The immature cells lie outside the sinusoidal wall.

The portal tracts are enlarged with myelocytes and polymorphs, both neutrophil and eosinophil; round cells are also conspicuous. The liver cell cords are compressed by the leukaemic deposits.

Lymphoid

Macroscopically, the liver is moderately enlarged, with pale areas on section.

Microscopically, the leukaemic infiltration involves only the portal tracts—the normal site of lymphoid tissue in the liver. The portal areas are enlarged and contain both mature and immature cells of the lymphatic series. The sinusoids are not affected. The liver cells are normal.

Hairy cell leukaemia

The liver is usually involved although specific clinical and biochemical features are rare. Sinusoidal and portal infiltration with mononuclear 'clear' cells is seen with sinusoidal congestion and beading. Angiomatous lesions, usually peri-portal, consist of blood spaces lined by hairy cells.

Bone marrow transplantation

Liver abnormalities occur at some time in the majority of patients within 12 months of bone marrow transplantation [10]. The changes range from abnormal liver function tests alone, to coagulation abnormalities, ascites and hepato-renal failure. There are many possible causes (table 4.3); more than one may be responsible at any one time. Pre-existing liver disease increases the risk.

In the first 15 weeks, the most common causes of liver abnormality are acute graft-versus-host disease (GVHD), intra-hepatic veno-occlusive disease, drug-induced reactions and infection.

Jaundice and abnormal liver enzyme tests accompany the systemic manifestations of *acute GVHD*—rash and diarrhoea. This usually begins 3–8 weeks' post-transplant. The hepatic changes may persist to give cholestatic chronic GVHD with intra-hepatic bile duct damage. Chronic GVHD may also develop *de novo*.

The development of jaundice, painful hepatomegaly, weight gain and ascites in the first weeks after bone marrow transplantation suggests a diagnosis of *veno-occlusive disease*. This is due to high-dose cytoreductive therapy given 5–10 days before the marrow infusion. The incidence varies from one report to another, ranging from less than 5% to over 60%, probably reflecting different patient groups, conditioning regimens and diagnostic criteria. Mortality in severely affected individuals is high, around 50%. There is controversy whether histological evidence of venular occlusion is needed for diagnosis. Routine percutaneous liver biopsy is often contraindicated by a low platelet count, prolonged coagulation tests and ascites. Transjugular liver biopsy overcomes these problems, although bleeding complications may still occur [31]. This route also allows the wedged

Table 4.3. Hepato-biliary disease and bone marrow transplantation

Problem	Related to
Pre-existing	
Fungal	Granulocytopenia
Viral (hepatitis type B, C)	Blood products
Drug	Medication
Biliary	Stones
Post-transplantation	
Early neutropenic phase (up to 4 weeks)	
acute graft-versus-host disease	Donor marrow
veno-occlusive disease	Cytoreductive therapy
nodular regenerative hyperplasia	
drug induced	Including TPN
Extra-hepatic bacterial sepsis	Bacteria/endotoxin
fungal	
biliary disease	Sludge
Intermediate (4–15 weeks)*	
Viral	Cytomegalovirus
	Hepatitis type B, C
Late (>15 weeks)	
chronic graft-versus-host disease	Multi-organ disease
chronic viral infection	
fungal	Immunosuppression
tumour recurrence	

* As well as continuing early problems.

hepatic venous pressure to be measured [31]. Four histological abnormalities correlate with the clinical severity of disease: occluded hepatic venules, eccentric luminal narrowing/phlebosclerosis, hepatocyte necrosis and sinusoidal fibrosis [30]. These findings suggest that there is extensive injury to zone 3 structures by the cytoreductive therapy. Studies suggest that ursodeoxycholic acid [8], defibrotide [5] and tissue plasminogen activator [34] may be useful in the prevention or treatment of veno-occlusive disease.

Opportunistic *fungal* and *bacterial infections* occur during neutropenic periods and may cause abnormal liver function; *viral infections* occur later.

Helpful data to identify the cause of the hepatic abnormality include: (a) timing of the changes related to drugs, chemotherapy, radiation and bone marrow infusion; (b) the dose of cytoreductive (conditioning) therapy; (c) the source of donor marrow; (d) pre-treatment viral serology; (e) the degree of immunosuppression; and (f) evidence of systemic disease. Bacteriological and virological data are important. Often more than one process is involved. In one series transvenous liver biopsy provided useful data for patient management in over 80% of cases [31].

After bone marrow transplantation, hepato-biliary scintiscanning and ultrasound commonly show abnormalities of questionable clinical significance. Doppler ultrasonography is not reliable for the diagnosis of veno-occlusive disease [28].

Lymphoma

Hepatic involvement occurs in about 70% of cases and immediately puts the patient into stage IV [14]. It may be seen as diffuse infiltrates, as focal tumour-like masses, as portal zone cellularity (fig. 4.4), as an epithelioid cell reaction or as lymphoid aggregates [14]. Rarely, lymphomatous infiltration presents as acute liver failure [40].

In *Hodgkin's disease*, typical tissue is seen spreading out from the portal tracts, with lymphocytes, large pale epithelioid cells, eosinophils, plasma cells and giant Reed–Sternberg cells (fig. 4.5). Later, fibroblasts are found in a supporting connective tissue reticulum.

In patients with known extra-hepatic Hodgkin's disease, but without obvious Reed–Sternberg cells in sections of the liver, hepatic involvement is suggested by portal infiltrates larger than 1 mm in diameter, changes of acute cholangitis, portal oedema and portal infiltrates with a predominance of atypical lymphocytes. These changes should stimulate a wider search for the diagnostic Reed–Sternberg cell in further sections [6].

In *non-Hodgkin's lymphoma*, the portal zones are usually involved. In small cell lymphocytic lymphoma, a dense, monotonous proliferation of normal-appearing lymphocytes is seen. The more aggressive lymphomas also involve portal zones and form tumour nodules. Large cell lymphoma may infiltrate sinusoids.

In *histiocytic medullary reticulosis*, large numbers of reticulum cells fill the sinusoids and portal tracts. Occasionally, the deposits may be single and large.

Liver granulomas with or without hepatic involvement are found with most lymphomas. Caseation without evidence of tuberculosis has been reported [15].

Paraproteinaemia and amyloidosis may be complications.

Diagnosis of hepatic involvement

Detection of hepatic involvement can be extremely difficult. It is unlikely if hepatomegaly is not found. Fever, jaundice and splenomegaly increase the likelihood. Increases in serum γ-GT and transaminase values are suggestive, although often non-specific.

Focal defects may be shown by ultrasound, CT and MRI scanning. Enlarged abdominal lymph nodes may also be seen.

Needle liver biopsy rarely reveals Hodgkin's tissue if the CT scan is normal. Ultrasound or CT-guided liver biopsy add to the chances of obtaining Hodgkin's tissue. Laparoscopy with liver biopsy may establish the diagnosis in the absence of positive CT scans [26]. Needle biopsy does not exclude hepatic involvement if only an

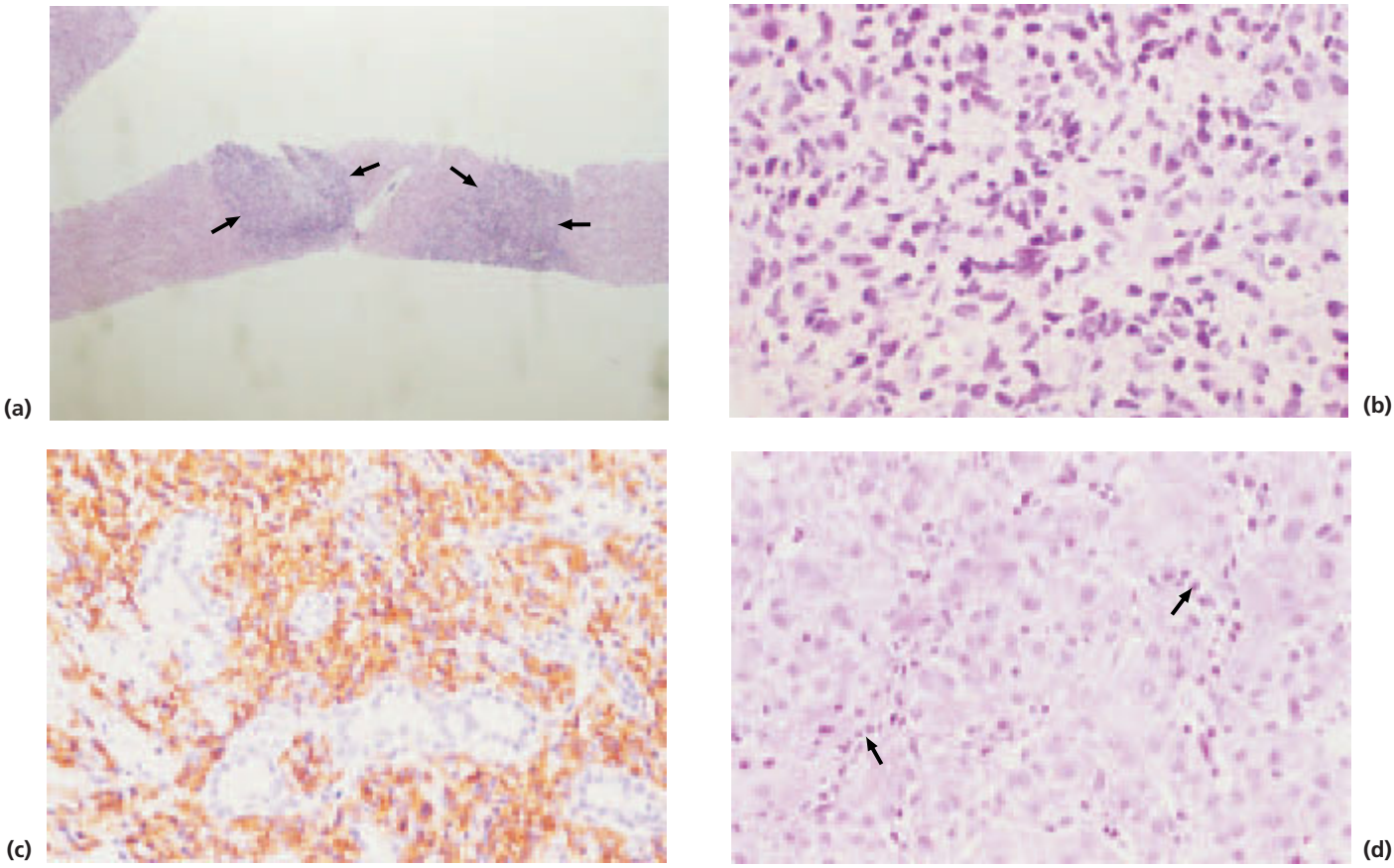


Fig. 4.4. Patterns of hepatic histology in lymphoma. (a) Low power showing dense portal cellular infiltrates (arrows) (H & E). (b) Higher power of portal area showing intermediate and large mononuclear cells. (c) Immunohistochemistry showing that the cells have a B cell phenotype (stained brown with antibody to CD20). Bile ducts are not stained. (d) Sinusoidal pattern of infiltration by lymphoma cells. Occasional atypical mononuclear cells are seen within the hepatic sinusoids (arrows).

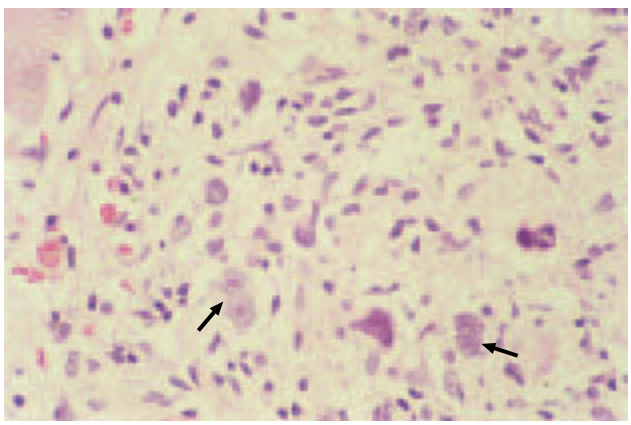


Fig. 4.5. Infiltration of portal zones by Hodgkin's cells including large Reed–Sternberg like cells (arrow) (H & E).

epithelioid histiocyte reaction is seen. Sinusoidal dilatation in zone 2 and 3 is found in 50% and may give a clue to the diagnosis [3].

Presentation as jaundice may provide great diagnostic difficulties (table 4.4). Lymphoma should always be considered in patients with jaundice, fever and weight loss.

Jaundice in lymphoma (table 4.4)

Hepatic infiltrates may be massive or present as space-occupying lesions. Large intra-hepatic deposits are the commonest cause of deep jaundice. Histological evidence is essential for diagnosis.

Biliary obstruction is more frequent with non-Hodgkin's lymphoma than with Hodgkin's disease [9]. It is usually due to hilar glands which are less mobile than those along the common bile duct which can be pushed aside. Occasionally the obstructing glands are peri-ampullary. Primary lymphoma of the bile duct itself is reported [20]. Investigations include endoscopic or percutaneous cholangiography and brush cytology. Known lymphoma elsewhere draws attention to this as a possible cause of bile duct obstruction. Differentiation from other causes of extra-hepatic biliary obstruction is difficult, and depends on the appearances on scanning

Table 4.4. Features of jaundice in lymphoma

Related to lymphoma	
Hepatic infiltrates massive tumour mass	Scans Liver biopsy
Biliary obstruction	Usually hilar Investigate endoscopic or percutaneous cholangiography Non-Hodgkin's usually
Intra-hepatic cholestasis	Rare Liver biopsy 'pure' cholestasis loss of bile ducts Usually Hodgkin's
Haemolysis	Autoimmune haemolytic anaemia Positive Coombs' test
Related to therapy	
Chemotherapy	High dose can cause fulminant liver failure (Chapter 20)
Hepatic irradiation	More than 35Gy(3500 rad) (Chapter 20)
Post-transfusion (hepatitis C)	(Chapter 18)
Hepatitis B reactivation	(Chapter 17)
Opportunist infections	(Chapter 29)

and at cholangiography, and the results of cytology and biopsy.

Rarely, an idiopathic intra-hepatic, usually cholestatic, jaundice may be seen in Hodgkin's [12] and non-Hodgkin's lymphoma [38]. It is unrelated to deposits in the liver or bile duct compression. Hepatic histology shows canalicular cholestasis. These changes are unrelated to therapy. The diagnosis is difficult and is made after full investigation. Liver histology may show loss of intra-hepatic bile ducts [12].

Rarely haemolysis causes deep jaundice. It may be due to Coombs' positive autoimmune haemolytic anaemia. Jaundice is exacerbated by bilirubin overload following blood transfusion.

Chemotherapy may cause jaundice. Almost all the cytotoxic drugs can be incriminated if given in sufficient dose. Common culprits include methotrexate, 6-mercaptopurine, cytosine arabinoside, procarbazine and vincristine. Hepatic irradiation in a dose usually exceeding 35 Gy (3500 rad) may cause jaundice.

Post-transfusion viral hepatitis B, C or non-A, non-B, non-C, may affect the immunocompromised patient. Opportunist infections are also encountered.

Primary hepatic lymphoma [1, 41]

This rare lymphoma by definition affects only the liver. There is a solitary mass in 60%, multiple masses in 35% and diffuse disease in 5% [24]. Histologically, it is a non-Hodgkin's large cell B- or less often T-cell lymphoma. Primary low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) also occurs [19]. Presentation is mainly with pain, hepatomegaly, a palpable mass and elevated alkaline phosphatase and bilirubin. Fever, night sweats and weight loss occur in 50% of cases. There is no lymphadenopathy. Ultrasound and CT show a non-specific space-occupying lesion in the liver in the majority but there may be diffuse hepatomegaly without tumour. Diagnosis is by liver biopsy. Sometimes histology may initially be confusing suggesting carcinoma or chronic hepatitis, or showing extensive haemorrhagic necrosis suggesting Budd–Chiari syndrome. The destructiveness of the infiltrate is a helpful diagnostic feature.

Primary lymphoma of the liver may be found incidentally or complicating acquired immune deficiency syndrome (AIDS) [27]. Patients with pre-existing cirrhosis have a poor prognosis. Negative α-fetoprotein and carcino-embryonic antigen (CEA) with a high LDH level in a patient with a liver mass should raise the possibility of lymphoma.

Treatment of hepatic involvement

More aggressive combination chemotherapy has considerably improved the prognosis of intra-hepatic Hodgkin's deposits causing jaundice. Treatment is the same as for other stage IV patients regardless of the jaundice. Similarly, those with 'idiopathic' cholestasis should receive the therapy appropriate for their lymphoma. If MOPP (mechlorethamine, Oncovin, procarbazine and prednisone) has failed, ABVD (Adriamycin, bleomycin, vinblastine and dacarbazine) should be tried. If jaundice is persistent, some palliation may be achieved by moderate local irradiation.

Extra-hepatic biliary obstruction is treated by external radiation and, if necessary, the insertion of temporary internal stents by the endoscopic or percutaneous route.

If drug toxicity is the cause, treatment may have to be changed or doses reduced.

Treatment for non-Hodgkin's lymphoma causing jaundice is the same as that for Hodgkin's disease.

Primary hepatic lymphoma is treated by chemotherapy or occasionally by lobectomy [1].

Lymphosarcoma

Nodules of lymphosarcomatous tissue may be found in the liver, especially in the portal tracts. Macroscopically

they resemble metastatic carcinoma. The liver may also be involved in giant follicular lymphoma.

Multiple myeloma

The liver may be involved in plasma cell myeloma, the portal tracts and sinusoids being filled with plasma cells. Associated amyloidosis may involve the hepatic arterioles.

Angio-immunoblastic lymphadenopathy

This resembles Hodgkin's disease. The liver shows a pleomorphic portal zone infiltrate (lymphocytes, plasma cells and blast cells) without histiocytes or Reed–Sternberg cells.

Extra-medullary haemopoiesis

The primitive reticulum cells of hepatic sinusoids and portal tracts possess the capacity to mature into adult erythrocytes, leucocytes or platelets. If the stimulus for blood regeneration is sufficiently strong, this function can be resumed. This is rare in the adult although myeloid metaplasia in the liver of the anaemic infant is not unusual. In the adult, it occurs with bone marrow replacement or infiltration, and especially in association with secondary carcinoma of bone, myelofibrosis, myelosclerosis, multiple myeloma and the marble bone disease of Albers-Schoenberg. It complicates all conditions associated with a leucoerythroblastic anaemia.

The condition is well exemplified by myelofibrosis and myelosclerosis, where the liver is enlarged, with a smooth firm edge. The spleen is enormous, and its removal results in even greater enlargement of the liver with increased liver enzymes. The mortality after splenectomy is 10–20%, some caused by hepatic dysfunction due to the increase in extra-medullary haemopoiesis.

Ascites occurs in a low percentage of patients with extra-medullary haemopoiesis, and may be due to portal hypertension, or, after splenectomy, peritoneal deposits of extra-medullary haemopoiesis.

Microscopic features

The conspicuous abnormality is a great increase in the cellular content, both in the portal tracts and in the distended sinusoids (fig. 4.6). The cells are of all types and varying maturity. The distribution of cells may reflect the type of underlying sinusoidal endothelial cell [4]. There are many reticulum cells and these may be converted into giant cells. The haemopoietic tissue may form discrete foci in the sinusoids. Rarely, larger foci may be seen on CT or MRI scanning [39].

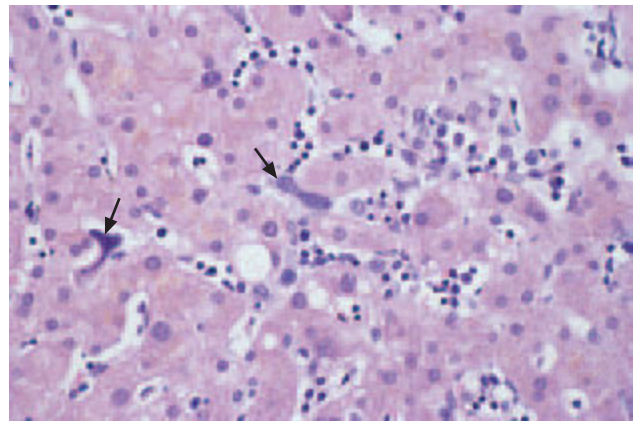


Fig. 4.6. Extra-medullary haemopoiesis—megakaryocytes (arrows), erythroblasts, normoblasts and polymorphs are seen in the hepatic sinusoids (H & E).

Electron microscopy shows haematological cells in the sinusoids with transformation of peri-sinusoidal cells into fibroblasts and myofibroblast-like cells.

Portal hypertension. This may be due to portal vein thrombosis or sinusoidal infiltration with haemopoietic cells. Disse's space fibrosis contributes. Nodular regenerative hyperplasia may also cause portal hypertension (Chapter 10).

Systemic mastocytosis

This is a disease of mast cell hyperplasia that may affect several organ systems. It can present with hepatomegaly as well as lymphadenopathy and skin lesions. Liver biopsy, stained with haematoxylin and eosin, shows polygonal cells with eosinophilic granules predominantly in portal tracts, with fewer in the sinusoids [11]. On staining with Giemsa and toluidine blue, the typical metachromatic cytoplasmic granules may be identified. Mast cell infiltration is a common finding, but severe liver disease is unusual except in those with haematological involvement or aggressive mastocytosis. Nodular regenerative hyperplasia, portal venopathy and veno-occlusive disease are reported [21] and may be responsible for portal hypertension and ascites. The latter carries a poor prognosis. Cirrhosis occurs in up to 5% of patients [11].

Langerhans' cell histiocytosis (histiocytosis X)

The underlying pathology of this rare condition is proliferation and aggregation of Langerhans' cells in the reticulo-endothelial system. Electron microscopy shows trilamellar rod-shaped structures (Birbeck granules) within the cells which also contain the neural-specific

protein S-100. Langerhans' cell histiocytosis comprises several entities (which overlap) including eosinophilic granuloma (bone lesions), Hand–Schüller–Christian disease (endocrine lesions; skin) and Letterer–Siwe disease (disseminated type; lungs, bone marrow, skin, lymph nodes, spleen, liver). The mechanism of liver injury is not known. Cholestasis is due to sclerosing cholangitis affecting intra-hepatic ducts or proliferating histiocytic cells in peri-portal areas [13]. Liver disease is present in one-third of patients. Portal hypertension and variceal haemorrhage may develop. Liver failure due to biliary cirrhosis is unusual. Transplantation has been successful with no evidence of recurrent disease up to 7 years later [42].

Lipid storage diseases

The lipidoses are disorders in which abnormal amounts of lipids are stored in the cells of the reticulo-endothelial system. They may be classified according to the lipid stored: xanthomatosis, cholesterol; Gaucher's disease, cerebroside; or Niemann–Pick disease, sphingomyelin.

Primary and secondary xanthomatosis

Cholesterol is stored mainly in the skin, tendon sheaths, bone and blood vessels. The liver is rarely involved but there may be isolated nests of cholesterol-containing foamy histiocytes in the liver. Investigation of the liver is of little diagnostic value.

Cholesteryl ester storage disease [7]

This rare, autosomal recessive, relatively benign disease is due to a deficiency of lysosomal acid lipase/cholesteryl ester hydrolase. It presents with symptomless hepatomegaly. The liver is orange in colour and hepatocytes contain excess cholesteryl ester and triglyceride. A septate fibrosis may lead to cirrhosis and patients may have early vascular disease. Complete enzyme deficiency (Wolman's disease) results in death in early infancy due to involvement of the liver, adrenals and histiocytes.

Gaucher's disease [22]

This rare, autosomal recessive disease was first described in 1882. It is the commonest lysosomal storage disorder. It is due to a deficiency of lysosomal acid β-glucosidase so that glucosylceramide, derived from membrane glycosphingolipids of time-expired white and red blood cells, accumulates in the reticulo-endothelial system throughout the body, particularly in the liver, bone marrow and spleen.

Three types are recognized:

- Type 1 (adult, chronic, non-neuronopathic) is the mildest and most common form of Gaucher's disease. It occurs rarely in all ethnic groups (non-Jewish: 1 in 40 000) but is most common in Ashkenazi Jews (1 in 850). The central nervous system is spared.
- Type 2 (infantile, acute, neuronopathic) is rare. In addition to the visceral involvement there is massive fatal neurological involvement, with death in infancy.
- Type 3 (juvenile, sub-acute, neuronopathic) is also rare. There is gradual and heterogeneous neurological involvement.

The various forms represent different mutations in the structural gene for acid β-glucosidase on chromosome 1, although there is a variability in severity of disease within a specific genotype [23]. Four mutations account for over 95% of disease alleles in Ashkenazi patients, but only 75% of non-Jewish patients. Patients homozygous for the L444P mutation are at high risk of neurological disease, whereas the presence of at least one allele with N370S precludes this form of disease [22]. Variation in tissue damage within each genotype is probably due to individual differences in the macrophage response to glucosylceramide accumulation, but the mechanisms are unknown.

The characteristic Gaucher cell is approximately 70–80 μm in diameter, oval or polygonal in shape and with pale cytoplasm. It contains two or more peripherally placed hyperchromatic nuclei between which fibrils pass parallel to each other (fig. 4.7). It is quite different from the foamy cell of xanthomatosis or Niemann–Pick disease.

Electron microscopy. The accumulated glycolipid formed from degraded cell membranes precipitates within the lysosomes and forms long (20–40 nm) rod-like tubules. These are seen by light microscopy. A somewhat similar cell is seen in chronic myeloid leukaemia and in

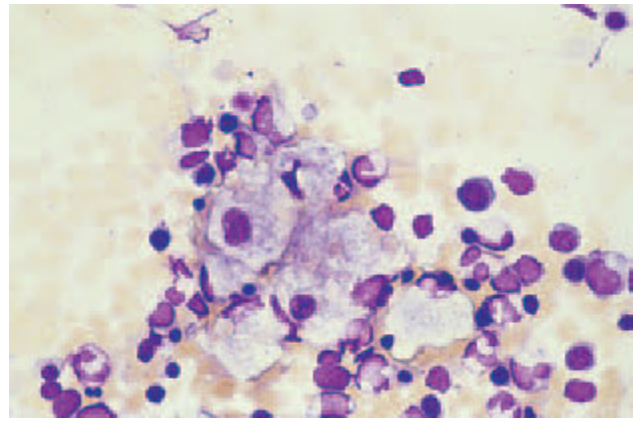


Fig. 4.7. Gaucher's disease. Smears of sternal bone marrow show large pale Gaucher cells with fibrillary cytoplasm and eccentric hyperchromatic nuclei. (Coutesy of Dr Atul Mehta.)

multiple myeloma due to increased turnover of β-glucocerebroside.

Chronic adult form (type 1)

This is the most common type. It is of variable severity and age of onset but usually commences insidiously before the age of 30 years. It is chronic and may be recognized in quite old people.

The mode of presentation is variable, with unexplained hepato-splenomegaly (especially in children), spontaneous bone fractures, or bone pain with fever. Alternatively there may be a bleeding diathesis, with non-specific anaemia.

The clinical features include pigmentation which may be generalized or a patchy, brownish tan. The lower legs may have a symmetrical pigmentation, leaden grey in colour and containing melanin. The eyes show yellow pingueculae.

The spleen is enormous and the liver is moderately enlarged, smooth and firm. Superficial lymph glands are not usually involved.

Hepatic involvement is often associated with fibrosis and abnormal liver function tests. Serum alkaline phosphatase is usually increased, sometimes with a rise in transaminase. Cirrhosis may develop but life-threatening liver disease affects only a small minority. Ascites and portal hypertension with variceal bleeding are associated with large areas of confluent fibrosis with a characteristic MRI appearance [16].

Bone X-rays. The long bones, especially the lower ends of the femora, are expanded, so that the waist normally seen above the condyles disappears. The appearance has been likened to that of an Erlenmeyer flask or hock bottle.

Sternal marrow shows the diagnostic Gaucher cells (fig. 4.7).

Aspiration liver biopsy should be performed if sternal puncture has yielded negative results. The liver is diffusely involved (fig. 4.8)

Peripheral blood changes. With diffuse bone marrow involvement, a leucoerythroblastic picture may be seen. Alternatively leucopenia and thrombocytopenia with prolonged bleeding time may be associated with only a moderate hypochromic microcytic anaemia [29].

Diagnosis may be made by measuring acid β-glucosidase activity in leukocytes.

Blood biochemical changes. Serum alkaline phosphatase is usually increased, sometimes with a rise in transaminase. Serum cholesterol is normal.

Treatment

Enzyme replacement therapy is now available. The acid β-glucosidase was first prepared from pooled human placentae, though most patients now receive enzyme made by recombinant technology. It is given by intravenous infusion. Several treatment regimens have been shown to be effective. After endogenous enzymatic deglycosylation, exogenous enzyme is taken up by mannose receptors on macrophages, in the liver, spleen and skeleton, where it is highly effective in reversing the haematological and visceral (liver, spleen) features. Skeletal disease is slow to respond.

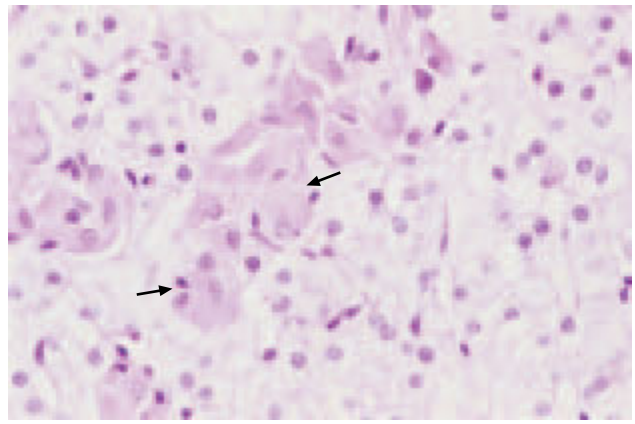


Fig. 4.8. Gaucher's disease. Liver section showing large pink-staining Gaucher cells (arrowed) between the pale liver cells. (Periodic acid–Schiff after diastase digestion (DPAS) stain.).

Splenectomy, partial or total, has been done for the very large spleen causing abdominal discomfort, and occasionally for thrombocytopenia or an acquired haemolytic anaemia. Total splenectomy is followed by more aggressive bone disease and pre-planned enzyme therapy is needed to prevent this.

Liver transplantation for decompensated cirrhosis has been done [32]. This does not correct the metabolic defect, and enzyme replacement therapy remains necessary. Bone marrow transplantation has been done, but the risks are considered prohibitive in comparison with enzyme replacement therapy.

Acute infantile Gaucher's disease (type 2)

This acute form of the disease presents within the first 6 months of life and is usually fatal before 2 years. The child appears normal at birth. There is cerebral involvement, progressive cachexia and mental deterioration. The liver and spleen are enlarged and superficial lymph nodes may also be palpable.

Autopsy shows Gaucher cells throughout the reticuloendothelial system. They are, however, not found in the brain and the pathogenesis of the cerebral disease is not understood.

Niemann–Pick disease

This rare, familial disease, inherited as autosomal

recessive, mainly affects the Jewish race. The deficiency is in the enzyme sphingomyelinase, in the lysosomes of the reticulo-endothelial system. This results in the lysosomal storage of sphingomyelin. The liver and spleen are predominantly involved.

The characteristic cell is pale, ovoid or round, 20–40 μm in diameter. In the unfixed state it is loaded with granules; when fixed in fat solvents the granules are dissolved, giving a vacuolated and foamy appearance. There are usually only one or two nuclei. Electron microscopy shows lysosomes as laminated myelin-like figures. These contain the abnormal lipid.

Niemann–Pick disease *type A* (acute, neuronopathic form) occurs in infants, who die before the age of 2 years. The condition starts in the first 3 months, with anorexia, weight loss and retardation of growth. The liver and spleen enlarge, the skin becomes waxy and acquires a yellowish-brown coloration on exposed parts. The superficial lymph nodes are enlarged. There are pulmonary infiltrates. The patient is blind, deaf and mentally retarded.

The fundus may show a cherry-red spot due to retinal degeneration at the macula.

The peripheral blood shows a microcytic anaemia and in the later stages the foamy Niemann–Pick cell may be found.

The disease may present as *neonatal cholestatic jaundice* which remits. Progressive neurological deterioration appears in late childhood.

A further *type B* (chronic, non-neuronopathic form) is associated with neonatal cholestasis which resolves. Cirrhosis develops slowly and may lead to portal hypertension, ascites and liver failure [25]. Liver transplantation for hepatic failure has been successful [32]. Although hepatic lipid accumulation was not seen at 10 months, longer follow-up is needed to assess the metabolic outcome.

Diagnosis is made by marrow puncture, which reveals characteristic Niemann–Pick cells, or by finding a low level of sphingomyelinase in leucocytes.

Bone marrow transplant has been done for patients with early severe liver disease [36]. Preliminary reports were promising with reduction of sphingomyelin from liver, spleen and bone marrow, but longer follow-up is needed.

Sea-blue histiocyte syndrome

This rare condition is characterized by histiocytes staining a sea-blue colour with Wright or Giemsa stain in bone marrow and in reticulo-endothelial cells of the liver. The cells contain deposits of phosphosphingolipid and glucosphingolipid. Clinically the liver and spleen are enlarged. The prognosis is usually good although thrombocytopenia and hepatic cirrhosis have been reported. It probably represents adult Niemann–Pick disease [18].

References

1 Anthony PP, Sarsfield P, Clarke T. Primary lymphoma of the liver: clinical and pathological features of 10 patients. *J. Clin. Pathol*. 1990; **43**: 1007.

2 Bird GLA, Smith H, Portmann B *et al*. Acute liver decompensation on withdrawal of cytotoxic chemotherapy and immunosuppressive therapy in hepatitis B carriers. *Q. J. Med*. 1989; **73**: 895.

3 Bruguera M, Caballero T, Carreras E *et al*. Hepatic sinusoidal dilatation in Hodgkin's disease. *Liver* 1987; **7**: 76.

4 Cardier JE, Barbera-Guillem E. Extramedullary haematopoiesis in the adult mouse liver is associated with specific hepatic sinusoidal endothelial cells. *Hepatology* 1997; **26**: 165.

5 Chopra R, Eaton JD, Grassi A *et al*. Defibrotide for the treatment of hepatic veno-occlusive disease: results of the European compassionate-use study. *Br. J. Haematol*. 2000; **111**: 1122.

6 Dich NH, Goodman ZD, Klein MA. Hepatic involvement in Hodgkin's disease: clues to histological diagnosis. *Cancer* 1989; **64**: 2121.

7 Elleder M, Chlumska A, Hyanek J *et al*. Subclinical course of cholesteryl ester storage disease in an adult with hypercholesterolemia, accelerated atherosclerosis, and liver cancer. *J. Hepatol*. 2000; **32**: 528.

8 Essell JH, Schroeder MT, Harman GS *et al*. Ursodiol prophylaxis against hepatic complications of allogenic bone marrow transplantation—a randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med*. 1998; **128**: 975.

9 Feller E, Schiffman FJ. Extrahepatic biliary obstruction by lymphoma. *Arch. Surg*. 1990; **125**: 1507.

10 Forbes GM, Davies JM, Herrmann RP *et al*. Liver disease complicating bone marrow transplantation: a clinical audit. *J. Gastroenterol. Hepatol*. 1995; **10**: 1.

11 Horny H-P, Kaiserling E, Campbell M *et al*. Liver findings in generalized mastocytosis: a clinicopathologic study. *Cancer* 1989; **63**: 532.

12 Hubscher SG, Lumley MA, Elias E. Vanishing bile duct syndrome: a possible mechanism for intrahepatic cholestasis in Hodgkin's lymphoma. *Hepatology* 1993; **17**: 70.

13 Iwai M, Kashiwadani M, Okuno T *et al*. Cholestatic liver disease in a 20 yr old woman with histiocytosis X. *Am. J. Gastroenterol*. 1988; **83**: 164.

14 Jaffe ES. Malignant lymphomas: pathology of hepatic involvement. *Semin. Liver Dis*. 1987; **7**: 257.

15 Johnson LN, Iseri O, Knodell RG. Caseating hepatic granulomas in Hodgkin's lymphoma. *Gastroenterology* 1990; **99**: 1837.

16 Lachmann RH, Wight DGD, Lomas DJ *et al*. Massive hepatic fibrosis in Gaucher's disease: clinico-pathological and radiological features. *Q. J. Med*. 2000; **93**: 237.

17 Lau JYN, Lai CL, Lin HJ *et al*. Fatal reactivation of chronic hepatitis B virus infection following withdrawal of chemotherapy in lymphoma patients. *Q. J. Med*. 1989; **73**: 911.

18 Long RG, Lake BD, Pettit JE *et al*. Adult Niemann–Pick disease: its relationship to the syndrome of the sea-blue histiocyte. *Am. J. Med*. 1977; **62**: 627.

19 Maes M, Depardieu C, Dargent JL *et al*. Primary low-grade

B-cell lymphoma of MALT-type occurring in the liver: a study of two cases. *J. Hepatol.* 1997; **27**: 922.
20 Maymind M, Mergelas JE, Seibert DG *et al.* Primary non-Hodgkin's lymphoma of the common bile duct. *Am. J. Gastroenterol.* 1997; **92**: 1543.
21 Mican JM, Di Bisceglie AM, Fong T-L *et al.* Hepatic involvement in mastocytosis: clinicopathologic correlations in 41 cases. *Hepatology* 1995; **22**: 1163.
22 Mistry PK. Gaucher's disease: a model for modern management of a genetic disease. *J. Hepatol.* 1999; **30**: 1.
23 Mistry PK. Genotype/phenotype correlations in Gaucher's disease. *Lancet* 1995; **346**: 982.
24 Ohsawa M, Aozasa K, Horiuchi K *et al.* Malignant lymphoma of the liver: report of five cases and review of the literature. *Dig. Dis. Sci.* 1992; **37**: 1105.
25 Putterman C, Zelingher J, Shouval D. Liver failure and the sea-blue/adult Niemann–Pick disease. Case report and review of the literature. *J. Clin. Gastroenterol.* 1992; **15**: 146.
26 Sans M, Andreu V, Bordas JM *et al.* Usefulness of laparoscopy with liver biopsy in the assessment of liver involvement at diagnosis of Hodgkin's and non-Hodgkin's lymphomas. *Gastrointest. Endosc.* 1998; **47**: 391.
27 Scoazec J-Y, Degott C, Brousse N *et al.* Non-Hodgkin's lymphoma presenting as a primary tumour of the liver: presentation, diagnosis and outcome in eight patients. *Hepatology* 1991; **13**: 870.
28 Sharafuddin MJA, Foshager MC, Steinbuch M *et al.* Sonographic findings in bone marrow transplant patients with symptomatic hepatic veno-occlusive disease. *J. Ultrasound Med.* 1997; **16**: 575.
29 Sherlock SPV, Learmonth JR. Aneurysm of the splenic artery; with an account of an example complicating Gaucher's disease. *Br. J. Surg.* 1942; **30**: 151.
30 Shulman HM, Fisher LB, Schoch LG *et al.* Veno-occlusive disease of the liver after marrow transplantation: histological correlates of clinical signs and symptoms. *Hepatology* 1994; **19**: 1171.
31 Shulman HM, Gooley T, Dudley MD *et al.* Utility of transvenous liver biopsies and wedged hepatic venous pressure measurements in 60 marrow transplant recipients. *Transplantation* 1995; **59**: 1015.
32 Smanik EJ, Tavill AS, Jacobs GH *et al.* Orthotopic liver transplantation in two adults with Niemann–Pick and Gaucher's diseases: implications for the treatment of inherited metabolic disease. *Hepatology* 1993; **17**: 42.
33 Souto P, Romaozinho JM, Figueiredo P *et al.* Severe acute liver failure as the initial manifestation of haematological malignancy. *Eur. J. Gastroenterol. Hepatol.* 1997; **9**: 1113.
34 Terra SG, Spitzer TR, Tsunoda SM. A review of tissue plasminogen activator in the treatment of veno-occlusive liver disease after bone marrow transplantation. *Pharmacotherapy* 1997; **17**: 929.
35 Valla D, Casadevall N, Huisse MG *et al.* Etiology of portal vein thrombosis in adults. *Gastroenterology* 1988; **94**: 1063.
36 Vellodi A, Hobbs JR, O'Donnell NM *et al.* Treatment of Niemann–Pick disease type B by allogeneic bone marrow transplantation. *Br. Med. J.* 1987; **295**: 1375.
37 Walz-Mattmòlla R, Horny HP, Ruck P *et al.* Incidence and pattern of liver involvement in haematological malignancies. *Pathol. Res. Pract.* 1998; **194**: 781.
38 Watterson J, Priest JR. Jaundice as a paraneoplastic phenomenon in a T-cell lymphoma. *Gastroenterology* 1989; **97**: 1319.
39 Wong Y, Chen F, Tai KS *et al.* Imaging features of focal intrahepatic extramedullary haematopoiesis. *Br. J. Radiol.* 1999; **72**: 906.
40 Woolf GM, Petrovic LM, Rojter SE *et al.* Acute liver failure due to lymphoma: a diagnostic concern when considering liver transplantation. *Dig. Dis. Sci.* 1994; **39**: 1351.
41 Zafrani ES, Gaulard P. Primary lymphoma of the liver. *Liver* 1993; **13**: 57.
42 Zandi P, Panis Y, Debray D *et al.* Paediatric liver transplantation for Langerhans' cell histiocytosis. *Hepatology* 1995; **21**: 129.

Chapter 5
Ultrasound, Computed Tomography and Magnetic Resonance Imaging

Hepato-biliary scanning can detect and characterize tumours in the liver, and demonstrate obstruction of blood vessels and bile ducts. It is an essential step in the diagnostic work-up of most hepatic problems. It may show some types of diffuse disease. Ultrasound (US) and computed tomography (CT) are most often used; magnetic resonance imaging (MRI) is increasingly available and experience is growing rapidly. Radio-isotope scanning as a screening approach for space-occupying lesions and diffuse disease has been superseded by the other scanning techniques. It retains a role for biliary tract imaging (Chapter 32), and also for scanning of metastases using specialized ligands.

US, CT and MRI all perform well with the optimal equipment, technique and operator. Selection of the method used will depend to an extent on the availability and cost. The clinician plays a major role in maintaining the quality of the report by specifying clearly the clinical problem.

Radio-isotope scanning

^{99m}*Tc-labelled tin colloid and colloids of human albumin* are taken up by reticulo-endothelial cells. Introduced in the 1960s they were used to detect hepatic tumours, but could not differentiate between cysts and tissue. Lesions 4 cm in diameter are usually demonstrated, but sensitivity falls below this size. Reduced patchy hepatic uptake with increased activity from bone marrow and spleen denotes chronic liver disease. US has replaced isotope scanning for the detection of space-occupying lesions, and can show the irregular liver outline and change in echogenicity in cirrhosis. Isotope scanning has also been replaced in other situations such as Budd–Chiari syndrome where the characteristic findings (preferential uptake by the caudate lobe) are not reliable enough to be of routine clinical value.

^{67}*Gallium citrate* is taken up by liver tumours and by inflammatory processes, for example abscess, but again the newer techniques, US and CT, are more appropriate for the majority of patients and centres. Gallium scanning retains a role in the complex patient with chronic sepsis of unknown origin when a focus of increased radio-activity may suggest an inflammatory collection.

^{99m}*Tc-IDA derivatives* have a role in the imaging of the biliary tract (Chapter 32).

^{99m}*Tc-labelled red blood cells* can be used to establish the diagnosis of cavernous haemangioma. A dynamic scan after intravenous injection will show an area of low activity initially. The lesion will then fill in as pooling of the red cells occurs. The delayed film will show an area of higher activity than the surrounding liver. Such a dynamic scan is equivalent to the appearances with CT following enhancement.

^{111}In-DTPA octreotide binds to somatostatin receptors which are expressed on neuroendocrine tumours, and scintigraphy with this agent will demonstrate over 90% of carcinoid tumours [3]. Its particular value is in showing unexpected lesions, extra-hepatic and in lymph nodes, not shown by MRI and CT (fig. 5.1) [26].

Positron emission tomography (PET)

This is based upon the principle that a positron emitted from a radio-active substance combines with an electron to form two photons travelling in opposite directions and that these can be localized by confidence detection. Positron-emitting radionuclides (synthesized in a cyclotron) include ^{15}O, ^{13}N, ^{11}C and ^{18}F, and these can be used to study regional blood flow and metabolism. This technique has been used to study hepatic blood flow. Because of increased glucose utilization in malignant tissue, PET scanning with 2[^{18}F]-fluoro-2-deoxy-D-glucose can detect carcinomas. This method has only a 55% sensitivity in detecting hepato-cellular carcinoma, compared with 90% for CT [11]. Poorly differentiated tumours have greater activity than well-differentiated types. PET scanning shows distant metastases from the primary tumour not seen by CT. This is also a useful property in the management of patients with recurrent colo-rectal carcinoma [7].

Ultrasound

Most imaging units use real-time high resolution US scanners. These are inexpensive compared with CT and MRI. US takes only a few minutes to perform. Dilated bile ducts, gallbladder disease, hepatic tumours and

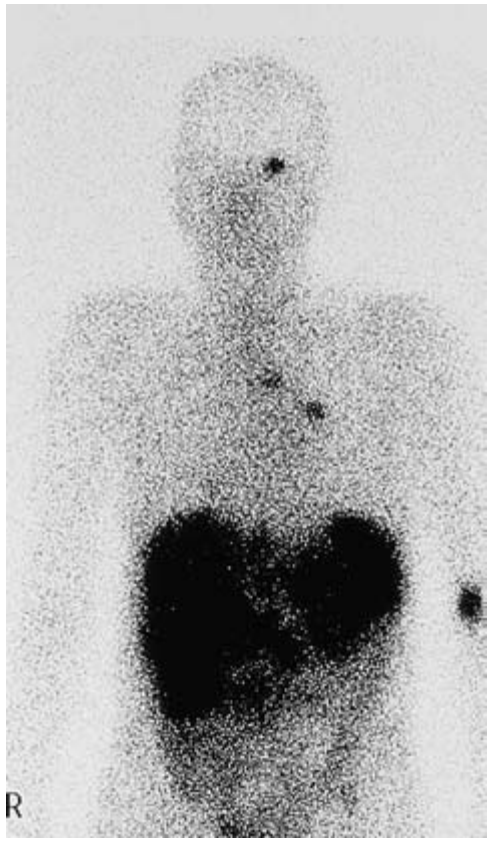


Fig. 5.1. ^{111}In-DTPA octreotide scan in a patient with carcinoid syndrome. Apart from the large intra-hepatic tumour, the scan shows metastases in the skull, mediastinum and left arm.

some diffuse hepatic abnormalities are shown. Residents who are not specialists in US can master the basic technique and apply it in the outpatient department or on the ward, for example to image liver and gallbladder before liver biopsy or to detect dilated bile ducts.

US has problems with hepato-biliary examination in the fat or gaseous patient, those with a high liver lying entirely covered by the rib margin and post-operative patients with dressings and painful scars.

A normal US shows the liver to have mixed echogenicity (fig. 5.2). Portal and hepatic veins, inferior vena cava and aorta are shown. The normal intra-hepatic bile ducts are thin and run parallel to large portal vein branches. The right and left hepatic ducts are 1–3 mm in diameter and the common duct 2–7 mm in diameter. US is the screening investigation of choice for patients with cholestasis (Chapter 13). The gallbladder is an ideal organ for sonography (Chapter 32).

The portal vein originates at the junction of the superior mesenteric and splenic veins. US can show a dilated portal vein and collaterals in portal hypertension, an obstructed or scarred portal vein due to tumour or thrombus, and the bunch of vessels of cavernomatous transformation in chronic portal vein thrombosis. Assessment of portal vein patency by real-time US, however, is not always accurate, particularly in patients with previous portal or biliary surgery. Doppler US has a greater sensitivity and specificity. In the absence of Doppler US, real-time US remains a useful first investigation in patients who have bled from oesophageal varices, to assess patency of the portal vein. The patency of portal systemic shunts can also be confirmed.

In heart failure, US shows dilated hepatic veins and inferior vena cava. In Budd–Chiari syndrome, hepatic veins may not be seen. Doppler US again adds diagnostic information over and above real-time US [2].

Focal hepatic lesions are better detected by US than diffuse disease. Lesions down to 1 cm in diameter can be seen. Simple cysts have smooth walls and echo-free contents with through transmission of the sound waves (fig. 33.4). The appearance is diagnostic and with small cysts more accurate than CT. Hydatid cysts produce a characteristic appearance with the contained daughter cysts. Cavernous haemangioma, the commonest liver neoplasm, is usually hyperechoic often with through transmission (fig. 5.3). Such a lesion less than 3 cm in diameter detected incidentally in a patient with normal liver function tests and defined by an experienced ultrasonographer generally needs no further investigation. Lesions more than 3 cm or where the appearances are not classic, or where metastases (especially hypervascular) are suspected, would need further confirmation by dynamic enhanced CT, red blood cell scintiscan or MRI.

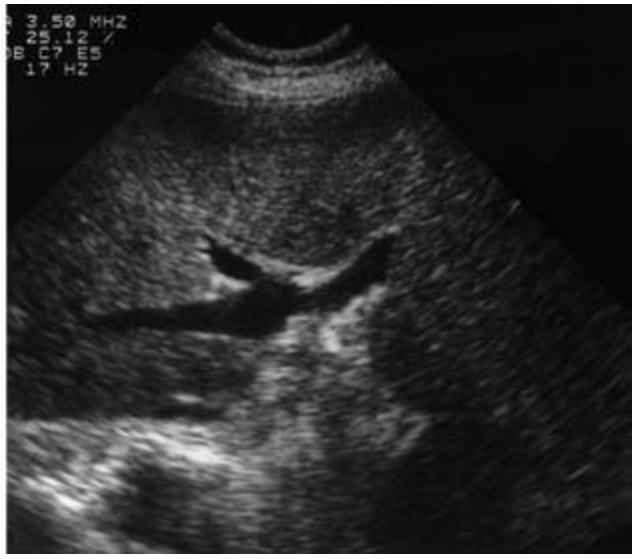
Malignant masses (primary or secondary carcinoma) produce a range of appearances on US including a hyper- or hypoechoic pattern (fig. 5.4), well circumscribed or infiltrative. Appearances highly suggestive of metastases include the bull's eye appearance (a hyperechoic rim surrounding a hypoechoic centre). Necrotic tumours may mimic abscess or cyst. Clinical data are paramount—underlying cirrhosis, a proven primary tumour or raised tumour markers in the serum being important. Guided biopsy or aspiration will usually follow to establish the actual pathology.

Diffuse hepatic disease may be detected by US as may anatomical anomalies. In cirrhosis the edge of the liver may be irregular and/or small (fig. 5.5), the hepatic echo pattern coarse (i.e. increased irregular echogenicity) and there may be splenomegaly ascites [1].

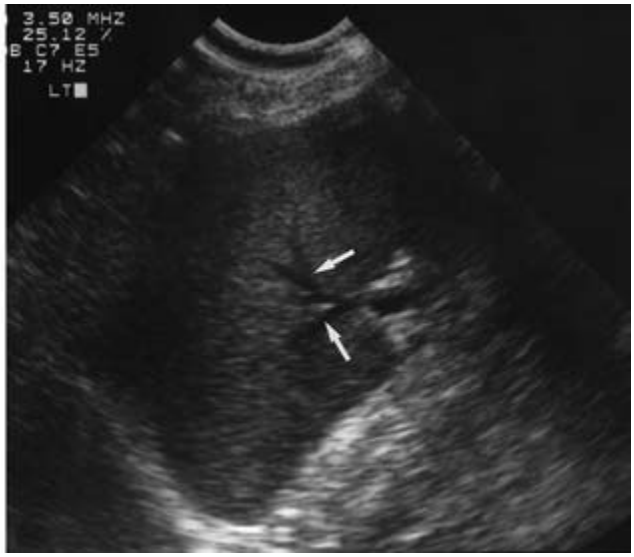
A fatty liver may show bright echoes [19]. Accurate quantification of fat, however, is not possible, partly because of the normal variation in echo pattern between normal individuals.

US is the current first choice (together with α-fetoprotein) to screen for the development of hepatocellular carcinoma in patients with cirrhosis.

US is the first choice examination when a hepatic



(a)



(b)

Fig. 5.2. Ultrasound appearance of normal liver. (a) Normal homogeneous echo pattern and the echo-free portal vein and its intra-hepatic branches. (b) Hepatic veins (arrowed) converge to enter the inferior vena cava.

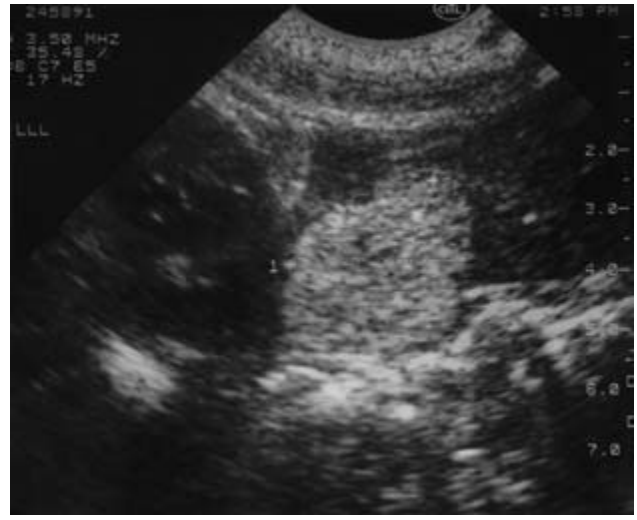


Fig. 5.3. Ultrasonography showing a 3-cm hyperechoic mass in the liver. This is characteristic of a cavernous haemangioma.

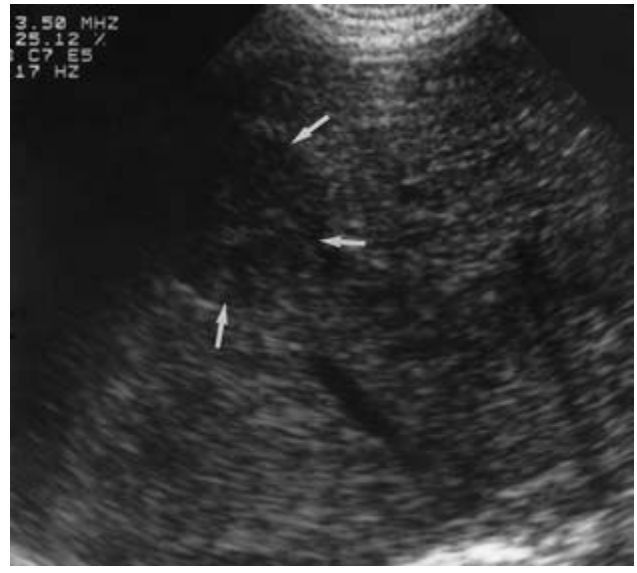


Fig. 5.4. Ultrasound of a liver showing a round hypoechoic mass (arrowed) with altered echo pattern—hepato-cellular carcinoma within a cirrhotic liver.

abscess is suspected. There is an area of reduced echogenicity with or without a surrounding capsule. Sometimes the pus has a similar echogenicity to liver and the abscess is not detected. Clinical features should draw attention to the possibility of a false negative result and CT ordered as a second option. US-guided aspiration for microbiology is necessary. Therapeutic aspiration or catheter drainage may follow.

Doppler ultrasound [12]

Doppler US depends upon the principle that the velocity and direction of flow in a vessel can be derived from the difference between the frequency of the US signal emitted from the transducer and that reflected back (echo) from the vessel. The technique is difficult and needs an experienced sonographer. Hepatic veins, hepatic artery and portal vein (fig. 10.23) each have unique Doppler signals (Chapter 10). This technique may aid diagnosis in suspected hepatic vein block [2], hepatic artery thrombosis (after liver transplantation) and portal vein thrombosis. In portal hypertension the direction of portal flow and the patency of porto-

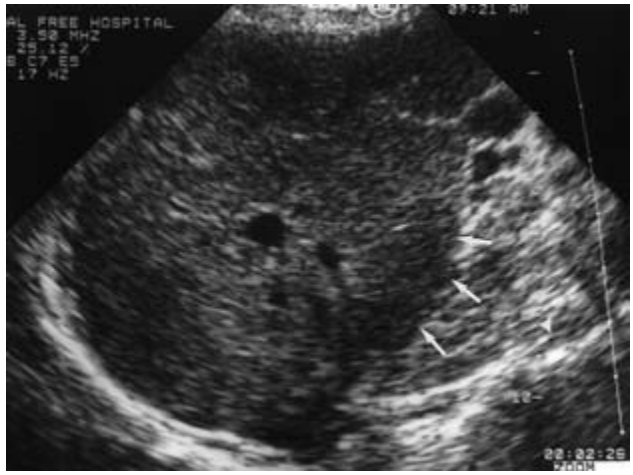


Fig. 5.5. Ultrasound scan in cirrhosis showing irregular edge of liver (arrowed) together with coarse echo pattern.

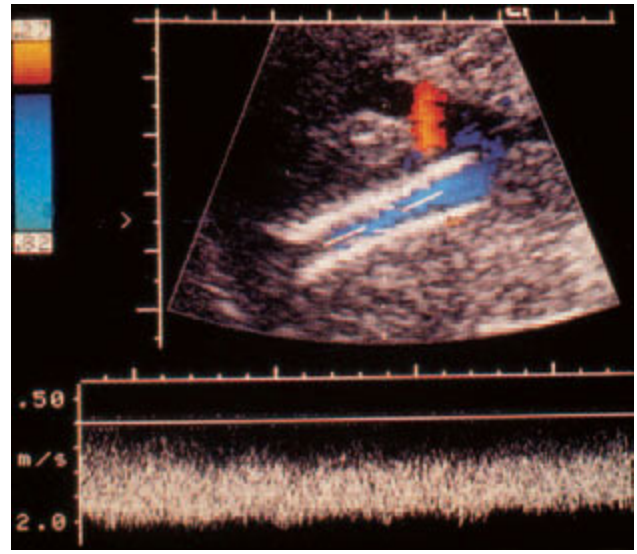


Fig. 5.6. Doppler US scan showing blood flow (blue) through a TIPS shunt.

systemic shunts can be seen. Flattening of the Doppler waveform from the hepatic veins suggests the presence of cirrhosis [4].

Monitoring of flow through transjugular intrahepatic portosystemic shunts (TIPS) by 2–3 monthly Doppler US is useful in detecting shunt dysfunction before clinical signs occur (fig. 5.6).

Endoscopic ultrasound

This technique can detect small peri-ampullary carcinomas and demonstrate the bile duct and gallbladder better than transcutaneous US (Chapter 32). Its use is restricted, however, by the availability of the equipment, and endoscopic and ultrasonic expertise.

Computed tomography [6, 25]

The liver is displayed as a series of adjacent cross-sectional slices. The hard copy scan is depicted as if seen from below. Typically 10–12 images are needed to examine the whole liver. Conventional CT has been replaced by spiral CT. In the conventional method, individual exposures are taken at 7–10-mm intervals through the area of interest. The breath must be held for each slice.

Spiral CT, where a continuous spiral exposure is made, can be completed during a single breath-hold, and thus more quickly (15–30 s). Images are still reconstructed as individual cross-sections. The great advantage of this method is that the scan can be completed while there is peak concentration of contrast medium in the blood vessels of interest. The detail is superior to conventional CT, particularly for small blood vessels. Tumour detection is improved. Computer reconstruction allows three-dimensional pictures which show the relationship of blood vessels to tumours, and, with intravenous cholangiographic medium, the biliary tree.

The CT scan demonstrates detailed anatomy across the whole abdomen at the level of the slice (fig. 5.7). Oral contrast is usually given to help identify stomach and duodenum. Enhancement by intravenous contrast medium, given as a bolus, an infusion or by arterioportography, demonstrates blood vessels, followed by the hepatic parenchyma. There is renal excretion of contrast. Intravenous cholangiography as a source of contrast is very occasionally used to delineate the biliary system but is restricted to patients with normal liver function tests. CT gives good visualization of adjacent organs, particularly kidneys, pancreas, spleen and retroperitoneal lymph nodes.

CT demonstrates focal hepatic lesions and some diffuse conditions. Advantages over US are that it is less operator dependent and hard copy films can be more readily understood by the clinician. It is more reproducible and obese patients are well suited for CT. Gas-filled bowel may rarely produce some artefacts—solved by altering the patient's position. Pain, post-operative scars and dressings are no hindrance. CT-guided biopsy and aspiration are accurate.

Disadvantages are cost, the exposure to radiation and lack of portability—the patient must be brought to the scanner.

The liver appears homogeneous with an attenuation value (in Hounsfield units) similar to kidney and spleen. Portal vein branches are seen at the hilum. Intravenous enhancement is necessary to differentiate these from dilated bile ducts confidently. Hepatic veins are usually seen. Enhanced CT shows the portal vein and can be used to check patency. Invading tumour or obstructing

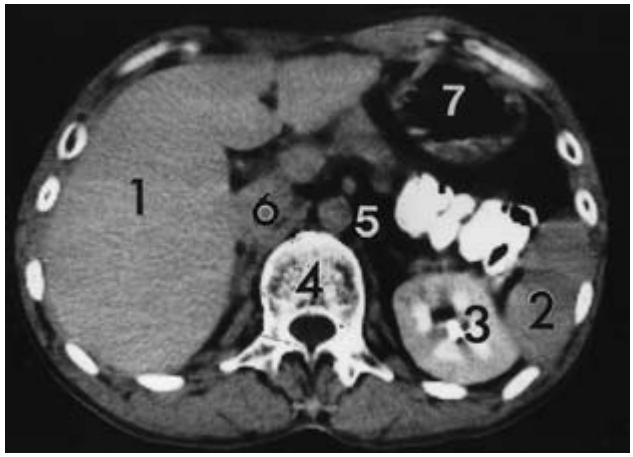


Fig. 5.7. CT scan (enhanced by contrast) showing the liver (1), spleen (2), kidney (3), vertebral body (4), aorta (5), head of the pancreas (6) and stomach (7).

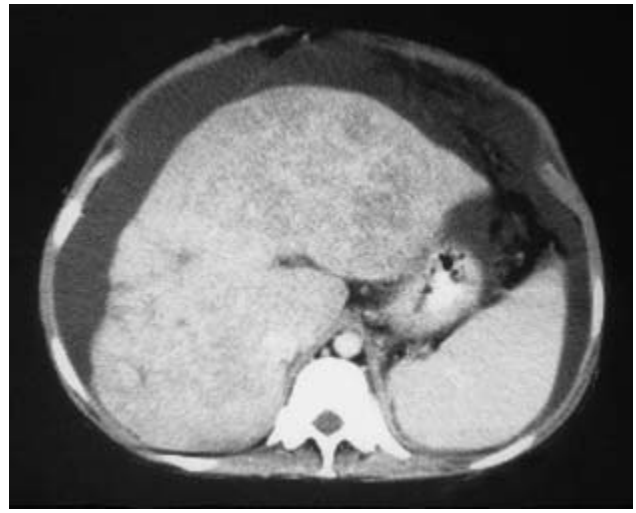


Fig. 5.8. Enhanced CT scan showing patchy areas of low attenuation in the liver (pseudo-tumour appearance) and ascites in a patient with Budd–Chiari syndrome.

thrombus may be seen. Cavernomatous transformation can be recognized with two or more enhancing vessels in place of the obstructed portal vein. Doppler US, however, remains the better technique to demonstrate abnormalities of the portal vein.

In Budd–Chiari syndrome there may be a patchy pattern of hepatic enhancement ('pseudo-tumour' appearance) (fig. 5.8) which may wrongly be interpreted as tumour within the liver. The caudate lobe is enlarged.

An enhanced CT demonstrates the splenic vein and in portal hypertension the collaterals around the spleen and retroperitoneum (fig. 5.9). Spontaneous and surgical shunts can be demonstrated.

Normal bile ducts, both intra- and extra-hepatic, are difficult to see. In the gallbladder, calcified stones are demonstrated and CT is used in the evaluation of patients for non-surgical therapy of gallbladder stones. US rather than CT, however, is the technique of choice to search for gallbladder stones.

The shape of the liver, any anatomical abnormalities or lobe atrophy are seen. Liver volume can be calculated from the slices taken but is a research tool.

CT demonstrates diffuse liver disease due to cirrhosis (fig. 5.10), fat (fig. 5.11) and iron (fig. 5.12). A nodular, uneven edge to the liver which may be shrunken suggests cirrhosis. Ascites and splenomegaly support this diagnosis. CT is of particular value in suspected cirrhosis when clotting deficiencies preclude routine percutaneous liver biopsy.

Fatty liver shows a lower attenuation value than normal (fig. 5.11). Even in an unenhanced scan the blood vessels stand out with a higher attenuation value than liver parenchyma. Thus fatty liver may be diagnosed without the need for liver biopsy. CT measurements correlate with histological steatosis. Single energy CT scan-

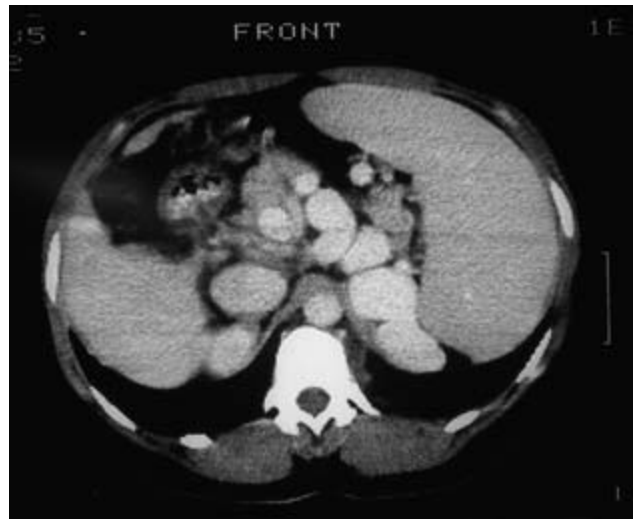


Fig. 5.9. Enhanced CT scan showing massive collaterals (white) around the large spleen due to portal hypertension.

ning is better than dual-energy CT which has a lower sensitivity, particularly when there is increased hepatic iron. However, overall, US is better than either CT method for diffuse steatosis [19].

In iron overload, hepatic density is increased on CT and the unenhanced liver is brighter than the spleen or kidney (fig. 5.12). Using dual-energy CT there is a correlation with liver iron but this is insufficient with moderate siderosis to make the method of practical value in the management of patients with haemochromatosis.

Liver with a high copper content usually has a normal attenuation value.

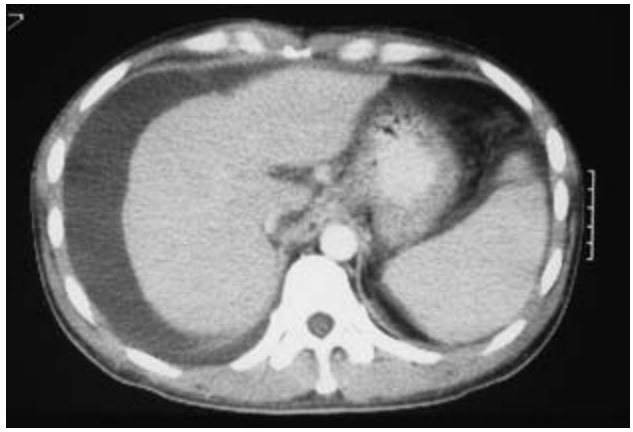


Fig. 5.10. Enhanced CT scan showing a shrunken liver with a nodular margin and ascites due to cirrhosis.

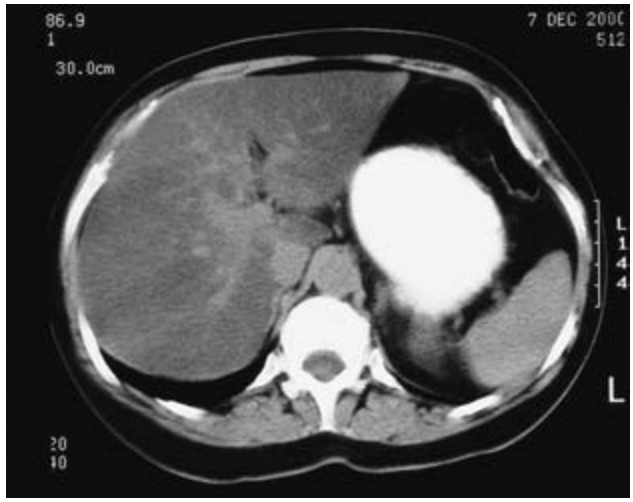


Fig. 5.11. Unenhanced CT scan in a patient with a fatty liver showing blood vessels outlined within the hepatic parenchyma which has a very low attenuation value.

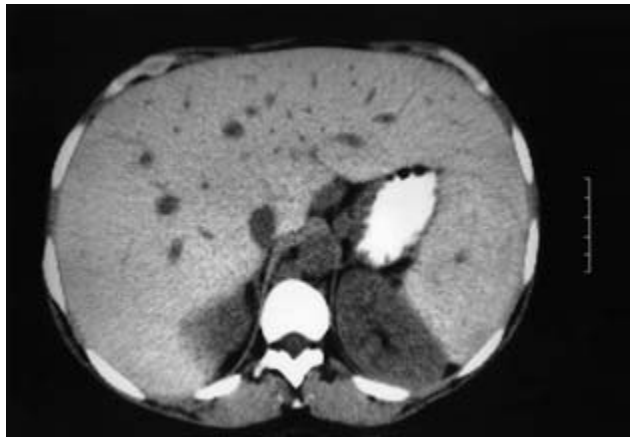


Fig. 5.12. Unenhanced CT scan of secondary iron overload in thalassaemia major. The liver shows increased density, greater than that of the kidney. Portal vein radicles are very prominent.

Space-occupying lesions of 1 cm and more in diameter can be detected by CT. Both unenhanced and enhanced scans should be done. Thus a filling defect on an unenhanced scan may be rendered isodense by intravenous contrast injection and missed. Conversely, an area isodense with normal liver on the unenhanced scan may only be seen after enhancement.

Benign lesions (often detected by chance) include simple cysts and cavernous haemangioma. Simple cysts can usually be confidently identified because of the low attenuation value of the centre, equivalent to water (fig. 33.5). Smaller cysts, however, may suffer from a partial volume effect (i.e. an artificially high attenuation value because of averaging with the surrounding block of normal tissue). US is necessary to confirm the small cyst.

Cavernous haemangioma appears as a low attenuation area on an unenhanced scan which subsequently fills in with contrast from the periphery (fig. 5.13). In the majority of cases the CT appearance is unequivocal. Where there is any question of the aetiology of the lesion, an MRI scan may be necessary.

CT scans can detect solid lesions greater than 1 cm in diameter due to primary or secondary malignant tumour (fig. 5.14). They usually have a lower attenuation value than normal liver that remains on enhancement. Calcification is present in some metastases such as from colon. Highly vascular metastases (kidney, choriocarcinoma, carcinoid) may fill in with enhancement. Most primary tumours do not. Whether confirmation by image-guided biopsy is necessary will depend upon the clinical situation and the results of tumour markers, α-fetoprotein and carcino-embryonic antigen (CEA). The sensitivity of CT in showing hepato-cellular carcinoma is 87%, compared with 80% for US and 90% for hepatic angiography [23]. The sensitivity for satellite lesions is lower at 59% for CT and angiography, and 17% for US. Injection of iodized oil (lipiodol) into the hepatic artery followed by CT 2 weeks later (fig. 31.12) may be used to detect small lesions [20], but many still escape detection—the sensitivity in a study of lesions 9–40 mm in diameter being only 53% [29].

CT scanning after injection of contrast into the splenic or superior mesenteric artery (CT arterio-portography) is the most sensitive method for detecting hepatic metastases (fig. 5.15) and also shows benign and malignant primary hepatic tumours [28]. Because it is invasive it is generally reserved for candidates for surgical resection. CT portography detects 75% of hepato-cellular carcinomas less than 2 cm in diameter [8] and 88% of primary and secondary hepatic malignant lesions [9].

Adenomas and focal nodular hyperplasia usually give negative defects but can be missed both by CT and US because they have characteristics close to that of normal liver tissue. Focal nodular hyperplasia classically has

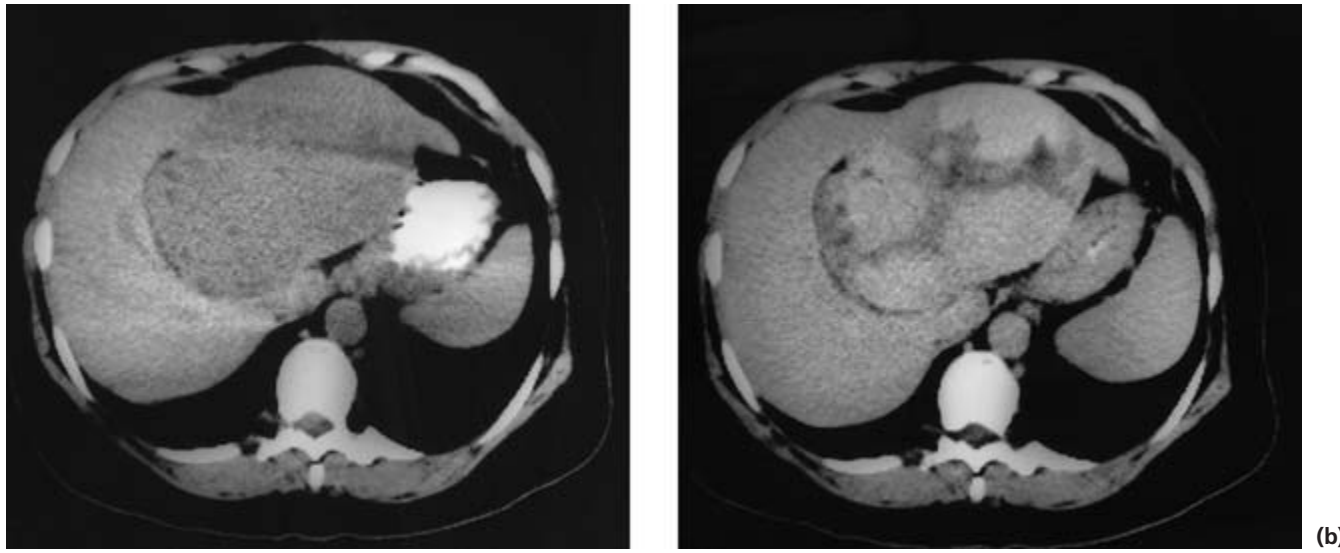


Fig. 5.13. (a) An unenhanced CT scan showing a large, low attenuation lesion in the left lobe of the liver. (b) Following enhancement, dynamic scanning shows gradual infilling of the lesion which eventually became isodense with the remainder of the liver. These are the characteristic appearances of a cavernous haemangioma.

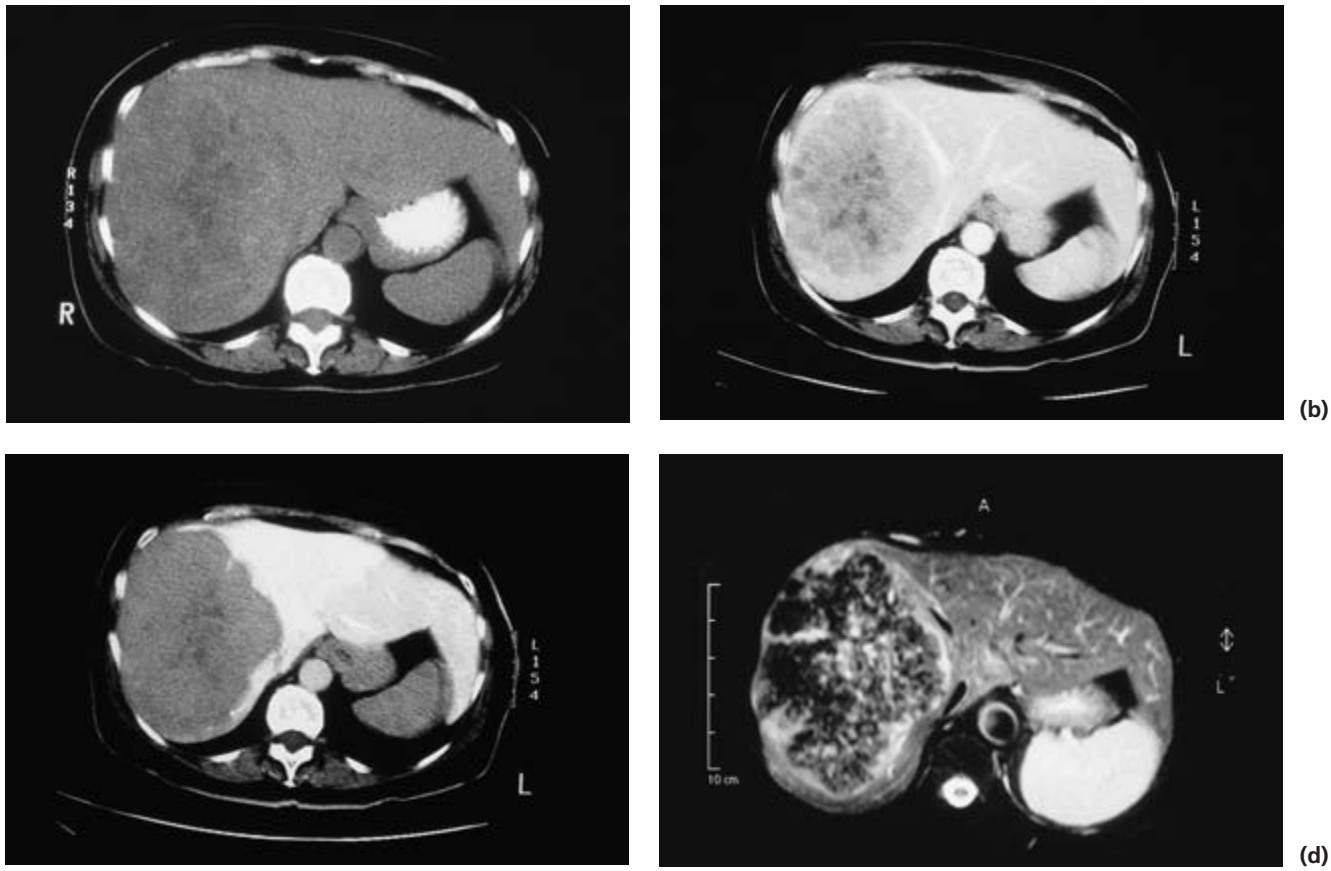


Fig. 5.14. Hepato-cellular carcinoma appearances on CT and MRI. (a) Unenhanced CT scan. Low attenuation area in right lobe. (b) Contrast enhanced CT scan. (c) CT portogram. (d) MRI scan (T_2-weighted) showing a predominantly low intensity lesion.

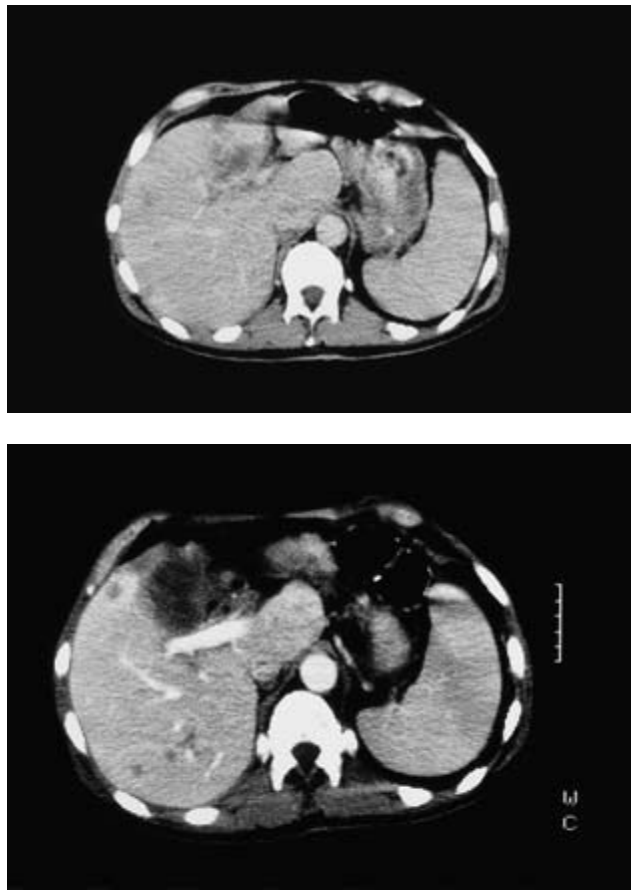


Fig. 5.15. Value of CT portography. (a) Conventional enhanced CT scan of the liver in a patient with cholangiocarcinoma in the left lobe. There was a suspicion of metastases in the right lobe. (b) CT portography clearly showing multiple small metastases in the right lobe. The portal vein is well seen as is the lesion in the left lobe.

a central scar but this is not specific enough to be of guaranteed diagnostic value.

Abscesses usually show a lower attenuation than normal liver (fig. 5.16). Aspiration under guidance is possible as with US. An enhanced rim around the abscess on CT is said to be more characteristic of amoebic abscess. Hydatid cysts, particularly those that are old and inactive, may have a calcified rim (fig. 29.21). Daughter cysts can be seen in active disease (fig. 29.22).

Enhanced CT is a valuable aid in abdominal trauma, the size of any laceration or contusion being noted, and the extent of any haemoperitoneum [21]. False aneurysms of the hepatic artery should be searched for.

An important function of CT, more so than US, is to define the anatomy for the surgeon considering hepatic resection. The segmental position of the lesion can be identified. CT portography will show whether more lesions exist than seen on the conventionally enhanced scan (fig. 5.15).

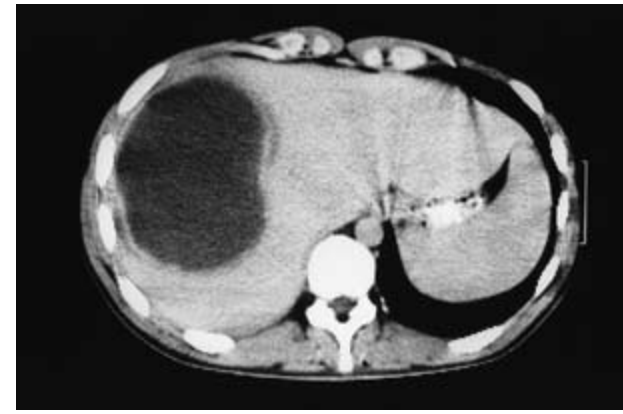


Fig. 5.16. CT scan of the liver in a 21-year-old man with fever and right upper quadrant pain. The CT shows a large space-occupying lesion from which 1 litre of pus was drained. This was an infected amoebic abscess.

Magnetic resonance imaging [10, 16]

This is the most expensive scanning technique, at approximately six times the cost of US and twice that of CT. The detection of lesions with MRI is comparable to that with CT, although most protocols for MRI at present have lower edge definition than that available for CT. The detection and characterization of lesions less than 1 cm in diameter is difficult. Respiratory gating is overcoming the problem of breathing artefacts. Some hepatic lesions have specific MRI signal characteristics, but others do not. Tissue-specific contrast agents may refine this in the future. Both CT and MRI show wider fields of anatomy and pathology than the liver alone.

MRI depends upon detection of energy released from hydrogen protons after forcible alignment in a strong magnetic field. The technique is safe with certain provisos. Patients with cardiac pacemakers and internal magnetic material (clips, metallic foreign bodies) are excluded, as are pregnant patients; it is difficult to scan and monitor the ventilated patient from intensive care.

Several measurements of tissue can be made but those most commonly employed are the relaxation times T_1 and T_2, and proton density. Tissues appear greatly different according to the mode used and the appearance of some organs may reverse. Blood vessels and bile ducts are visualized without the need for contrast material. There is excellent contrast resolution (better than CT) and good spatial resolution (not as good as CT). As scanning times (currently 5–10 min for each sequence) shorten with technological advances, artefacts from respiratory movement particularly in the breathless patient will decrease and spatial resolution will improve. Multiple planes (axial, coronal, sagittal) can be reconstructed

according to need. Reproducibility is good. Tissue characterization is possible.

T_1 relaxation time is the time taken for hydrogen protons to realign within the external magnetic field after a radio-frequency pulse. T_2 relaxation time describes the rate at which the axes of the protons move out of phase with each other because of the differing electromagnetic influence of adjacent protons. Protein density simply depicts the number of protons per unit area. Tissues respond differently to the MRI process and scans can therefore characterize cyst fluid, subacute and chronic haematoma, fat, neoplasm, fibrotic tissue and vessels.

On T_1-weighted scans the liver usually appears grey and homogeneous, with a signal greater than spleen. On T_2-weighted scans the hepatic signal is less than that from spleen (fig. 5.17). Dilated bile ducts are easily seen.

Normal blood vessels usually appear black with T_1-weighted scans because the energy donated during the radiopulse has passed out of the slice with blood flow by the time the return signal is recorded.

Whichever technique is used, portal vein, hepatic veins, inferior vena cava, aorta and biliary tract are seen. Note that no contrast injection is needed for blood vessel or bile duct visualization (fig. 5.18).

MRI can show cysts, haemangioma, primary and secondary tumour (fig. 5.14d). Malignant tumour usually appears dark (low signal) on T_1-weighted scan and bright (high signal) on T_2-weighted, similar to the signal from the spleen. Differentiation between hepatocellular carcinoma and metastases is not always possible although contrast agents targeting functional hepatocytes, such as gadolinium benyloxypropionictetraacetate (Gd-BOPTA) are useful. Tumours containing functional hepatocytes, such as hepato-cellular carcinoma, focal nodular regenerative hyperplasia and regenerating nodules should appear different from metastases which do not contain hepatocytes and will not take up contrast [15, 22, 27]. Contrast agents (such as ferumoxides) that home to the reticulo-endothelial system can differentiate focal nodular hyperplasia (containing Kupffer cells) from both metastases and primary liver carcinoma in which uptake of these agents is not expected. Preliminary reports suggest that adenomatous hyperplastic nodules without dysplasia are low signal on T_2-weighted scans, differentiating them from hepato-cellular carcinoma [18]. MRI is insensitive for the diagnosis of small (< 2 cm) hepato-cellular carcinomas and dysplastic nodules [14]. Cavernous haemangioma is particularly bright on T_2-weighted scans and can be distinguished from carcinoma using a spin-echo sequence of 2000/150 [5]. Following contrast, there is characteristic infilling from the periphery (fig. 5.19), equivalent to that seen with CT after enhancement.

MRI detects increased hepatic iron and the liver appears darker or black on all sequences (fig. 5.20).

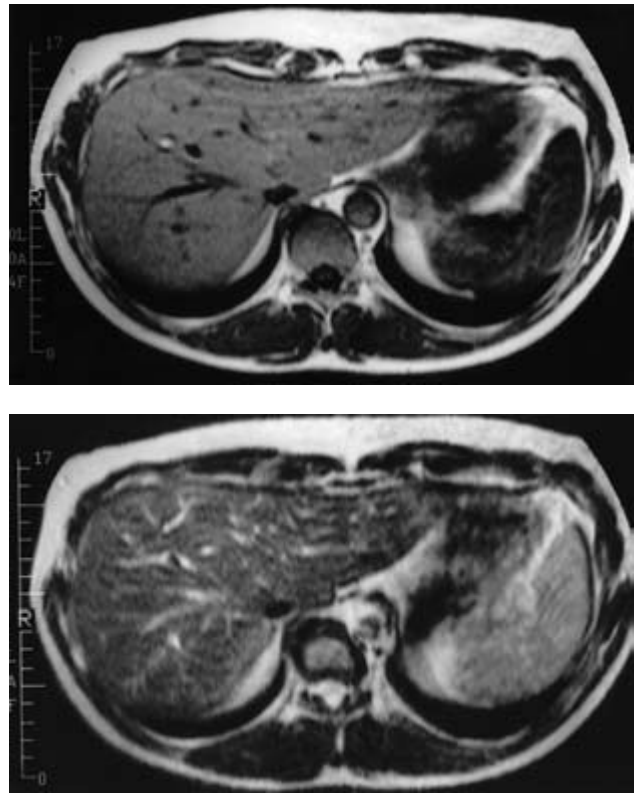


Fig. 5.17. MRI scan in a normal adult volunteer. (a) T_1-weighted scan (spin-echo 300/12). (b) T_2-weighted scan (spin-echo 1500/80). Note than in the T_2-weighted scan the spinal canal contents are bright (white) as are the blood vessels in the homogeneous liver (left).

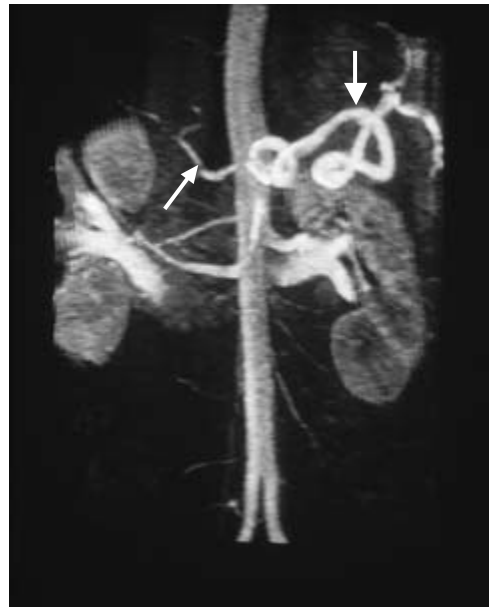


Fig. 5.18. MRI (T_2-weighted) angiogram showing the hepatic artery (small arrow) and tortuous splenic artery (large arrow) as well as the renal vessels below.

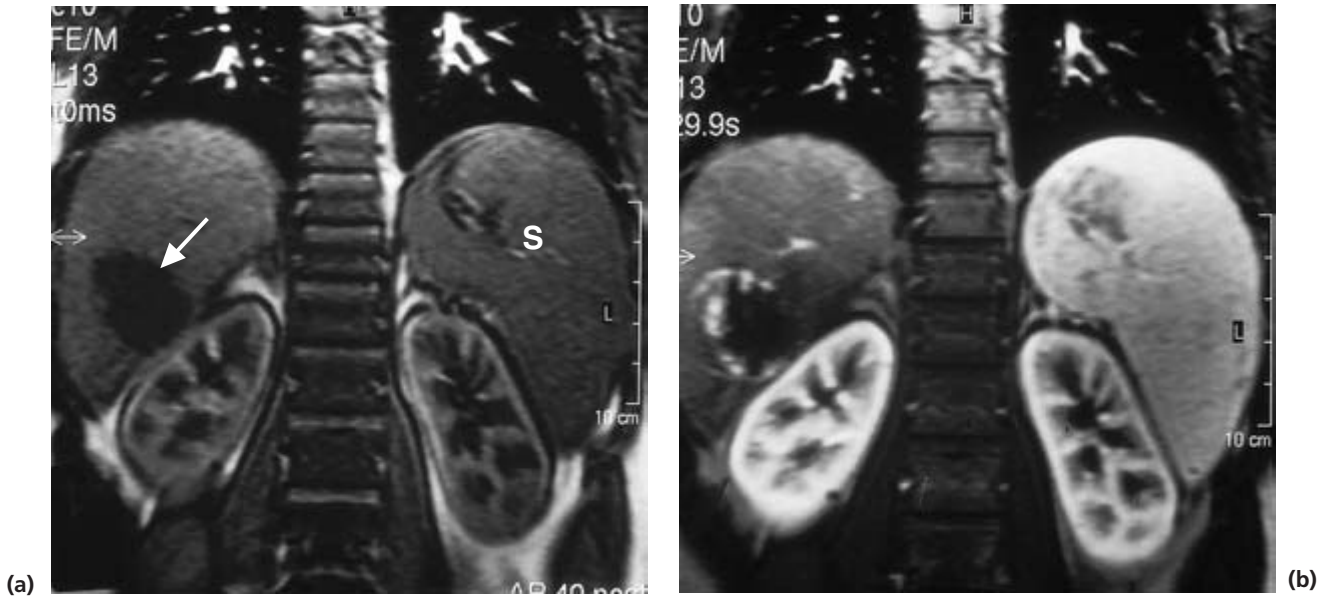


Fig. 5.19. MRI of hepatic haemangioma. (a) T_1-weighted scan showing a typical low intensity lesion in the right lobe (arrow). (b) There is bright high intensity infilling at the periphery after gadolinium enhancement. Note incidental splenomegaly (S).

Several approaches can be used to quantify the iron concentration by, for example, comparing the signal from liver with that of muscle on specific sequences [13]. Accurate quantification is likely only to be possible in units with a specific interest, and MRI is not currently widely used in the management of patients with haemochromatosis.

MR cholangiopancreatography (MRCP) has emerged as a valuable technique for showing pathology in the intra- and extra-hepatic biliary tree (fig. 5.21) (Chapter 32) [17, 24]. No contrast is required. The peripheral radicals of the intra-hepatic bile ducts are usually more fully demonstrated than on contrast cholangiography (percutaneous transhepatic cholangiography, endoscopic retrograde cholangiopancreatography). MR angiography allows non-invasive investigation of arterial and venous anatomy, and pathology (Figs 5.22, 5.23).

MRI techniques are advancing rapidly. Developments will include optimizing the spin–echo sequence, using fast imaging sequences and applying new contrast media such as gadolinium and manganese derivatives and ferrite [22]. At present the results for MRI of the liver are comparable to CT. MRI promises much for the future but its use may well be limited geographically by cost, availability and expertise.

CT remains the better choice if scanning of the chest or bones is needed to evaluate malignant hepatic disease, or if guided biopsy is necessary.

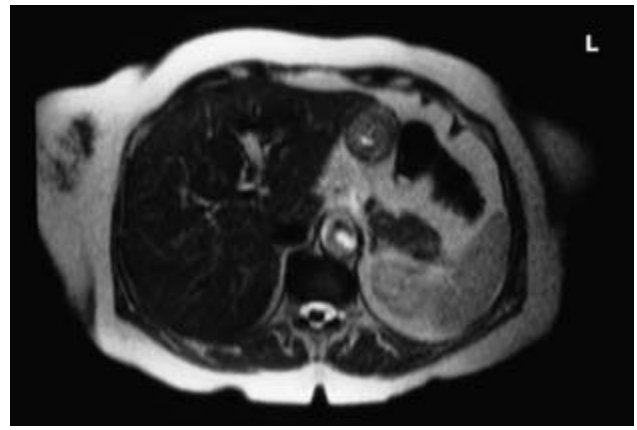


Fig. 5.20. MRI scan (T_2-weighted) showing black low intensity liver due to iron in a patient with haemochromatosis.

MR spectroscopy

MR spectroscopy allows non-invasive evaluation of biochemical changes in tissue *in vivo*. Changes in molecules involved in selected areas of cellular metabolism can be detected. The technique currently remains experimental, but has been applied to patients with liver disease [30]. Phosphorus-31 spectroscopy shows an increase in phospholipid membrane precursors (phosphomonoester or PME peak) and a decrease in phospholipid membrane degradation products and endoplasmic reticulum (phosphodiester or PDE peak). These changes correlate with severity of liver disease and may reflect increased turnover of cell membranes as the liver regenerates. Clinical application of the technique remains elusive but

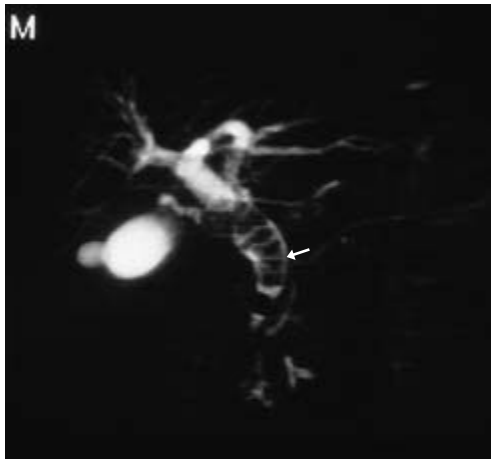


Fig. 5.21. MRCP showing the bile duct packed full of stones (arrow).

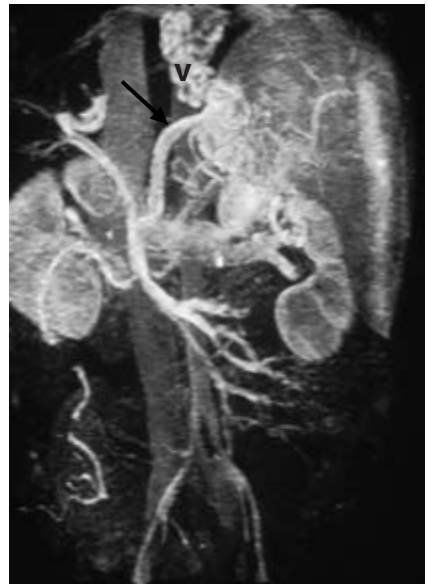
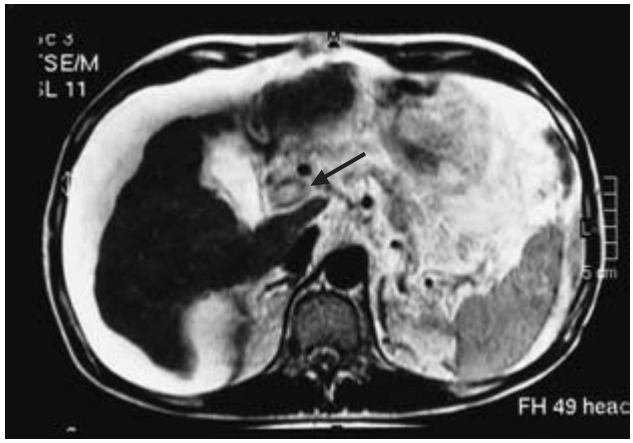
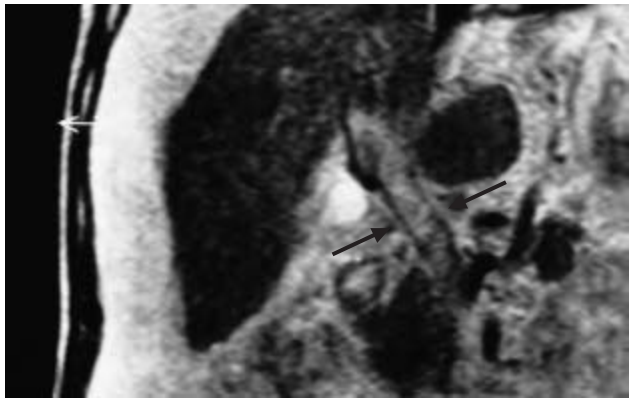


Fig. 5.23. MR angiogram in a patient with hepatitis C cirrhosis, showing a large collateral vein (arrow) feeding a leash of varices (v).



(a)



(b)

Fig. 5.22. MR angiography. T_1-weighted scan. (a) Cross-section in a patient with cirrhosis and ascites, showing thrombus in the portal vein (arrow). (b) Coronal scan, showing thrombus between a rim of blood (arrows) in a partially patent portal vein.

a role in acute liver failure and assessment of donor liver tissue is possible.

Conclusions and choice

The choice of technique for hepato-biliary imaging depends upon the problem that has to be solved and the availability of the appropriate apparatus, operator and interpreter (table 5.1). Strict diagnostic algorithms cannot be formulated that will service *all units*. Radio-isotope scanning has been superseded by US, CT and MRI which are better in detecting lesions and characterizing them. With an experienced ultrasonographer, this technique is the initial examination of choice for the majority of problems. Equivocal results can be further studied by CT or MRI as necessary.

CT and MRI characterize most lesions better than US but are more costly and less widely available. In some centres CT replaces US as the primary procedure, often more out of availability and convenience (for the clinician) than need.

For the diagnosis of jaundice, US is the preferred screening investigation. If necessary this may be followed by MRI and/or MRCP scanning to help in the diagnosis and to show the extent of disease.

For the diagnosis of gallbladder stones, US is the primary method of choice.

Tc-IDA scanning provides an alternative non-invasive method to US for diagnosing acute cholestasis, and is used to demonstrate post-operative biliary patency and

Table 5.1. Non-invasive imaging for hepato-biliary disease

	Choice		
Question	First	Second	Third
Mass in liver	US	CT/MRI	
Hepatic metastases	US	CT/MRI	
Screen cirrhotic for HCC	US	CT	
Tumour resectable	CT*	MRI	
Haemangioma	US	MRI	
Abscess	US/CT		
Hydatid cyst	US	MRI/CT	
Portal vein patent	USDop	US/CT/MRI	
Portal hypertension	USDop	US	CT
Budd–Chiari	USDop	US	CT/MRI
Shunt patent	USDop	US/CT/MRI	
Assessment of trauma	US/CT		
Cirrhosis	US	CT	
Fatty liver	US	CT/MRI	
Iron	CT	MRI	
Gallbladder stone	US		
Acute cholecystitis	US/IDA		
Dilated bile ducts	US	MRCP	
Duct stone	US†	MRCP	
Bile leak	IDA		
Pancreatic tumour	US/CT	EUS	

*CT portography.
†Only of value if positive.
CT, computed tomography; EUS, endoscopic ultrasound; HCC, hepato-cellular carcinoma; IDA, scintiscan with iminodiacetic acid derivative; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; US, ultrasound; USDop, Doppler ultrasound.

leaks. It is also used in infants in the diagnostic work-up of possible biliary atresia (see fig. 32.9).

References

1 Aubé C, Oberti F, Korali N *et al*. Ultrasonographic diagnosis of hepatic fibrosis or cirrhosis. *J. Hepatol*. 1999; **30**: 472.
2 Bolondi L, Gaiani S, Li Bassi S *et al*. Diagnosis of Budd–Chiari syndrome by pulsed Doppler ultrasound. *Gastroenterology* 1991; **100**: 1324.
3 Caplin ME, Buscombe JR, Hilson AJ *et al*. Carcinoid tumour. *Lancet* 1998; **352**: 799.
4 Colli A, Cocciolo M, Riva C *et al*. Abnormalities of Doppler waveform of hepatic veins in patients with chronic liver disease: correlation with histological findings. *Am. J. Roentgenol*. 1994; **162**: 833.
5 de Beeck BO, Luypaert R, Dujardin M *et al*. Benign liver lesions: differentiation by magnetic resonance. *Eur. J. Radiol*. 1999; **32**: 52.
6 El Sherif A, McPherson SJ, Dixon AK. Spiral CT of the abdomen: increased diagnostic potential. *Eur. J. Radiol*. 1999; **31**: 43.
7 Huebner RH, Park KC, Shepherd JE *et al*. A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. *J. Nucl. Med*. 2000; **41**: 1177.
8 Ikeda K, Saitoh S, Koida I *et al*. Imaging diagnosis of small hepatocellular carcinoma. *Hepatology* 1994; **20**: 82.
9 Irie T, Takeshita K, Wada Y *et al*. CT evaluation of hepatic tumours: comparison of CT with arterial portography, CT with infusion hepatic arteriography, and simultaneous use of both techniques. *Am J. Roentgenol*. 1995; **164**: 1407.
10 Ito K, Mitchell DG, Matsunaga N. MR imaging of the liver: techniques and clinical applications. *Eur. J. Radiol*. 1999; **32**: 2.
11 Khan MA, Combs CS, Brunt EM *et al*. Positron emission tomography in the evaluation of hepatocellular carcinoma. *J. Hepatol*. 2000; **32**: 792.
12 Killi RM. Doppler sonography of the native liver. *Eur. J. Radiol*. 1999; **32**: 21.
13 Kreeftenberg HG, Mooyaart EL, Huizenga JR *et al*. Quantification of liver iron concentration with magnetic resonance imaging by combining T1-, T2-weighted spin echo sequences and a gradient echo sequence. *Neth. J. Med*. 2000; **56**: 133.
14 Krinsky GA, Lee VS, Theise ND *et al*. Hepatocellular carcinoma and dysplastic nodules in patients with cirrhosis: prospective diagnosis with MR imaging and explantation correlation. *Radiology* 2001; **219**: 445.
15 Li KC, Chan F. New approaches to the investigation of focal hepatic lesions. *Bailliéres Best Pract. Res. Clin. Gastroenterol*. 1999; **13**: 529.
16 Macdonald GA, Peduto AJ. Magnetic resonance imaging (MRI) and diseases of the liver and biliary tract. Part 1. Basic principles, MRI in the assessment of diffuse and focal hepatic disease. *J. Gastroenterol. Hepatol*. 2000; **15**: 980.
17 Macdonald GA, Peduto AJ. Magnetic resonanace imaging and diseases of the liver and biliary tract. Part 2. Magnetic resonance cholangiography and angiography and conclusions. *J. Gastroenterol. Hepatol*. 2000; **15**: 992.
18 Matsui O, Kadoya M, Kameyama T *et al*. Adenomatous hyperplastic nodules in the cirrhotic liver: differentiation from hepatocellular carcinoma with MR imaging. *Radiology* 1989; **173**: 123.
19 Mendler M-H, Bouillet P, Le Sidaner A *et al*. Dual energy CT in the diagnosis and quantification of fatty liver: limited clinical value in comparison to ultrasound scan and single-energy CT, with special reference to iron overload. *J. Hepatol*. 1998; **28**: 785.
20 Palma LD. Diagnostic imaging and interventional therapy of hepatocellular carcinoma. *Br. J. Radiol*. 1998; **71**: 808.
21 Poletti PA, Mirvis SE, Shanmuganathan K *et al*. CT criteria for management of blunt liver trauma: correlation with angiographic and surgical findings. *Radiology* 2000; **216**: 418.
22 Reimer P, Jähnke N, Fiebich M *et al*. Hepatic lesion detection and characterization: value of nonenhanced MR imaging, superparamagnetic iron oxide-enhanced MR imaging, and spiral CT-ROC analysis. *Radiology* 2000; **217**: 152.
23 Rizzi PM, Kane PA, Ryder SD *et al*. Accuracy of radiology in detection of hepatocellular carcinoma before liver transplantation. *Gastroenterology* 1994; **107**: 1425.
24 Sackmann M, Beuers U, Helmberger T. Biliary imaging: magnetic resonance cholangiography vs. endoscopic retrograde cholangiography. *J. Hepatol*. 1999; **30**: 334.
25 Savci G. The changing role of radiology in imaging liver tumours: an overview. *Eur. J. Radiol*. 1999; **32**: 36.

26 Shi W, Johnston CF, Buchanan KD *et al*. Localization of neuroendocrine tumours with ^{111}In DTPA-octreotide scintigraphy (Octreoscan): a comparative study with CT and MR imaging. *Q. J. Med*. 1998; **91**: 295.
27 Sica GT, Ji H, Ros PR. CT and MR imaging of hepatic metastases. *Am. J. Roentgenol*. 2000; **174**: 691.
28 Soyer P, Bluemke DA, Fishman EK. CT during arterial portography for the preoperative evaluation of hepatic tumours: how, when, and why? *Am. J. Roentgenol*. 1994; **163**: 1325.
29 Taourel PG, Pageaux GP, Coste V *et al*. Small hepatocellular carcinoma in patients undergoing liver transplantation: detection with CT after injection of iodized oil. *Radiology* 1995; **197**: 377.
30 Taylor-Robinson SD. Applications of magnetic resonance spectroscopy to chronic liver disease. *Clin. Med*. 2001; **1**: 54.

Chapter 6
Hepato-cellular Failure

Hepato-cellular failure can complicate almost all forms of liver disease. It may follow virus hepatitis, or the cirrhoses, fatty liver of pregnancy, hepatitis due to drugs, overdose with drugs such as acetaminophen (paracetamol), ligation of the hepatic artery near the liver, or occlusion of the hepatic veins. The syndrome does not complicate portal venous occlusion alone. Circulatory failure, with hypotension, may precipitate liver failure.

It may be terminal in chronic cholestasis, such as primary biliary cirrhosis or cholestatic jaundice associated with malignant replacement of liver tissue or acute cholangitis. It should be diagnosed cautiously in a patient suffering from acute biliary obstruction.

Although the clinical features may differ, the overall picture and treatment are similar, irrespective of the aetiology. Acute liver failure poses special problems (Chapter 8).

There is no constant hepatic pathology and in particular necrosis is not always seen. The syndrome is therefore functional rather than anatomical. It comprises some or all of the following features.

- General failure of health.
- Jaundice.
- Hyperdynamic circulation and cyanosis.
- Fever and septicaemias.
- Neurological changes (hepatic encephalopathy).
- Ascites (Chapter 9).
- Changes in nitrogen metabolism.
- Skin and endocrine changes.
- Disordered blood coagulation (Chapter 4).

General failure of health

The most conspicuous feature is easy fatiguability. Wasting can be related to difficulty in synthesizing tissue proteins. Anorexia and poor dietary habits add to the malnutrition.

Jaundice

Jaundice is largely due to failure of the liver cells to metabolize bilirubin, so it is some guide to the severity of liver cell failure.

In acute failure, due to such causes as virus hepatitis, jaundice parallels the extent of liver cell damage. This is not so evident in cirrhosis, where jaundice may be absent or mild. When present it represents active hepatocellular disease and indicates a bad prognosis. Diminished erythrocyte survival adds a haemolytic component to the jaundice.

Vasodilatation and hyperdynamic circulation

This is associated with all forms of hepato-cellular failure, but especially with decompensated cirrhosis [33]. It is shown by flushed extremities, bounding pulses and capillary pulsations. Peripheral blood flow is increased. Arterial blood flow is increased in the lower limbs. Portal blood flow is increased. Renal blood flow, and particularly cortical perfusion, is reduced. Cardiac output is raised [11, 24] and evidenced by tachycardia, an active precordial impulse and frequently an ejection systolic murmur (figs 6.1, 6.2). These circulatory changes only rarely result in heart failure.

The blood pressure is low and, in the terminal phase, further reduces kidney function. At this stage the impaired liver blood flow contributes to hepatic failure and the fall in cerebral blood flow adds to the mental changes [8]. Such hypotension is ominous and attempts at elevation by raising circulatory volume by blood

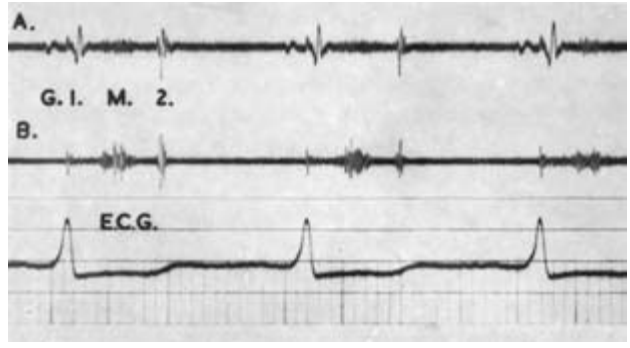


Fig. 6.1. Cirrhosis. Phonocardiogram at apex (A) and base (B) shows ejection-type systolic murmur (M) and an auricular sound (pre-systolic gallop) (G) [19].

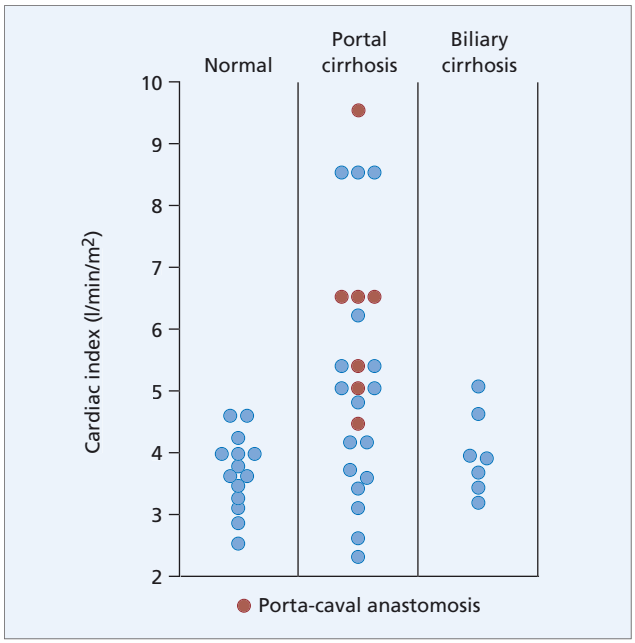


Fig. 6.2. The cardiac output is raised in many patients with hepatic cirrhosis but within normal limits in biliary cirrhosis. Mean normal cardiac index is 3.68±0.601/min/m². Mean in hepatic cirrhosis is 5.36±1.981/min/m² [24].

transfusion or by such drugs as dopamine are of only temporary benefit.

Systemic vascular peripheral resistance is reduced as is the arteriovenous oxygen difference. In patients with cirrhosis, whole body oxygen consumption is decreased and tissue oxidation is abnormal. This has been related to the hyperdynamic circulation and to arteriovenous shunting. Thus, the vasodilator state of liver failure may contribute to general tissue hypoxia.

Vasomotor tone is decreased as shown by reduced vasoconstriction in response to mental exercise, the Valsalva manoeuvre and tilting from horizontal to vertical [19, 20]. Autonomic neuropathy is a poor prognostic indicator [6]. Large numbers of normally present, but functionally inactive, arteriovenous anastomoses may have opened under the influence of a vasodilator substance. The effective arterial blood volume falls as a consequence of the enlargement of the arterial vascular compartment induced by arterial vasodilatation. This activates the sympathetic and renin–angiotensin systems and is important in sodium and water retention and ascites formation (Chapter 9). The hyperdynamic splanchnic circulation is related to portal hypertension (Chapter 10).

The nature of the vasodilators concerned remains speculative. They are likely to be multiple. The substances might be formed by the sick hepatocyte, fail to be inactivated by it or bypass it through intra- or extrahepatic portal-systemic shunts. The vasodilators are likely to be of intestinal origin. In cirrhosis, increased permeability of the intestinal mucosa and portosystemic shunting allow endotoxin and cytokines to reach the systemic circulation and these could be responsible (see fig. 6.9) [17, 18].

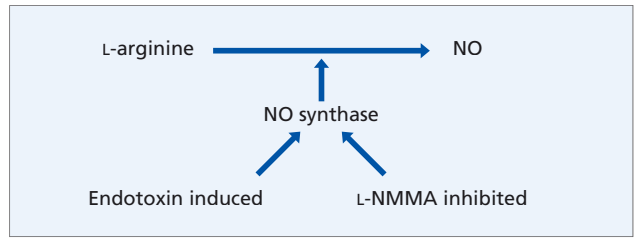


Fig. 6.3. Nitric oxide (NO) is a general vasodilator. It is produced from L-arginine, NO synthase being the responsible enzyme. This is induced by endotoxin and inhibited by L-NMMA.

Nitric oxide (NO). This endothelium-derived potent vasodilator may be involved in the hyperdynamic circulation [26]. It is released from L-arginine by a family of NO synthase enzymes encoded by different genes (fig. 6.3). The endothelial constituent, NO synthase (NO S3), plays an important part in regulating normal vasoconstrictor tone [3].

L-arginine analogues such as NG-monomethyl-L-arginine (L-NMMA) inhibit NO release. They have been shown to reverse many of the vasodilator effects of NO. Inhibitors have been shown to reverse the hyperdynamic circulation in portal-hypertensive rats [16]. Cirrhotic rats show increased sensitivity to the pressor effect of NO inhibition and portal pressure rises [25]. NO synthase is inducible after stimulation with bacterial endotoxin or cytokines. NO is important in ascites formation and the hepato-renal syndrome (Chapter 9), and in portal hypertension (Chapter 10) [36].

Various gastrointestinal peptides, such as vaso-active intestinal polypeptide (VIP) type II, have little effect on the portal circulation. Glucagon is unlikely to be the sole vasodilator responsible.

Prostaglandins (E_1, E_2 and E_{12}) have vasodilatory actions and prostanoids are released into the portal vein in patients with chronic liver disease [38]. They may play a part in vasodilatation.

The cirrhotic shows arterial hyporeactivity to endogenous vasoconstrictors [23].

After hepatic transplantation, portal pressure becomes normal, and the cardiac index and splanchnic flow remain high due to the persistence of portal-systemic collateral flow [9].

Hepato-pulmonary syndrome

About a third of patients with decompensated cirrhosis

Table 6.1. Pulmonary changes complicating chronic hepato-cellular disease

Hypoxia
Intra-pulmonary shunting
Ventilation–perfusion mismatch
Reduced transfer factor
Pleural effusion
Raised diaphragms
Basal atelectasis
Primary pulmonary hypertension
Porto-pulmonary shunting
Chest X-ray mottling

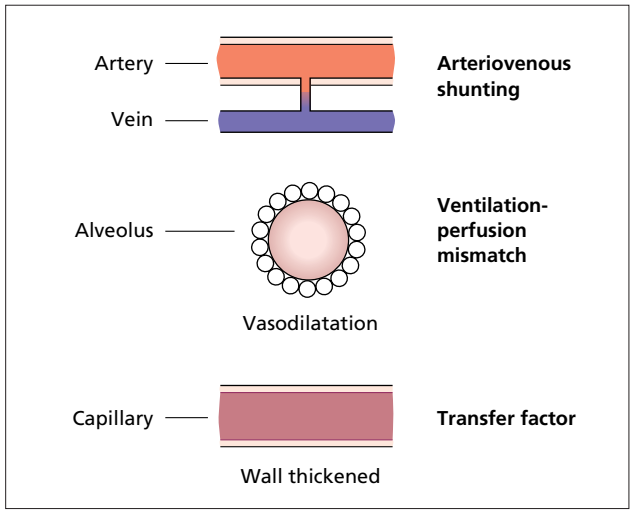


Fig. 6.4. Pulmonary changes in liver failure.

Table 6.2. Hepato-pulmonary syndrome

Advanced chronic liver disease
Arterial hypoxaemia
Intra-pulmonary vascular dilatation
No primary cardiopulmonary disease

have reduced arterial oxygen saturation and are sometimes cyanosed (table 6.1, fig. 6.4) [29]. Causes include the hepato-pulmonary syndrome (table 6.2) [32]. This is defined as a clinical disorder associated with advanced liver disease and with disturbed pulmonary gas exchange leading to hypoxaemia and with widespread intra-pulmonary vascular dilatations in the absence of detectable primary cardio-pulmonary disease [13, 30, 32]. The alveolar–arterial oxygen gradient ($Aa\mathit{P}o_2$) exceeds 15 mmHg (breathing room air). The intra-pulmonary shunting is through microscopic arteriovenous fistulae. The peripheral branches of the pulmonary artery are markedly dilated in the lungs and in the pleura where spider naevi may sometimes be seen (fig. 6.5) [1]. Arterial right-to-left large shunts causing cyanosis are rare (fig. 6.6) [1].

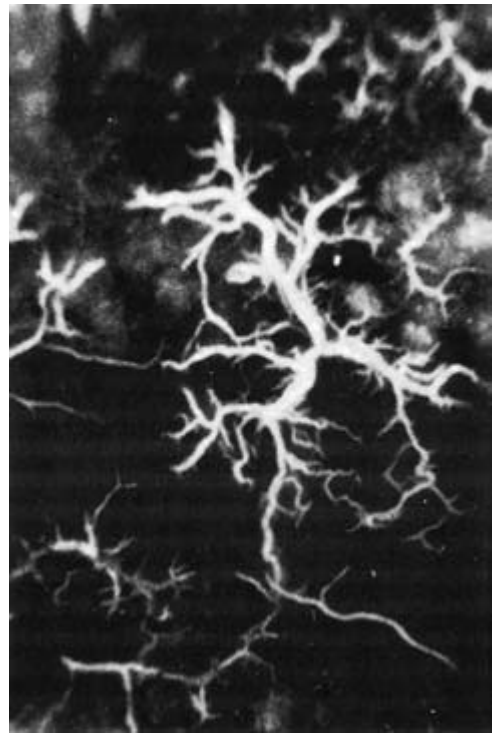


Fig. 6.5. Cirrhosis. Macroscopic appearances of the pleura showing dilated pleural vessels resembling a spider naevus [1].

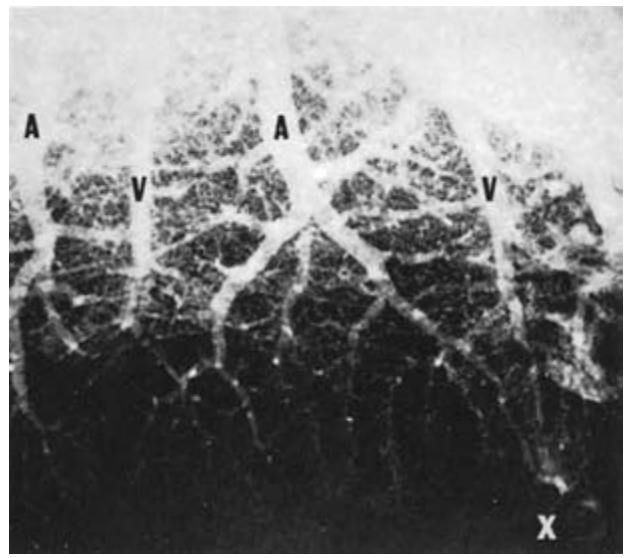


Fig. 6.6. Arteriogram from a patient with cirrhosis showing a slice of the basal region of the left lung. Arteries (A) and veins (V) alternate: X is the site of the arteriovenous shunting, into which a large arterial branch can be directly traced. The injection medium was barium suspension [1].

Reduction of diffusing capacity is present without a restrictive ventilatory defect [35]. This is likely to be due

to dilatation of small pulmonary blood vessels, a complication both of advanced cirrhosis and fulminant hepatic failure [1, 34]. A reduction in transfer factor is related to thickening of the walls of the small veins and capillaries by a layer of collagen [34].

The pulmonary vasodilatation is associated with a low pulmonary vascular resistance which fails to respond to hypoxia or exercise. This also leads to failure of the lung to match perfusion with ventilation [31]. Even in those who retain hypoxic pulmonary vasoconstriction, the pulmonary artery pressure is low in the face of hypoxia and a raised carbon dioxide. Porto-pulmonary anastomoses have been demonstrated but are unlikely to contribute to arterial oxygen desaturation as the portal vein has a high oxygen content. Moreover, the flow from them is probably small.

The vasoactive substances that could induce pulmonary vasodilatation in cirrhosis are unknown [10]. Candidates include NO [4], endothelin-1 [21, 40] and arachidonic acid and its metabolites.

Pulmonary function in cirrhotics may be reduced by a high diaphragm (secondary to hepatomegaly or massive ascites), a pleural effusion or the chronic lung disease of the heavily smoking alcoholic.

Finger clubbing is a frequent but inconstant association. Platypnoea and orthodeoxia are usual [12].

The most profound cyanosis and clubbing are associated with chronic autoimmune hepatitis and long-standing cirrhosis.

Diagnosis demands demonstration of pulmonary vasodilatation and an increased alveolar–arterial oxygen gradient on breathing room air. Other diagnostic methods include trans-thoracic contrast-enhanced echocardiography [14] and technetium 99m (^{99m}Tc) macro-aggregated albumin lung scanning. Pulmonary angiography shows the spongy appearance of the basal pulmonary vessels which corresponds to the infiltrates seen on a chest X-ray.

Improvement in liver function is associated with both lessening of the cyanosis and of the nodularity on the chest radiograph.

No pharmacological therapy is effective.

Progressive and severe hypoxaemia may be the indication for liver transplant. This results in resolution of intra-pulmonary shunting especially the diffuse precapillary dilatations (fig. 6.7) [37]. Meta-analysis of trials in 81 patients with hepato-pulmonary syndrome showed improvement or normalization of hypoxaemia in 66 within 15 months of a successful liver transplant [13]. Post-transplant mortality was 16% and was associated with the severity of the hypoxaemia. In paediatrics, pulmonary shunting reversed within weeks of the operation [15]. Reversal is not always the case when pulmonary arteriovenous shunts are large and these may require coil embolotherapy which should precede transplant [27].

Transjugular intrahepatic portosystemic shunt (TIPS) has improved arterial oxygen saturation and has been used for successful palliation in a patient awaiting transplant [28].

Pulmonary hypertension

This affects 2% of patients with portal hypertension both intra- and extra-hepatic [7]. Histometric study of the muscular pulmonary arteries shows dilatation and thickening of the wall and, rarely, thrombi [22]. Plexogenic pulmonary arteriopathy, involving arteries 10–200 mm in diameter and once thought to be diagnostic of pulmonary hypertension, has been found at autopsy [22].

The pulmonary hypertension may be part of the general hyperdynamic circulatory state of cirrhosis (fig. 6.8).

Pulmonary hypertension should be suspected in hypoxaemic patients without pulmonary vascular dilatation. It is confirmed by echocardiography with Doppler assessment of pulmonary artery pressures [12]. If positive, measurements of the pulmonary circulation should be made by right heart catheterization.

Pulmonary hypertension is a contraindication to liver transplant, which can result in peri-operative deaths from acute right ventricular failure [2].

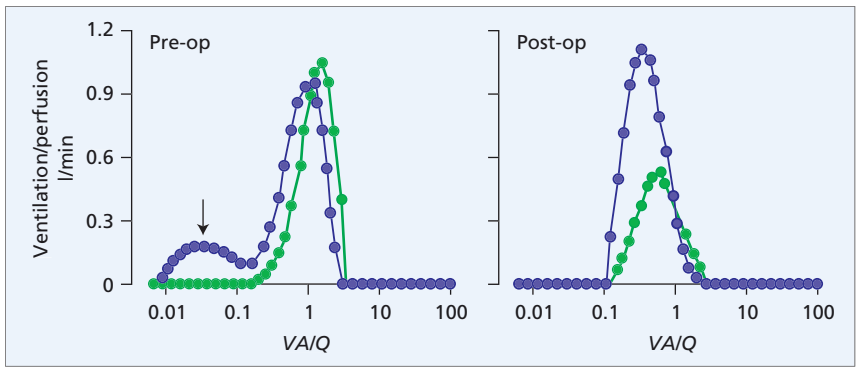


Fig. 6.7. Using the multiple inert gas elimination technique, intra-pulmonary shunting and ventilation (●)–perfusion (●) (*VA*/*Q*) mismatch (arrow) disappeared after liver transplant [5].

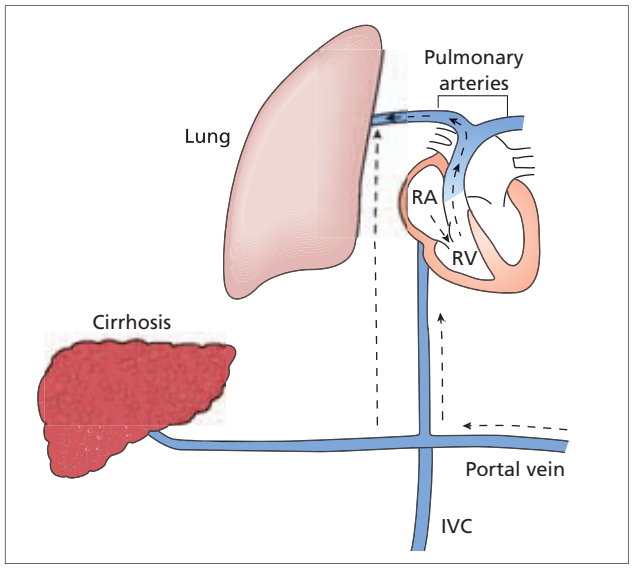


Fig. 6.8. Pulmonary hypertension in cirrhosis might be related to portal-systemic and porto-pulmonary shunting of vasoconstrictor substances. IVC, inferior vena cava; RA, right auricle; RV, right ventricle.

Pulmonary hypertention can also follow multiple tumour emboli to the pulmonary microvasculature in patients with hepato-cellular carcinoma [39].

References

1 Berthelot P, Walker JG, Sherlock S *et al*. Arterial changes in the lungs in cirrhosis of the liver—lung spider nevi. *N. Engl. J. Med*. 1966; **274**: 291.

2 Cheng EY, Woehlck HJ. Pulmonary artery hypertension complicating anaesthesia for liver transplantation. *Anaesthesiology* 1992; **77**: 389.

3 Clemens MG. Nitric oxide in liver injury. *Hepatology* 1999; **30**: 1.

4 Dinh-Xuan AT. Endothelial modulation of pulmonary vascular tone. *Eur. Resp. J*. 1992; **5**: 757.

5 Eriksson LS, Söderman C, Ericzon B-G *et al*. Normalization of ventilation/perfusion relationships after liver transplantation in patients with decompensated cirrhosis: evidence for a hepatopulmonary syndrome. *Hepatology* 1990; **12**: 1350.

6 Fleckenstein JF, Frank SM, Thuluvath PJ. Presence of autonomic neuropathy is a poor prognostic indicator in patients with advanced liver disease. *Hepatology* 1996; **23**: 471.

7 Hadengue A, Benhayoun MK, Lebrec D *et al*. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic haemodynamics. *Gastroenterology* 1991; **100**: 520.

8 Hecker R, Sherlock S. Electrolyte and circulatory changes in terminal liver failure. *Lancet* 1956; **ii**: 1121.

9 Henderson JM. Abnormal splanchnic and systemic haemodynamics of end-stage liver disease: what happens after liver transplantation? *Hepatology* 1993; **17**: 514.

10 King PD, Rumbaut R, Sanchez C. Pulmonary manifestations of chronic liver disease. *Dig. Dis*. 1996; **14**: 73.

11 Kowalski HJ, Abelman WH. The cardiac output at rest in Laennec's cirrhosis. *J. Clin. Invest*. 1953; **32**: 1025.

12 Krowka MJ, Dickson ER, Cortese DA. Hepatopulmonary syndrome: clinical observations and lack of therapeutic response to somatostatin analogue. *Chest* 1993; **104**: 515.

13 Krowka MJ, Porayka MK, Plevak DJ *et al*. Hepatopulmonary syndrome with progressive hypoxemia as an indication for liver transplantation: case reports and literature review. *Mayo Clin. Proc*. 1997; **72**: 44.

14 Krowka MJ, Tajik AJ, Dickson ER *et al*. Intrapulmonary vascular dilatations (IPVD) in liver transplant candidates. Screening by two-dimensional contrast-enhanced echocardiography. *Chest* 1990; **97**: 1165.

15 Laberge J-M, Brandt ML, Lebecque P *et al*. Reversal of cirrhosis-related pulmonary shunting in two children by orthotopic liver transplantation. *Transplantation* 1992; **53**: 1135.

16 Lee F-Y, Colombato LA, Albillos A *et al*. N-ω-nitro-L-arginine administration corrects peripheral vasodilation and systemic capillary hypotension and ameliorates plasma volume expansion and sodium retention in portal hypertensive rats. *Hepatology* 1993; **17**: 84.

17 Lin R-S, Lee F-Y, Lee S-D *et al*. Endotoxemia in patients with chronic liver disease: relationship to severity of liver diseases, presence of esophageal varices, and hyperdynamic circulation. *J. Hepatol*. 1995; **22**: 165.

18 Lopez-Talavera JC, Merrill WW, Groszmann RJ. Tumor necrosis factor alpha: a major contributor to the hyperdynamic circulation in prehepatic portal-hypertensive rats. *Gastroenterology* 1995; **108**: 761.

19 Lunzer MR, Manghani KK, Newman SP *et al*. Impaired cardiovascular responsiveness in liver disease. *Lancet* 1975; **ii**: 382.

20 Lunzer MR, Newman SP, Sherlock S. Skeletal muscle blood flow and neurovascular reactivity in liver disease. *Gut* 1973; **14**: 354.

21 Luo B, Abrams GA, Fallon MB. Endothelin-1 in the rat liver bile duct ligation model of hepato-pulmonary syndrome: correlation with pulmonary dysfunction. *J. Hepatol*. 1998; **29**: 571.

22 Matsubara O, Nakamura T, Uehara T *et al*. Histometrical investigation of the pulmonary artery in severe hepatic disease. *J. Pathol*. 1984; **143**: 31.

23 Moreau R, Lebrec D. Endogenous factors involved in the control of arterial tone in cirrhosis. *J. Hepatol*. 1995; **22**: 370.

24 Murray JF, Dawson AM, Sherlock S. Circulatory changes in chronic liver disease. *Am. J. Med*. 1958; **24**: 358.

25 Niederberger M, Gines P, Tsai P *et al*. Increased aortic cyclic guanosine monophosphate concentration in experimental cirrhosis in rats: evidence for a role of nitric oxide in the pathogenesis of arterial vasodilation in cirrhosis. *Hepatology* 1995; **21**: 1625.

26 Niederberger M, Martin PY, Gines P *et al*. Normalization of nitric oxide production corrects arterial vasodilation and hyperdynamic circulation in cirrhotic rats. *Gastroenterology* 1995; **109**: 1624.

27 Poterucha JJ, Krowka MJ, Dickson ER *et al*. Failure of hepatopulmonary syndrome to resolve after liver transplantation and successful treatment with embolotherapy. *Hepatology* 1995; **21**: 96.

28 Riegler JL, Lang KA, Johnson SP *et al*. Transjugular intrahep-

atic porto systemic shunt improves oxygenation in hepato-pulmonary syndrome. *Gastroenterology* 1998; **109**: 987.
29 Rodman T, Sobel M, Close HP. Arterial oxygen unsaturation and the ventilation perfusion defect of Laennec's cirrhosis. *N. Engl. J. Med*. 1960; **263**: 73.
30 Rodriguez-Roisin R, Agusti AGN, Roca J. The hepato-pulmonary syndrome: new name, old complexities. *Thorax* 1992; **47**: 897.
31 Ruff F, Hughes JMB, Stanley N *et al*. Regional lung function in patients with hepatic cirrhosis. *J. Clin. Invest*. 1971; **50**: 2403.
32 Sherlock S. The liver–lung interface. *Semin. Resp. Med*. 1988; **9**: 247.
33 Sherlock S. Vasodilatation associated with hepatocellular disease: relation to functional organ failure. *Gut* 1990; **31**: 365.
34 Stanley NN, Williams AJ, Dewar CA *et al*. Hypoxia and hydrothoraces in a case of liver cirrhosis: correlation of physiological, radiographic, scintigraphic and pathological findings. *Thorax* 1977; **32**: 457.
35 Stanley NN, Woodgate DJ. Mottled chest radiograph and gas transfer defect in chronic liver disease. *Thorax* 1972; **27**: 315.
36 Stark ME, Szurszewski JH. Role of nitric oxide in gastrointestinal and hepatic function and disease. *Gastroenterology* 1992; **103**: 1928.
37 Stoller JK, Moodie D, Schiavone WA *et al*. Reduction of intrapulmonary shunt and resolution of digital clubbing associated with primary biliary cirrhosis after liver transplantation. *Hepatology* 1990; **11**: 54.
38 Wernze H, Tittor W, Goerig M. Release of prostanoids into the portal and hepatic vein in patients with chronic liver disease. *Hepatology* 1986; **6**: 911.
39 Willett IR, Sutherland RC, O'Rourke MF *et al*. Pulmonary hypertension complicating hepato-cellular carcinoma. *Gastroenterology* 1984; **87**: 1180.
40 Wong J, Vanderford PA, Fineman JR *et al*. Endothelin-1 produces pulmonary vasodilation in the intact unborn lamb. *Am. J. Physiol*. 1993; **265**: H1318.

Fever and septicaemia

About one-third of patients with decompensated cirrhosis show a continuous low-grade fever which rarely exceeds 38°C. This is unaffected by antibiotics or by altering dietary protein. It seems to be related to the liver disease. Cytokines such as tumour necrosis factor may be responsible, at least in alcoholics (fig. 6.9) [8]. Cytokines released as part of the inflammatory response have undesirable effects, particularly vasodilatation, endothelial activation and multi-organ failure.

The human liver is bacteriologically sterile and the portal venous blood only rarely contains organisms. However, in the cirrhotic, bacteria, particularly intestinal, could reach the general circulation either by passing through a faulty hepatic filter or through porto-systemic collaterals [2].

Septicaemia is frequent in terminal hepato-cellular failure. Multiple factors contribute. Kupffer cell and polymorphonuclear function are impaired [3, 5]. Serum

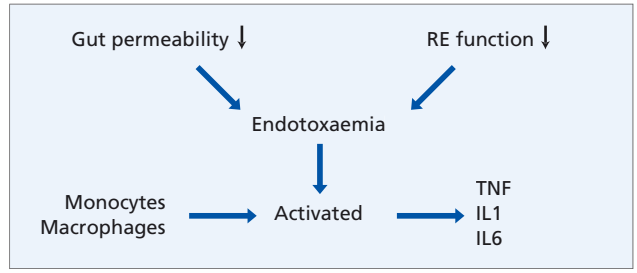


Fig. 6.9. Anorexia, fever, weight loss and a fatty liver in patients with hepato-cellular failure may be related to endotoxaemia with production of cytokines: tumour necrosis factor (TNF), interleukin-1 (IL1) and IL6. RE, reticulo-endothelial.

shows a reduction in factors such as fibronectin, opsonins and chemo-attractants, including members of the complement cascade. Systemic toxaemia of intestinal origin results in deterioration of the scavenger functions of the reticulo-endothelial system and also to renal damage (fig. 6.9) [6]. These factors contribute to blood culture positive episodes. They are particularly important in spontaneous bacterial peritonitis which affects 75% of cirrhotic patients with ascites (Chapter 9).

Urinary tract infections are particularly common in cirrhotic patients and are usually Gram-negative. Indwelling urinary catheters play a part.

Pneumonia especially affects alcoholics. Other infections include lymphangitis and endocarditis [4]. Of patients with acute liver failure, 50% show infections, often arising from soft tissues, the respiratory or urinary tract or central venous cannulas [7]. Clinical features may be atypical with inconspicuous fever, no rigors and only slight leucocytosis.

In both acute and chronic liver failure, about two-thirds of the infections are Gram-positive, often staphylococcal, and Gram-negative in one-third [1, 7]. Grade C cirrhotics are usually affected. The hospital mortality is 38%. Bad prognostic features are an absence of fever, elevated serum creatinine and marked leucocytosis [1]. Recurrent infections are ominous and sufferers should be considered for liver transplant.

Patients with liver failure should receive prophylactic antibiotics during invasive practical procedures and after gastrointestinal bleeding. Parenteral broad-spectrum antibiotics should be commenced when infection is suspected.

References

1 Barnes PF, Arevalo C, Chan LS *et al*. A prospective evaluation of bacteremic patients with chronic liver disease. *Hepatology* 1988; **8**: 1099.

2 Caroli J, Platteborse R. Septicémie porto-cave. Cirrhosis du foie et septicémie à colibacille. *Sem. Hôp. Paris* 1958; **34**: 472.
3 Imawari M, Hughes RD, Gove CD *et al*. Fibronectin and Kupffer cell function in fulminant hepatic failure. *Dig. Dis. Sci*. 1985; **30**: 1028.
4 McCashland TM, Sorrell MF, Zetterman RK. Bacterial endocarditis in patients with chronic liver disease. *Am. J. Gastroenterol*. 1994; **89**: 924.
5 Rajkovic IA, Williams R. Abnormalities of neutrophil phagocytosis, intracellular killing, and metabolic activity in alcoholic cirrhosis and hepatitis. *Hepatology* 1986; **6**: 252.
6 Rimola A, Soto R, Bory F *et al*. Reticuloendothelial system phagocytic activity in cirrhosis and its relation to bacterial infections and prognosis. *Hepatology* 1984; **4**: 53.
7 Rolando N, Harvey F, Brahm J *et al*. Prospective study of bacterial infection in acute liver failure: an analysis of 50 patients. *Hepatology* 1990; **11**: 49.
8 Yoshioka K, Kakumu S, Arao M *et al*. Tumor necrosis factor α production by peripheral blood mononuclear cells of patients with chronic liver disease. *Hepatology* 1989; **10**: 769.

Fetor hepaticus

This is a sweetish, slightly faecal smell of the breath which has been likened to that of a freshly opened corpse, or mice. It complicates severe hepato-cellular disease especially with an extensive collateral circulation. It is presumably of intestinal origin, for it becomes less intense after defaecation or when the gut flora is changed by wide-spectrum antibiotics. Methyl mercaptan has been found in the urine of a patient with hepatic coma who exhibited fetor hepaticus [1]. This substance can be exhaled in the breath and might be derived from methionine, the normal demethylating processes being inhibited by liver damage.

In patients with acute liver disease, fetor hepaticus, particularly if so extreme that it pervades the room, is a bad omen and often precedes coma. It is very frequent in patients with an extensive portal-collateral circulation, when it is not such a grave sign. Fetor may be a useful diagnostic sign in patients seen for the first time in coma.

Reference

1 Challenger F, Walshe JM. Fœtor hepaticus. *Lancet* 1995; **i**: 1239.

Changes in nitrogen metabolism

Ammonia metabolism (Chapter 7). The failing liver is unable to convert ammonia to urea.

Urea production is impaired, but the reserve powers of synthesis are so great that the blood urea concentration in hepato-cellular failure is usually normal. Low values may be found in fulminant hepatitis. Maximal rate of urea synthesis is a good measure of hepato-cellular function, but is too complicated for routine use [2].

Amino acid metabolism. An excess of amino acid in the urine is usual [3]. In both acute and chronic liver disease a common pattern of plasma amino acids is found. The aromatic amino acids, tyrosine and phenylalanine, are raised together with methionine. The concentration of the three branched-chain amino acids, valine, isoleucine and leucine, is reduced [1]. This results in a lowering of the ratio of branched-chain to aromatic amino acids and this is irrespective of the presence or absence of hepatic encephalopathy.

Serum albumin level falls in proportion to the degree of hepato-cellular failure and its duration. Protein is absorbed and retained, but is not used for serum protein manufacture. The low serum protein values may also reflect an increased plasma volume.

Plasma prothrombin falls with the serum protein levels. The consequent prolonged prothrombin time is not restored to normal by vitamin K therapy. Other proteins concerned in blood clotting may be deficient. In terminal liver failure the bleeding diathesis may be so profound that the patient is exsanguinated by such simple procedures as a paracentesis abdominis (Chapter 4).

References

1 Morgan MY, Milsom JP, Sherlock S. Plasma amino acid patterns in liver disease. *Gut* 1982; **23**: 362.
2 Rudman D, Di Fulco TJ, Galambos JT *et al*. Maximal rates of excretion and synthesis of urea in normal and cirrhotic subjects. *J. Clin. Invest*. 1973; **52**: 2241.
3 Walshe JM. Disturbances of amino-acid metabolism following liver injury. *Q. J. Med*. 1953; **22**: 483.

Skin changes

An older Miss Muffett
Decided to rough it
And lived upon whisky and gin.
Red hands and a spider
Developed outside her—
Such are the wages of sin. [1]

Vascular spiders [1, 3, 5]

Synonyms: *arterial spider, spider naevi spider telangiectasis, spider angioma*

Arterial spiders are found in the vascular territory of the superior vena cava and very rarely below a line joining the nipples. Common sites are the necklace area, the face, forearms and dorsum of the hand (fig. 6.10). They fade after death.

An arterial spider consists of a central arteriole, radiating from which are numerous small vessels resembling a spider's legs (fig. 6.11). It ranges in size from a pinhead to 0.5 cm in diameter. When sufficiently large it can be seen

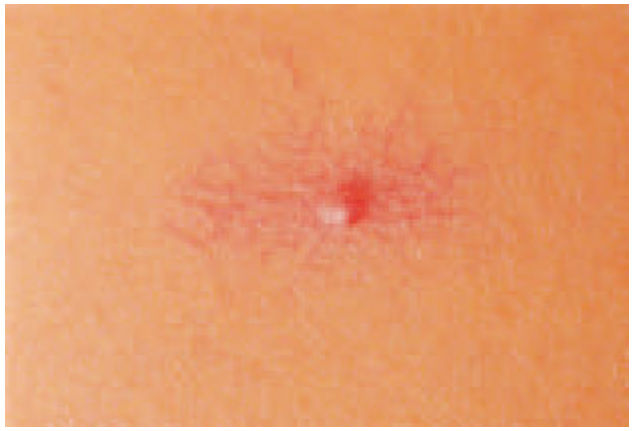


Fig. 6.10. A vascular spider. Note the elevated centre and radiating branches.

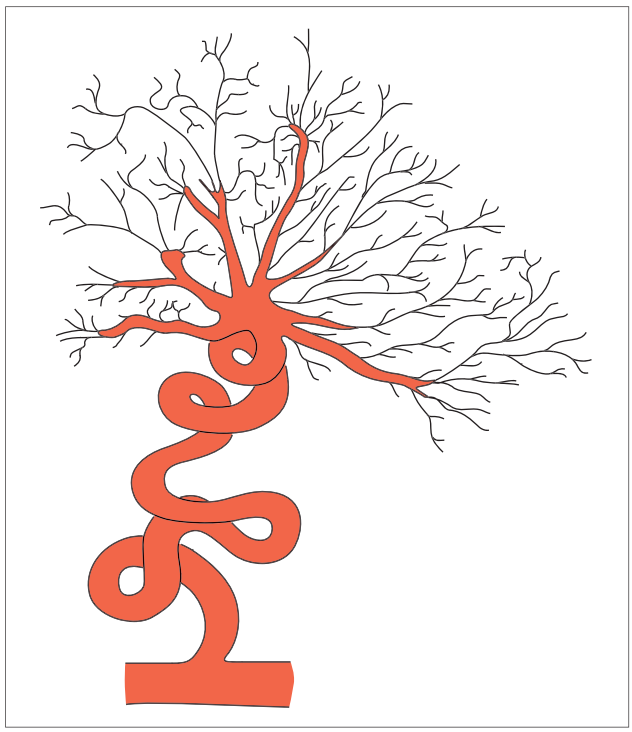


Fig. 6.11. Schematic diagram of an arterial spider [3].

or felt to pulsate, and this effect is enhanced by pressing on it with a glass slide. Pressure on the central prominence with a pinhead causes blanching of the whole lesion, as would be expected from an arterial lesion.

Arterial spiders may disappear with improving hepatic function, whereas the appearance of fresh spiders is suggestive of progression. The spider may also disappear if the blood pressure falls. Spiders can bleed profusely.

In association with vascular spiders, and having a similar distribution, numerous small vessels may be scattered in random fashion through the skin, usually on the upper arms. These resemble the silk threads in American dollar bills and the condition is called *paper money skin*.

A further association is the appearance of *white spots* on the arms and buttocks on cooling the skin [3]. Examination with a lens shows that the centre of each spot represents the beginnings of a spider.

Vascular spiders are most frequently associated with cirrhosis, especially of the alcoholic. They may appear transiently with viral hepatitis. Rarely they are found in normal persons, especially children. During pregnancy, they appear between the second and fifth months, disappearing within 2 months of delivery. A few spiders are not sufficient to diagnose liver disease, but many new ones, with increasing size of old ones, should arouse suspicion.

Differential diagnosis

Hereditary haemorrhagic telangiectasis. The lesions are usually on the upper body. Mucosal ones are common inside the nose, on the tongue, lips and palate, and in the pharynx, oesophagus and stomach. The nail beds, palmar surfaces and fingers are frequently involved. Visceral angiography usually shows lesions elsewhere.

The telangiectasis is punctiform, flat or a little elevated, with sharp margins. It is connected with a single vessel, or with several, which makes it resemble the vascular spider. Pulsation is difficult to demonstrate.

The lesion is a thinning of the telangiectatic vessel but the veins show muscular hypertrophy [4].

Telangiectasia may be associated with cirrhosis. Calcinosis, Raynaud's phenomenon, sclerodactyly and telangiectasia (*CRST syndrome*) may be found in patients with primary biliary cirrhosis.

Campbell de Morgan's spots are very common, increasing in size and number with age. They are bright red, flat or slightly elevated and occur especially on the front of the chest and the abdomen.

The venous star is found with elevation of venous pressure. It usually overlies the main tributary to a vein of large size. It is 2–3 cm in diameter and is not obliterated by pressure. Venous stars are seen on the dorsum of the foot, legs, back and on the lower border of the ribs.

Palmar erythema (liver palms)

The hands are warm and the palms bright red in colour, especially the hypothenar and thenar eminences and pulps of the fingers (fig. 6.12). Islets of erythema may be found at the bases of the fingers. The soles of the feet may be similarly affected. The mottling blanches on pressure and the colour rapidly returns. When a glass slide is pressed on the palm it flushes synchronously with the

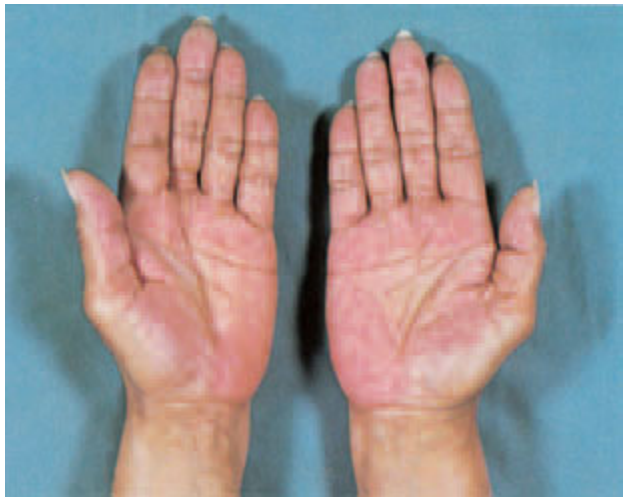


Fig. 6.12. Palmar erythema ('liver palms') in a patient with hepatic cirrhosis.

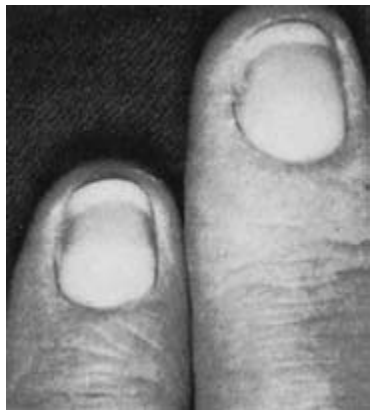


Fig. 6.13. White nails in a patient with hepatic cirrhosis.

pulse rate. The patient may complain of throbbing, tingling palms.

Palmar erythema is not so frequently seen in cirrhosis as are vascular spiders. Although both may be present, they may appear independently, making it difficult to define a common aetiology.

Many normal people have *familial* palmar flushing, unassociated with liver disease. A similar appearance may be seen in prolonged rheumatoid arthritis, in pregnancy, with chronic febrile diseases, leukaemia and thyrotoxicosis.

White nails

White nails, due to opacity of the nail bed, were found in 82 of 100 patients with cirrhosis and occasionally in certain other conditions (fig. 6.13) [2]. A pink zone is seen at the tip of the nail and in a severe example the lunula cannot be distinguished. The lesions are bilateral, with the thumb and index finger being especially involved.

Mechanism of skin changes

The selective distribution of vascular spiders is not understood. Exposure of upper parts of the body to the elements may damage the skin so that it becomes susceptible to the development of spiders when the appropriate internal stimulus exists. Children may develop spiders on the knees and one nudist with cirrhosis was said to be covered with vascular spiders. The number of spiders does not correlate with the hyperdynamic circulation, although when the cardiac output is very high the spiders pulsate particularly vigorously.

The vascular spiders and palmar erythema have been traditionally attributed to oestrogen excess. They are also seen in pregnancy when circulating oestrogens are increased. Oestrogens have an enlarging, dilating effect on the spiral arterioles of the endometrium, and such a mechanism may explain the closely similar cutaneous spiders [1]. Oestrogens have induced cutaneous spiders in men [1], although this is not usual when such therapy is given for prostatic carcinoma. The liver certainly inactivates oestrogens, although oestradiol levels in cirrhosis are often normal. The ratio between oestrogens and androgens may be more important. In male cirrhotics, although the serum oestradiol was normal, free serum testosterone was reduced. The oestradiol/free testosterone ratio was highest in male cirrhotics with spiders [5].

The aetiology of the other skin lesions remains unknown.

References

1 Bean WB. *Vascular Spiders and Related Lesions of the Skin*. Blackwell Scientific Publications, Oxford, 1959.
2 Lloyd CW, Williams RH. Endocrine changes associated with Laennec's cirrhosis of the liver. *Am. J. Med*. 1948; **4**: 315.
3 Martini GA. Über Gefässveränderungen der Haut bei Leberkranken. *Z. Klin. Med*. 1955; **150**: 470.
4 Martini GA, Straubesand J. Zur Morphologie der Gefässpinnen ('vascular spiders') in der Haut Leberkranker. *Virchows Arch*. 1953; **324**: 147.
5 Pirovino M, Linder R, Boss C *et al*. Cutaneous spider nevi in liver cirrhosis: capillary microscopical and hormonal investigations. *Klin. Wochenschr*. 1988; **66**: 298.

Endocrine changes

Endocrine changes may be found in association with cirrhosis. They are more common in cirrhosis of the alcoholic and if the patient is in the active, reproductive phase of life. In the male, the changes are towards feminization. In the female, the changes are less and are towards gonadal atrophy.

Hypogonadism

Diminished libido and potency are frequent in men with active cirrhosis and a large number are sterile. The impotence and its severity are greater if the cirrhotic patient is alcoholic [7]. Patients with well-compensated disease may have large families.

The testes are soft and small. Seminal fluid is abnormal in some cases. Secondary sexual hair is lost and men shave less often. Prostatic hypertrophy has a lower incidence in men with cirrhosis [5].

Other signs include female body habitus and a female escutcheon. Gynaecomastia is particularly common in alcoholics.

The female has ovulatory failure. The pre-menopausal patient loses feminine characteristics, particularly breast and pelvic fat. She is usually infertile; menstruation is erratic, diminished or absent, but rarely excessive. Any breast or uterine atrophy is of little significance in the post-menopausal woman.

In women with non-alcoholic liver disease, sexual behaviour, desire, frequency and performance are not impaired [1].

Gynaecomastia, sometimes unilateral, is rare, and the incidence in cirrhotics may not differ from that of controls [6] (fig. 6.14). Total oestrogen/free testosterone and oestradial/free testosterone ratios are higher in cirrhotic patients, but cannot be correlated with the presence of gynaecomastia.

The breasts may be tender. Enlargement is caused by hyperplasia of the glandular elements [5]. Young men with chronic autoimmune hepatitis may develop gynaecomastia but alcoholic liver disease is the commonest association.

Spironolactone therapy is the commonest cause of gynaecomastia in cirrhotic patients. This decreases serum testosterone levels and reduces hepatic androgen-receptor activity [10].

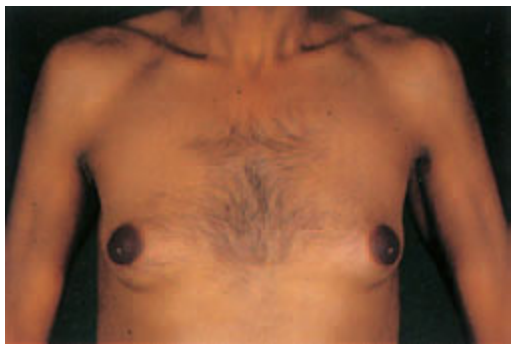


Fig. 6.14. Gynaecomastia in a patient with cirrhosis.

Relation to alcohol

It is difficult to disentangle the hypothalamic–pituitary–gonadal dysfunction in patients with chronic liver disease from the aetiology of the liver disease and particularly from the effects of alcohol.

Feminization is more frequent with alcoholic cirrhosis than with other types. Acute administration of alcohol to normal men increases the hepatic metabolism of testosterone.

The hepatic uptake of sex steroids depends on liver function. Chronic administration of alcohol raises sex hormone binding globulin (SHBG) so reducing the free fraction of plasma testosterone and the amount presented to the liver [11]. However, low dehydroepiandrosterone with raised oestradiol and androstenedione are found in patients with non-alcoholic liver disease [3]. The direct effect of alcohol on the testes may add to the general effects of liver disease. Acutely, alcohol also raises plasma gonadotrophins. Impotence is greater if the cirrhotic patient is alcoholic [7].

Mechanism

The three principal unconjugated oestrogens (oestrone, oestradiol and oestriol) are found in the plasma of normal men. They are produced by the testes and adrenals and also from peripheral conversion of the major circulating androgens. Oestradiol is the most biologically potent oestrogen. It is bound to SHBG and to albumin. The biologically active unbound form is marginally raised in patients with cirrhosis and the total only minimally increased. The changes in plasma oestrogens are insufficient to account for the degree of feminization.

The human liver has both androgen and oestrogen receptors which render it sensitive to androgens and oestrogens [9, 15]. Reduced oestrogen receptor concentrations in patients with chronic liver disease reflect the degree of liver dysfunction and not the specific type of liver disease [4]. In cirrhosis, the end organ sensitivities to sex hormones may be changed. Hepatic androgen receptors fall and hepatic oestrogen receptor concentrations increase [15].

Feminization may be related to hepatic regeneration [16]. Partial hepatic resection or liver transplantation are associated with increases in serum oestrogens and reductions in testosterone, while oestrogen receptors increase [13].

Primary liver cancer occasionally presents with feminization [14]. Serum oestrone levels are high and can return to normal when the tumour is removed. The tumour can be shown to function as trophoblastic tissue.

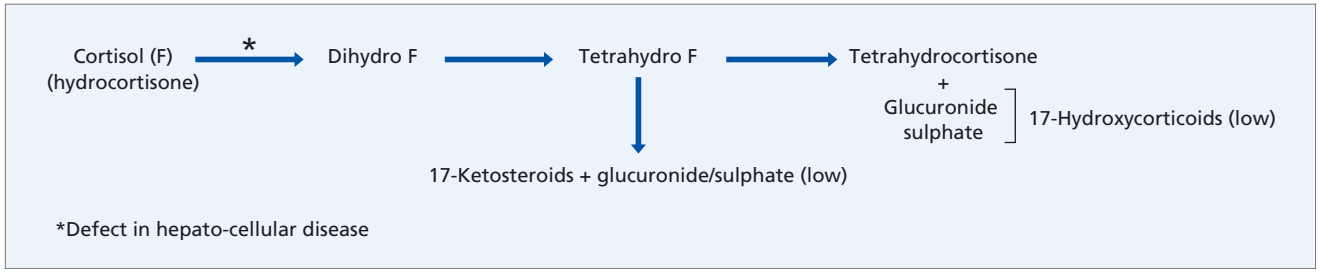


Fig. 6.15. The metabolism of cortisol by the liver. In hepato-cellular disease there is difficulty in reducing the 4–3 ketonic group but not in conjugation. Urinary 17-ketosteroids and 17-hydroxycorticoids are therefore reduced.

Hypothalamic–pituitary function

Plasma gonadotrophins are usually normal although a minority of cirrhotic patients have high values. These normal levels, in spite of testicular failure, suggest either a primary testicular defect or a failure of the pituitary–hypothalamus. Impaired release of luteinizing hormone suggests a possible hypothalamic defect, at least in those with alcoholic liver disease [2].

Hypothalamic–pituitary dysfunction in some women with non-alcoholic liver disease may lead to amenorrhoea and oestrogen deficiency and also to osteoporosis [8].

Metabolism of hormones [12]

A reduced rate of hormonal metabolism might be related to a decrease in hepatic blood flow, to shunting of blood through or around the liver or to an increase in SHBG which would reduce the free diffusible fraction of circulating hormone [11].

Steroid hormones are conjugated in the liver. Derivatives of oestrogens, cortisol and testosterone are conjugated as a glucuronide or sulphate and so excreted in the bile or urine. There seems to be little difficulty in the process even in the presence of hepato-cellular disease. The conjugated hormones excreted in the bile undergo an entero-hepatic circulation. In cholestasis the biliary excretion of oestrogens, and especially of polar conjugates, is greatly reduced. There are changes in the urinary pattern of excretion. Any failure of hormone metabolism results in a rise in blood hormone levels. This alters the normal homeostatic balance between secretion rates of hormones and their utilization. These feedback mechanisms between plasma hormone levels and hormone secretion prevent any but temporary rises in circulating levels. This may explain some of the difficulty in relating plasma hormone levels to clinical features.

Testosterone is converted to a more potent metabolite —dihydrotestosterone. It is degraded in the liver and conjugated for urinary excretion as 17-oxysteroids.

Oestrogens are metabolized and conjugated for excretion in urine or bile.

Cortisol is degraded primarily in the liver by a ring reduction to tetrahydrocortisone and subsequently conjugated with glucuronic acid (fig. 6.15).

Prednisone is converted to prednisolone.

References

1 Bach N, Schaffner F, Kapelman B. Sexual behaviour in women with nonalcoholic liver disease. *Hepatology* 1989; **9**: 698.

2 Bannister P, Handley T, Chapman C *et al*. Hypogonadism in chronic liver disease: impaired release of luteinizing hormone. *Br. Med. J*. 1986; **293**: 1191.

3 Bannister P, Oakes J, Sheridan P *et al*. Sex hormone changes in chronic liver disease: a matched study of alcoholic vs. nonalcoholic liver disease. *Q. J. Med*. 1987; **63**: 305.

4 Becker U, Andersen J, Poulsen HS *et al*. Variation in hepatic oestrogen receptor concentrations in patients with liver disease. A multivariate analysis. *Scand. J. Gastroenterol*. 1992; **27**: 355.

5 Bennett HS, Baggenstoss AH, Butt HR. The testis, breast and prostate of men who die of cirrhosis of the liver. *Am. J. Clin. Pathol*. 1950; **20**: 814.

6 Cavanaugh J, Niewoehner CB, Nuttall FQ. Gynecomastia and cirrhosis of the liver. *Arch. Intern. Med*. 1990; **150**: 563.

7 Cornely CM, Schade RR, Van Thiel DH *et al*. Chronic advanced liver disease and impotence: cause and effect? *Hepatology* 1984; **4**: 1227.

8 Cundy TF, Butler J, Pope RM *et al*. Amenorrhoea in women with nonalcoholic chronic liver disease. *Gut* 1991; **32**: 202.

9 Eagon PK, Elm MS, Stafford EA *et al*. Androgen receptor in human liver: characterization and quantification in normal and diseased liver. *Hepatology* 1994; **19**: 92.

10 Francavilla A, Di Leo A, Eagon PK *et al*. Effect of spironolactone and potassium canrenoate on cytosolic and nuclear androgen and oestrogen receptors of rat liver. *Gastroenterology* 1987; **93**: 681.

11 Guechot J, Vaubourdolle M, Ballet F *et al*. Hepatic uptake of sex steroids in men with alcoholic cirrhosis. *Gastroenterology* 1987; **92**: 203.

12 Johnson PJ. Sex hormones and the liver. *Clin. Sci*. 1984; **66**: 369.

13 Kahn D, Makowka L, Zeng P *et al*. Estrogen and androgen

receptors in the liver after orthotopic liver transplantation. *Transplant Proc*. 1989; **21**: 409.
14 Kew MC, Kirschner MA, Abrahams GE *et al*. Mechanism of feminization in primary liver cancer. *N. Engl. J. Med*. 1977; **296**: 1084.
15 Porter LE, Elm MS, Van Thiel DH *et al*. Hepatic oestrogen receptor in human liver disease. *Gastroenterology* 1987; **92**: 735.
16 Van Thiel DH, Stauber RE, Gavaler JS *et al*. Evidence for modulation of hepatic mass by oestrogens and hepatic 'feminization'. *Hepatology* 1990; **12**: 547.

General treatment

Results are at the same time depressing and encouraging. Once the liver is disorganized, as in cirrhosis, it will never regain normal structure. Much can be achieved by symptomatic measures. The liver cells retain such an enormous regenerative capacity that, even though liver structure may not return to normal, functional compensation may be achieved.

Precipitating factors

Any factor depressing hepato-cellular function may throw the patient with hitherto compensated liver disease into failure. Gastrointestinal haemorrhage or the fall in blood pressure following surgical operation may necessitate blood transfusion. An acute infection must be treated. If failure has followed an alcoholic episode, the patient is denied alcohol. Electrolyte disturbances, whether diuretic-induced or due to some other factor such as vomiting or diarrhoea, must be corrected.

General measures

Bed rest reduces the functional demands on the liver. In the acute case, it is advisable; in the subacute and chronic case, bed rest is continued while improvement is maintained. If, after 4 weeks of bed rest, the condition remains static, the patient should be allowed moderate activity.

Diet. A high-protein diet may be of particular value in the alcoholic. In most cirrhotic patients 80–100 g protein and 2500 calories suffice. Fat need not be restricted within the calorie total. Folic acid may be deficient. Meals must be attractively presented—the patient with hepato-cellular failure has a fickle appetite, but if he can be persuaded to eat well clinical improvement will follow.

Diet is more important in the alcoholic who has been depriving himself of food than in the non-alcoholic who has usually been eating well.

Dietary supplements. Methionine, choline and amino acid supplements do not increase the rate of recovery. Very high methionine and cystine levels are found in the plasma in severe hepatitis and cirrhosis. There is no deficiency but rather difficulty in utilization.

Alcohol. Patients with acute hepato-cellular failure should abstain from all alcohol for between 6 months and 1 year after recovery. If alcoholism can be incriminated the patient should, if possible, become a total and life-long abstainer. If the chronic liver disease is non-alcoholic, one glass of wine or beer daily will not be harmful.

Anaemia. The haemoglobin level must be kept above 10 g/100 ml. The anaemia may remit only when liver function improves.

Corticoid hormones. Prednisolone and adrenocorticotrophic hormone (ACTH) do not affect the basic cirrhotic process. They have complications including an increased risk of serious infection.

Sex hormones. Hormone therapy to impotent men suffering from alcoholic cirrhosis may lead to the plasma hormone levels returning to normal but normal sexual potency is not restored. Cessation of alcohol and attention to social problems are more important than hormone therapy.

Oral testosterone has no beneficial effect in alcoholic cirrhosis other than to cause a slight decrease in gynaecomastia [1]. Mortality is increased.

Sedatives (Chapter 7). Morphine is very likely to precipitate coma.

Barbiturates vary in their mode of excretion. The long-acting, short-chain barbiturates such as barbitone or phenobarbitone are excreted largely by the kidney and small doses are reasonably well tolerated by the patient with cirrhosis. The short-acting, long-chain barbiturates such as pentobarbitone and the thiobarbitones such as pentothal are metabolized largely by the liver and should be avoided. If a barbiturate is used, the initial dose must be small.

Chlordiazepoxide (Librium) may lead to oversedation in patients with liver disease [2]. The disposition of oxazepam is normal and this may be the drug of choice in cirrhosis [3].

References

1 Copenhagen Study Group for Liver Diseases. Testosterone treatment of men with alcoholic cirrhosis: a double blind study. *Hepatology* 1986; **6**: 807.
2 Roberts RK, Wilkinson GR, Branch RA *et al*. Effect of age and parenchymal liver disease on the disposition and elimination of chlordiazepoxide (Librium). *Gastroenterology* 1978; **75**: 479.
3 Shull HJ, Wilkinson GR, Johnson R *et al*. Normal disposition of oxazepam in acute viral hepatitis and cirrhosis. *Ann. Intern. Med*. 1976; **84**: 420.

Chapter 7
Hepatic Encephalopathy

Hepatic encephalopathy is a reversible neuropsychiatric state that complicates liver disease. The pathogenetic mechanism is not fully understood. Studies show derangement of several neurotransmitter systems. The changes are complex and no one defect provides a unifying explanation. The brain is exposed to increased levels of ammonia, neurotransmitters and their precursors because of failed hepatic clearance or the abnormal peripheral metabolism of the cirrhotic.

A spectrum of syndromes exists (table 7.1). In acute (fulminant) hepatic failure, encephalopathy accompanies the features of a virtual hepatectomy (Chapter 8). The encephalopathy of cirrhosis has portal-systemic shunting as a component but hepato-cellular dysfunction is also important; various precipitating factors play a part. Chronic neuropsychiatric states exist, usually in those with chronic portal-systemic shunting, and may be associated with irreversible brain damage. In these cases the hepato-cellular disease is relatively mild.

The different syndromes of hepatic encephalopathy also probably reflect the amount and range of 'toxic' metabolites/transmitters produced. The coma of acute liver failure, often with manic features and cerebral oedema, contrasts with the hypomanic lethargic picture of chronic encephalopathy.

Historical perspective

The relationship of the liver to mental function has been recognized from earliest times. The Babylonians (*c.* 2000 BC) attributed powers of augury and divination to the liver, designating it by the term also used for 'soul' or 'mood'. In the medicine of ancient China (Neiching 1000 BC) the liver was regarded as the storer of blood containing the soul. Hippocrates (460–370 BC) described a patient with hepatitis who 'barked like a dog, could not be held and said things which could not be comprehended'. Frerichs, the father of modern hepatology, described the terminal mental changes in patients with liver disease [21].

> Cases have occurred to me in which individuals who for a long period have suffered from cirrhosis of the liver have suddenly presented a series of morbid symptoms which are foreign to that disease. They have become unconscious, and have been afterwards seized with noisy delirium, from which they passed into deep coma and in this state have died.

It is now recognized that a neuropsychiatric syndrome of the same basic pattern may complicate liver disease of almost all types. It can culminate in coma and death.

Clinical features

The picture is complex and affects all parts of the brain. There are neurological and psychiatric components. Variability between patients is a marked feature. The diagnosis may be easy—for example in the known cirrhotic admitted with gastrointestinal haemorrhage or sepsis, who is confused and on examination has a 'flapping' tremor. Without the clinical background data and obvious precipitating event, however, the slide into early hepatic encephalopathy may go unrecognized unless subtle changes of the syndrome are appreciated. A history obtained from a family member who has noticed a change may be valuable.

However, in cirrhotics with neuropsychiatric deterio-

Table 7.1. Types of hepatic encephalopathy

Type of encephalopathy	% Survival	Aetiological factors
Acute liver failure	20*	Viral hepatitis Alcoholic hepatitis Drug reactions and overdose
Cirrhosis with precipitant	70–80	Diuresis Haemorrhage Paracentesis Diarrhoea and vomiting Surgery Alcoholic excess Sedatives Infections Constipation
Chronic portal-systemic encephalopathy	100	Portal-systemic shunting Dietary protein intake Intestinal bacteria

*Without transplantation.

ration, particularly when sudden, the clinician should be on guard for the occasional patient with intracranial haemorrhage, trauma, infection or tumour with the associated neurological signs, as well as a drug-induced or other metabolic cause.

With hepatic encephalopathy, differences in clinical history and examination are usual, particularly in the more chronic cases. The picture depends on the nature and severity of aetiological and precipitating factors. Children may show a particularly acute reaction, often with mania.

For descriptive purposes, features of encephalopathy can be separated into changes in consciousness, personality, intellect and speech.

Disturbed consciousness with disorder of sleep is usual. Hypersomnia appears early and progresses to reversal of the normal sleep pattern. Reduction of spontaneous movement, a fixed stare, apathy, and slowness and brevity of response are early signs. Further deterioration results in reaction only to intense or noxious stimuli. Coma at first resembles normal sleep, but progresses to complete unresponsiveness. Deterioration may be arrested at any level. Rapid changes in the level of consciousness are accompanied by delirium.

Personality changes are most conspicuous with chronic liver disease. These include childishness, irritability and loss of concern for family. Even in remission the patient may present similar personality features suggesting frontal lobe involvement. They are usually co-operative, pleasant people with an ease in social relationships and frequently a jocular, euphoric mood.

Intellectual deterioration varies from slight impairment of organic mental function to gross confusion. Isolated abnormalities appearing in a setting of clear consciousness relate to disturbances in visual spatial gnosis. These are most easily elicited as constructional apraxia, shown by an inability to reproduce simple designs with blocks or matches (fig. 7.1). Number connection tests (fig. 7.2) may be used serially to assess progress but to be most informative should be compared with normal values for the same age group [66, 86].

Writing is oblivious of ruled lines and a daily writing chart is a good check of progress (fig. 7.1). Failure to distinguish objects of similar size, shape, function and position may lead to symptoms such as micturating and defaecating in inappropriate places. Insight into such anomalies of behaviour is frequently preserved.

Speech is slow and slurred and the voice is monotonous. In deep stupor, dysphasia becomes marked and is always combined with perseveration.

Some patients have *fetor hepaticus*. This is a sour, faecal smell in the breath, due to volatile substances normally formed in the stool by bacteria. These mercaptans if not removed by the liver are excreted through the lungs and appear in the breath. Fetor hepaticus does not correlate with the degree or duration of encephalopathy and its absence does not exclude hepatic encephalopathy.

The most characteristic neurological abnormality is the 'flapping' tremor (*asterixis*). This is due to impaired inflow of joint and other afferent information to the brainstem reticular formation resulting in lapses in posture. It is demonstrated with the patient's arms outstretched and fingers separated or by hyperextending the wrists with the forearm fixed (fig. 7.3). The rapid flexion–extension movements at the metacarpophalangeal and wrist joints are often accompanied by lateral movements of the digits. Sometimes arms, neck, jaw, protruded tongue, retracted mouth and tightly closed eyelids are involved and the gait is ataxic. Absent at rest, less marked on movement and maximum on sustained

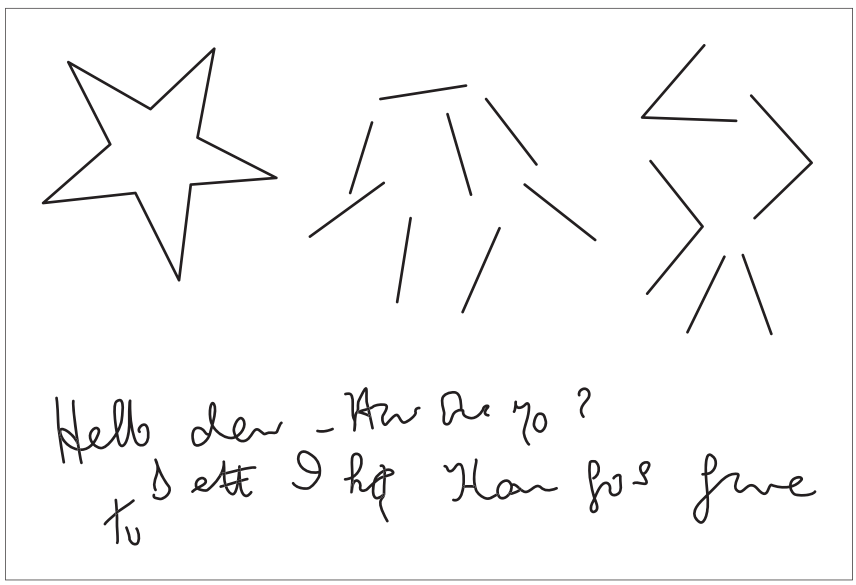


Fig. 7.1. Focal disorders in chronic portal-systemic encephalopathy elicited in patients with full consciousness and minimal intellectual defect, in the absence of gross tremor or visual disorder. Above: constructional apraxia. Below: writing difficulty. 'Hello dear. How are you? Better I hope. That goes for me too'.

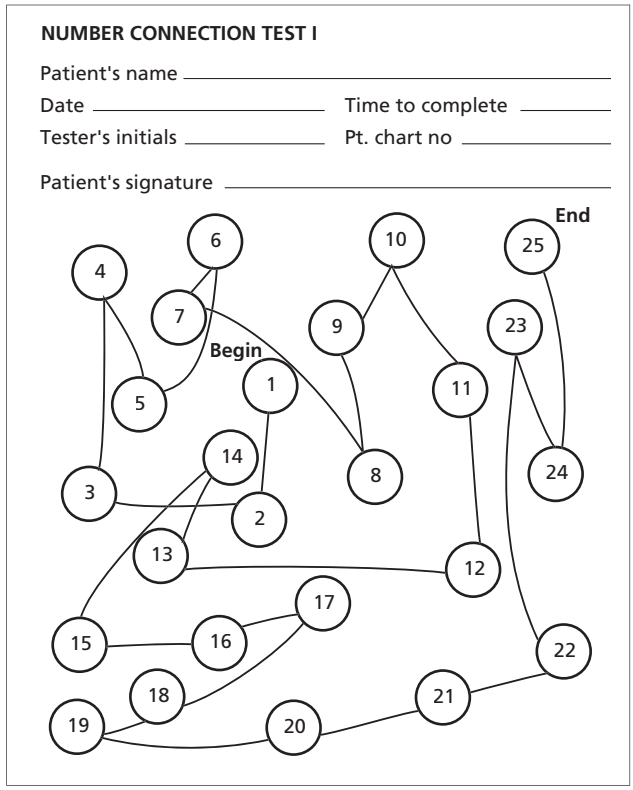


Fig. 7.2. The Reitan number connection test.

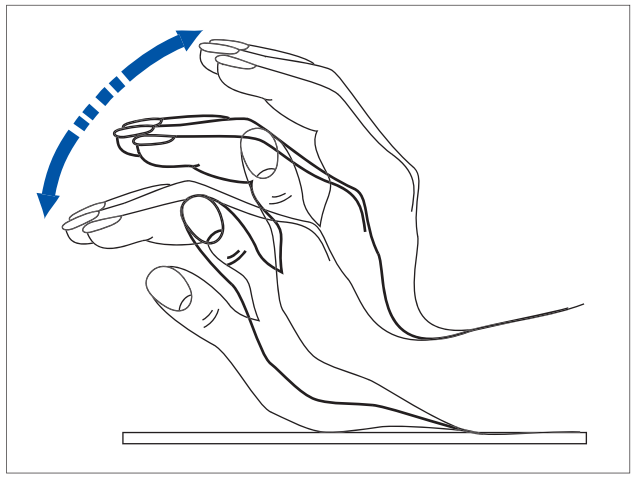


Fig. 7.3. 'Flapping' tremor elicited by attempted dorsiflexion of the wrist with the forearm fixed.

posture, the tremor is usually bilateral, although not bilaterally synchronous, and one side may be affected more than the other. It may be appreciated by gentle elevation of a limb or by the patient gripping the doctor's hand. In coma the tremor disappears. A 'flapping' tremor is not specific for hepatic pre-coma. It can also be observed in uraemia, in respiratory failure and in severe heart failure.

Table 7.2. The clinical grades of hepatic encephalopathy

I	Mild confusion, euphoria, anxiety or depression Shortened attention span Slowing of ability to perform mental tasks (addition/subtraction) Reversal of sleep rhythm
II	Drowsiness, lethargy, gross deficits in ability to perform mental tasks Obvious personality changes Inappropriate behaviour Intermittent disorientation of time (and place) Lack of sphincter control
III	Somnolent but rousable Persistent disorientation of time and place Pronounced confusion Unable to perform mental tasks
IV	Coma with (IVa) or without (IVb) response to painful stimuli

Deep tendon reflexes are usually exaggerated. Increased muscle tone is present at some stage and sustained ankle clonus is often associated with rigidity. During coma patients become flaccid and lose their reflexes.

The plantar responses are usually flexor becoming extensor in deep stupor or coma. Hyperventilation and hyperpyrexia may be terminal. The diffuse nature of the cerebral disturbance is further shown by excessive appetite, muscle twitchings, grasping and sucking reflexes. Disorders of vision include reversible cortical blindness [45].

The clinical course fluctuates, and frequent observation of the patient is necessary. Clinical grading should be used as a part of the clinical record of neuropsychiatric signs (table 7.2).

Investigations

Cerebrospinal fluid

This is usually clear and under normal pressure. Patients in hepatic coma may show an increased CSF protein concentration, but the cell count is normal. Glutamic acid and also glutamine may be increased.

Electroencephalogram

There is a bilateral synchronous slowing of the wave frequency (with an increase in wave amplitude) from the normal α-rhythm of 8–13 cycles per second (Hz) down to the δ range of below 4 cycles per second (fig. 7.4). This is best graded using frequency analysis. Alerting stimuli, such as opening the eyes, fail to reduce the background rhythmic activity. The change starts in the frontal or central region and progresses posteriorly.

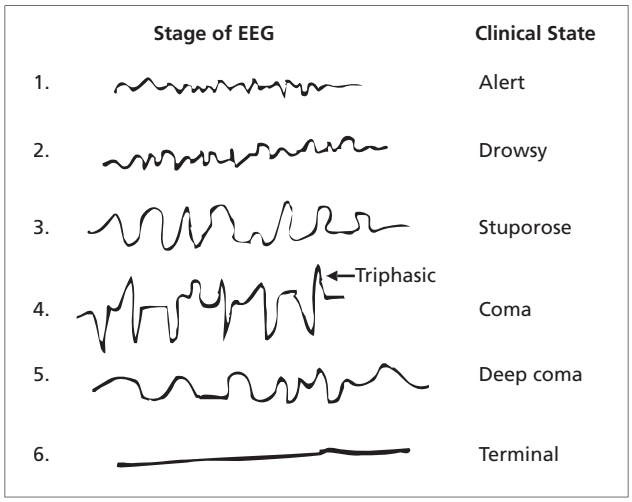


Fig. 7.4. Changes in EEG during phases of encephalopathy. There is a slowing in frequency with increasing amplitude until in stage 4 triphasic waves appear. The amplitude then decreases. Finally there is absence of rhythmic activity.

This technique is useful for diagnosis and to assess treatment.

In very chronic cases with permanent neuronal damage, the tracing may be slow or rapid and flat. Such changes may be 'fixed' and unaltered by diet.

EEG changes occur very early even before psychological or biochemical disturbances. They are non-specific, being found also in conditions such as uraemia, CO_2 retention, vitamin B_{12} deficiency or hypoglycaemia. These changes, however, in a conscious patient with liver disease are virtually diagnostic.

Evoked potentials

These are electrical potentials from the subcortical and cortical neurons triggered by visual or auditory stimuli, or stimulation of somatosensory nerves. They test the conduction and function of afferent pathways between the stimulated peripheral tissue and the cortex. Abnormalities of visual (VEPs), brainstem auditory (BAEPs) and somatosensory (SEPs) evoked potentials have been found in clinical and subclinical encephalopathy. They remain a research rather than clinical tool. Because the sensitivity has varied from one study to another, VEPs and BAEPs have little place in the evaluation of subclinical encephalopathy particularly compared with psychometric testing. SEPs are more sensitive than psychometric tests in the assessment of subclinical encephalopathy [88].

A newer method recording event-related *endogenous* potentials is under study. The patient's co-operation is needed, limiting it to encephalopathy grade 0–2. Such visual P300 potentials have been found to be more sensitive than psychometric tests in cirrhotics with subclinical encephalopathy [38].

Brain scans

CT and MRI show cerebral atrophy even with apparently well-compensated cirrhosis and results are related to the severity of the liver dysfunction. Atrophy is particularly marked in those with chronic persistent encephalopathy and may be potentiated by alcoholism [79]. The CT scan can be quantified to show cerebral oedema and cortical atrophy even in those with subclinical portal-systemic encephalopathy [9].

In cirrhotic patients there is increased signal in the basal ganglia on T_1-weighted MRI images, thought to be due to the deposition of manganese [64]. This finding is not directly related to hepatic encephalopathy, occurring in patients with complete portal vein thrombosis, cavernomatous transformation and no evidence of liver disease, suggesting a relationship to shunting rather than disturbed liver function or encephalopathy [58, 69].

Magnetic resonance spectroscopy

This approach has been used to study cerebral intracellular metabolism in patients and experimental models with hepatic encephalopathy [48, 74, 78]. Changes in intra-cellular glutamine have been demonstrated. Preliminary studies of the changes that occur during treatment of human hepatic encephalopathy may provide an approach to dissect the pathogenetic mechanisms [25].

Neuropathological changes

Grossly the brain may be normal, but cerebral oedema (see fig. 8.3) is seen in about half of the patients, particularly the younger cases dying with prolonged deep coma.

Microscopically, the characteristic changes in patients with cirrhosis who die in hepatic coma are in astrocytes rather than neurons. The astrocytes proliferate and develop enlarged nuclei, prominent nucleoli, margination of chromatin and accumulation of glycogen—changes referred to as Alzheimer type 2 astrocytosis. These changes are found particularly in the cerebral cortex and basal ganglia and are related to hyperammonaemia. Neurons show minor alterations. Early astrocyte changes are probably reversible.

In very long-standing cases, the structural changes may be irreversible and the patient unresponsive to treatment (chronic hepato-cerebral degeneration). Apart from the astrocytic changes there is cortical thinning with loss of neurons in cortex, basal ganglia and cerebellum.

Demyelination in the pyramidal tracts is associated with spastic paraplegia.

Blood–brain barrier

In experimental acute liver failure some studies show a change in the blood–brain barrier [89] while others do not [42]. In patients with severe liver disease and minimal encephalopathy an increased permeability–surface area product for ammonia has been described [43]. There are difficulties in equating animal models with humans, also whether these are early primary changes or later secondary effects, or related to liver failure rather than encephalopathy. Most clinical data do not suggest early changes in the blood–brain barrier.

Clinical variants in cirrhotics

Subclinical

Clinically inapparent impairment in mental functions, sufficient to cause disruption in the routine of everyday living, is frequent in patients with cirrhosis. Between 15 and 60% of patients with cirrhosis, and seemingly normal neurological and mental status, fail psychometric tests, impairment of performance being more marked than for verbal skills [18, 22]. The prevalence depends on the Child–Pugh score and the methodology used.

This mild form of hepatic encephalopathy is identified by psychometric testing and/or electroencephalography (EEG) and has been called *subclinical encephalopathy*. However, more critical analysis of *quality of life* in these patients shows significant differences compared with those without any evidence of hepatic encephalopathy [23, 24]. Multivariate analysis shows that male sex, the Child–Pugh score (B/C) and the presence of varices, together with five statements from the Sickness Impact Profile (SIP) identify patients at risk [23]. The five SIP statements found to have independent predictive value for subclinical hepatic encephalopathy are [23]:

- I spend much of the day lying down in order to rest (statement of highest value).
- I am confused and start several actions at a time.
- I forget a lot, e.g. things that happened recently, where I put things, appointments.
- I have difficulty doing handwork, for example, turning faucets, using kitchen gadgets, sewing, carpentry.
- I am not working at all.

Regular employment is less frequent in cirrhotics with mild encephalopathy (50% compared to 85% in those without impairment). Cirrhotic patients with subclinical encephalopathy have a significantly lower 1-year survival compared with those without this finding [2]. Treatment with lactulose is beneficial [30, 83]. It is therefore important to consider the possibility of unrecognized mild hepatic encephalopathy in patients with cirrhosis since the impact on quality of life may be substantial.

Acute type

The syndrome may appear spontaneously, without a precipitant, usually in a deeply jaundiced patient with ascites and in the terminal stages. Most cases are related to a precipitating factor (table 7.3). These act by depressing liver cell or cerebral function, increasing nitrogenous material in the intestine, or raising the portal–collateral flow.

A brisk response to a potent *diuretic* may be responsible. Large *paracenteses* may also precipitate coma; the mechanism is uncertain. Electrolyte imbalance following removal of large quantities of electrolytes and water, changes in hepatic circulation and hypotension may contribute. Other causes of fluid and electrolyte depletion, such as *diarrhoea* or *vomiting*, may be precipitants.

Gastrointestinal haemorrhage, usually from oesophageal varices, is a common precipitating cause. Coma results from the large protein meal (as blood) in addition to depression of hepato-cellular function due to anaemia and reduction in liver blood flow.

Surgical procedures are tolerated extremely poorly. Hepatic function is depressed by the blood loss, anaesthesia and 'shock'.

Acute alcoholism precipitates coma both by depressing cerebral function and by the associated acute alco-

Table 7.3. Precipitants of acute hepatic encephalopathy in the cirrhotic patient

Electrolyte imbalance
Diuretics
Vomiting
Diarrhoea
Bleeding
Oesophageal and gastric varices
Gastro-duodenal erosions
Mallory–Weiss tear
Drugs
Alcohol withdrawal
Infection
Spontaneous bacterial peritonitis
Urinary
Chest
Constipation
Large protein meal

holic hepatitis. *Opiates*, *benzodiazepines* and *barbiturates* depress cerebral function and have a prolonged action when hepatic detoxication is delayed.

Infections, especially with bacteraemia and including 'spontaneous' bacterial peritonitis, may be the precipitant.

Coma may occasionally be initiated by a large *protein meal* or *severe constipation*.

Transjugular intrahepatic portal-systemic shunts (TIPS) precipitate or worsen hepatic encephalopathy in about 20–30% of cases. This incidence varies depending on the patient population and selection [31, 72]. As with surgical shunts, the wider the diameter of TIPS inserted, the more likely is encephalopathy. Independent predictors of post-TIPS hepatic encephalopathy are the presence of encephalopathy before the procedure and reduced liver function [59]. There is a decline in the frequency of hepatic encephalopathy 3 months after TIPS despite a sustained increase in arterial ammonia. This is not totally explained by a reduction in shunt flow or alteration in liver function. Cerebral adaptation to the effect of toxins has been suggested [59].

Chronic type

This relates to extensive portal-systemic shunting, which may consist simply of the myriad of small anastomotic vessels developing in the cirrhotic patient or, more often, one major collateral channel, such as the spleno-renal, gastro-renal, umbilical or inferior mesenteric vein.

Fluctuations in encephalopathy are related to dietary protein and diagnosis can be confirmed by noting the effect clinically and on the EEG of a precipitant such as a high-protein diet or by demonstrating improvement by protein withdrawal. Clinical and biochemical evidence of liver disease may be equivocal or absent, and the neuropsychiatric disorder may dominate the picture.

The intermittent neuropsychiatric disturbance may continue for many years and the diagnosis is very likely to fall between various specialist interests. The psychiatrist is interested in the non-specific organic reaction and may not consider underlying liver disease. The neurologist focuses attention on the neurological features, while the hepatologist, recognizing the cirrhosis, fails to elicit the neurological signs or assumes that the patient is just 'odd' or an alcoholic. The patient may be seen for the first time in coma or in remission, adding to the diagnostic difficulty.

The *acute psychiatric states* often present shortly (2 weeks to 8 months) after porta-caval anastomosis as a paranoid–schizophrenic picture or as hypomania. 'Classic' portal-systemic encephalopathy, with EEG slowing, is usually present in addition. Formal psychiatric treatment may be required as well as treatment of the hepatic encephalopathy.

Hepato-cerebral degeneration: myelopathy

More persistent neuropsychiatric syndromes are probably related to organic changes in the central nervous system, not only in the brain but also in the spinal cord. Progressive *paraplegia* may commence insidiously in those with a large portal-systemic collateral circulation. The encephalopathy is not severe. The spinal cord shows demyelination. The paraplegia is progressive and the usual treatment for portal-systemic encephalopathy is ineffective.

Chronic cerebellar and *basal ganglia* signs with parkinsonism, the tremor being unaffected by intention, may develop after some years of chronic hepatic encephalopathy. Permanent cerebral damage is probably present, for treatment has little effect on the tremor.

Focal cerebral symptoms, epileptic attacks and dementia have also been noted.

Differential diagnosis

A *low sodium state* can develop in cirrhotic patients on a restricted sodium diet and having diuretics and abdominal paracenteses. This is shown by apathy, headache, nausea and hypotension. The diagnosis is confirmed by finding low serum sodium levels with a rise in blood urea concentration. The condition may be combined with impending hepatic coma.

Acute alcoholism provides a particularly difficult problem especially as the two syndromes may coexist (Chapter 22). Many symptoms attributed to alcoholism may be due to portal-systemic encephalopathy. Delirium tremens is distinguished by continuous motor and autonomic over-activity, total insomnia, terrifying hallucinations and a finer, more rapid tremor. The patient is flushed, agitated, inattentive and perfunctory in his replies. Tremor, absent at rest, becomes coarse and irregular on activity. Profound anorexia, often with retching and vomiting, is common.

Portal-systemic encephalopathy in an alcoholic has similar features to that in the non-alcoholic except for the frequent absence of rigidity, hyper-reflexia and ankle clonus due to concomitant peripheral neuritis. An EEG is helpful, as is the observation of a favourable response to dietary protein withdrawal and lactulose.

Wernicke's encephalopathy is common with profound malnutrition and with alcoholism.

Hepato-lenticular degeneration (*Wilson's disease*) is found in young people, often with a family history. The symptoms do not fluctuate, the tremor is choreo-athetoid rather than 'flapping', the Kayser–Fleischer corneal ring is seen and disturbances in copper metabolism can usually be demonstrated.

Latent *functional psychoses*, such as depression or paranoia, are frequently released by impending hepatic

coma. The type of reaction is related to the previous personality, and to intensification of personality traits. The psychiatric importance of the syndrome is emphasized by such patients often being admitted to mental hospitals. Conversely, a chronic psychiatric state in patients with known liver disease may not be related to the liver dysfunction. In such patients investigations are designed to demonstrate the chronic syndrome and in particular a large collateral circulation by arterioportography or by CT scanning after intravenous contrast enhancement. Clinical and EEG changes induced by high and low protein feeding may also be useful.

Prognosis

Prognosis depends on the extent of liver cell failure. The chronic group with relatively good liver function but with an extensive collateral circulation combined with increased intestinal nitrogen have the best prognosis and the acute hepatitis group the worst. In cirrhosis, the outlook is poor if the patient has ascites, jaundice and a low serum albumin level—all indicative of liver failure. The survival probability in cirrhotic patients after the first episode of acute hepatic encephalopathy is 42% at 1 year and 23% at 3 years [12].

Assessment of therapy is made difficult by fluctuations in the clinical course. The value of any new method can only be assessed after large numbers of patients have been treated by controlled regimes. Results in patients with chronic encephalopathy (largely related to porto-systemic shunting) with recovery as the rule, must be separated from acute hepato-cellular failure in which recovery is rare.

Older patients have the added disadvantage of cerebral vascular disease. Children with portal vein obstruction having a portal-systemic shunt develop no intellectual or psychological side-effects [1].

Pathogenetic mechanisms [28, 33]

The essentially reversible nature of the syndrome with such widespread cerebral changes suggests a metabolic mechanism. However, no single metabolic derangement accounts for hepatic encephalopathy. The basic processes are failure of hepatic clearance of gut-derived substances, either through hepato-cellular failure or shunting, and altered amino acid metabolism, both of which result in changes in cerebral neurotransmission. Several neuroactive toxins, in particular ammonia, and neurotransmitter systems (table 7.4) are thought to be involved and inter-relate. Reduced cerebral metabolic rates for oxygen and glucose found in hepatic encephalopathy are thought to be due to the reduced neuronal activity.

Table 7.4. Neurotransmitters implicated in hepatic encephalopathy

Neurotransmitter system	Normal action	Hepatic encephalopathy
Glutamate	Neuro-excitation	Dysfunction ↓ receptors interference by NH^+_4
GABA/BZ	Neuro-inhibitor	Increased endogenous BZs ?GABA
Dopamine Noradrenaline	Motor/cognitive	Inhibition false neurotransmitters (aromatic amino acids)
Serotonin	Arousal	?Dysfunction synaptic deficit? ↑serotonin turnover

BZ, benzodiazepine; GABA, γ-aminobutyric acid.

Portal-systemic encephalopathy

Every patient with hepatic pre-coma or coma has a circulatory pathway through which portal blood may enter the systemic veins and reach the brain without being metabolized by the liver.

In patients with poor hepato-cellular function, such as acute hepatitis, the shunt is through the liver itself. The damaged cells are unable to metabolize the contents of the portal venous blood completely so that they pass unaltered into the hepatic veins (fig. 7.5).

In patients with more chronic forms of liver disease, such as cirrhosis, the portal blood bypasses the liver through enlarged natural 'collaterals'. The portal–hepatic vein anastomoses, developing around the nodules in a cirrhotic liver, may also act as internal shunts. The picture is a common complication of porta-caval anastomosis and TIPS. The condition is analogous to the neuropsychiatric disturbance developing in a dog with an Eck fistula (porta-caval shunt) if it is fed meat.

Encephalopathy is unusual if liver function is adequate. In hepatic schistosomiasis, where the collateral circulation is great and liver function good, coma is rare. If shunting is sufficiently great, however, encephalopathy may develop in the absence of obvious liver disease, for instance in extra-hepatic portal hypertension and congenital shunts [82].

Patients going into hepatic coma are suffering from cerebral intoxication by intestinal contents which have not been metabolized by the liver (*portal-systemic encephalopathy*). The nature of the cerebral intoxicant is nitrogenous. A picture indistinguishable from impending hepatic coma can be induced in some patients with

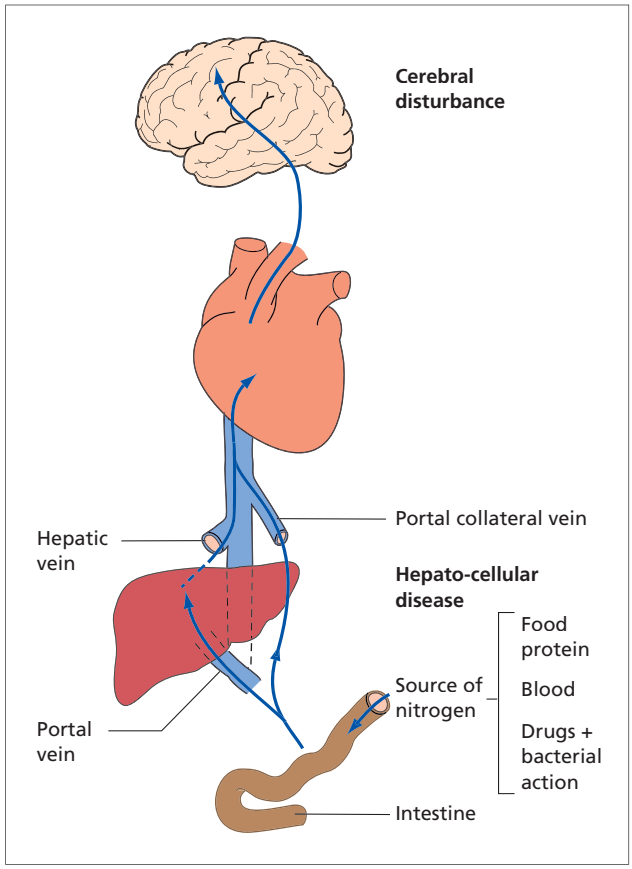


Fig. 7.5. The mechanism of portal-systemic encephalopathy.

cirrhosis by the oral administration of a high-protein diet, ammonium chloride, urea or methionine.

Intestinal bacteria

Symptoms can often be relieved by oral antibiotics. The intoxicants therefore seem to be produced by intestinal bacteria. Other measures which diminish the colonic flora, for instance colonic exclusion or purgation, may also be effective. Moreover, urea-splitting bacteria and the small intestinal flora generally are increased in patients with liver disease. Some ammonium may be derived by metabolism of glutamine by small intestinal mucosa [63].

Neurotransmission

Although there are many studies in experimental and human encephalopathy, the overall picture remains complex and in many areas conflicting and controversial. Definitive data are difficult to collect (table 7.5). Ammonia is thought to play an important role; other neurotransmitter systems are strongly implicated.

Ammonia and glutamine

Ammonia has been the most widely studied factor in the pathogenesis of hepatic encephalopathy. There is a considerable bank of data implicating it in the neuronal dysfunction that occurs (fig. 7.6) [56].

Ammonia is produced from the breakdown of proteins, amino acids, purines and pyrimidines. About half of the ammonia arising from the intestine is synthesized by bacteria, the remainder coming from dietary protein and glutamine. There is no consensus as to the contribution of *Helicobacter pylori*, which has urease activity, to ammonia levels and encephalopathy [11].

The liver normally converts ammonia to urea and glutamine through the urea cycle. Disorders of the urea cycle (congenital defects, Reye's syndrome) lead to an encephalopathy.

In hepatic encephalopathy blood ammonia levels are elevated in 90% of patients. Brain levels are also increased. Encephalopathy can be reproduced in some patients by oral ammonium salts. There is an increase in

Table 7.5. Problem of investigating neurotransmitters in hepatic encephalopathy

Access to cerebral tissue
Lability of factors, e.g. NH_3
Complexity of neurotransmitters
Applicability of animal models
Spectrum of human disease
Difficulty of interpreting ligand data which depend on
release
metabolism (enzymes)
removal/re-uptake
receptor binding

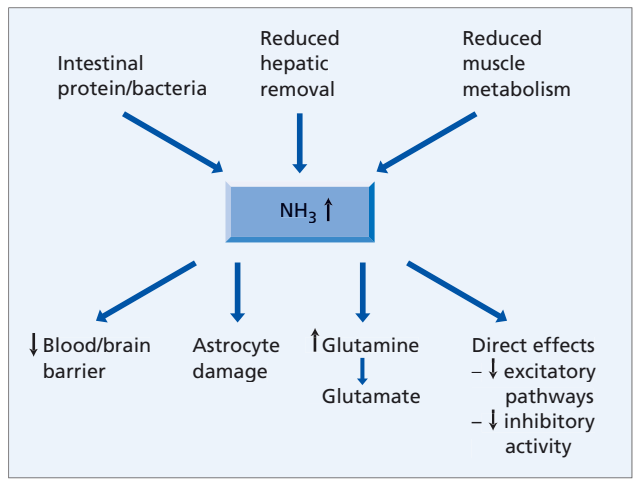


Fig. 7.6. Ammonia: source and potential role in hepatic encephalopathy.

the cerebral metabolic rate for ammonia and an increase in the blood–brain barrier permeability to ammonia [43].

Hyperammonaemia *per se* is associated with decreased excitatory neurotransmission. Ammonia intoxication leads to a hyperkinetic preconvulsive state which cannot be equated with hepatic coma.

The primary mechanisms proposed for ammonia in hepatic encephalopathy are a *direct* effect on neural membranes or on post-synaptic inhibition [77], and an *indirect* neuronal dysfunction due to disturbance of glutamate neurotransmission.

There is no urea cycle in the brain, and ammonia removal involves a different pathway. In astrocytes, glutamine synthetase converts glutamate plus ammonia to glutamine (fig. 7.7). With excess ammonia, glutamate (an important excitatory neurotransmitter) is depleted, and glutamine accumulates. ^{1}H (proton) MRS studies in hepatic encephalopathy show changes consistent with an increase in cerebral glutamine [40]. Cerebrospinal fluid (CSF) levels of glutamine and α-ketoglutarate correlate with the degree of encephalopathy. This description is, however, a simplification of the complex changes in glutamine/glutamate that have been found [56].

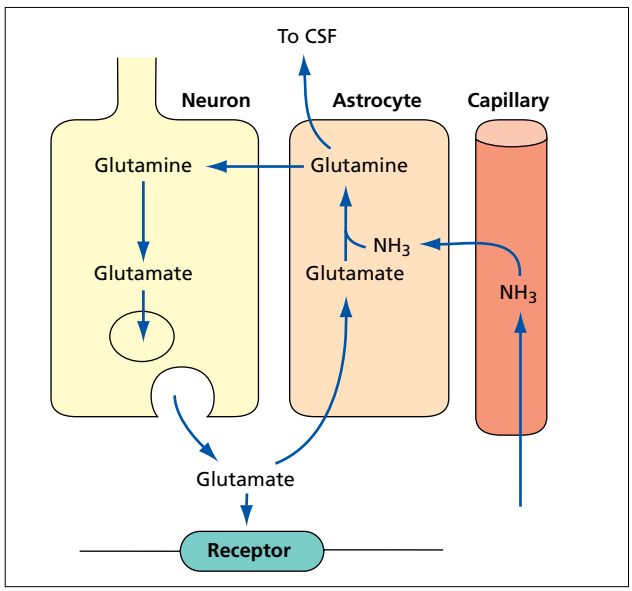


Fig. 7.7. Key steps in glutamatergic synaptic regulation and removal of ammonia by the brain. In the neuron, glutamate is synthesized from its precursor glutamine, stored in synaptic vesicles and ultimately released via a calcium-dependent mechanism. Once released glutamate can act upon any of the types of glutamate receptors found in the synaptic cleft. In the astrocyte, glutamate is taken up and converted to glutamine by glutamine synthetase using NH_3. In hepatic encephalopathy changes include increased cerebral NH_3, astrocyte damage, and a reduced number of glutamate receptors. (From [56] with permission.)

Changes in glutamate binding sites [29] and in glutamate re-uptake by astrocytes have been suggested.

The overall contribution of ammonia to the development of hepatic encephalopathy is difficult to quantify, particularly since there are also changes in other neurotransmitter systems. That other mechanisms are involved is underlined by the finding that in 10% of patients with hepatic encephalopathy, blood ammonia values are within the normal range regardless of the depth of coma. The pH-dependent partial pressure of gaseous ammonia in arterial blood correlates more closely than total ammonia with clinical and EEG changes in hepatic encephalopathy [37].

Methionine derivatives, mainly mercaptans, induce hepatic encephalopathy. This has led to the view that certain toxins, particularly ammonia, mercaptans, fatty acids and phenols, act synergistically. These observations need extension with the better techniques now available.

Manganese

Blood and brain concentrations of manganese are increased in chronic liver failure. Manganese deposition is the most likely explanation for the hyper-intensity on MRI of the globus pallidus [13]. Exposure of astrocytes to manganese produces Alzheimer type 2 changes as seen in hepatic encephalopathy. Current evidence, however, suggests that manganese accumulation is due to portal-systemic shunting, and that it is not a prime player in hepatic encephalopathy [58, 59].

False neurotransmitters

It has been proposed that dopamine and catecholamine-mediated cerebral neurotransmission is inhibited by amines generated either by bacterial action in the colon or by altered cerebral metabolism of precursors. The original hypothesis [20] suggested that decarboxylation of some amino acids in the colon leads to the formation of β-phenylethanolamine, tyramine and octopamine—so-called false neurotransmitters. These might replace the true transmitter (fig. 7.8).

An alternative approach to interference with normal neurotransmission is based on a change in the availability of precursors. Thus plasma aromatic amino acids, tyrosine, phenylalanine and tryptophan, are increased in patients with liver disease probably due to failure of hepatic deamination. The branched-chain amino acids, valine, leucine and isoleucine, are decreased, perhaps due to increased metabolism by skeletal muscle and kidneys, secondary to the hyperinsulinaemia of chronic liver disease. The two groups of amino acids compete for uptake into the brain. The imbalance in plasma levels allows more aromatic amino acids to pass an

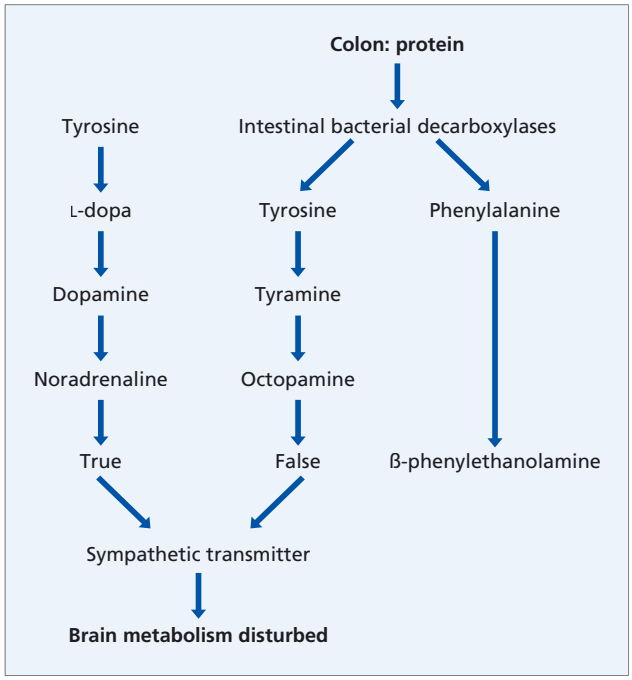


Fig. 7.8. The possible role of false sympathetic neurotransmitters in the disturbed cerebral metabolism in liver disease.

abnormal blood–brain barrier. There may also be reduced efflux of aromatic amino acids from the brain [36]. An increase in phenylalanine level in the brain leads to inhibition of dopa production and the formation of false neurotransmitters such as phenylethanolamine and octopamine.

A change in this neurotransmitter system in hepatic encephalopathy has some support from the improvement after L-dopa and bromocriptine treatment, but the number of patients who improve is limited and the results are equivocal. Serum and urinary octopamine levels are increased in hepatic encephalopathy. However, intraventricular infusion of enormous quantities of octopamine, with resulting depression of brain dopamine and adrenaline, failed to cause coma in normal rats. Moreover, when brain catecholamines were measured post-mortem in cirrhotic patients with encephalopathy, no reduction was found compared with cirrhotics who were not encephalopathic at the time of death [17].

Serotonin

The neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) is involved in the control of cortical arousal and thus the conscious state and the sleep/wake cycle. The precursor tryptophan is one of the aromatic amino acids increased in the plasma in liver disease. It is also increased in the CSF and brain of patients with hepatic coma and therefore has the potential to increase brain serotonin synthesis. In hepatic encephalopathy there are also other changes in serotonin metabolism including related enzymes (monoamine oxidase, MAO), receptors and metabolites (5-hydroxyindole acetic acid, 5-HIAA). There is increased expression of the neuronal isoform of the monoamine-metabolizing enzyme MAO-A [55]. These changes, together with the appearance of encephalopathy in patients with chronic liver disease treated with ketanserin (a 5-HT blocker) for portal hypertension [81], implicate the serotonin system in hepatic encephalopathy. Where the dysfunction in this system primarily lies awaits further study.

γ-Aminobutyric acid (GABA) and endogenous benzodiazepines

GABA is the principal inhibitory neurotransmitter in the brain [7]. It is usually synthesized from glutamate by glutamate dehydrogenase in presynaptic nerves and stored in vesicles. It binds to a specific GABA receptor in the postsynaptic membrane. This receptor is part of a larger receptor complex which also has binding sites for benzodiazepines and barbiturates (fig. 7.9). The binding of any of these ligands opens a chloride channel and after the influx of chloride there is hyperpolarization of the postsynaptic membrane, and neuroinhibition.

GABA is synthesized by gut bacteria, and that entering the portal vein is metabolized by the liver. In the presence of liver failure or portal-systemic shunting it enters the systemic circulation. There are increased GABA levels in the plasma of patients with liver disease and hepatic encephalopathy [41]. Suggestions that GABA might be involved in hepatic encephalopathy came mainly from experimental models of acute liver failure, but in subsequent studies in autopsied brain tissue from cirrhotic patients with encephalopathy, GABA *per se* does not seem to be involved.

However, the focus on the GABA–benzodiazepine receptor complex led to data suggesting that endogenous benzodiazepines are present in patients with hepatic encephalopathy and that these may interact with the receptor complex and cause neuroinhibition. Benzodiazepine-like compounds have been detected in the plasma and CSF of patients with hepatic encephalopathy due to cirrhosis [57] and in the plasma in fulminant hepatic failure [6]. Cirrhotics with hepatic encephalopathy who had taken no synthetic benzodiazepines for at least 3 months showed significantly higher values for benzodiazepine-like activity than controls without liver disease, using a radio-receptor assay [57]. Stool from cirrhotic patients contains five times the benzodiazepine-like activity as stool from controls [3]. The relationship between plasma endogenous benzodiazepines and encephalopathy is controversial.

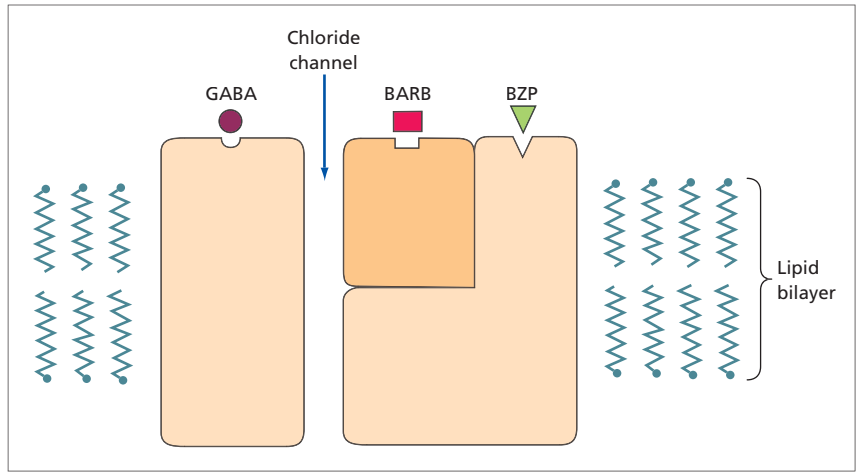


Fig. 7.9. Simplified model of the GABA-receptor/ionophore complex embedded in a postsynaptic neural membrane. Binding of any of the depicted ligands, γ-aminobutyric acid (GABA), barbiturates (BARB) or benzodiazepines (BZP), to its specific binding site increases chloride-ion conductance through the membrane with resultant hyperpolarization and neuroinhibition [73].

Some studies show a correlation [57] while others do not [4]. However, both central benzodiazepine receptors (coupled GABA-A receptors) and peripheral type benzodiazepine receptors are increased in the brain in chronic liver failure [13, 32].

It remains unclear whether the changes in the benzodiazepine receptor or endogenous ligands are significant pathogenetically or are simply associated phenomena. Nevertheless involvement of this neurotransmitter system is consistent with the increased sensitivity to benzodiazepines of cirrhotic patients [8]. Also the benzodiazepine antagonist flumazemil reverses encephalopathy temporarily (the drug has a short half-life) in some patients. [5]

Other metabolic abnormalities

Neuronal nitric oxide synthase may be increased in hepatic encephalopathy and make a contribution to the altered cerebral perfusion in chronic liver disease [67].

These patients are often alkalotic. This may result from toxic stimulation of the respiratory centre by ammonium, from administration of alkalis such as citrate in transfusions or with potassium supplements, or from hypokalaemia. Urea synthesis consumes bicarbonate. Progressive loss of urea cycle capacity is associated with increased plasma bicarbonate levels (and metabolic alkalosis) and ammonia excretion by the kidney increases. [27]

Hypoxia increases cerebral sensitivity to ammonia. The stimulation of the respiratory centre results in increase in depth and rate of respiration. Hypocapnia follows and this reduces cerebral blood flow. The increase in the blood organic acids (lactate and pyruvate) is correlated with the reduction in CO_2 tension.

Any potent diuretic can precipitate hepatic coma. This may be related to hypokalaemia [15] and to readier penetration of ammonium ions through the blood–brain barrier in the presence of alkalosis. In addition to hypokalaemia, other electrolyte disturbances or a profound diuresis seem to initiate encephalopathy.

Changes in carbohydrate metabolism

The hepatectomized dog dies in hypoglycaemic coma. Hypoglycaemic episodes are rare in chronic liver disease but may complicate fulminant hepatitis (Chapter 8).

α-Ketoglutaric and pyruvic acids are transported from the periphery to the metabolic pool in the liver, and blood levels increase as the neurological state deteriorates. These levels probably reflect severe liver damage. The fall in blood ketones also reflects severity of hepatic dysfunction. There is progressive impairment of intermediate carbohydrate metabolism as the liver fails.

Astrocyte swelling

Studies using MR spectroscopy show a depletion of myoinositol and an increase in glutamine/glutamate ('osmolytes'). It has been suggested that an associated increase in astrocyte hydration may be a major pathogenetic event in the development of hepatic encephalopathy [26].

Conclusions

No unifying mechanism explains hepatic encephalopathy. The brain controls neuropsychiatric behaviour through multiple inhibitory and stimulatory receptor-mediated pathways. Although neurotransmitters are produced locally they depend upon substrates and influences from further afield (fig. 7.10). When the liver fails or there is portal-systemic shunting there is a complex pattern of changes which influence multiple neurotransmitter systems.

Of the systems discussed, the effects of ammonia

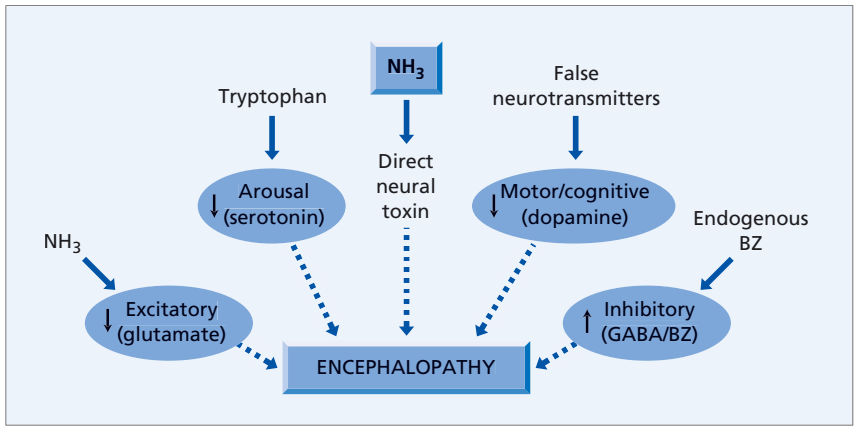


Fig. 7.10. Multifactorial mechanism of hepatic encephalopathy. The altered neurotransmitter state leaves the brain more sensitive to other insults including narcotics, sepsis, hypoxia and hypotension. BZ, benzodiazepines; GABA, γ-aminobutyric acid.

appear central to hepatic encephalopathy, with changes in glutamate, serotonin and endogenous benzodiazepine-mediated neurotransmission awaiting further study. The place of false neurotransmitters and GABA appears less persuasive than initially thought.

Cerebral metabolism is undoubtedly abnormal in liver disease. This is thought to be an effect rather than the cause of neurotransmitter-mediated changes. In the chronic case, actual structural changes in the brain can be demonstrated. The end result is a brain with abnormal neurotransmitter function, which is unduly sensitive to insults (opiates, electrolyte imbalance, sepsis, hypotension, hypoxia) that would be without effect in the normal patient.

Treatment of hepatic encephalopathy [16]

Treatment broadly divides into three areas.

1 Identification and treatment of the precipitating cause.

2 Intervention to reduce the production and absorption of gut-derived ammonia and other toxins. This involves reduction and modification of dietary protein, alteration of enteric bacteria and the colonic environment (antibiotics, lactulose/lactilol), and stimulation of colonic emptying (enemas, lactulose/lactilol).

3 Prescription of agents to modify neurotransmitter balance directly (bromocriptine, flumazemil), or indirectly (branched-chain amino acids). These are of limited clinical value at present.

The choice of treatment (table 7.6) depends on the clinical picture: subclinical, acute or persistent chronic encephalopathy.

Table 7.6. Treatment of hepatic pre-coma and coma

Acute
Identify precipitating factor
Empty bowels of nitrogen-containing materials
stop haemorrhage
phosphate enema
Protein-restricted diet; raise dietary protein slowly with recovery
Lactulose or lactilol
Neomycin 1 g four times a day by mouth for 1 week
Maintain calorie, fluid and electrolyte balance
Stop diuretics, check serum electrolyte levels
Chronic
Avoid nitrogen-containing drugs
Protein, largely vegetarian intake, at limit of tolerance
Ensure at least two free bowel movements daily
Lactulose or lactilol
If symptoms worsen adopt the regime for acute coma

Diet [46, 62]

In the acute attack dietary protein is reduced to 20 g/day. Calorie intake is maintained at 2000 cal/day or above, orally or intravenously. During recovery, protein is added in 10 g increments on alternate days. Any relapse is treated by a return to the previous level. In patients after an acute episode of coma, a normal protein intake is soon achieved.

It is important in cirrhotic patients to avoid protein restriction for any longer than is necessary since these patients have a higher than normal protein requirement (1.2 g/kg/day) to remain in positive balance. Guidelines recommend that the daily protein intake in patients with liver disease should if possible be around 1.0–1.5 g/kg depending upon the degree of hepatic decompensation [46, 62]. In the acute case, a short period of protein deprivation may not be harmful but prolonged restriction of protein in the cirrhotic patient without encephalopathy is inappropriate [75].

If animal protein is not well tolerated, vegetable protein may be used. The latter is less ammoniagenic and contains small amounts of methionine and aromatic amino acids. It is also more laxative and increases the intake of dietary fibre so that there is increased incorporation and elimination of nitrogen contained in faecal

bacteria [84]. It may be difficult to take because of flatulence, diarrhoea and bulk.

Antibiotics

Neomycin, given orally, is very effective in decreasing gastrointestinal ammonium formation. Little neomycin is absorbed from the gut although blood levels have been detected and impaired hearing or deafness may follow its long-term use. Thus it should only be used for the acute case for 5–7 days (4–6 g/day in divided doses). Neomycin should be used with particular caution in patients with renal insufficiency. In acute hepatic coma, lactulose is given, and neomycin added if the response is slow or partial. Surprisingly the two drugs seem to act synergistically [85], perhaps because of action on different bacterial populations.

Metronidazole (200 mg four times per day orally) seems to be as effective as neomycin [53]. Because of dose-related central nervous system toxicity, it should not be used long term.

Rifaximin, a non-absorbed derivative of rifamycin, is effective for grade 1–3 hepatic encephalopathy at a dose of 1200 mg/day [87].

Lactulose and lactilol

The human intestinal mucosa does not have an enzyme to split these synthetic disaccharides. When given by mouth *lactulose* reaches the caecum where it is broken down by bacteria predominantly to lactic acid (fig. 7.11). The osmotic volume of the colon is increased. The faecal pH drops. The growth of lactose-fermenting organisms is favoured and organisms such as bacteroides, which are ammonia formers, are suppressed. It may be of particular value in hepatic encephalopathy induced by bleeding. The colonic fermentative bacteria prefer lactulose to blood when both are present [54]. It may 'detoxify' short-chain fatty acids produced in the presence of blood and proteins.

The mode of action is uncertain. Faecal acidity would reduce the ionization and hence absorption of ammonia (also amines and other toxic nitrogenous compounds); faecal ammonia is not increased. Lactulose more than doubles the colonic output of bacterial mass and 'soluble' nitrogen [84] which is then no longer available for absorption as ammonia.

The aim of treatment with lactulose is to produce acid stools without diarrhoea. The dose is 10–30 ml three times a day and is adjusted to produce two semi-soft stools daily.

Side-effects include flatulence, diarrhoea and intestinal pain. Diarrhoea can be so profound that serum sodium increases to over 145 mmol/l, serum potassium falls and alkalosis develops. The blood volume falls and may impair renal function. These side-effects are particularly likely if the daily dose exceeds 100 ml. Some of the side-effects may be related to contamination of lactulose syrup with other sugars. Crystalline lactulose may be less toxic.

Lactilol (β-galactoside sorbitol) is a second-generation disaccharide easily produced in chemically pure crystalline form, which can be dispensed as a powder. It is not broken down or absorbed in the small intestine, but is metabolized by colonic bacteria [61].

Lactilol seemed to be as effective as lactulose in chronic and acute portal-systemic encephalopathy [51]. Patients responded more quickly to lactilol than lactulose, and there was less diarrhoea and flatulence (table 7.7) [10, 51].

However, lactitol is no longer routinely available on prescription, but can be obtained from the manufactuer under special circumstances for patients intolerant of lactulose.

Lactilol and lactulose have been used for the treatment of subclinical hepatic encephalopathy [50]. Psycho-

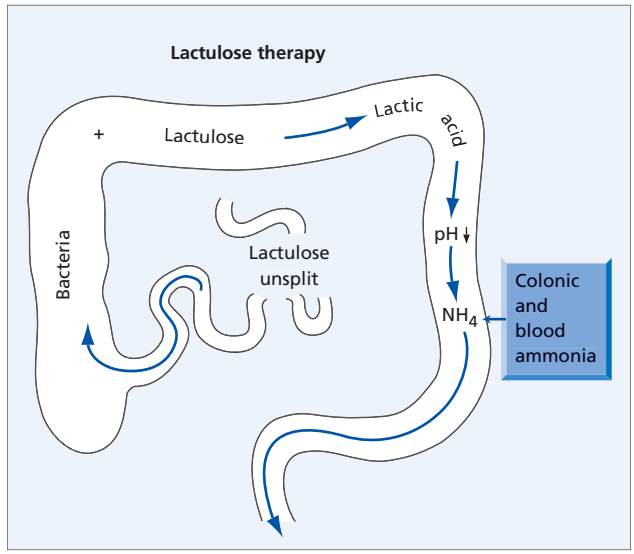


Fig. 7.11. Lactulose reaches the colon unsplit. It is then converted by bacteria to organic acids and an acid stool results. This may also affect the ionization of ammonia in the colon and reduce its absorption.

Table 7.7. The effects of lactilol compared with lactulose

Colonic effects similar
As effective in encephalopathy
Quicker action
More convenient (powder)
Less sweet
Less diarrhoea and flatulence

metric performance improved. A dose of lactitol of 0.3–0.5 g/kg/day was well tolerated and effective [71].

Purgation. Hepatic encephalopathy follows constipation and remissions are associated with return to a normal bowel action. The value of enemas and purgation with magnesium sulphate in patients with hepatic coma must be emphasized. Lactulose or lactose enemas may be used and are superior to water [80]. All enemas must be neutral or acid to reduce ammonium absorption. Magnesium sulphate enemas can cause dangerous hypermagnesaemia [14]. Phosphate enemas are safe.

Sodium benzoate and L-ornithine -L-aspartate

Sodium benzoate promotes urinary excretion of ammonia and is as effective as lactulose and is less expensive.

L-ornithine-L-aspartate treatment promotes hepatic removal of ammonia by stimulating residual hepatic urea cycle activity and promoting glutamine synthesis, particularly in skeletal muscle [70]. Control studies show that both oral and intravenous administration reduce ammonia levels and improve encephalopathy in patients with cirrhosis [35, 76].

Levodopa and bromocriptine

If portal-systemic encephalopathy is related to a defect in dopaminergic neurotransmission then replenishment of cerebral dopamines should be beneficial. Dopamine does not pass the blood–brain barrier, but its precursor, levodopa, does and can cause temporary arousal in acute hepatic encephalopathy [44]. However, only a few patients benefit.

Bromocriptine is a specific dopamine receptor agonist with a prolonged action. As an adjunct to protein restriction and lactulose it has given clinical, psychometric and EEG improvement in chronic portal-systemic encephalopathy [52]. It should be considered in the rare patient with intractable chronic portal-systemic encephalopathy and good, stable liver function resistant to dietary protein restriction and lactulose.

Flumazenil

This is a benzodiazepine-receptor antagonist which can induce transient, variable but distinct improvement in some patients with hepatic encephalopathy associated with fulminant liver failure or cirrhosis. A randomized, double-blind study of flumazenil was only beneficial in a subgroup of cirrhotic patients with severe hepatic encephalopathy [5]. Overall results showed improvement in neurological score in 15% of treated patients compared with 3% on placebo. EEG improved in 25% of treated patients compared with 4% on placebo. The place of this group of compounds in the clinical situation has yet to be established.

Branched-chain amino acids

In cirrhotic patients the serum branched chain amino acids valine, leucine and isoleucine are low, and aromatic amino acid levels are increased. The reduced ratio of branched-chain to aromatic amino acids has been related to the development of hepatic encephalopathy through increased supply of precursors of neurotransmitters. Infusions of solutions containing a high concentration of branched-chain amino acids have been used to treat acute and chronic hepatic encephalopathy. Results have been extremely conflicting, perhaps related to differences in the nature of amino acid solutions, the ways of administration and the patients studied. Analysis of controlled trials shows that there is no consensus that intravenous branched-chain amino acids control hepatic encephalopathy [47].

Despite individual studies showing benefit of oral branched-chain amino acid treatment the benefit of this expensive treatment also remains controversial [19, 49].

Other precipitating factors

Patients are extremely sensitive to sedatives and whenever possible these are avoided. If an overdose is suspected, the appropriate antagonist should be given. If the patient is uncontrollable and some sedation is necessary, a small dose of temazepam or oxazepam is given; morphine and paraldehyde are absolutely contraindicated. Chlordiazepoxide and heminevrin used with caution are valuable in the alcoholic with impending hepatic coma. Drugs known to induce hepatic coma such as oral amino acids and diuretics are disallowed.

Potassium deficiency can be treated by fruit juices or by effervescent or slow-release potassium chloride. If it is urgent, potassium chloride may be added to an intravenous infusion.

Zinc deficiency in patients with cirrhosis should be treated with supplementation. Theoretically deficiency may reduce metabolism of ammonia to urea because of the dependency on zinc of some of the enzymes involved, but studies of zinc therapy in hepatic encephalopathy have not established benefit [68].

Shunt occlusion

Surgical shunt occlusion can reverse the severe portal-systemic encephalopathy following a porta-caval anastomosis. Alternatively the shunt may be occluded by

invasive radiology with the insertion of a balloon or a steel coil. This may also be done for a spontaneous gastro-spleno-renal shunt [34, 39].

Temporary hepatic support

Complicated methods of temporary hepatic support are not applicable to hepatic coma in the cirrhotic. Such a patient is either terminal or can be expected to come out of coma without them.

Hepatic transplantation

This may be the ultimate answer to the problem of chronic hepatic encephalopathy. One patient with a history of 3 years showed marked improvement lasting 9 months following transplantation [60]. Another patient with chronic hepato-cerebral degeneration and spastic paraparesis showed remarkable improvement after orthotopic liver transplantation [65].

References

1 Alagille D, Carlier J-C, Chiva M *et al*. Long-term neuropsychological outcome in children undergoing portal-systemic shunts for portal vein obstruction without liver disease. *J. Pediatr. Gastroenterol. Nutr.* 1986; **5**: 861.

2 Amodio P, Del Piccolo F, Marchetti P *et al*. Clinical features and survival of cirrhotic patients with subclinical cognitive alterations detected by the number connection test and computerized psychometric tests. *Hepatology* 1999; **29**: 1662.

3 Aronson L, Gacad RC, Kaminsky-Russ K *et al*. Evidence of gut production of 'endogenous' benzodiazepines: implications for hepatic encephalopathy. *Gastroenterology* 1996; **110**: A1144.

4 Avallone R, Zeneroli ML, Venturini I *et al*. Endogenous benzodiazepine-like compounds and diazepam binding inhibitor in serum of patients with liver cirrhosis with and without overt encephalopathy. *Gut* 1998; **42**: 861.

5 Barbaro G, Di Lorenzo G, Soldini M *et al*. Flumazenil for hepatic encephalopathy grade III and IVa in patients with cirrhosis: an Italian multicentre double-blind, placebo-controlled, cross-over study. *Hepatology* 1998; **28**: 374.

6 Basile AS, Harrison PM, Hughes RD *et al*. Relationship between plasma benzodiazepine receptor ligand concentrations and severity of hepatic encephalopathy. *Hepatology* 1994; **19**: 112.

7 Basile AS, Jones EA. Ammonia and GABA-ergic neurotransmission: interrelated factors in the pathogenesis of hepatic encephalopathy. *Hepatology* 1997; **25**: 1303.

8 Batki G, Fisch HU, Karlaganis G *et al*. Mechanism of the excessive sedative response of cirrhotics to benzodiazepines. Model experiments with triazolam. *Hepatology* 1987; **7**: 629.

9 Bernthal P, Hays A, Tarter RE *et al*. Cerebral CT scan abnormalities in cholestatic and hepato-cellular disease and their relationship to neuro-psychologic test performance. *Hepatology* 1987; **7**: 107.

10 Blanc P, Daures J-P, Rouillon J-M *et al*. Lactitol or lactulose in the treatment of chronic hepatic encephalopathy: results of a meta-analysis. *Hepatology* 1992; **15**: 222.

11 Blei AT. *Helicobacter pylori*, harmful to the brain? *Gut* 2001; **48**: 590.

12 Bustamante J, Rimola A, Ventura P-J *et al*. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. *J. Hepatol.* 1999; **30**: 890.

13 Butterworth RF. Complications of cirrhosis III. Hepatic encephalopathy. *J. Hepatol.* 2000; **32** (Suppl. 1): 171.

14 Collinson PO, Burroughs AK. Severe hypermagnesaemia due to magnesium sulphate enemas in patients with hepatic coma. *Br. Med. J.* 1986; **293**: 1013.

15 Conn HO. Effects of high–normal and low–normal serum potassium levels on hepatic encephalopathy: facts, half-facts or artifacts? *Hepatology* 1994; **20**: 1637.

16 Cordoba J, Blei AT. Treatment of hepatic encephalopathy. *Am. J. Gastroenterol.* 1997; **92**: 1429.

17 Cuilleret G, Pomier-Layrargues G, Pons F *et al*. Changes in brain catecholamine levels in human cirrhotic hepatic encephalopathy. *Gut* 1981; **21**: 565.

18 Das A, Dhiman RK, Saraswat VA *et al*. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. *J. Gastroenterol. Hepatol.* 2001; **16**: 531.

19 Fabbri A, Magrini N, Bianchi G *et al*. Overview of randomized clinical trials of oral branched-chain amino acid treatment in chronic hepatic encephalopathy. *J. Parenter. Enterol. Nutr.* 1996; **20**: 159.

20 Fischer JE, Baldessarini RJ. False neurotransmitters and hepatic failure. *Lancet* 1971; **2**: 75.

21 Frerichs FT. *A Clinical Treatise on Diseases of the Liver*, Vol. I. Translated by C Murchison. New Sydenham Society, London, 1960, p. 241.

22 Gitlin N, Lewis DC, Hinkley L. The diagnosis and prevalence of subclinical hepatic encephalopathy in apparently healthy, ambulant nonshunted patients with cirrhosis. *J. Hepatol.* 1986; **3**: 75.

23 Groeneweg M, Moerland W, Quero JC *et al*. Screening of subclinical hepatic encephalopathy. *J. Hepatol.* 2000; **32**: 748.

24 Groeneweg M, Quero JC, Bruijn ID *et al*. Subclinical hepatic encephalopathy impairs daily functioning. *Hepatology* 1998; **28**: 45.

25 Haseler LJ, Sibbitt WL Jr, Mojtahedzadeh HN *et al*. Proton MR spectroscopic measurement of neurometabolities in hepatic encephalopathy during oral lactulose therapy. *Am. J. Neuroradiol.* 1998; **19**: 1681.

26 Haussinger D, Kircheis G, Fischer R *et al*. Hepatic encephalopathy in chronic liver disease: a clinical manifestation of astrocyte swelling and low-grade cerebral oedema? *J. Hepatol.* 2000; **32**: 1035.

27 Haussinger D, Steeb R, Gerok W. Ammonium and bicarbonate homeostasis in chronic liver disease. *Klin. Wochenschr.* 1990; **68**: 75.

28 Hazell AS, Butterworth RF. Hepatic encephalopathy: an update of pathophysiologic mechanisms. *Proc. Soc. Exp. Biol. Med.* 1999; **222**: 99.

29 Hermengildo C, Monfort P, Felipo V. Activation of *N*-methyl-D-aspartate receptors in rat brain *in vivo* following acute ammonia intoxication: characterization by *in vivo* brain microdialysis. *Hepatology* 2000; **31**: 709.

30 Horsmans Y, Solbreux PM, Daenens C *et al*. Lactulose

improves psychometric testing in cirrhotic patients with subclinical encephalopathy. *Aliment. Pharmacol. Therapeut.* 1997; **11**: 165.
31 Jalan R, Gooday R, O'Carroll RE *et al*. A prospective evaluation of changes in neuropsychological and liver function tests following transjugular intrahepatic portosystemic stent-shunt. *J. Hepatol.* 1995; **23**: 697.
32 Jalan R, Turjanski N, Taylor-Robinson SD *et al*. Increased availability of central benzodiazepine receptors in patients with chronic hepatic encephalopathy and alcohol related cirrhosis. *Gut* 2000; **46**: 546.
33 Jones EA, Weissenborn K. Neurology and the liver. *J. Neurol. Neurosurg. Psychiatr.* 1997; **63**: 279.
34 Kawanaka H, Ohta M, Hashizume M *et al*. Portosystemic encephalopathy treated with balloon-occluded retrograde transvenous obliteration. *Am. J. Gastroenterol.* 1995; **90**: 508.
35 Kircheis G, Nilius R, Held C *et al*. Therapeutic efficacy of L-ornithine-L-aspartate infusions in patients with cirrhosis and hepatic encephalopathy: results of a placebo-controlled, double-blind study. *Hepatology* 1997; **25**: 1351.
36 Knudsen GM, Schmidt J, Almdal T *et al*. Passage of amino acids and glucose across the blood–brain barrier in patients with hepatic encephalopathy. *Hepatology* 1993; **17**: 987.
37 Kramer L, Tribl B, Gendo A *et al*. Partial pressure of ammonia vs. ammonia in hepatic encephalopathy. *Hepatology* 2000; **31**: 30.
38 Kügler CFA, Lotterer E, Petter J *et al*. Visual event-related P300 potentials in early portosystemic encephalopathy. *Gastroenterology* 1992; **103**: 302.
39 Kuramitsu T, Komatsu M, Matsudaira N *et al*. Portal-systemic encephalopathy from a spontaneous gastrorenal shunt diagnosed by three-dimensional computed tomography and treated effectively by percutaneous vascular embolization. *Liver* 1998; **18**: 208.
40 Laubenberger J, Haussinger D, Boyer S *et al*. Proton magnetic resonance spectroscopy of brain in symptomatic and aysmptomatic patients with liver cirrhosis. *Gastroenterology* 1997; **112**: 1610.
41 Levy LJ, Leek J, Losowsky MS. Evidence for gamma aminobutyric acid as the inhibitor of gamma aminobutyric acid binding in the plasma of humans with liver disease and hepatic encephalopathy. *Clin. Sci.* 1987; **73**: 531.
42 Lo WD, Ennis SR, Goldstein GW *et al*. The effects of galactosamine-induced hepatic failure upon blood–brain barrier permeability. *Hepatology* 1987; **7**: 452.
43 Lockwood AH, Yap EWH, Wong WH. Cerebral ammonia metabolism in patients with severe liver disease and minimal hepatic encephalopathy. *J. Cereb. Blood* 1991; **11**: 337.
44 Lunzer M, James IM, Weinman J *et al*. Treatment of chronic hepatic encephalopathy with levodopa. *Gut* 1974; **15**: 555.
45 Miyata Y, Motomura S, Tsuji Y *et al*. Hepatic encephalopathy and reversible cortical blindness. *Am. J. Gastroenterol.* 1988; **83**: 780.
46 Mizock BA. Nutrition support in hepatic encephalopathy. *Nutrition* 1999; **15**: 220.
47 Morgan MY. Branched-chain amino acids in the management of chronic liver disease. Facts and fantasies. *J. Hepatol.* 1990; **11**: 133.
48 Morgan MY. Cerebral magnetic resonance imaging in patients with chronic liver disease. *Metab. Brain Dis.* 1998; **13**: 273.
49 Morgan MY. The treatment of chronic hepatic encephalopathy. *Hepatogastroenterology* 1995; **38**: 377.
50 Morgan MY, Alonso M, Stranger LC. Lactilol and lactulose for the treatment of subclinical hepatic encephalopathy in cirrhotic patients. A randomized, cross-over study. *J. Hepatol.* 1989; **8**: 208.
51 Morgan MY, Hawley KM. Lactilol vs. lactulose in the treatment of acute hepatic encephalopathy in cirrhotic patients: a double-blind, randomized trial. *Hepatology* 1987; **7**: 1278.
52 Morgan MY, Jakobovits AW, James IM *et al*. Successful use of bromocriptine in the treatment of chronic hepatic encephalopathy. *Gastroenterology* 1980; **78**: 663.
53 Morgan MH, Read AE, Speller DCE. Treatment of hepatic encephalopathy with metronidazole. *Gut* 1982; **23**: 1.
54 Mortensen PB, Rasmussen HS, Holtug K. Lactulose detoxifies *in vitro* short-chain fatty acid production in colonic contents induced by blood: implications for hepatic coma. *Gastroenterology* 1988; **94**: 750.
55 Mousseau DD, Baker GB, Butterworth RF. Increased density of catalytic sites and expression of brain monoamine oxidase A in humans with hepatic encephalopathy. *J. Neurochem.* 1997; **68**: 1200.
56 Mousseau DD, Butterworth RF. Current theories on the pathogenesis of hepatic encephalopathy. *Proc. Soc. Exp. Biol. Med.* 1994; **206**: 329.
57 Mullen KD, Szauter KM, Kaminsky-Russ K. 'Endogenous' benzodiazepine activity in body fluids of patients with hepatic encephalopathy. *Lancet* 1990; **336**: 81.
58 Nolte W, Wiltfang J, Schindler CG *et al*. Bright basal ganglia in T1-weighted magnetic resonance images are frequent in patients with portal vein thrombosis without liver cirrhosis and not suggestive of hepatic encephalopathy. *J. Hepatol.* 1998; **29**: 443.
59 Nolte W, Wiltfang J, Schindler C *et al*. Portosystemic hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in patients with cirrhosis: clinical, laboratory, psychometric and electroencephalographic investigations. *Hepatology* 1998; **28**: 1215.
60 Parkes JD, Murray-Lyon IM, Williams R. Neuropsychiatric and electroencephalographic changes after transplantation of the liver. *Q. J. Med.* 1970; **39**: 515.
61 Patil DH, Westaby D, Mahida YR *et al*. Comparative modes of action of lactilol and lactulose in the treatment of hepatic encephalopathy. *Gut* 1987; **28**: 255.
62 Plauth M, Merli M, Kondrup J *et al*. ESPEN guidelines for nutrition in liver disease and transplantation. *Clin. Nutr.* 1997; **16**: 43.
63 Plauth M, Roske A-E, Romaniuk P *et al*. Post-feeding hyperammonaemia in patients with transjugular intrahepatic portosystemic shunt and liver cirrhosis: role of small intestinal ammonia release and route of nutrient administration. *Gut* 2000; **46**: 849.
64 Pomier Layrargues G, Spahr L, Butterworth RF. Increased manganese concentrations in pallidum of cirrhotic patients. *Lancet* 1995; **345**: 735.
65 Powell EE, Pender MP, Chalk JB *et al*. Improvement in chronic hepatocerebral degeneration following liver transplantation. *Gastroenterology* 1990; **98**: 1079.
66 Quero JC, Hartmann IJC, Meulstee J *et al*. The diagnosis of subclinical hepatic encephalopathy in patients with cirrhosis using neuropsychological tests and automated electroencephalogram analysis. *Hepatology* 1996; **24**: 556.

67 Raghavendra Rao VL, Butterworth RF. Neuronal nitric oxide synthase and hepatic encephalopathy. *Metab. Brain Dis*. 1998; **12**: 175.

68 Riordan SM, Williams R. Treatment of hepatic encephalopathy. *New Engl. J. Med*. 1997; **337**: 473.

69 Rose C, Butterworth RF, Zayed J *et al*. Manganese deposition in basal ganglia structures results from both portal-systemic shunting and liver dysfunction. *Gastroenterology* 1999; **117**: 640.

70 Rose C, Michalak A, Pannunzio P *et al*. Ornithine-L-aspartate in experimental portal-systemic encephalopathy: therapeutic efficacy and mechanism of action. *Metab. Brain Dis*. 1998; **13**: 147.

71 Salerno F, Moser P, Maggi A *et al*. Effects of long-term administration of low-dose lactilol in patients with cirrhosis but without overt encephalopathy. *J. Hepatol*. 1994; **21**: 1092.

72 Sanyal AJ, Freedman AM, Shiffman ML *et al*. Portosystemic encephalopathy after transjugular portosystemic shunt: results of a prospective controlled study. *Hepatology* 1994; **20**: 46.

73 Schafer DF, Jones EA. Hepatic encephalopathy and the γ-aminobutyric-acid neurotransmitter system. *Lancet* 1982; **i**: 18.

74 Seery JP, Taylor-Robinson SD. The application of magnetic resonance spectroscopy to the study of hepatic encephalopathy. *J. Hepatol*. 1996; **25**: 988.

75 Soulsby CT, Morgan MY. Dietary management of hepatic encephalopathy in cirrhotic patients: survey of current practice in United Kingdom. *Br. Med. J*. 1999; **318**: 1391.

76 Stauch S, Kircheis G, Adler G *et al*. Oral L-ornithine-L-aspartate therapy of chronic hepatic encephalopathy: results of a placebo-controlled double-blind study. *J. Hepatol* 1998; **28**: 856.

77 Szerb JC, Butterworth RF. Effect of ammonium ions on synaptic transmission in the mammalian central nervous system. *Prog. Neurobiol*. 1992; **39**: 135.

78 Taylor-Robinson SD, Buckley C, Changani KK *et al*. Cerebral proton and phosphorus-31 magnetic resonance spectroscopy in patients with subclinical hepatic encephalopathy. *Liver* 1999; **19**: 389.

79 Thuluvath PJ, Edwin D, Yue CN *et al*. Increased signals seen in globus pallidus in T_1-weighted magnetic resonance imaging in cirrhotics are not suggestive of chronic hepatic encephalopathy. *Hepatology* 1995; **21**: 440.

80 Uribe M, Campoll O, Vargas F *et al*. Acidifying enemas (lactilol and lactulose) vs. nonacidifying enemas (tap-water) to treat acute portal–systemic encephalopathy: a double-blind, randomised clinical trial. *Hepatology* 1987; **7**: 639.

81 Vorobioff J, Garcia-Tsao G, Groszmann R *et al*. Long-term haemodynamic effects of ketanserin, a 5-hydroxytryptamine blocker, in portal hypertensive patients. *Hepatology* 1988; **9**: 88.

82 Watanabe A. Portal-systemic encephalopathy in non-cirrhotic patients: classification of clinical types, diagnosis and treatment. *J. Gastroenterol. Hepatol*. 2000; **15**: 969.

83 Watanabe A, Sakai T, Sato S *et al*. Clinical efficacy of lactulose in cirrhotic patients with and without subclinical hepatic encephalopathy. *Hepatology* 1997; **26**: 1410.

84 Weber FL, Banwell JG, Fresard KM *et al*. Nitrogen in fecal bacterial fibre, and soluble fractions of patients with cirrhosis: effects of lactulose and lactulose plus neomycin. *J. Lab. Clin. Med*. 1987; **110**: 259.

85 Weber FL, Fresard KM, Lally BR. Effects of lactulose and neomycin on urea metabolism in cirrhotic subjects. *Gastroenterology* 1982; **82**: 213.

86 Weissenborn K, Rockert N, Hecker H *et al*. The number connection tests A and B: interindividual variability and use for the assessment of early hepatic encephalopathy. *J. Hepatol*. 1998; **28**: 646.

87 Williams R, James OFW, Warnes TW *et al*. Evaluation of the efficacy and safety of rifaximin in the treatment of hepatic encephalopathy: a double-blind, randomized, dose-finding multicentre study. *Eur. J. Gastroenterol. Hepatol*. 2000; **12**: 203.

88 Yang S-S, Wu C-H, Chiang T-R *et al*. Somatosensory evoked potentials in subclinical portosystemic encephalopathy: a comparison with psychometric tests. *Hepatology* 1998; **27**: 357.

89 Zaki AEO, Ede RJ, Davis M *et al*. Experimental studies of blood brain barrier permeability in acute hepatic failure. *Hepatology* 1984; **4**: 359.

Chapter 8
Acute Liver Failure

Acute liver failure describes the clinical syndrome of severe impairment of liver function (encephalopathy, coagulopathy and jaundice) within 6 months of the onset of symptoms. Although usually due to an acute insult (most frequently virus or drug) in a previously healthy person, acute liver failure may be the presenting feature of chronic liver disease in particular Wilson's disease, autoimmune chronic hepatitis or delta superinfection in a patient with chronic hepatitis B.

Acute liver failure developing within a few days or weeks after the acute insult has a high incidence of cerebral oedema and a risk of dying from brainstem herniation ('coning'). Other complications that may lead to death include bacterial and fungal infections, circulatory instability, renal and pulmonary failure, acid–base and electrolyte disturbances and coagulopathy. These make intensive care, referral to a specialist unit, the availability of liver transplantation and temporary hepatic support vitally important. The survival of patients has improved with such facilities, rising from about 20% in the early 1970s to 50% in the 1990s [90].

The key to optimizing treatment is early recognition of acute liver failure and transfer of the patient to a liver unit with facilities for liver transplantation. In a recent study of patients with acetaminophen (paracetamol) induced acute liver failure, 56 of the 124 patients who met the criteria for transplantation were not listed because of the rapid development of contraindications (multi-organ failure, cerebral oedema). Of those 68 patients listed for transplantation 24 developed contraindications while awaiting transplant [9]. This outcome highlights the need for rapid referral of patients with acute liver failure to a transplant centre to maximize the chance of survival.

Definition

The original definition of fulminant hepatic failure by Trey and Davidson in 1970 stipulated an onset of hepatic encephalopathy within 8 weeks of the first symptoms of illness, in patients without pre-existing liver disease. The recognition that different clinical patterns of acute liver failure relate to aetiology and prognosis, and that patients may have underlying chronic liver disease, has led to revision of this definition and the development of several classifications [10, 60].

One widely used classification broadly separates acute liver failure into hyper-acute, acute and sub-acute, based on the time interval between the development of jaundice and encephalopathy (table 8.1) [60]. An alternative classification [12] is fulminant and sub-fulminant liver failure (time from jaundice to encephalopathy less or more than 2 weeks). Late onset liver failure describes encephalopathy developing more than 8 weeks (but less than 24 weeks) after the first symptoms [32]. Classification of the patient into a particular subgroup has value in the assessment of prognosis and the urgency with which intervention is needed. In rapidly developing liver failure (hyper-acute) the chance of survival without transplantation is more than in acute liver failure. Classifications also have an important role in the interpretation of data from different units and countries and in the planning of trials.

Causes (tables 8.2, 8.3)

The most common cause of acute liver failure worldwide is viral hepatitis. The exception to this pattern is in the UK where acetaminophen self-poisoning has been the most frequent cause of acute liver failure.

Table 8.1. Classification of acute liver failure [60]

	Interval: jaundice to encephalopathy	Cerebral oedema	Prognosis	Leading causes
Hyper-acute	<7 days	Common	Moderate	Virus A, B; acetaminophen
Acute	8–28 days	Common	Poor	Non-A/B/C; drugs
Sub-acute	29 days to 12 weeks	Poor	Poor	Non-A/B/C; drugs

Table 8.2. Causes of acute liver failure

Infective
Hepatitis virus A, B, C, D, E, transfusion-transmitted virus (TTV)
Herpes simplex
Drug reactions and toxins
Acetaminophen (paracetamol) overdose
Antidepressants
Halothane
Isoniazid–rifampicin
Non-steroidal anti-inflammatory drugs
Mushroom poisoning
Herbal remedies
Ecstasy
Ischaemic
Ischaemic hepatitis
Surgical 'shock'
Acute Budd–Chiari syndrome
Metabolic
Wilson's disease
Fatty liver of pregnancy
Reye's syndrome
Miscellaneous (rare)
Massive malignant infiltration
Severe bacterial infection
Heat stroke

Table 8.3. Causes of acute liver failure: geographical variation

Cause	USA [77] 1994–1996 $n = 295$ (%)	India [1, 2] 1987–1993 $n = 423$ (%)	UK [8] 1991–1997 $n = 989$ (%)
Acetaminophen (paracetamol)	20	–	71
Viral (A, B, E*)	17	80	5
Non-A/B/C/E	15	12	7
Drug	12	5	5
Other	36	–	12

* Hepatitis E is rare in the USA and UK.

The hepatitis virus responsible varies from one geographical location to another. In the United States 30% of acute liver failure is due to virus, half being from hepatitis A and B and the remainder non-A/B/C/E [77]. The latter have typical prodromal symptoms and biochemical profiles, but no viral agent can be identified. In India, virtually all acute liver failure is viral with 40% being due to hepatitis E and 25–30% to hepatitis B [1, 2]. In Greece, the high carrier rate of hepatitis B is reflected in a greater proportion of patients having hepatitis B-related acute liver failure [61].

If appropriate testing is not done hepatitis B may not be diagnosed since one-third to one-half of patients with acute liver failure due to this virus become seronegative for hepatitis B surface antigen (HBsAg) after a few days [76]. Hepatitis B virus (HBV) core mutants may complicate the picture further because of defective production of the normal viral antigens. They are an important aetiology in cases of acute hepatitis B related acute liver failure in India [2]. In about 50% of hepatitis B patients the acute liver failure is precipitated by another factor, usually acute infection or superinfection with delta virus [76]. Reactivation of viral replication in carriers of hepatitis B or C may lead to liver failure [36, 85] after antitumour chemotherapy or following cessation of immunosuppressive therapy.

The contribution of hepatitis C varies geographically being low (0–10%) in the USA and Europe and higher (around 20%) in Taiwan [19]. Patients with superinfection of chronic hepatitis C with acute hepatitis A may be at risk of acute liver failure [86]. This risk is the basis for offering hepatitis vaccination to patients with chronic liver disease, although the cost-effectiveness of this strategy has been questioned [56].

Hepatitis E causes epidemics of acute hepatitis not only in India but also in central Asia, Mexico and China. Pregnant women are particularly at risk of acute liver failure. In Western countries acute liver failure due to hepatitis E has been reported in individuals with links to endemic areas [49].

Hepatitis G infection does not appear to be responsible for fulminant hepatic failure [78]. Transfusion-transmitted virus (TTV) has been implicated in 25% of cases of idiopathic acute liver failure [17].

Other viruses can cause a fatal hepatic necrosis especially in immunocompromised individuals. These include herpes simplex, cytomegalovirus, adenoviruses, Epstein–Barr and parvovirus B19 [46].

Acetaminophen is predictably hepato-toxic in overdose and has been the most common suicidal agent taken in the UK (Chapter 20). Since 1998 there has been a reduction in the frequency of severe acetaminophen-related hepato-toxicity [64, 83] due the sale of acetaminophen in blister packs rather than bottles, and a restriction in the number of tablets obtainable without prescription.

Acetaminophen may be hepato-toxic when taken in therapeutic doses in patients concurrently drinking excess alcohol. The characteristic picture is of very high serum aspartate transaminase levels (reported up to 48 000 iu/l) usually accompanied by a lower level of alanine transaminase [93]. Alcohol-enhanced acetaminophen hepato-toxicity, however, appears to be a less frequent clinical event in the UK [51].

Idiosyncratic drug reactions may cause acute liver failure. The most frequent culprits are anti-tuberculosis medication [1, 8], non-steroidal agents [6], anaesthetic agents and antidepressants. Acute liver failure is also reported with the recreational drug 'ecstasy' (3,4-methylene dioxymetamphetamine) [4]. Herbal remedies have been associated with hepato-cellular damage and acute liver failure [81]. Carbon tetrachloride poisoning

usually causes more renal than hepatic damage. This is true of most industrial poisons although acute liver failure can follow occupational exposure to the solvent 2-nitropropane [39].

Mushroom poisoning is common in France and in areas where unusual fungi are gathered and eaten. Hepatic failure is preceded by muscarinic effects, such as profuse sweating, vomiting and diarrhoea. Early recognition is important to optimize supportive measures and to be alerted to the possibility of liver failure [45].

Pregnant women may develop hepatic necrosis due to eclampsia or fatty liver (Chapter 27).

Vascular causes of ischaemic hepatitis include low cardiac output in a patient with underlying cardiac disease, acute Budd–Chiari syndrome, and surgical shock with or without Gram-negative septicaemia.

Massive infiltration of the liver with tumour such as in lymphoma [74] can lead to acute liver failure. Such a cause should be considered in the differential diagnosis since liver transplantation is contraindicated, and specific therapy may be life saving.

Acute Wilson's disease must always be excluded in any patient who is less than 35 years old, particularly if haemolysis is associated. In these patients acute liver failure may result from a superimposed acute viral hepatitis [75].

Autoimmune hepatitis may rarely present as subfulminant hepatic failure [40].

Clinical features

The patient, previously having been well, typically develops non-specific symptoms such as nausea and malaise. Jaundice follows and then features of hepatic encephalopathy. Coma may develop rapidly within a few days. Transfer of the patient to a specialist liver centre with a transplantation service needs to be done earlier rather than later. It must be realized that a patient with acute liver disease and prolonged coagulation can deteriorate and die. Advice from a liver centre should be sought. If on admission there is encephalopathy, immediate transfer should be discussed.

In the early stages, jaundice bears little relation to neuropsychiatric changes which may even develop before jaundice. Later, jaundice is deep. Liver size is usually small.

Vomiting is common but abdominal pain rare. Tachycardia, hypotension, hyperventilation and fever are later features. The clinician must be alert to the delay between acetaminophen overdose and liver damage which may present after a period of 2–3 days or apparent clinical recovery.

Focal neurological signs, high fever or a slow response to conventional treatment should prompt a search for alternative causes for encephalopathy.

Patients with a more gradual onset of hepatic insufficiency (over weeks rather than days, and variously called sub-fulminant, sub-acute or late onset) infrequently develop cerebral oedema. Ascites and renal failure appear, and the prognosis is worse than in those patients with a more rapid course.

Common complications of acute liver failure include infections, haemodynamic disturbances and cerebral oedema. These complications together with hepatic encephalopathy and other related problems are discussed below.

The overall mortality of an attack of acute hepatitis is about 1%, with the risk for non-A, non-B (1.5–2.5%) being greater than that for hepatitis B (1%) or A (0.2–0.4%) [41]. The short-term prognosis for acute liver failure is much worse than for liver failure associated with chronic liver disease, but in acute liver failure the hepatic lesion is potentially reversible, and survivors usually recover completely.

Late onset hepatic failure. This term refers to a group of patients in whom encephalopathy develops after an illness of more than 8 weeks but less than 24 weeks from the first symptoms, in the absence of pre-existing liver disease. In most patients, the cause cannot be found [31]. Nausea, malaise and abdominal discomfort are followed by ascites, encephalopathy and renal impairment. Survival was about 20% without transplantation. A 1-year survival of 55% has been reported after transplantation [31].

Distinction from chronic liver disease

A note should be made of any history of liver disease, the duration of symptoms and the presence of a hard liver, marked splenomegaly and vascular spiders on the skin (table 8.4). A problem arises in the alcoholic where recent heavy drinking adds acute hepatitis to underlying chronic liver disease. In these circumstances the liver is large. Potential reversibility of acute alcoholic hepatitis merits more supportive effort than could be given to the usual end-stage cirrhosis where the liver would not be expected to regenerate.

Investigations (table 8.5)

Blood is taken to identify problems needing immediate

Table 8.4. Liver failure: distinction between acute and acute-on-chronic types

	Acute	Acute-on-chronic
History	Short	Long
Nutrition	Good	Poor
Liver	±	+ hard
Spleen	±	+
Spiders	o	++

Table 8.5. Investigations of acute liver failure

Haematology
Haemoglobin, platelets, WBC, prothrombin, blood group
Biochemical
Blood glucose, serum bilirubin, aspartate transaminase, alkaline phosphatase, albumin, globulin, immunoglobulins
Serum urea, sodium, potassium, bicarbonate, chloride, calcium, phosphate
Serum amylase
Store 8 ml serum for later use
Microbiology, virology
Hepatitis B antigen and IgM anticore
Hepatitis A (IgM) antibody
Hepatitis C antibody
Hepatitis E antibody
Serum anti-delta
Blood culture, aerobic and anaerobic
Sputum, urine, stool (culture and microscopy)
Store serum for virological studies
Other essential
Chest X-ray, electrocardiogram, fluid intake and output, blood gases
Additional (not always necessary)
Blood alcohol or other drug level
Urine electrolyte concentration
Plasma fibrin degradation products
Hepatic scan

attention, to establish a baseline for hepatic and renal function, to establish the cause and to check criteria for survival/transplantation.

Haematology

The prothrombin time (together with the degree of encephalopathy) is central to the assessment of the severity of the clinical situation, and its progress. Haemoglobin and white count are obtained. A falling platelet count may reflect disseminated intravascular coagulation.

Biochemistry

Blood glucose, blood urea, electrolytes and creatinine are measured. Bilirubin, albumin, transaminase, alkaline phosphatase and amylase are routinely done. Serum bilirubin is important prognostically for non-acetaminophen patients. Serum albumin is usually initially normal, but later a low albumin reflects a poor prognosis. The transaminases are of little prognostic value. Levels tend to fall as the patient's condition worsens. Blood gas analysis for pH is important in the prognostic evaluation of acetaminophen-related liver failure.

Virological markers

Acute hepatitis A should be diagnosed by a serum IgM anti-A antibody. Serum HBsAg is checked, but the IgM core antibody is necessary for certain diagnosis. HBsAg may have been cleared and hepatitis B surface antibody (HBsAb) will not have appeared. Serum HBV DNA is then usually negative. Such rapid viral clearance indicates a favourable prognosis, perhaps because it implies a good immune response to the HBV. In those positive for HBV, serum anti-delta should be sought. Anti-hepatitis C virus (anti-HCV) should be performed, but is likely to be negative this early in the disease (Chapter 18). PCR for HCV RNA is required for diagnosis of HCV-related acute hepatic failure.

Hepatitis E serology should be done if geographically appropriate.

Electroencephalogram (EEG)

This has been used to assess the clinical state and determine prognosis (fig. 8.1). However, the guidelines now used for decisions on clinical management, and in particular liver transplantation, no longer depend on the EEG. Repeated measurement may, however, be necessary when clinical and laboratory features do not move in the same direction.

Continuous EEG recording, however, has shown 50% of patients with acute liver failure to have sub-clinical seizure/epileptiform activity. This is not recognized clinically without EEG because the patient is paralysed and ventilated. EEG monitoring has been recommended for patients reaching stage 3 or 4 encephalopathy [32].

Scanning and liver biopsy

Scanning will show a reduction in liver size. However, correlation of liver size with survival is imprecise. Liver histology shows considerable variability of necrosis from area to area which may be prognostically misleading [38].

In a retrospective study a liver volume of less than 1000 ml and/or hepatic parenchymal necrosis of greater than 50% indicated a poor prognosis, but findings above these two thresholds did not necessarily indicate a good outcome [79]. Hepatic regenerative changes on histology (associated with less than 50% parenchymal necrosis) were present in the good prognostic group. However, both CT scanning and transjugular liver biopsy are done in the radiology department and transfer of the patient can worsen haemodynamic instability and intercranial hypertension. From the practical point of view clinical and laboratory data rather than scanning and biopsy are used for decision making.

CT of the brain is unreliable in detecting early cerebral

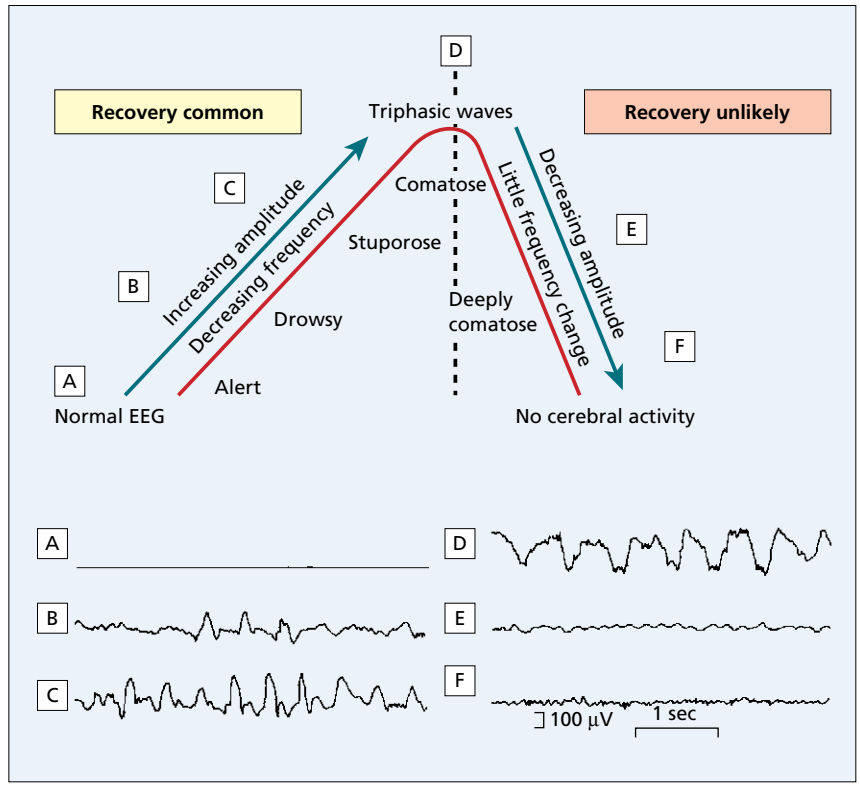


Fig. 8.1. Evolution of the EEG in liver failure. The progression from grade A to D is marked by increasing amplitude, decreasing frequency and increasing drowsiness. At D, triphasic waves appear and the interrupted line indicates the limit beyond which recovery is unlikely. From E to F amplitude decreases with little frequency change and at F there is no cerebral activity.

oedema, and the movement of the patient to the radiology unit carries the risk of deterioration.

Associations

Hepatic encephalopathy

The neurological sequelae of acute liver failure are hepatic encephalopathy and cerebral oedema with raised intracranial pressure (ICP). Clinically they overlap (fig. 8.2). Early in the clinical course encephalopathy usually develops without evidence of increased ICP. Once stupor to deep coma with or without decerebrate posturing (grade 3–4 encephalopathy) develops, the patient is at high risk of developing cerebral oedema.

The pathogenesis of hepatic encephalopathy is multifactorial (Chapter 7) and centres on failure of the liver to remove toxic, mainly nitrogenous, substances from the circulation. In contrast to the coma of cirrhotic patients, portal-systemic encephalopathy due to shunting of blood past the liver is of minor importance. Blood ammonia (and presumably amine) levels are increased but do not correlate with the depth of coma or the prognosis. Measurement of blood ammonia is not necessary for management.

The onset of encephalopathy is often sudden. It may precede jaundice. The features are unlike those seen in chronic liver disease with agitation, changes in personality, delusions and restlessness. The patient may show

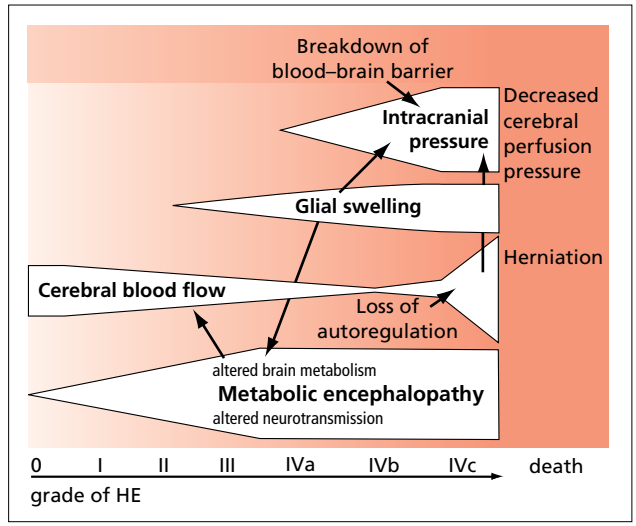


Fig. 8.2. Brain dysfunction in acute liver failure. Proposed interrelation of metabolic encephalopathy, ICP and changes in cerebral blood flow during the progression of the disease. HE, hepatic encephalopathy. (From [33] with permission.)

antisocial behaviour or character disturbance. Nightmares, headaches and dizziness are other inaugural, non-specific symptoms. Delirium, mania and fits indicate stimulation of the reticular system. Unco-operative behaviour often continues while consciousness is clouded. The delirium is of the noisy, restless variety and

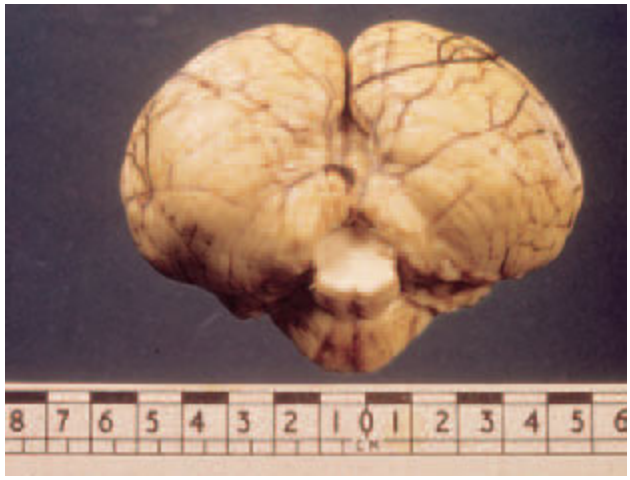


Fig. 8.3. Cerebral oedema in a patient who died in hepatic coma. Note the indented cerebellum.

attacks of screaming are spontaneous or induced by minor stimuli. Violent behaviour is common. 'Flapping' tremor may be transient and overlooked. Fetor hepaticus is usually present.

The prognosis for patients with grade 1 or 2 encephalopathy (confused or drowsy) is good. For grade 3 or 4 it is much poorer.

Cerebral oedema (intracranial hypertension)

Acute liver failure is associated with cerebral oedema, which can lead to an increase in intracerebral pressure. This is uncommon in patients with grade 1 or 2 encephalopathy, but develops in the majority with grade 4. Raised intracerebral pressure can lead to brainstem herniation (fig. 8.3) and is the most common cause of death, being found in 80% of fatal cases. There is a generalized or focal increase in brain volume due to an increase in water content. The cause is probably multifactorial and currently not fully understood [15, 48]. Two mechanisms have been proposed: cytotoxic and vasogenic.

The *cytotoxic* hypothesis depends on the accumulation of osmolytes such as glutamine, particularly in astrocytes, with subsequent osmotic uptake of water into the cells. In the brain astrocytes are the site of ammonia metabolism by amidation of glutamate to glutamine. In acute liver failure cerebral glutamine concentrations rise. Brain-stem herniation correlates with arterial ammonia concentration [20].

The *vasogenic* hypothesis depends on changes in cerebral blood flow and the blood–brain barrier. Cerebral blood flow has a wide variation between individuals with acute liver failure and it is not clear whether this is related to systemic changes or is locally induced. Cerebral vasodilatation is associated with a poor prognosis. Hypoxia and prostaglandins may be involved. It is possible that the changes in cerebral blood flow may also be related to glutamine through the production of nitric oxide. Surges of intracranial hypertension may result from vascular engorgement secondary to inappropriate vasodilatation.

Disruption of the blood–brain barrier with leakage of plasma into the cerebrospinal fluid has been proposed as a mechanism for cerebral oedema but this hypothesis has not been substantiated.

The net blood supply to the brain depends on the balance between carotid arterial pressure and intracerebral pressure. Cerebral blood flow appears to be inadequate in most patients with grade 4 encephalopathy resulting in cerebral hypoxia [89], and these changes may be related to the development of cerebral oedema. Cerebral blood flow autoregulation (maintained blood flow despite falling or rising blood pressure) is lost in patients with fulminant hepatic failure [47]. Loss of this protective mechanism could exacerbate cerebral changes due to systemic hypotension (giving cerebral ischaemia) and cerebral hyperperfusion (increasing cerebral blood volume and interstitial water) [48].

Clinically, raised intracerebral pressure is suggested by systolic hypertension (sustained or intermittent), increased muscle tone and myoclonus which progress to extension and hyperpronation of the arms and extension of the legs (decerebrate posturing). Dysconjugate eye movements and skewed positions of the eyes may be seen. If not controlled by treatment, this clinical picture progresses to loss of pupillary reflexes and respiratory arrest from brainstem herniation.

Coagulopathy

The liver synthesizes all the coagulation factors (except factor VIII), inhibitors of coagulation and proteins involved in the fibrinolytic system (Chapter 4). It is also involved in the clearance of activated clotting factors. The coagulopathy of fulminant hepatic failure is thus complex and due not only to factor deficiency, but also to enhanced fibrinolytic activity most likely caused by intravascular coagulation [63]. The platelet count may fall due to increased consumption or reduced production, and platelet function is also abnormal in fulminant hepatic failure.

The resulting coagulopathy predisposes to bleeding. This is a potential cause of death; it may be spontaneous, from the mucous membranes, from the gastrointestinal tract or into the brain.

The prothrombin time is the most widely used test to assess coagulation. It is a guide to prognosis and is one of the criteria used in deciding whether transplantation should be done (see table 8.7) [58].

Hypoglycaemia, hypokalaemia, metabolic changes

Hypoglycaemia is found in 40% of patients with acute liver failure. It may be persistent and intractable. Plasma insulin levels are high due to reduced hepatic uptake; gluconeogenesis is reduced in the failing liver. Hypoglycaemia can cause rapid neurological deterioration and death and is one aspect of the condition which can be treated satisfactorily.

Hypokalaemia is common and due in part to urinary losses with inadequate replacement, and administration of glucose. Serum sodium levels tend to be low, falling markedly in the terminal stages. Other electrolyte changes include hypophosphataemia, hypocalcaemia and hypomagnesaemia.

Acid–base changes are common. Respiratory alkalosis is due to hyperventilation, probably related to direct stimulation of the respiratory centre by unknown toxic substances. Respiratory acidosis can be caused by elevated ICP and respiratory depression, or pulmonary complications. Lactic acidosis develops in about half of the patients reaching grade 3 coma. It is related to inadequate tissue perfusion due to hypotension and hypoxaemia. A metabolic acidosis is more frequent in acetaminophen-induced acute liver failure; the fall in pH is one of the criteria used in transplant decisions (see table 8.7).

Infection [70]

Ninety per cent of patients with acute liver failure and grade 2 or more encephalopathy have clinical or bacteriological evidence of infection (fig. 8.4) [68]. Twenty-five per cent have associated bacteraemia. The majority of infections are respiratory. The high rate of infection can be related to poor host defences with impaired Kupffer cell and polymorph function and to the reduction of factors such as fibronectin, opsonins and chemoattractants, including components of the complement system. Poor respiratory effort and cough reflex, and the presence of endotracheal tubes, venous lines and urinary catheters place the patient at increased risk.

Infections in the blood, respiratory tract and urine are usually detected within 3 days of admission. In some cases the source of infection may never be found, but tips of intravenous catheters should be cultured after removal, and are often incriminated. The typical manifestations of sepsis, such as fever and leucocytosis, may be absent (fig. 8.4). More than two-thirds of infections are due to Gram-positive organisms, usually staphylococci, but streptococci and Gram-negative bacilli are also found.

Fungal infections are found in about one-third of patients, often unrecognized and ominous [69]. These patients share particular clinical features (table 8.6). Fungal resistance to short-term prophylaxis with fluconizole is unlikely [35].

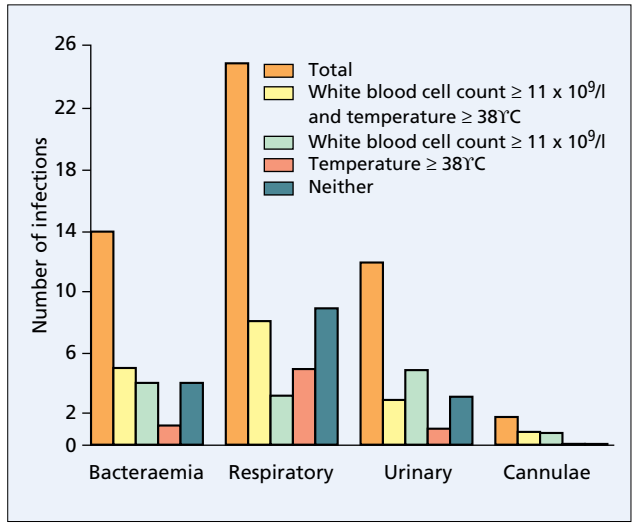


Fig. 8.4. Clinical signs of bacterial infection related to significant microbiological cultures in 50 patients with acute liver failure. Raised temperature and white cell count were poor indicators of bacterial infection. (From [68] with permission.)

Table 8.6. Features of systemic fungal infection [69]

Deterioration in coma grade after initial improvement
Pyrexia unresponsive to antibiotics
Established renal failure
Markedly elevated white cell count

Overall, infections make a major contribution to clinical deterioration and death. The severity of the systemic inflammatory response relates to prognosis [72].

Renal

Due to decreased urea synthesis by the liver, the blood urea concentration may not be a good indicator of kidney function, and the serum creatinine is preferred. Renal failure, which develops in about 55% of patients, may be related to liver cell failure itself (hepato-renal syndrome), to acute tubular necrosis secondary to complications of acute liver failure (sepsis, endotoxaemia, bleeding, hypotension), or direct nephrotoxicity of the drug or other insult responsible for the hepatic damage (e.g. acetaminophen overdose). The hepato-renal syndrome (Chapter 9) results from a combination of factors including a hyperdynamic circulation with lowered renal perfusion pressure, activation of the sympathetic nervous system, and increased synthesis of vasoactive mediators which decrease glomerular capillary ultrafiltration [54].

Haemodynamic changes: systemic hypotension

Hypotension is a feature of liver failure. It is associated with a low peripheral vascular resistance and increased cardiac output which relate to the degree of hepatic damage. Apart from sepsis and endotoxaemia, the cause is unclear but possible mediators include prostaglandins and nitric oxide. There is covert tissue hypoxia at the microcirculatory level with conse-quent lactic acidosis. The circulatory changes are associated with decreased cerebral perfusion and renal vasoconstriction.

Cardiac dysrhythmias of most types are noted in the later stages and relate to electrolyte abnormalities, acidosis, hypoxia and the insertion of catheters into the pulmonary artery.

Depression of brainstem function due to cerebral oedema and herniation eventually leads to circulatory failure.

Pulmonary complications

These include aspiration of gastric contents or blood, atelectasis, infection and respiratory depression due to brainstem compression. Intrapulmonary arteriovenous shunting adds to the hypoxia. There may be pulmonary oedema. Adult respiratory distress syndome (ARDS) is usually refractory to treatment and fatal.

Chest X-rays show abnormalities in over half of patients. These include lobar collapse, patchy consolidation, aspiration pneumonia and, in one-quarter, non-cardiogenic pulmonary oedema.

Acute pancreatitis

Acute haemorrhagic and necrotizing pancreatitis is frequent in patients dying with acute liver failure. It is difficult to recognize in the comatose patient but, rarely, it may be the cause of death. Serum amylase levels are raised in about one-third of patients and should be monitored.

Aetiological factors include haemorrhage into and around the pancreas, the causative virus, corticosteroid therapy and shock.

Prognosis

The overall survival for those reaching grade 3 or 4 encephalopathy is 20% without transplantation. If only grade 1 or 2 coma is reached, survival is around 65%. Those who survive do not develop cirrhosis.

The advent of successful liver transplantation for acute liver failure has made prediction of survival particularly important. Indications, whether clinical or laboratory, that spontaneous recovery is unlikely are therefore of vital importance. Prognosis is worse in older patients, although under 10 year olds are also at particular risk [58]. Coexistence of other disease worsens the prognosis.

Aetiology is important. In one series, 12.5% of halothane-related patients survived without transplantation compared with 66% for hepatitis A, 38.9% for hepatitis B and 50% for acetaminophen overdose [59].

If any precipitant of encephalopathy can be identified, particularly the administration of sedatives, the prognosis is better. The patient improves as the drug is eliminated.

Unfavourable clinical signs include a small liver and ascites. Decerebrate rigidity, with loss of the oculovestibular reflex and respiratory failure are particularly ominous. Such patients, if they survive, may rarely be left with residual brainstem and cerebral cortical injury [57].

Prothrombin time is the best indicator of survival [58]. The association of a clotting factor V concentration of less than 15% with coma is also ominous [11]. At this level survival is only 10% for all aetiologies except hepatitis A and acetaminophen overdose where the outlook is better. Hypoglycaemia is another bad sign.

Liver biopsy is rarely indicated but, if necessary, can be performed by the transjugular route. The extent of hepato-cellular necrosis and interlobular confluent necrosis is related to outcome. Hepatic parenchymal necrosis of more than 50% is associated with a reduced survival [79].

An important univariate and multivariate analysis was made of predictive factors in 586 patients with acute liver failure managed medically (table 8.7) [58]. In patients with viral hepatitis and drug reactions, three static variables—aetiology (non-A–E hepatitis or drug), age (less than 10 years and more than 40 years) and duration of jaundice before encephalopathy (greater than 7 days)—and two dynamic variables, a serum bilirubin exceeding 18 mg (300 µmol/l) and a prothrombin time exceeding 50 s, indicated a poor prognosis. In acetaminophen overdose, survival correlated with arterial blood pH, peak prothrombin time and serum creatinine.

These criteria have been validated by other centres and some have found a slightly lower predictive accuracy (71 and 68% for acetaminophen-induced and non-acetaminophen-induced acute liver failure) [3]. Acute Physiology and Chronic Health Evaluation scores (APACHE II and III) may improve decision making and the defining of patients in clinical trials [9, 52].

Another commonly applied set of criteria uses the concurrent presence of confusion or coma and an age-corrected factor V between 20 or 30% of normal [14].

These criteria use clinical and laboratory data that are straightforward to collect and there is currently no other generally accepted system in use. The King's College criteria are most widely used.

Assessment of hepatocyte necrosis on liver biopsy, or reduced liver volume on CT scanning, are used in some

Table 8.7. King's College Hospital criteria for liver transplantation in acute liver failure [58]

Acetaminophen (paracetamol)
pH < 7.30 (irrespective of grade of encephalopathy)
or
Prothrombin time >100 s (INR > 7) and serum creatinine >300 μmol/l in patients with grade III or IV encephalopathy

Non-acetaminophen patients
Prothrombin time >100 s (INR > 7) (irrespective of grade of encephalopathy)
or
Any three of the following variables (irrespective of grade of encephalopathy)
- age <10 or >40 years
- aetiology: non-A–E hepatitis, 'viral' hepatitis no agent identified, halothane hepatitis, idiosyncratic drug reaction
- duration of jaundice before onset of encephalopathy >7 days
- prothrombin time >50 s (INR > 3.5)
- serum bilirubin >300 μmol/l

centres, and in the case of biopsy may alter the diagnosis in 17% of cases [27]. However, debate as to their discriminant value and practical problems in arranging them safely, at the appropriate time, have limited their use.

The causes of death are: cerebral oedema, infection, bleeding, respiratory and circulatory failure, renal failure, hypoglycaemia and pancreatitis.

Survival depends on the capacity of the liver to regenerate and this is almost impossible to predict. It is probably under humoral control and a hepatocyte growth factor has been identified. Human hepatocyte growth factor is increased in the blood in patients with acute liver failure, but is not a useful prognostic measure.

No criteria are ever likely to predict the outcome of acute liver failure with certainty. However, prediction of a low chance of survival, for example 20%, is clinically useful in directing a decision to transplant with a 60–80% chance of survival.

Treatment [8]

Over the years survival of patients with acute liver failure has improved due to meticulous attention to the detail of good supportive care combined with better knowledge of the most important functions lost when the liver cell fails. These patients are mercifully rare, and should be treated in a special unit with experience in the management of acute liver failure and facilities for liver transplantation. The complex problems associated with multiple organ failure require close monitoring and prompt treatment (table 8.8). The clinical state of the patient may change rapidly. Frequent review is essential. Such patients should be managed in a high dependency or intensive care area by an appropriately trained team of nurses.

Table 8.8. Management of acute liver failure

Problem	Treatment
Hepatic encephalopathy	Reduce protein by mouth Phosphate enema twice daily No sedation Lactulose 30 ml dose
Cerebral oedema	Intravenous mannitol Avoid hyperthermia Monitor ICP
Hypoglycaemia	100 ml 50% glucose if blood glucose falls below 3 mmol/l Check blood glucose hourly Infusion 10–50% dextrose Check hypokalaemia
Hypocalcaemia	10 ml 10% calcium gluconate i.v. daily
Renal failure	Haemofiltration
Respiratory failure	Intubation Ventilation Oxygen Maintain normal blood gases
Hypotension	Albumin Vaso-constrictors
Infection	Frequent cultures Prophylactic antibiotics (see text) Specific antibiotics later
Bleeding	No arterial puncture H_2 blocker Sulcralfate Fresh frozen plasma and platelets

ICP, intracranial pressure.

The measures described below apply predominantly to patients in grade 3 and 4 coma and must be modified for those in the lower grades.

The patient is barrier nursed. Attendants should wear gloves, gowns and masks and should have been vaccinated against hepatitis B. The grade of encepalopathy (Chapter 7) must be charted hourly.

Temperature, pulse and blood pressure should be recorded at least hourly and preferably continuously. A strict fluid balance chart recording input and output is imperative. Care should be taken to avoid fluid overload.

A naso-gastric tube is passed. An H_2-antagonist or proton pump inhibitor is given to reduce the risk of gastroduodenal erosions and bleeding. Lack of acid may increase gastric bacteria. Prophylaxis using sulcralfate is an alternative. Enteral nutrition should be given containing calories appropriate to the individual patient. Earlier in the course of the illness oral supplements should be given.

To detect early evidence of complications, such as renal and respiratory failure, monitoring using invasive

methods is necessary so that preventative measures can be taken. A urinary catheter, central venous catheter and arterial line should be placed, the last two after clotting factor and if necessary platelet infusion.

Hypoglycaemia is frequent, and on arrival the blood sugar is estimated; 100 ml of 50% glucose is given intravenously if the blood glucose is less than 60 mg/dl (3.5 mmol/l). A continuous infusion of dextrose 5 or 10% is given, the volume according to fluid needs. If enteral nutrition is given hypoglycaemia is less likely.

The blood sugar is checked every hour and further 50% glucose given if hypoglycaemia recurs. If it is necessary to move a patient from one centre to another, a 20% dextrose infusion should be given during the journey.

Hypomagnesaemia is a frequent finding often associated with hypokalaemia.

Respiratory status is monitored using pulse oximetry. Oxygen by mask is given. Mechanical ventilation is necessary if respiratory failure is shown by a rise in arterial P_{CO_2} (>6.5 kPa) or fall in P_{O_2} (<10 kPa), although this is a rare indication. More often endotracheal intubation is necessary for the comatose patient to prevent aspiration or when sedation is becoming necessary because of agitation.

Infections occur in up to 90% of patients with acute liver failure [68]. Particular risk factors are a high maximum INR and intubation of the trachea [67].

To pre-empt *septic complications*, sputum and urine should be sent for culture daily. Venous and arterial line sites should be inspected regularly; cannulas should be replaced if inflamed, or if fever develops, or otherwise routinely every 3–5 days. The tip of the catheter is sent for culture.

Studies of prophylactic selective systemic antibiotics and intestinal decontamination have shown benefit both individually and in combination. Their use is, however, controversial. Prophylactic intravenous antibiotics reduce infection by 80% but do not improve outcome or reduce the length of stay. Selective enteric decontamination adds no benefits to parenteral antibiotics (fig. 8.5) [71]. In this study multi-resistant bacteria were found and were thought to be related to the third-generation cephalosporin used. The most appropriate antibiotic regimen will depend on the incidence, type and sensitivity of bacteria on the individual liver unit. Regular microbiological surveillance is essential. Blanket use of broad-spectrum antibiotics should be narrowed down to a specific choice once positive cultures are available.

Without prophylaxis fungal infections are found in about 30% of patients [69]. Trials in which oral amphotericin B have been used have reduced the rate of fungal infection below 5% (fig. 8.5) [71]. Treatment of systemic fungal infection is with amphotericin B and flucytosine.

Hypotension is extremely difficult, if not impossible to control. When crystalloid or albumin infusions do not correct the fall in blood pressure, a vaso-constrictor agent such as noradrenaline (norepinephrine) may be given although combinations of vaso-active drugs may be more useful [8].

When *renal failure* develops, monitoring of fluid balance becomes even more critical. Dopamine infusion may slow or reverse the change in renal function although its use is questionable in critically ill patients [8, 54]. Continuous arteriovenous haemofiltration [22] is indicated when the serum creatinine rises above about 400 µmol/l (4.5 mg/dl), and to correct fluid overload, acidosis and hyperkalaemia. Haemodialysis on an intermittent basis causes haemodynamic instability. It may increase ICP.

Coagulopathy is managed by routine intravenous vitamin K. Fresh frozen plasma and platelets are given if there is bleeding or for invasive procedures such as insertion of an arterial line or extradural pressure transducer.

Hepatic encephalopathy is treated by the usual routine (Chapter 7) with no protein by mouth, and phosphate enemas. Lactulose is given via the naso-gastric tube (initially 15–30 ml). Exacerbating factors, such as sepsis, electrolyte imbalance and haemorrhage, should be treated. Sedation must be avoided if at all possible. If absolutely necessary, if the patient is violent, a small dose of a short-acting benzodiazepine (e.g. midazolam) may be given. Neomycin is avoided because of possible nephrotoxicity. Antibiotics given to prevent or treat infection will also serve to treat the encephalopathy. Flumazemil is a benzodiazepine-receptor antagonist which can produce variable, short-lived but distinct improvement in some patients with hepatic encephalopathy. This drug at present, however, has no defined role in the management of encephalopathy.

Cerebral oedema is an important cause of death. *ICP monitoring* with an epidural pressure transducer is used in specialist units [16, 43, 50] allowing detection of subclinical episodes of intracranial hypertension. Control of cerebral oedema may prolong survival giving a greater chance of the patient reaching transplantation [43]. Complications of transducer insertion, including intracranial bleeding and sepsis, occur in about 4%, with fatal haemorrhage in 1% [16]. The type of transducer chosen depends on local expertise, although the complication rate with epidural placement is less than with sub-dural bolts and parenchymal monitors [16]. A platelet count of less than 50×10^9/litre is regarded as a contraindication because of the risk of bleeding [43]. Increases of ICP to 25–30 mmHg sustained for more than 5 min are treated with mannitol 1 g/kg body weight (up to 100 g given in a 20% solution as an intravenous bolus). Urine output must be monitored to confirm a diuresis. In patients with renal failure, mannitol should only be used in combina-

tion with ultrafiltration, to avoid hyperosmolarity and fluid overload.

ICP monitoring allows the cerebral perfusion pressure (mean arterial pressure minus ICP) to be calculated. A pressure of less than 50 mmHg has been considered a contraindication to transplantation because of a poor neurological outcome. However, patients with a lower perfusion pressure and prolonged intracranial hypertension (greater than 35 mmHg for 24–38 h) have survived with complete neurological recovery [23].

Monitoring of the *jugular bulb venous oxygen saturation* may be used but this approach is not widespread. The jugular vein is catheterized retrogradely until the catheter tip sits in the jugular bulb. Samples of blood are taken; oxygen saturations of less than 55% indicate cerebral ischaemia. This is managed either by increasing blood flow, decreasing ICP or using agents to reduce the metabolic demands of the brain. Oxygen saturations of greater than 85% may reflect a hyperaemic cerebral circulation which similarly needs correcting [48].

It is important to nurse the patient with the upper trunk and head elevated between 20 and 30° above the horizontal since this lowers ICP. Further elevation may raise ICP and lower mean arterial pressure [21]. Corticosteroids are not effective. Hyperventilation, to induce cerebral vasoconstriction and reduce cerebral blood volume, has an effect which is not sustained [29]. Thiopental infusion by decreasing the cerebral metabolic rate, is effective in some patients where mannitol and haemofiltration have failed [37] but because of possible haemodynamic effects should be done with ICP monitoring.

Hypothermia prevents brain oedema experimentally either by reducing blood–brain transfer of ammonia and/or by reducing extra-cellular brain glutamate concentrations [73]. Preliminary studies in patients with acute liver failure also show a reduction in ICP. Further studies are needed to optimize this approach and determine whether it can be used to stabilize patients until a donor liver is available [42]. These results emphasize however, that hyperthermia should be avoided.

When ICP monitoring cannot be done, the clinical team should be alert for signs of raised ICP (see above), and administer mannitol if this is suspected.

Epileptiform activity detected by EEG should be treated with phenytoin, to reduce the increase in cerebral oxygen consumption that occurs [32].

N-acetylcysteine, initially introduced and validated for the acute treatment (12–15 h) of acetaminophen self-poisoning, has been shown to be of value in patients with acetaminophen-induced acute liver failure when continued for longer than the first 16 h [44]. Survival is increased, and cerebral oedema, hypotension and renal failure reduced. A previous study suggesting that *N*-acetylcysteine improves blood flow and oxygen delivery and extraction in acute liver failure has not been substantiated [87].

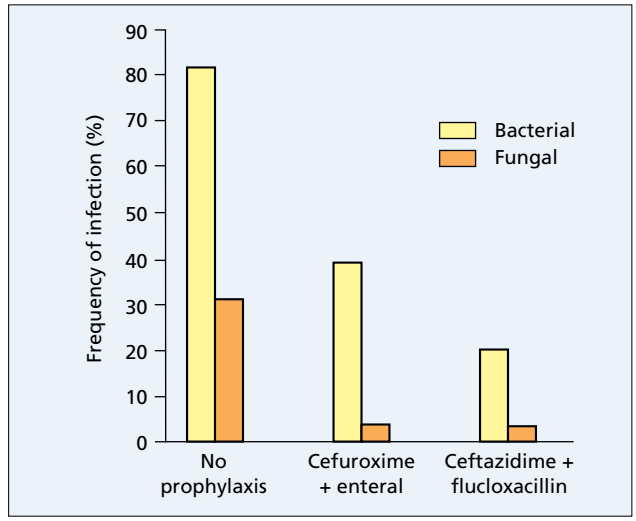


Fig. 8.5. Prevention of sepsis in acute liver failure: comparison of results from studies at King's College Hospital. Prophylactic parenteral antibiotics reduced infections. Enteral decontamination had no additional benefit. Oral amphotericin B (antifungal) was given with both antimicrobial regimens. (Data from [67, 68, 70, 71] courtesy of Dr N. Rolando.)

Corticosteroids. Large doses of corticosteroids are of no benefit in acute liver failure. They may even be of negative value. The complications include infections and gastric erosions.

Artificial and bio-artificial liver support

The aim is to provide support until the native liver recovers its function spontaneously, or until a donor liver is available. Much research has focused on the use of columns or membranes that would allow removal of toxic metabolites. Charcoal haemoperfusion, despite early promise, has not shown benefit in controlled trials [59]. More recent *artificial liver support* systems (Bio-Logic-DT™ and the Molecular Absorbent Recirculating System [MARS]) [65] use systems which attempt to remove tightly protein-bound toxins by perfusion over resins or albumin. The MARS system uses an albumin-impregnated dialysis membrane and a dialysate containing 5% human albumin. The dialysate is perfused over charcoal and resin adsorbents and finally dialysed to remove water-soluble toxins including ammonia. Preliminary experience with both of these artificial liver support systems have shown some benefit but controlled studies in the setting of acute liver failure are awaited.

Bio-artificial liver support systems use bio-reactors containing viable hepatocytes in culture. Three systems have reached an advanced stage of clinical assessment:

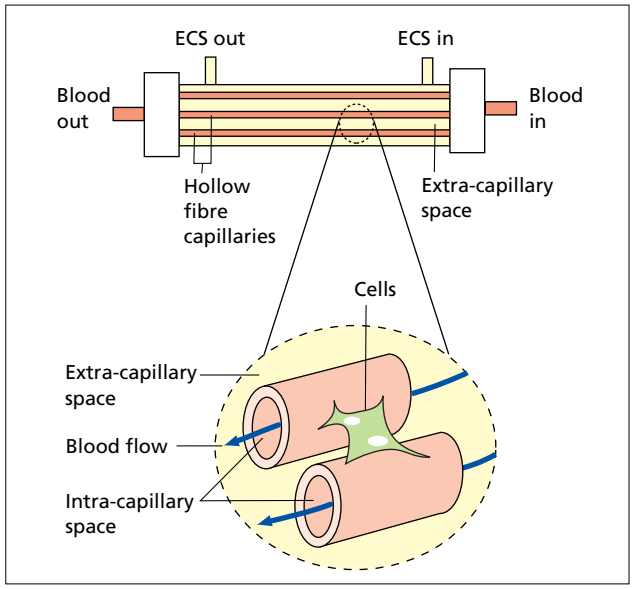


Fig. 8.6. Bio-artificial liver support. Diagram of hollow fibre cartridge device. Cells are cultured on the extra-capillary side of the semipermeable fibres while blood or medium flows through the lumen. ECS, extra-capillary space. (From [82] with permission.)

the 'Bio-artificial Liver' (BAL), the 'Extra-corporeal Liver Assist Device' (ELAD) [30] and the 'Berlin Extra-corporeal Liver support System' (BELS) [28, 65]. The BAL and BELS systems use primary porcine hepatocytes, while the ELAD system uses a hepatoblastoma cell line. Anticoagulated plasma or whole blood is passed through a device allowing metabolic transfer between cells and perfusate (fig. 8.6). Protocols differ as to whether the plasma or blood is first passed over a charcoal column or other device. None of the systems use primary human hepatocytes. Whether the use of a mixture of parenchymal and non-parenchymal cells is more effective is not yet known.

The function of such bio-artificial liver devices has been shown experimentally. Preliminary results in patients with acute liver failure have been encouraging with a reduction in encephalopathy, serum ammonia and ICP, an increase in cerebral perfusion and an improvement in prothrombin time, factor 5 level and galactose elimination capacity. A pilot controlled study of the ELAD system showed no statistically significant benefit. In patients with acute liver failure treated with the BAL system, 18 showed statistically significant improvement in level of consciousness, a reduction in intracranial hypertension and an increase in cerebral perfusion pressure [88]. A randomized control trial is in progress. These techniques hold promise for the future but whether the results will ever regularly lead to a recovery of the native liver rather than bridge the gap to successful transplantation remains to be seen.

Liver transplantation

Hepatic transplantation has to be considered for patients reaching grade 3 and 4 coma due to fulminant hepatic failure. The survival rate for these patients without transplantation is usually less than 20%. Survival rates with transplantation are 60–80%. However, it is frequently difficult to judge both the right time and the necessity for transplant. If too early, the operation may be unnecessary and the patient will be committed to lifetime immunosuppression; if too late, the chances of successful transplantation are reduced.

Indications [92]. The decision to select ('list') an individual for potential transplant is based on validated criteria (see prognosis section above). These include pH, age, aetiology, time between onset of jaundice and encephalopathy, prothrombin time and serum bilirubin level [58], or a plasma factor V level of less than 20% of normal [11]. In the original studies, use of these criteria identified about 95% of fatal cases. The predictive accuracy of these criteria in subsequent studies is in some cases above and in others below the original report, but the criteria remain central to the assessment of the patient admitted with acute liver failure [3, 62, 80].

However, there is a delay on average of about 2 days in obtaining an acceptable donor liver after putting out the request. Although the majority will have survived and still require a transplant, and some will have improved and not need a transplant, some will have died (table 8.9) or developed problems that make them inappropriate to transplant. The prognostic criteria have a lower predictive value (around 50%; range 17–82%) in identifying which patients will not need a transplant [66]. This has led to the suggestion that all patients with hyper-acute and acute (fulminant and sub-fulminant) liver failure should be listed for transplantation on admission to hospital, or when they reach grade 3 encephalopathy [62], and that the decision as to whether or not transplantation is necessary should be reviewed when the donor liver becomes available.

These prognostic uncertainties emphasize the need for early dialogue and transfer of patients with acute liver failure to a specialist liver unit with the facilities for transplantation (table 8.10). Children in particular

Table 8.9. Hepatic transplantation for acute liver failure (Paris experience) [7]

Number of patients	112
Died waiting	18%
Transplanted	92
Alive	71%

Table 8.10. Checklist of information when referring patient with fulminant hepatic failure to liver unit

Patient details
Probable cause of liver failure
Risk factors
Drug overdose, when taken, blood levels, treatment
Past medical history
Previous surgery
Previous psychiatric history
Cardiorespiratory status
Current grade of encephalopathy
Assessment of renal and septic status
Obvious Kayser–Fleischer rings
Weight and height
Investigations
Full blood count, platelets
Prothrombin time (fibrin degradation products)
Urea, sodium, potassium, bicarbonate, creatinine, blood glucose, amylase
Bilirubin, transaminase, alkaline phosphatase, albumin
Blood gases
Urine output
Positive bacteriological culture
Viral serology (HAV IgM, HBsAg, HB core IgM)
Chest X-ray
Central venous pressure
Current medication/fluid regime
Scanning data: liver, brain
Electroencephalogram

should be transferred before the development of hepatic encephalopathy.

Contraindications. Absolute contraindications are active ongoing infection; ARDS and inspired oxygen of greater than 60%; fixed dilated pupils for prolonged periods of time (1 h or more); and cerebral perfusion pressure <40 mmHg or ICP >35 mmHg for longer than 1–2 h [92]. Relative contraindications are a rapidly increasing requirement for vasopressor support, infection under treatment and a history of psychiatric problems [55].

Results. Technically the operation is less difficult than that for chronic liver disease as portal venous collaterals and adhesions are not present. Coagulation defects can be controlled with plasma derivatives and platelets.

Published results worldwide show a survival between 60 and 90% (table 8.11), the variation probably reflecting the severity of illness at the time of transplantation and the criteria for proceeding with transplantation. Survival is less than that seen overall when transplantation is done for liver cirrhosis [34]. The results in acute liver failure compare with an estimated 20% survival of patients reaching this stage of disease who are not transplanted. Donor livers are hard to find at short notice, and livers that are not ideal, e.g. with an incompatible blood group or steatosis, may be used. This worsens the results [14].

Table 8.11. Transplantation for fulminant hepatic failure

Centre	References	Date	Number	Survival (%)
London/ Cambridge	Williams and O'Grady [91]	1990	56	58
Paris	Devictor *et al*. [24]	1992	19	68
San Francisco	Ascher *et al*. [5]	1995	35	92
Pittsburgh	Dodson *et al*. [26]	1994	115	60
Paris	Bismuth *et al*. [14]	1995	116	68
USA (12 centres)	Schiødt *et al*. [77]	1999	121	76
European Registry	Fischer *et al*. [34]	1999	2205	61

Analysis of the influence of pre-transplantation status on outcome in acute liver failure has shown that in non-acetaminophen-induced liver failure, survival is related to aetiology and serum creatinine [25]. At the time of transplant indices of the severity of systemic illness (organ system failure and APACHE III score) and serum creatinine discriminated survivors from non-survivors. In the acetaminophen group, time from ingestion to transplantation was significantly shorter in the survivors than non-survivors (4±1 vs. 6±1 days). At the time of transplantation serum bilirubin and APACHE III score correlated with survival [25].

Liver transplantation has been performed in patients with fulminant hepatitis A, B and presumed non-A–E. Results in patients with hepatitis B are particularly satisfactory as the disease does not usually recur in the transplanted liver.

Auxiliary liver transplantation

The native liver is left in place, and the donor liver graft either placed in the right upper quadrant alongside the native liver (heterotopic), or part of the native liver is resected and replaced with a reduced size graft (orthotopic). The intention is to provide viable liver function from the graft, giving the native liver time to recover and regenerate. The advantage over conventional transplantation is the temporary need for immunosuppression.

Analysis of 47 patients transplanted in 12 European centres showed no difference in 1-year patient survival between those having a conventional orthotopic liver transplant (61% survival) compared with auxiliary liver transplantation (62%) [84]. Of patients surviving 1 year after auxiliary liver transplantation, 65% were free of immunosuppressive treatment. These results suggest that auxiliary liver transplantation (particularly partial orthotopic) may have an advantage over conventional

orthotopic liver transplantation in acute liver failure because with a similar 1-year survival there is a chance of life free of immunosuppression. Reliable criteria to indicate which patients are most likely to benefit from this technique are needed. Factors associated with a high likelihood of complete liver regeneration include an age less than 40 years, liver failure due to acetaminophen or hepatitis A or B infection, and a delay between the onset of jaundice and encephalopathy of less than 7 days [18]. The problem with these criteria, however, is that they have been recognized as indicating favourable outcome even in patients with conservative management [34].

Living related liver transplantation

This is a well-established procedure of liver transplantation for children using a left or left lateral lobe from a living donor. It has been used in patients with fulminant/sub-fulminant hepatic failure [53] with a 90% 1-year survival in 14 recipients. The post-operative course in all donors was uneventful. Concerns with this approach for acute liver failure include issues of informed consent under the pressure of an emergency situation which may interfere with a potential donor's ability to make a well-considered decision. Additionally there are issues as to whether the hepatocyte mass from a left or left lateral hepatic lobe is always able to sustain recovery in such patients [34].

Hepatocyte transplantation

In experimental animals with acute liver failure hepatocyte transplantation may improve survival. Only a small number of cells is necessary, between 0.5 and 3% of the normal hepatocyte mass. A limited number of studies have been done in patients with acute liver failure who were not candidates for liver transplantation [13, 65]. There was an improvement in encephalopathy score, arterial ammonia, prothrombin time, and aminopyrine and caffeine clearances. No clinical improvement was seen in the first 24 h after hepatocyte transplantation. None of the patients survived. Immunosuppression is necessary for the survival of the transplanted cells. Complications include hypoxaemia and infiltrates on chest X-ray after intraportal hepatocyte transplantation. No randomized, controlled data are available. Developments are needed in the method of delivery of hepatocytes, the prophylaxis of infections and strategies for preventing rejection without the need for immunosuppressive drugs.

Conclusion

Liver transplantation cannot be accepted as the perfect and ideal treatment for fulminant hepatic failure, but it gives survival to many patients who otherwise would have died. Early referral of patients to a specialist centre must be emphasized. This will increase the chance of the patient being fit enough for transfer. Delayed action loses the window of opportunity for safe transfer and greater success of transplantation. There are still considerable selection difficulties. Some patients will clearly be candidates for transplant, some will obviously be unsuitable. The doubt lies in the intermediate cases and how many in this category will recover with conservative treatment alone. The initial selection of potential candidates for transplantation is separate from the final decision to proceed. The success and role of artificial liver support systems and of auxiliary and living related liver transplantation await further evaluation.

References

1 Acharya SK, Dasarathy S, Kumer TL *et al*. Fulminant hepatitis in a tropical population: clinical course, and early predictors of outcome. *Hepatology* 1996; **23**: 1448.
2 Acharya SK, Panda SK, Saxena A *et al*. Acute hepatic failure in India: a perspective from the East. *J. Gastroenterol. Hepatol.* 2000; **15**: 473.
3 Anand AC, Nightingale P, Neuberger JM. Early indicators of prognosis in fulminant hepatic failure: an assessment of the King's criteria. *J. Hepatol.* 1997; **26**: 62.
4 Andreu V, Mas A, Bruguera M *et al*. Ecstasy: a common cause of severe acute hepatotoxicity. *J. Hepatol*. 1998; **29**: 394.
5 Ascher NL, Lake JR, Emond JC *et al*. Liver transplantation for fulminant hepatic failure. *Arch. Surg*. 1995; **128**: 677.
6 Banks AT, Zimmerman HJ, Ishak KG *et al*. Diclofenac-associated hepatotoxicity: analysis of 180 cases reported to the Food and Drug Administration as adverse reactions. *Hepatology* 1995; **22**: 820.
7 Benhamou JP. *Fulminant Hepatic Failure*. American Association for the Study of the Liver Disease Course Syllabus, 1990.
8 Bernal W, Wendon J. Acute liver failure; clinical features and management. *Eur. J. Gastroenterol. Hepatol.* 1999; **11**: 977.
9 Bernal W, Wendon J, Rela M *et al*. Use and outcome of liver transplantation in acetaminophen-induced acute liver failure. *Hepatology* 1998; **27**: 1050.
10 Bernuau J, Benhamou JP. Classifying acute liver failure. *Lancet* 1993; **342**: 252.
11 Bernuau J, Goudeau A, Poynard T *et al*. Multivariate analysis of prognostic factors in fulminant hepatitis B. *Hepatology* 1986; **6**: 648.
12 Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: definitions and causes. *Semin. Liver Dis.* 1986; **6**: 97.
13 Bilir BM, Guinette D, Karrer F *et al*. Hepatocyte transplantation in acute liver failure. *Liver Transplant*. 2000; **6**: 32.
14 Bismuth H, Samuel D, Castaing D *et al*. Orthotopic liver transplantation in fulminant and subfulminant hepatitis. The Paul Brousse experience. *Ann. Surg*. 1995; **222**: 109.
15 Blei AT, Larsen FS. Pathophysiology of cerebral oedema in fulminant hepatic failure. *J. Hepatol.* 1999; **31**: 771.
16 Blei AT, Olafsson S, Webster S *et al*. Complications of intracranial pressure monitoring in fulminant hepatic failure. *Lancet* 1993; **341**: 157.

17 Charlton M, Adjei P, Poterucha J *et al*. TT-virus infection in North American blood donors, patients with fulminant hepatic failure, and cryptogenic cirrhosis. *Hepatology* 1998; **28**: 839.

18 Chenard-Neu MP, Boudjema K, Bernuau J *et al*. Auxiliary liver transplantation: regeneration of the native liver and outcome in 30 patients with fulminant hepatic failure—a multicentre European study. *Hepatology* 1996; **23**: 1119.

19 Chu C-M, Sheen I-S, Liaw Y-F. The role of hepatitis C virus in fulminant viral hepatitis in an area with endemic hepatitis A and B. *Gastroenterology* 1994; **107**: 189.

20 Clemmesen JO, Larsen FS, Kondrup J *et al*. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. *Hepatology* 1999; **29**: 648.

21 Davenport A, Will EJ, Davison AM. Effect of posture on intracranial pressure and cerebral perfusion pressure in patients with fulminant hepatic and renal failure after acetaminophen self-poisoning. *Crit. Care Med.* 1990; **18**: 286.

22 Davenport A, Will EJ, Losowsky MS *et al*. Continuous arteriovenous haemofiltration in patients with hepatic encephalopathy and renal failure. *Br. Med. J.* 1987; **295**: 1028.

23 Davies M, Mutimer D, Lowes J *et al*. Recovery despite impaired cerebral perfusion in fulminant hepatic failure. *Lancet* 1994; **343**: 1329.

24 Devictor D, Desplanques L, Debray D *et al*. Emergency liver transplantation for fulminant liver failure in infants and children. *Hepatology* 1992; **16**: 1156.

25 Devlin J, Wendon J, Heaton N *et al*. Pretransplantation clinical status and outcome of emergency transplantation for acute liver failure. *Hepatology* 1995; **21**: 1018.

26 Dodson SF, Dehara K, Iwatsuki S. Liver transplantation for fulminant hepatic failure. *ASAIO J.* 1994; **40**: 86.

27 Donaldson BW, Gopinath R, Wanless IR *et al*. The role of transjugular liver biopsy in fulminant liver failure: relation to other prognostic indicators. *Hepatology* 1993; **18**: 1370.

28 Dowling DJ, Mutimer DJ. Artificial liver support in acute liver failure. *Eur. J. Gastroenterol. Hepatol.* 1999; **11**: 991.

29 Ede RJ, Gimson AES, Bihari D *et al*. Controlled hyperventilation in the prevention of cerebral oedema in fulminant hepatic failure. *J. Hepatol.* 1986; **2**: 43.

30 Ellis AJ, Hughes RD, Wendon JA *et al*. Pilot controlled trial of the extracorporeal liver assist device in acute liver failure. *Hepatology* 1996; **24**: 1446.

31 Ellis AJ, Saleh M, Smith H *et al*. Late-onset hepatic failure: clinical features, serology and outcome following transplantation. *J. Hepatol.* 1995; **23**: 363.

32 Ellis AJ, Wendon JA, Williams R. Subclinical seizure activity and prophylactic phenytoin infusion in acute liver failure: a controlled clinical trial. *Hepatology* 2000; **32**: 536.

33 Ferenci P. Brain dysfunction in fulminant hepatic failure. *J. Hepatol.* 1994; **21**: 487.

34 Fischer L, Sterneck M, Rogiers X. Liver transplantation for acute liver failure. *Eur. J. Gastroenterol. Hepatol.* 1999; **11**: 985.

35 Fisher NC, Cooper MA, Hastings JGM *et al*. Fungal colonization and fluconazole therapy in acute liver disease. *Liver* 1998; **18**: 320.

36 Flowers MA, Heathcote J, Wanless IR *et al*. Fulminant hepatitis as a consequence of reactivation of hepatitis B virus infection after discontinuation of low-dose methotrexate therapy. *Ann. Intern. Med.* 1990; **112**: 381.

37 Forbes A, Alexander GJM, O'Grady JG *et al*. Thiopental infusion in the treatment of intracranial hypertension complicating fulminant hepatic failure. *Hepatology* 1989; **10**: 306.

38 Hanau C, Munoz SJ, Rubin R. Histopathological heterogeneity in fulminant hepatic failure. *Hepatology* 1995; **21**: 345.

39 Harrison R, Letz G, Pasternak G *et al*. Fulminant hepatic failure after occupational exposure to 2-nitropropane. *Ann. Intern. Med.* 1987; **107**: 466.

40 Herzog D, Rasquin-Weber A-M, Debray D *et al*. Subfulminant hepatic failure in autoimmune hepatitis type 1: an unusual form of presentation. *J. Hepatol.* 1997; **27**: 578.

41 Hoofnagle JH, Carithers RL, Shapiro C *et al*. Fulminant hepatic failure: summary of a workshop. *Hepatology* 1995; **21**: 240.

42 Jalan R, Damink SWMO, Deutz NEP *et al*. Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure. *Lancet* 1999; **354**: 1164.

43 Keays RT, Alexander GJM, Williams R. The safety and value of extradural intracranial pressure monitors in fulminant hepatic failure. *J. Hepatol.* 1993; **18**: 205.

44 Keays R, Harrison PM, Wendon JA *et al*. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *Br. Med. J.* 1991; **303**: 1026.

45 Klein AS, Hart J, Brems JJ *et al*. Amanita poisoning: treatment and the role of liver transplantation. *Am. J. Med.* 1989; **86**: 187.

46 Langnas AN, Markin RS, Cattral MS *et al*. Parvovirus B19 as a possible causative agent of fulminant liver failure and associated aplastic anaemia. *Hepatology* 1995; **22**: 1661.

47 Larsen FS, Ejlersen E, Clemmesen JO *et al*. Preservation of cerebral oxidative metabolism in fulminant hepatic failure: an autoregulation study. *Liver Transplant. Surg.* 1996; **2**: 348.

48 Larsen FS, Knudsen GM, Hansen BA. Pathophysiological changes in cerebral circulation, oxidative metabolism and blood–brain barrier in patients with acute liver failure. *J. Hepatol.* 1997; **27**: 231.

49 Lau JYN, Sallie R, Fang JWS *et al*. Detection of hepatitis E virus genome and gene products in two patients with fulminant hepatitis E. *J. Hepatol.* 1995; **22**: 605.

50 Lidofsky SD, Bass NM, Prager MC *et al*. Intracranial pressure monitoring and liver transplantation for fulminant liver failure. *Hepatology* 1992; **16**: 1.

51 Makin A, Williams R. Paracetamol hepatoxicity and alcohol consumption in deliberate and accidental overdose. *Q. J. Med.* 2000; **93**: 341.

52 Mitchell I, Bihari D, Chang R *et al*. Earlier identification of patients at risk from acetaminophen-induced acute liver failure. *Crit. Care Med.* 1998; **26**: 279.

53 Miwa S, Hashikura Y, Mita A *et al*. Living-related liver transplantation for patients with fulminant and subfulminant hepatic failure. *Hepatology* 1999; **30**: 1521.

54 Moore K. Renal failure in acute liver failure. *Eur. J. Gastroenterol. Hepatol.* 1999; **11**: 967.

55 Mutimer DJ, Ayres RCS, Neuberger JM *et al*. Serious paracetamol poisoning and the results of liver transplantation. *Gut* 1994; **35**: 809.

56 Myers RP, Gregor JC, Marotta PJ. The cost-effectiveness of hepatitis A vaccination in patients with chronic hepatitis C. *Hepatology* 2000; **31**: 834.

57 O'Brien CJ, Wise RJS, O'Grady JG *et al*. Neurological sequelae in patients recovered from fulminant hepatic failure. *Gut* 1987; **28**: 93.

58 O'Grady JG, Alexander GJM, Hayllar KM *et al*. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; **97**: 439.

59 O'Grady JG, Gimson AES, O'Brien CJ *et al*. Controlled trials of charcoal haemoperfusion and prognostic factors in fulminant hepatic failure. *Gastroenterology* 1988; **94**: 1186.

60 O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet* 1993; **342**: 273.

61 Papaevangelou G, Tassopoulos N, Roumeliotou-Karayannis A *et al*. Etiology of fulminant viral hepatitis in Greece. *Hepatology* 1984; **4**: 369.

62 Pauwels A, Mostefa-Kara N, Florent C *et al*. Emergency liver transplantation for acute liver failure: evaluation of London and Clichy criteria. *J. Hepatol.* 1993; **17**: 124.

63 Pernambuco JR, Langley PG, Hughes RD *et al*. Activation of the fibrinolytic system in patients with fulminant liver failure. *Hepatology* 1993; **18**: 1350.

64 Prince MI, Thomas SHL, James OFW *et al*. Reduction in incidence of severe paracetamol poisoning. *Lancet* 2000; **355**: 2047.

65 Riordan SM, Williams R. Acute liver failure: targeted artificial and hepatocyte-based support of liver regeneration and reversal of multiorgan failure. *J. Hepatol.* 2000; **32** (Suppl. 1**)**: 63.

66 Riordan SM, Williams R. Use and validation of selection criteria for liver transplantation in acute liver failure. *Liver Transplant.* 2000; **6**: 170.

67 Rolando N, Gimson A, Wade J *et al*. Prospective controlled trial of selective parenteral and enteral antimicrobial regimen in fulminant hepatic failure. *Hepatology* 1993; **17**: 196.

68 Rolando N, Harvey F, Brahm J *et al*. Prospective study of bacterial infection in acute liver failure: an analysis of 50 patients. *Hepatology* 1990; **11**: 49.

69 Rolando N, Harvey F, Brahm J *et al*. Fungal infection: a common, unrecognized complication of acute liver failure. *J. Hepatol.* 1991; **12**: 1.

70 Rolando N, Philpott HJ, Williams R. Bacterial and fungal infection in acute liver failure. *Semin. Liver Dis.* 1996; **16**: 389.

71 Rolando N, Wade JJ, Stangou A *et al*. Prospective study comparing the efficacy of prophylactic parenteral antimicrobials, with or without enteral decontamination, in patients with acute liver failure. *Liver Transplant. Surg.* 1996; **2**: 8.

72 Rolando N, Wade J, Davalos M *et al*. The systemic inflammatory response syndrome in acute liver failure. *Hepatology* 2000; **32**: 734.

73 Rose C, Michalak A, Pannunzio M *et al*. Mild hypothermia delays the onset of coma and prevents brain oedema and extracellular brain glutamate accumulation in rats with acute liver failure. *Hepatology* 2000; **31**: 872.

74 Rowbotham D, Wendon J, Williams R. Acute liver failure secondary to hepatic infiltration: a single centre experience of 18 cases. *Gut* 1998; **42**: 576.

75 Sallie R, Chiyende J, Tan KC *et al*. Fulminant hepatic failure resulting from coexistent Wilson's disease and hepatitis E. *Gut* 1994; **35**: 849.

76 Saracco G, Macagno S, Rosina F *et al*. Serologic markers with fulminant hepatitis in persons positive for hepatitis B surface antigen. A worldwide epidemiologic and clinical survey. *Ann. Intern. Med*. 1988; **108**: 380.

77 Schiødt FV, Atillasoy E, Shakil AO *et al*. Etiology and outcome for 295 patients with acute liver failure in the United States. *Liver Transplant. Surg.* 1999; **5**: 29.

78 Sergi C, Jundt K, Seipp S *et al*. The distribution of HBV, HCV and HGV among livers with fulminant hepatic failure of different aetiology. *J. Hepatol.* 1998; **29**: 861.

79 Shakil AO, Jones BC, Lee RG *et al*. Prognostic value of abdominal CT scanning and hepatic histopathology in patients with acute liver failure. *Dig. Dis. Sci.* 2000; **45**: 334.

80 Shakil AO, Kramer D, Mazariegos GV *et al*. Acute liver failure: clinical features, outcome analysis, and applicability of prognostic criteria. *Liver Transplant*. 2000; **6**: 163.

81 Sheikh NM, Philen RM, Love LA. Chaparral-associated hepatotoxicity. *Arch. Intern. Med*. 1997; **157**: 913.

82 Sussman NL, Chong MG, Koussayer T *et al*. Reversal of fulminant hepatic failure using an extracorporeal liver assist device. *Hepatology* 1992; **16**: 60.

83 Turvill JL, Burroughs AK, Moore KP. Change in occurrence of paracetamol overdose in UK after introduction of blister packets. *Lancet* 2000; **355**: 2048.

84 van Hoek B, de Boer J, Boudjema K *et al*. Auxiliary vs. orthotopic liver transplantation for acute liver failure. *J. Hepatol.* 1999; **30**: 699.

85 Vento S, Cainelli F, Mirandola F *et al*. Fulminant hepatitis on withdrawal of chemotherapy in carriers of hepatitis C virus. *Lancet* 1996; **347**: 92.

86 Vento S, Garofano T, Renzini C *et al*. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N. Engl. J. Med.* 1998; **338**: 286.

87 Walsh TS, Hopton P, Philips BJ *et al*. The effect of *N*-acetylcysteine on oxygen transport and uptake in patients with fulminant hepatic failure. *Hepatology* 1998; **27**: 1332.

88 Watanabe FD, Mullon CJ-P, Hewitt WR *et al*. Clinical experience with a bioartificial liver in the treatment of severe liver failure. *Ann. Surg.* 1997; **225**: 484.

89 Wendon JA, Harrison PM, Keays R *et al*. Cerebral blood flow and metabolism in fulminant liver failure. *Hepatology* 1994; **19**: 1407.

90 Williams R. New directions in acute liver failure. *J. R. Coll. Physicians Lond*. 1994; **28**: 552.

91 Williams R, O'Grady JG. Liver transplantation: results, advances and problems. *J. Gastroenterol. Hepatol.* 1990; **5** (Suppl. 1): 110.

92 Williams R, Wendon J. Indications for orthotopic liver transplantation in fulminant liver failure. *Hepatology* 1994; **20**: 5S.

93 Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. *Hepatology* 1995; **22**: 767.

Chapter 9
Ascites

Ascites is free fluid within the peritoneal cavity. It forms because of conditions directly involving the peritoneum (infection, malignancy), or diseases remote from the peritoneum (liver disease, heart failure, hypoproteinaemia). Cirrhosis is the commonest cause in the Western world, with malignancy, and less frequently cardiac failure and tuberculous peritonitis, being responsible for most other cases.

The pathophysiology underlying the formation of ascites in cirrhosis is complex. This is reflected in the number of theories put forward. There are many neurohormonal, renal and systemic vascular abnormalities. Theories have evolved as new observations are made to piece together the jigsaw of interactions leading to ascites.

The abnormalities associated with the formation of ascites in patients with cirrhosis are:

- portal hypertension
- renal retention of sodium
- splanchnic arterial vasodilatation
- systemic vascular changes
- increased splanchnic and hepatic lymph formation
- hypoalbuminaemia.

Portal hypertension and renal retention of sodium are universal. At their most extreme the abnormalities related to cirrhosis and ascites lead to the *hepato-renal syndrome*.

New avenues of treatment being explored have followed advances in knowledge, such as the use of splanchnic vasoconstrictors for hepato-renal syndrome. Drugs to increase water loss (aquaretics) are under investigation.

Liver transplantation is the ultimate therapy for ascites and hepato-renal syndrome. Replacement of the liver reverses the renal changes. However, this approach is only practical for the relatively stable patient. It is impracticable for rapidly progressing hepato-renal syndrome. New therapeutic strategies are needed to buy time before a donor liver becomes available.

Mechanism of ascites formation [27]

All proposed mechanisms involve inappropriate renal sodium and water retention, either secondary to vascular changes (*underfill and peripheral arterial vasodilatation hypotheses*) or as a primary event (*overfill theory*) (table 9.1). Liver disease and portal hypertenion are central to the process. Increased lymph production from the liver and splanchnic capillaries leads to ascites. Changes in the peritoneal membrane and its permeability may contribute.

Underfill and peripheral vasodilatation hypotheses

Vascular changes

Many circulatory changes are found in patients with cirrhosis, particularly as disease advances and there is decompensation (table 9.2). Theories of ascites formation based on vascular changes depend upon stimulation of the renin–angiotensin–aldosterone system (RAAS) as a result of a reduced effective circulating volume—that is, the compartment interacting with volume and baroreceptors.

The traditional *underfill theory* proposed sequestration of blood in the splanchnic venous bed, which with peripheral vasodilatation associated with arteriovenous shunting led to a reduction in the central vascular compartment.

The current modification of this theory is based upon *peripheral arterial vasodilatation* (fig. 9.1). Splanchnic arterial vasodilatation is found in some patients with cirrhosis and portal hypertension. Nitric oxide is thought to play a central role. This leads to net arterial vasodilatation, reduced arterial vascular resistance, increased cardiac output and reduced filling of the central pressure monitoring compartment. RAAS and sympathetic activity are increased. Splanchnic arterial vasodilatation is accompanied systemically by vasoconstriction in the renal, cerebral and muscle vascular beds.

Table 9.1. Sequence of events for the hypotheses of ascites formation

	Underfill/peripheral arterial vasodilatation	Overfill
Primary event	Vascular	Renal
Secondary event	Renal	Vascular

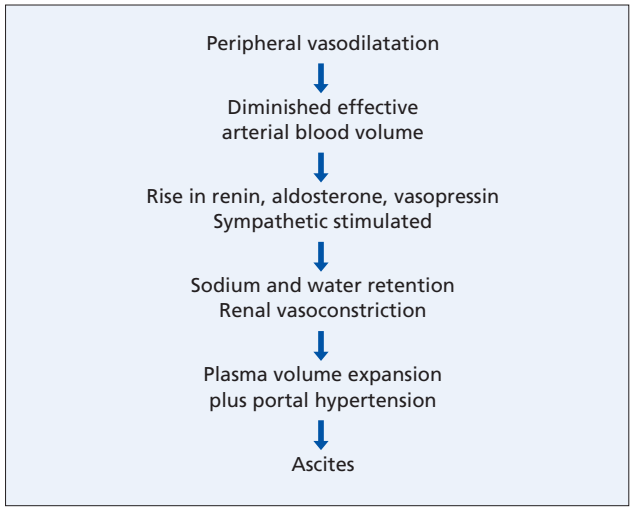


Fig. 9.1. The peripheral arterial vasodilatation hypothesis for ascites formation in cirrhosis [70].

Table 9.2. Circulatory changes in patients with cirrhosis

Increased	Plasma/total blood volume
	Non-central blood volume
	Cardiac output
	Portal pressure and flow
Reduced	Central blood volume
	Arterial blood pressure
	Splanchnic vascular resistance
	Systemic vascular resistance
	Renal blood flow

Vasodilators (table 9.3)

The factors responsible for splanchnic and peripheral arterial vasodilatation are not clearly understood. Some vasodilators may be of intestinal origin. Endothelial cells may respond to changes in shear stress, endotoxin or cytokines with the production of vasodilators such as nitric oxide. Nitric oxide synthesis is increased in cirrhotic patients. There is increased plasma nitric oxide and its metabolites, and increased nitric oxide in exhaled air [50]. Plasma concentrations of nitric oxide are higher in portal venous than peripheral venous blood, suggesting increased splanchnic production. In an experimental model of cirrhosis, inhibition of nitric oxide synthase significantly reduces plasma renin, aldosterone and vasopressin levels, and increases renal sodium and water excretion [51].

Another new potent vasodilator peptide, adrenomedullin, may also play a role. Plasma levels are increased in cirrhotic patients with ascites [31].

Table 9.3. Vasodilators implicated in vascular changes of cirrhosis and vasoconstrictors

	Vasodilators	Vasoconstrictors
Renal	Prostaglandin E_2	Endothelin-1
	Nitric oxide	Thromboxane A_2
	Kallikrein–kinin system	Angiotensin II
	Prostacyclin	Leukotrienes
		Adenosine
Systemic	Nitric oxide	Angiotensin II
	Atrial natruretic peptide	Noradrenaline
	Adrenomedullin	Antidiuretic hormone
	Calcitonin gene-related peptide	Neuropeptide Y

Renal changes

Total body sodium and water balance depends upon the control of sodium and water reabsorption in the distal tubule and collecting duct. This is regulated by the RAAS and anti-diuretic hormone (ADH, vasopressin).

Renin is produced by the kidney in response to stretching of the afferent glomerular arterioles, and to renal baroreceptor and β-adrenergic stimulation. Under the influence of renin, angiotensinogen (produced by the liver) is converted to angiotensin I (a decapeptide), which in turn is converted to angiotensin II (an octapeptide) by angiotensin-converting enzyme (ACE). Angiotensin II is the main stimulant to the synthesis and secretion of aldosterone, a mineralocorticoid, from the glomerular cells of the adrenal cortex.

Aldosterone acts on cells in the collecting duct(ule), and through a cytoplasmic interaction increases both luminal uptake and basolateral passage of sodium.

Other factors affecting renin release are angiotensin II, nitric oxide, atrial natriuretic peptide (ANP), vasopressin (ADH), and adenosine (inhibitory), and prostaglandins, kallikrein, calcitonin and TNF-α (stimulatory). Angiotensin II also stimulates sodium and water retention in the proximal tubule.

In patients with cirrhosis and ascites, the normal regulation of sodium balance is lost. Sodium is retained avidly, urinary sodium excretion often being less than 5 mmol/day.

There is increased activity of the RAAS (fig. 9.2). Plasma levels of these hormones are increased because of stimulation of volume receptors in the central circulation. This is due to a reduction in 'effective circulating blood volume', which also activates the sympathetic system (raised circulating noradrenaline).

Naturesis after spironolactone therapy (an aldosterone antagonist) supports hyperaldosteronism as having an active part in sodium retention of the cirrhotic.

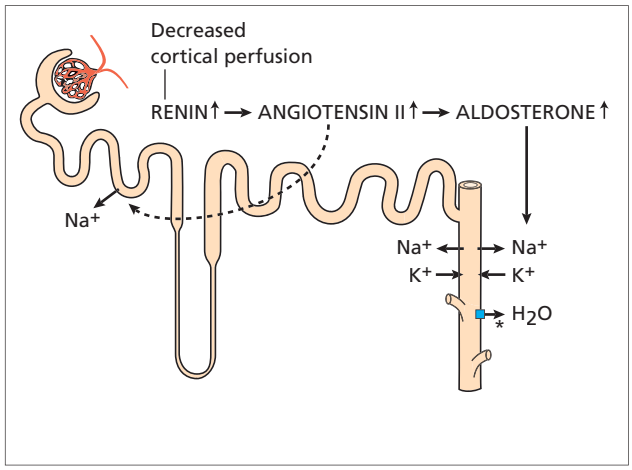


Fig. 9.2. Mechanisms of increased sodium and water reabsorption in cirrhosis. * Increased ADH-stimulated water reabsorption in collecting ducts.

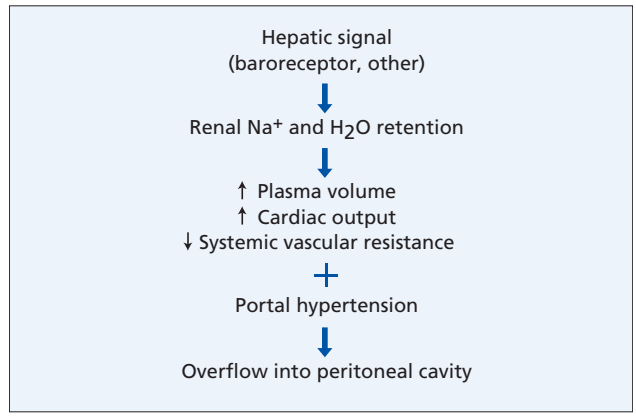


Fig. 9.3. Overfill hypothesis.

Overfill hypothesis (fig. 9.3)

A large proportion (30–60%) of cirrhotic patients do not have a measurable increase in the components of the RAAS. However, some of these patients have a defect of sodium handling even in the absence of ascites. Thus they do not excrete a sodium challenge appropriately and there is a tendency to sodium retention. This finding questions whether sodium and water retention in cirrhotics is truly related to prior systemic vascular changes followed by RAAS activation. An alternative proposal is that there is a primary renal change—responding to a hepatic signal—that leads to sodium retention (*overfill theory*) (fig. 9.3). Several signals have been suggested. Reduced hepatic synthesis of a natriuretic agent, reduced hepatic clearance of a sodium-retaining hormone, or a 'hepato-renal reflex' of unknown aetiology could be responsible. The hypothesis proposes that sodium and water retention lead to expansion of the plasma volume, an increase in cardiac output and a fall in systemic vascular resistance. The combination of portal hypertension and circulatory hypervolaemia lead to ascites. Central to the argument between this *overfill hypothesis* and the theories based on vascular abnormalities is whether or not changes in cardiovascular haemodynamics and in RAAS are present before the first evidence of renal sodium retention. Early involvement of angiotensin II in sodium retention is supported by data showing correction of the subtle renal sodium retention in pre-ascitic cirrhotic patients, with *low* systemic angiotensin II levels, by losartan, an angiotensin II receptor antagonist [28].

Other renal factors

Atrial natriuretic factor (ANF)

This is a potent vaso-relaxant natriuretic peptide released from the cardiac atria, probably in response to intravascular volume expansion. In early compensated cirrhosis, ANF may maintain sodium homeostasis despite the presence of mild anti-natriuretic factors. In the later stages renal resistance to ANF develops, rendering it ineffective. ANF probably has no primary role in the sodium retention of cirrhosis.

Prostaglandins

Several prostaglandins are synthesized in the kidney and although they are not primary regulators they modulate the effects of other factors and hormones locally.

Prostaglandin (PG) I_2 and E_2 are vasodilators, and also increase sodium excretion through vasodilatation and a direct effect on the loop of Henle. They stimulate renin production and inhibit cyclic adenosine monophostate (cAMP) synthesis, thereby interfering with the action of vasopressin (ADH).

Thromboxane A_2 is a vasoconstrictor, reducing renal blood flow, glomerular filtration and perfusion pressure.

$PGI_{2\alpha}$ is synthesized in the tubules and increases sodium and water excretion.

Prostaglandins therefore have a significant role in sodium and water homeostasis. In conditions where there is a reduced circulating volume, which includes cirrhosis, there is increased prostaglandin synthesis. This counterbalances renal vasoconstriction by antagonizing the local effects of renin, angiotensin II, endothelin 1, vasopressin and catecholamines.

The importance of this role is demonstrated clinically by the renal dysfunction seen in cirrhotics when

non-steroidal anti-inflammatory agents are given [82]. Without the vasodilatatory influence of prostaglandins renal blood flow and glomerular filtration rate fall because of unopposed vasoconstriction due to renin and other factors. Such an imbalance may be the trigger for the hepato-renal syndrome.

Circulation of ascites

Once formed, ascitic fluid can exchange with blood through an enormous capillary bed under the visceral peritoneum. This plays a vital, dynamic role, sometimes actively facilitating transfer of fluid into the ascites and sometimes retarding it. Ascitic fluid is continuously circulating, with about half entering and leaving the peritoneal cavity every hour, there being a rapid transit in both directions. The constituents of the fluid are in dynamic equilibrium with those of the plasma.

Summary (fig. 9.4)

The *peripheral arterial dilatation hypothesis* of ascites formation proposes that renal sodium and water retention is due to reduced effective blood volume secondary to peripheral arterial vasodilatation particularly in the splanchnic bed. The renal changes are mediated by stimulation of the RAAS, an increase in sympathetic function, and other systemic and local peptide and hormone disturbances.

The *overfill* view suggests that renal retention of sodium is primary with secondary vascular changes and accumulation of ascites and oedema.

The increase in intra-sinusoidal pressure found in cirrhosis and hepatic venous obstruction in Budd–Chiari syndrome stimulates hepatic lymph formation and this adds to the ascites. An active role of the peritoneal capillary membrane in controlling the passage of fluid is possible.

Thus several changes occurring in sequence are responsible for the clinical features. Different disturbances are emphasized according to the stage of liver disease. At the extreme end of the spectrum of renal and vascular changes, hepato-renal syndrome develops.

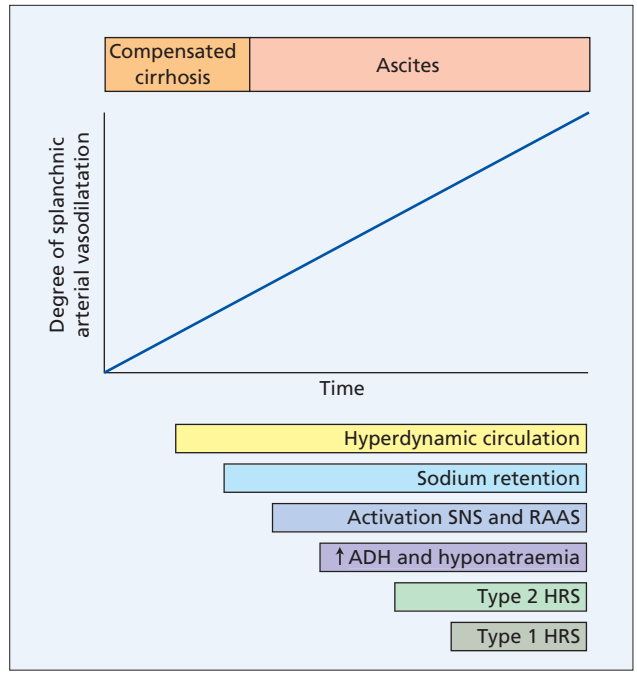


Fig. 9.4. Time course of circulatory, neurohormonal and renal function abnormalities in cirrhosis (in sequence of peripheral arterial vasodilation theory). ADH, antidiuretic hormone; HRS, hepato-renal syndrome; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system. (From [9] with permission.)

Clinical features

Onset

Ascites may appear suddenly or develop insidiously over the course of months with accompanying flatulent abdominal distension.

Ascites may develop suddenly when hepato-cellular function is reduced, for instance by haemorrhage, 'shock', infection or an alcoholic debauch. This might be related to the fall in serum albumin values and/or to intravascular fluid depletion. Occlusion of the portal vein may precipitate ascites in a patient with a low serum albumin level.

The insidious onset proclaims a worse prognosis, possibly because it is not associated with any rectifiable factor.

There is gradually increasing abdominal distension and the patient may present with dyspnoea.

Examination

The patient is sallow and dehydrated. Sweating is diminished. Muscle wasting is profound. The thin limbs with the protuberant belly lead to the description of the patient as a 'spider man'. The ascites may be classified into mild, moderate or tense.

The abdomen is distended not only with fluid but also by air in the dilated intestines. The fullness is particularly conspicuous in the flanks. The umbilicus is everted and the distance between the symphysis pubis and umbilicus seems diminished.

The increased intra-abdominal pressure favours the protrusion of hernias in the umbilical, femoral or inguinal regions or through old abdominal incisions. Scrotal oedema is frequent.

Distended abdominal wall veins may represent porto-systemic collateral channels which radiate from

the umbilicus and persist after control of the ascites. Inferior vena caval collaterals result from a secondary, functional block of the inferior vena cava due to pressure of the peritoneal fluid. They commonly run from the groin to the costal margin or flanks and disappear when the ascites is controlled and intra-abdominal pressure is reduced. Abdominal striae may develop.

Dullness on percussion in the flanks is the earliest sign and can be detected when about 2 litres are present. The distribution of the dullness differs from that due to enlargement of the bladder, an ovarian tumour or a pregnant uterus when the flanks are resonant to percussion. With tense ascites it is difficult to palpate the abdominal viscera, but with moderate amounts of fluid the liver or spleen may be ballotted.

A fluid thrill means much free fluid; it is a very late sign of fluid under tension.

The lung bases may be dull to percussion due to elevation of the diaphragm.

Secondary effects

A *pleural effusion* is found in about 5–10% of cirrhotics and in 85% of these it is right-sided [40]. It is due to defects in the diaphragm allowing ascites to pass into the pleural cavity (fig. 9.5). This can be shown by introducing ^{131}I albumin or air into the ascites and examining the pleural space afterwards. However, this technique only has a sensitivity of around 70%. Similarly, examination of pleural and ascitic fluid is not reliable to differentiate an effusion due to local pleural disease from that due to ascites [2].

Right hydrothorax may be seen in the absence of ascites due to the negative intra-thoracic pressure during breathing, drawing the peritoneal fluid through the diaphragmatic defects into the pleural cavity [37].

The pleural fluid is in equilibrium with the peritoneal fluid and control depends on medical treatment of the ascites. Aspiration is followed by rapid filling up of the pleural space by ascitic fluid. Transjugular intrahepatic portosystemic shunts (TIPS) have been successful [75].

Spontaneous bacterial empyema may be a complication [83].

Oedema usually follows the ascites and is related to hypoproteinaemia. A functional inferior vena caval block due to pressure of the abdominal fluid is an additional factor.

The *cardiac apex beat* is displaced up and out by the raised diaphragm.

The *neck veins* are distended. This is secondary to the increase in right atrial pressure and intra-pleural pressure which follows tense ascites and a raised diaphragm. A persisting increase in jugular venous pressure after ascites is controlled implies a cardiac cause for the fluid retention.

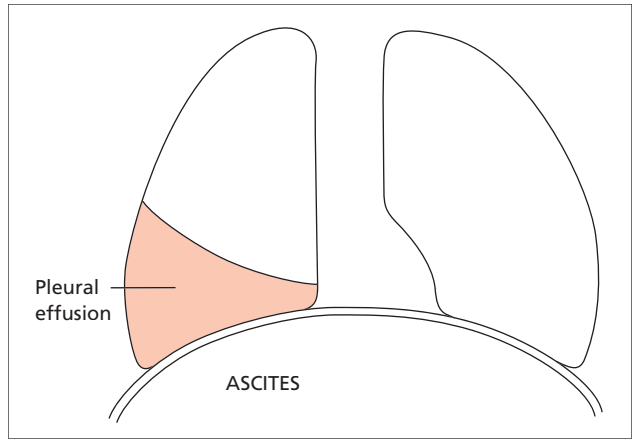


Fig. 9.5. A right-sided pleural effusion may accompany ascites and is related to defects in the diaphragm.

Ascitic fluid

Diagnostic paracentesis (of about 30 ml) is always performed, however obvious the cause of the ascites. Complications, including bowel perforation and haemorrhage can develop rarely after paracentesis in patients with cirrhosis.

Protein concentration rarely exceeds 1–2 g/100 ml. Higher values suggest infection. Obstruction to the hepatic veins (Budd–Chiari syndrome) is usually, but not always, associated with a very high ascitic fluid protein. Pancreatic ascites also has a high protein concentration.

If the serum albumin minus ascites albumin *gradient* is greater than 1.1 g/dl, the patient has portal hypertension.

Electrolyte concentrations are those of other extracellular fluids.

Ascitic fluid protein and white cell count, but not polymorph concentration, increase during a diuresis.

Fluid appears clear, green, straw-coloured or bile-stained. The volume is variable and up to 70 litre have been recorded. A blood-stained fluid indicates malignant disease or a recent paracentesis or an invasive investigation, such as liver biopsy or trans-hepatic cholangiography.

The *protein content* and *white cell count* should be measured and a *film* examined for organisms. Aerobic and anaerobic *cultures* should be performed.

The percentage of positive cultures can be markedly increased if ascitic fluid is inoculated directly into blood culture bottles at the bedside [62].

Cytology. The normal endothelial cells in the peritoneum can resemble malignant cells, so leading to an over-diagnosis of cancer.

The *rate of accumulation of fluid* is variable and depends on the dietary intake of sodium and the ability of the

kidneys to excrete it. Rate of ascitic fluid reabsorption is limited to 700–900 ml daily.

The *pressure* exerted by the ascitic fluid rarely exceeds 10 mmHg above the right atrium. At high pressures, discomfort makes paracentesis obligatory. Vasovagal fainting may follow too rapid release of ascites.

A *low sodium state* may follow a large paracentesis, especially if the patient has been on a restricted sodium intake. Approximately 1000 mmol of sodium is lost in every 7 litre of ascites. This is rapidly replenished from the blood and the serum sodium level falls. Water may be retained in excess of sodium.

Urine

The urine volume is diminished, deeply pigmented and of high osmolarity.

The daily urinary output of sodium is greatly reduced, usually less than 5 mmol and in a severe case less than 1 mmol.

Radiological features

Plain X-ray of the abdomen shows a diffuse ground-glass appearance. Distended loops of bowel simulate intestinal obstruction. Ultrasound and CT scans show a space around the liver and these can be used to demonstrate quite small amounts of fluid (fig. 9.6).

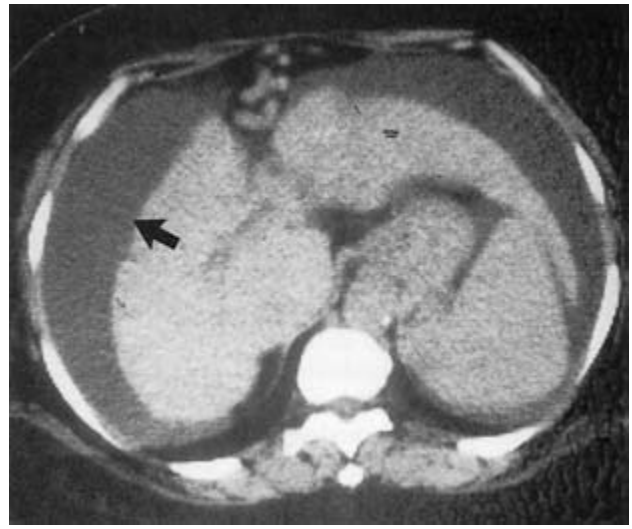


Fig. 9.6. CT scan showing an irregular cirrhotic small liver, splenomegaly and ascites (arrow).

Differential diagnosis

Malignant ascites. There may be symptoms and localizing signs due to the primary tumour. After paracentesis, the liver may be enlarged and nodular. The peritoneal fluid may be characteristic with a high protein content.

A low serum–ascites albumin gradient, less than 1.1 g/dl, suggests malignancy [3]. Lactic acid dehydrogenase levels are high.

Tuberculous ascites. This should be suspected particularly in the severely malnourished alcoholic. The patient is usually pyrexial. After paracentesis, lumps of matted omentum can be palpated. The ascitic fluid is of high protein content, usually with many lymphocytes and sometimes polymorphs. The deposit must always be stained for tubercle bacilli, and suitable cultures set up.

Chylous ascites results from accumulation of fat, predominantly chylomicrons, in the ascitic fluid [1]. The commonest cause is malignant lymphoma. It is a rare complication of advanced cirrhosis. Diagnosis is based on paracentesis with a high (2–8-fold) plasma triglyceride ratio, or a total ascitic triglyceride of greater than 110 mg/ml. It is associated with a 40–70% mortality. Management is of the underlying cause, and a low-fat medium chain triglyceride (MCT) diet for 3 weeks or if this fails total parenteral nutrition for 4–6 weeks.

Constrictive pericarditis. Diagnostic points include the very high jugular venous pressure, the paradoxical pulse, the radiological demonstration of a calcified pericardium and the characteristic electrocardiogram and echocardiograph. Right and left heart catheterization and MRI or cine CT of the heart may be necessary to confirm the diagnosis [81].

Hepatic venous obstruction (Budd–Chiari syndrome) must be considered, especially if the protein content of the ascitic fluid is high.

Pancreatic ascites. This is rarely gross. It develops as a complication of acute pancreatitis with pseudocyst rupture, or from pancreatic duct disruption. The amylase content of the ascitic fluid is very high.

Ovarian tumour is suggested by resonance in the flanks. The maximum bulge is antero-posterior and the maximum girth is below the umbilicus.

Bowel perforation, with infected ascites, is shown by a low glucose and high protein concentration in the fluid.

Spontaneous bacterial peritonitis

(table 9.4) [62]

Infection of the ascitic fluid may be spontaneous or follow a previous paracentesis. The spontaneous type develops in about 8% of cirrhotic patients with ascites. It is particularly frequent if the cirrhosis is severely decompensated. In most cases the complication develops *after* the patient is admitted to hospital. These patients are more likely to have gastrointestinal bleeding and renal failure and to require invasive procedures or therapy (fig. 9.7).

The infection is blood-borne and in 90% monomicrobial. The causative organisms are mainly of intestinal

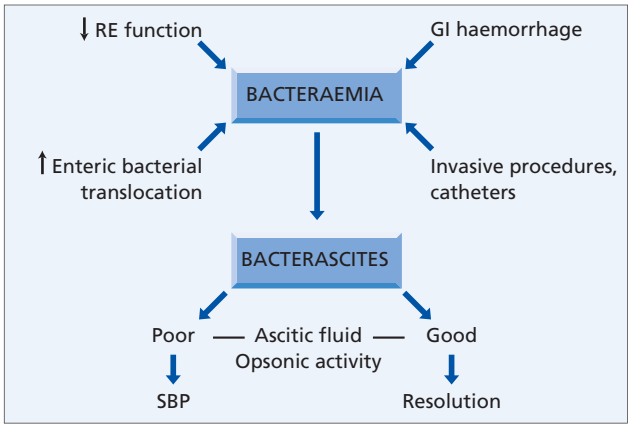


Fig. 9.7. The pathogenesis of spontaneous bacterial peritonitis (SBP) in patients with cirrhosis. GI, gastrointestinal; RE, reticulo-endothelial.

Table 9.4. Spontaneous bacterial peritonitis

Suspect grade B and C cirrhosis with ascites
Clinical features may be absent and peripheral WBC normal
Ascitic protein usually <1 g/dl
Usually monomicrobial and Gram-negative
Start antibiotics if ascites >250 mm polymorphs
50% die
69% recur in 1 year

origin with representatives of the normal aerobic flora. In cirrhotic patients bacterial overgrowth and small intestinal dysmotility may contribute [15]. Experimentally there is an increased rate of bacterial translocation of bacteria across the intestinal wall to mesenteric lymph nodes in models of portal hypertension and cirrhosis. Spontaneous bacterial peritonitis is associated with an increased bacterial translocation rate [44]. Malnutrition increases bacterial translocation and spontaneous bacterial peritonitis [14]. Bacterial translocation is reduced by selective intestinal decontamination with norfloxacin [45].

Host defences are abnormal. Reticulo-endothelial function is impaired. Neutrophils are abnormal in the alcoholic. There is intra-hepatic shunting and impairment of bactericidal activity in the ascites. Ascitic fluid favours bacterial growth and deficient ascitic opsonins lead to defective coating of bacteria which are indigestible by polymorphs. The opsonic activity of the ascitic fluid is proportional to protein concentration and spontaneous bacterial peritonitis is more likely if ascitic fluid protein is less than 1 g/dl [67].

Infection with more than one organism is likely to be associated with abdominal paracentesis, colonic perforation or dilatation, or any intra-abdominal source of infection.

The ascitic polymorph count exceeds 250 cells/mm^3 and culture is positive. Spontaneous bacterial peritonitis should be suspected if a patient with known cirrhosis deteriorates, particularly with encephalopathy. It can develop in a fulminant form in a patient who previously had no ascites. Ascitic fluid protein less than 1 g/dl and a high serum bilirubin level independently predict the first spontaneous bacterial peritonitis [4]. Patients with variceal bleeding or with previous spontaneous bacterial peritonitis are at particular risk. Pyrexia, local abdominal pain and tenderness, and systemic leucocytosis may be noted. These features, however, may be absent and the diagnosis is made on the index of suspicion with examination of the ascitic fluid.

Antibiotics should be started empirically in all those with more than 250 polymorphs/mm^3.

The bacterial count in the ascites is low. The infecting organisms are usually *Escherichia coli* or group D streptococci. Anaerobic bacteria are rarely found. Opportunistic organisms are identified in the immunosuppressed. Blood cultures are positive in 80%.

Monomicrobial, non-neutrocytic bacterascites may resolve without treatment but can progress to spontaneous bacterial peritonitis [66].

Patients with spontaneous bacterial peritonitis are particularly at risk of renal complications which is probably related to systemic vascular changes, including local production of nitric oxide [11], and the systemic inflammatory response to infection generated by tumour necrosis factor and interleukin 6 [56].

Prognosis

Deterioration is shown by marked increases in serum bilirubin and creatinine and by a very high white cell count in the blood.

Of patients with spontaneous bacterial peritonitis 30–50% will die during that hospital admission, and 69% will recur in 1 year, and again 50% will die [78].

The outlook depends on the association with recent gastrointestinal bleeding [10], the severity of the infection and the degree of renal and liver failure [47].

The prevalence of hepato-cellular carcinoma in patients with spontaneous bacterial peritonitis is approximately 20% [46].

Treatment

Five days of parenteral, third-generation cephalosporin such as cefotaxime is usually effective [63, 68]. For cefotaxime the optimal cost-effective dosage is 2 g every 12 h. A minimal duration of 5 days of treatment is recommended [62]. Amoxycillin-clavulanic acid is as effective

cefotaxime [61]. This study used intravenous amoxycillin-clavulanic acid followed by oral therapy. Intravenous ciprofloxacin followed by oral treatment is also effective [76].

These regimens are for the initial empirical therapy of spontaneous bacterial peritonitis but the antibiotic choice should be reviewed once results of ascitic culture and sensitivity of the bacterial isolates are known. Because of renal toxicity, aminoglycosides should be avoided.

In a randomized study the administration of intravenous albumin to patients with spontaneous bacterial peritonitis treated with cefotaxime significantly reduced the incidence of renal impairment (10 vs. 33%) and hospital mortality (10 vs. 29%) [73]. The use of albumin was expensive. This study provides the lowest reported hospital mortality for spontaneous bacterial peritonitis. Further trials with lower doses of albumin or synthetic plasma expanders are awaited.

Diuretic therapy increases the total protein and ascitic opsonic activity. Paracentesis does not seem to increase the early and long-term risk of spontaneous bacterial peritonitis [72].

Because of reduced survival, spontaneous bacterial peritonitis is an indication to consider hepatic transplantation, particularly if recurrent.

Prophylaxis

The risk of spontaneous bacterial peritonitis is particularly high in cirrhotic patients with upper gastrointestinal haemorrhage. Oral administration of norfloxacin (400 mg/12 h for a minimum of 7 days) is currently recommended for this group [62]. Spontaneous bacterial peritonitis and other infections should be ruled out before starting prophylaxis. The incidence of bacterial infections in patients with gastrointestinal haemorrhage is also reduced by combinations of ofloxacin with amoxycillin-clavulanic acid, ciprofloxacin with amoxycillin-clavulanic acid and oral ciprofloxacin alone [62].

In patients with a previous episode of spontaneous bacterial peritonitis the risk of recurrence during the subsequent year is 40–70%. Oral administration of norfloxacin (400 mg/day) is recommended in such patients who should then be evaluated for liver transplantation [62]. Trimethoprim-sulfamethoxazole is a less costly but effective alternative [71].

There is currently insufficient evidence to recommend prophylaxis for patients with a low ascitic fluid protein (< 1 g/dl) who have an increased risk of spontaneous bacterial peritonitis. There is a concern that long-term prophylaxis will lead to the emergence of resistant bacteria [57]. In patients with a high ascitic fluid protein (> 1 g/dl) without a past history of spontaneous bacterial peritonitis, prophylaxis is not thought necessary.

Treatment of cirrhotic ascites [7, 19, 65]

Therapy of ascites, whether by diuretics or paracentesis, reduces clinical symptoms and the patients is grateful. However, although the initial clinical response may be excellent, if fluid loss is excessive the result may be a patient in renal failure or with encephalopathy. Treatment must therefore be appropriate to the clinical state and the response properly monitored. The approach must be tailored to the patient. The spectrum of therapeutic intervention ranges from sodium restriction alone (rarely used), to diuretic use, therapeutic paracentesis, and for the most severe groups, TIPS and eventually liver transplantation.

Indications for treatment include the following:

Symptomatic ascites. Abdominal swelling sufficient to produce clinical symptoms, for example increasing girth or physical effort, requires treatment, most often with sodium restriction and diuretics. The presence of stable ascites *per se*, for example on scanning, without clinical symptoms, may not require active treatment, although to prevent deterioration advice on a reduction in sodium intake is wise. Inappropriate introduction of excessive treatment for ascites may lead to dizziness, muscle cramps, dehydration, hypotension and renal dysfunction.

Uncertain diagnosis. Control of ascites may allow such procedures as scanning and liver biopsy to be done. The urgency of the situation and degree of ascites will direct whether sodium restriction and diuretic is used, or paracentesis.

Gross ascites, causing abdominal pain and/or dyspnoea most often demands paracentesis.

Tense ascites with pain may lead to eversion and ulceration of an umbilical hernia, which is near to rupture. This complication has a very high mortality, due to shock, renal failure and sepsis, and urgent paracentesis is indicated.

Monitoring during treatment is mandatory. The patient is weighed daily. Fluid input as well as output is monitored. Urine volume and body weight provide a satisfactory guide to progress. Urinary electrolyte (sodium/potassium) determinations are helpful but not essential in determining therapy and monitoring the response. Serum electrolytes are measured two to three times per week while the patient is in hospital.

Treatment regimens include dietary sodium restriction, diuretics and abdominal paracentesis (table 9.5). Where liver disease is due to alcohol, the patient should be encouraged to abstain. The mild case is managed as an outpatient by diet and diuretics, but if admitted to hospital, paracentesis is usually a first procedure. In a survey of European hepatologists, 50% used paracentesis initially, to be followed by diuretics [7]. Fifty per cent regarded complete control of the ascites as desirable,

Table 9.5. General management of ascites

Bed rest. 70–90 mmol sodium diet. Check serum and urinary electrolytes. Weigh daily. Measure urinary volume. Sample ascites
Spironolactone 100–200 mg daily
If tense ascites consider paracentesis (see table 9.8)
After 4 days consider adding frusemide (furosemide) 40 mg daily. Check serum electrolytes
Stop diuretics if pre-coma ('flap'), hypokalaemia, azotaemia or alkalosis
Continue to monitor weight. Increase diuretics as necessary

Table 9.6. Advice for 'no added salt diet' (70–90 mmol/day)

Omit
Anything containing baking powder or baking soda (contains sodium bicarbonate): pastry, biscuits, crackers, cakes, self-raising flour and ordinary bread (see restriction below)
All commercially prepared foods (unless designated low salt—check packet)
Dry breakfast cereals except Shreaded Wheat, Puffed Wheat or Sugar Puffs
Tinned/bottled savouries: pickles, olives, chutney, salad cream, bottled sauces
Tinned meats/fish: ham, bacon, corned beef, tongue, oyster, shellfish
Meat and fish pastes; meat and yeast extracts
Tinned/bottled vegetables, soups, tomato juice
Sausages, kippers
Cheese, ice-cream
Candy, pastilles, milk chocolate
Salted nuts, potato crisps, savoury snacks
Drinks: especially Lucozade, soda water, mineral waters according to sodium content (essential to check sodium content of mineral waters, varies from 5 to 1000 mg/l)
Restrict
Milk (300 ml = half pint/day)
Bread (two slices/day)
Free use
Fresh and home-cooked fruit and vegetables of all kinds
Meat/poultry/fish (100 g/day) and one egg. Egg may be used to substitute 50 g meat (2 oz)
Unsalted butter or margarine, cooking oils, double cream
Boiled rice, pasta (without salt), semolina
Seasonings help make restricted salt meal more palatable: include lemon juice, onion, garlic, pepper, sage, parsley, thyme, marjoram, bay leaves
Fresh fruit juice, coffee, tea
Mineral water (check sodium content)
Marmalade, jam
Dark chocolate, boiled sweets, peppermints, chewing gum
Salt substitutes (not potassium chloride)
Salt-free bread, crispbread, crackers or matzos

whereas the other half were satisfied with symptomatic relief without removing all the ascites. Thus consensus on standardized treatment regimes is difficult to reach because of the clinical spectrum of ascites, the clinical success of the different regimens and the lack of evidence-based studies comparing individual approaches.

Bed rest used to be a feature of initial therapy. Evidence for benefit is sparse but as part of an overall strategy it has been found to be beneficial [20]. This may be related to increased renal perfusion and portal venous blood flow during recumbency. However, modern clinical medicine does not allow the luxury of observing clinical responses to bed rest and sodium restriction alone over even a few days of hospital stay because of cost, and the clinical effectiveness and relative safety of more active therapies.

Sodium restriction/diet

The cirrhotic patient who is accumulating ascites on an unrestricted sodium intake excretes less than 10 mmol (approximately 0.2 g) sodium daily in the urine. Extrarenal loss is about 0.5 g. Sodium taken in excess of 0.75 g will result in ascites, every gram retaining 200 ml of fluid. Historically, such patients were recommended a diet containing 22–40 mmol/day. Current opinion, however, supports a 'no added salt' diet (approximately 70–90 mmol) combined with diuretic to increase urinary sodium excretion (table 9.4). The diets restricting sodium to 22–40 mmol were unpalatable and also compromised protein and calorie intake, which in patients with cirrhosis is critical for proper nutrition. Occasionally restrictions between 40 and 70 mmol/day may be necessary.

The average daily intake of sodium is about 150–250 mmol. To reduce intake to 70–90 mmol/day (approximately 1600–2000 mg) salt should not be used at the table or when cooking. Also various foods containing sodium should be restricted or avoided (table 9.6). Many low-sodium foods are now available including soups, ketchups and crackers.

A few ascitic patients may respond to this regimen alone but usually the first line of treatment for ascites includes diuretics. Patients prefer the combination of diuretics and a modest restriction of sodium to severe sodium restriction alone. Very occasionally if there is a good response, diuretics may be withdrawn and the patient maintained on dietary sodium restriction alone.

Good responders are liable to be those:

- with ascites and oedema presenting for the first time in an otherwise stable patient—'virgin ascites'
- with a normal creatinine clearance (glomerular filtration rate)
- with an underlying reversible component of liver disease such as fatty liver of the alcoholic
- in whom the ascites has developed acutely in response to a treatable complication such as infection or bleeding, or after a non-hepatic operation

• with ascites following excessive sodium intake, such as in sodium-containing antacids or purgatives, or mineral (spa) waters with a high sodium content.

Diuretics

The major reason for sodium retention is hyperaldosteronism in cirrhotic patients, due to increased activity of the renin–angiotensin system. There is avid reabsorption of sodium from the distal tubule and collecting duct (fig. 9.2).

Diuretics can be divided into two main groups (fig. 9.8) according to their site of action. The first group inhibit Na^+–K^+–2 Cl^- co-transporter in the ascending limb of the loop of Henle and include frusemide (furosemide) and bumetamide. It is not appropriate to use these alone since the sodium remaining in the tubule as a result of diuretic action is reabsorbed in the distal tubule and collecting duct because of hyperaldosteronism. A randomized controlled trial has shown frusemide alone to be less effective than spironolactone [58]. Thiazides inhibit sodium in the distal convoluted tubule, have a longer half-life, and are not as a rule used in the treatment of ascites.

The second group, spironolactone (an aldosterone antagonist), amiloride and triamterene (inhibitors of the Na^+ channel) block sodium reabsorption in the distal tubule and collecting duct. They are central to the treatment of cirrhotic ascites. They are weakly natriuretic but conserve potassium. Potassium supplements are not usually necessary—indeed this type of diuretic sometimes needs to be temporarily stopped because of hyperkalaemia.

There are two therapeutic approaches which can be used initially: spironolactone alone, or a combination of spironolactone with frusemide. Both have their advocates [19, 65].

Spironolactone alone. The starting dose is 100–200 mg/day according to the degree of ascites. If there has been insufficient clinical response (less than 0.5 kg/day weight loss) after 3–4 days, then the dose is increased by 100 mg/day every 4 days to a maximum of 400 mg/day. Lack of clinical response indicates the need to check the urinary sodium output, because a high value will identify the occasional patient who is exceeding the prescribed low sodium diet.

If there is a lack of, or insufficient, clinical response on spironolactone alone (usually at the level of 200 mg/day) a loop diuretic such as frusemide is added at a dose of 20–40 mg/day.

Combination therapy. Treatment is started with the combination of spironolactone (100 mg) and frusemide (40 mg) daily [65]. There is no direct comparison between this and the use of spironolactone alone. The ease of control and choice of diuretics can be related to the 24-h urinary sodium content on admission to hospital (table 9.7). The disadvantage of starting with spironolactone alone is the delay before its clinical effect.

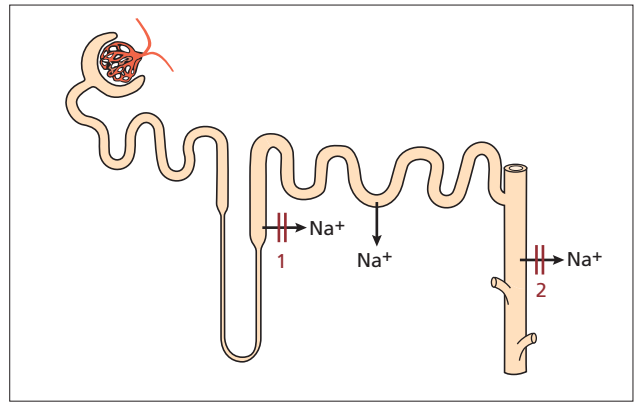


Fig. 9.8. Site of action of diuretics. 1 = loop diuretics: frusemide (furosemide), bumetamide. 2 = distal tubule/collecting duct: spironolactone, amiloride, triamterene.

Monitoring of daily weight is necessary. The rate of ascitic fluid reabsorption is limited to 700–900 ml/day. If a diuresis of 2–3 litre is induced, much of the fluid must come from non-ascitic, extra-cellular fluids including oedema fluid and the intravenous compartment. This is safe so long as oedema persists. Indeed diuresis may be rapid (greater than 2 kg daily) until oedema disappears [60]. Overall recommendations, however, to avoid the risk of renal dysfunction are a maximum daily weight loss of 0.5 kg/day, with a maximum of 1.0 kg/day in those with oedema.

Intravascular volume expansion with intravenous albumin increases the naturesis in response to diuretics, but is expensive and not cost-effective [20].

Long-term spironolactone causes painful gynaecomastia in cirrhotic males and should then be replaced by 10–15 mg/day of amiloride. However, this is less effective than spironolactone.

Longer acting diuretics such as thiazides and ethacrynic acid (a loop diuretic) are avoided in patients with liver disease because their action may continue after the drug is stopped because of side-effects. The patient may thus continue to lose urinary sodium and potassium and become hypovolaemic despite stopping the diuretic.

Before diuretic therapy is deemed to have failed (diuretic refractory ascites), non-compliance with sodium restriction should be ruled out by measuring a 24-h urinary sodium excretion. If this is greater than the 'prescribed dietary' sodium intake the patient is not complying with the restriction. Other causes of a lack of response to sodium restriction and diuretics are con-

Table 9.7. Treatment of ascites related to 24-h urinary sodium excretion

24-h urinary sodium (mmol)	Treatment
<5	Distal and loop diuretic
5–25	Distal diuretic
>25	Low-sodium diet only

comitant use of non-steroidal anti-inflammatory agents and spontaneous bacterial peritonitis.

Diuretic failures often occur in those with very poor hepato-cellular function who have a a poor prognosis without liver transplantation. In such refractory patients diuretics have eventually to be withdrawn because of intractable uraemia, hypotension or encephalopathy.

Complications

Rising urea and creatinine reflect contraction of the extracellular fluid volume and reduced renal circulation. It is necessary to interrupt or reduce diuretic therapy. Hepato-renal syndrome may be precipitated.

Encephalopathy may follow any profound diuresis and is usually associated with hypokalaemia and hypochloraemic acidosis.

Hyperkalaemia reflects the effect of spironolactone, which should be reduced or interrupted according to the level of serum potassium.

Hyponatraemia reflects reduced free water clearance. In the patient with severe hepato-cellular dysfunction it may also indicate the passage of sodium into the cells. If the serum sodium falls below 120 mmol/l, fluid intake should be restricted to 1 litre per day. Intravenous albumin is beneficial [52].

Muscle cramps may be a problem. They indicate the need to review the dose of diuretic. Quinine sulphate at night may help. Weekly intravenous albumin is beneficial [5].

Follow-up advice

The outpatient should adhere to the low-sodium diet, and abstain from alcohol where this is the cause of liver disease. Bathroom scales should be used to allow a record of weight to be made daily, nude or with consistent clothing. A daily record should be kept and brought to the physician at each visit.

The dose of diuretics depends upon the degree of ascites and the severity of the liver disease. A usual regime is 100–200 mg spironolactone (or 10–20 mg amiloride) daily with frusemide 40–80 mg daily for the patient with more marked ascites initially, or with a poor response to spironolactone alone. Serum electrolytes, creatinine, urea and liver function tests are monitored every 4 weeks for the stable outpatient. In the patient who has been treated initially as an inpatient an earlier check at 1 week after discharge allows an adjustment to the management plan before electrolyte or clinical imbalance has occurred. As liver function improves and the oedema and ascites resolve it may be possible to stop the frusemide first and then the spironolactone. Symptoms such as postural dizziness and thirst indicate over-enthusiastic treatment. The 'no added salt' (70–90 mmol) is maintained in the majority of patients.

Therapeutic abdominal paracentesis (table 9.8)

This procedure was abandoned in the 1960s because of the fear of causing acute renal failure. Moreover, the loss of approximately 50 g of protein in a 5-litre paracentesis led to patients becoming severely malnourished. New interest came with the observation that a 5-litre paracentesis was safe in fluid- and salt-restricted patients with *ascites and peripheral oedema* [38]. This work was extended to daily 4–5-litre paracenteses with 40 g salt-poor albumin infused intravenously over the same period. Finally, a single large paracentesis, about 10 litre in 1 h combined with intravenous albumin (6–8 g/l ascites removed) was shown to be equally effective (table 9.9) [25, 77].

In a controlled trial, paracentesis reduced hospital stay compared with traditional diuretic treatment [24]. The probability of requiring readmission to hospital, survival and causes of death did not differ significantly between the paracentesis and diuretic groups. The procedure is contraindicated in grade C patients with serum bilirubin greater than 10 mg/dl (170 μmol/l), prothrombin time less than 40%, platelets less than 40 000, creatinine greater than 3 mg/dl and urine sodium less than 10 mmol/day (table 9.8).

The complete, total paracentesis results in hypovolaemia as reflected by a rise in plasma renin levels [23].

Table 9.8. Therapeutic paracentesis

Selection
Tense ascites
Preferably with oedema
Child's grade B
Prothrombin >40%
Serum bilirubin <170 μmol/l (<10 mg/dl)
Platelets >40 000/mm^3
Serum creatinine <3 mg/dl (<260 μmol/l)
Urinary sodium >10 mmol/24 h
Routine
Volume removed: 5–10 litre
i.v. salt-poor albumin: 6–8 g/l removed

Table 9.9. Total paracentesis with intravenous albumin [77]

Volume; 10 litre
Time; 1 h
i.v. albumin (sodium-poor): 6 g/l removed
Candidates (see table 9.8)
Advantages
Comfort
Shortened hospital stay
But
Relapse, Survival } unchanged
Not in grade C patients

There is also some renal impairment proportional to the severity of the underlying liver disease. Its extent is a measure of survival.

Albumin replacement is more effective in preventing the hypovolaemia and post-paracentesis circulatory dysfunction than less costly plasma expanders such as dextran 70, dextran 40 and polygeline [22].

Total volume paracentesis decreases variceal pressure, size and wall tension in cirrhotic patients (prior to albumin replacement), suggesting benefit in patients with variceal bleeding with tense ascites [39].

Summary

Paracentesis is a safe, cost-effective treatment for cirrhotic ascites [7]. However, approximately 90% of patients with ascites respond to sodium restriction and diuretics, and paracentesis is generally a second-line treatment except for patients with tense and refractory ascites (see below). Despite this many clinicians opt for early paracentesis rather than waiting for diuretics to be effective [7]. It must not be done in end-stage cirrhotic patients or in those with renal failure. Intravenous salt-poor albumin replaces the protein lost in the ascitic fluid.

Sufficient ascitic fluid is removed to give the patient a flaccid, but not ascites-free, abdomen. The paracentesis must be followed by a good salt-restricted dietary and diuretic regime.

Refractory ascites [8]

This is defined as ascites that cannot be mobilized or the recurrence of which cannot be prevented by medical therapy. It is divided into diuretic-resistant ascites and diuretic-intractable ascites.

Diuretic-resistant ascites cannot be mobilized or the recurrence cannot be prevented (e.g. after therapeutic paracentesis) due to a lack of response (loss of weight, less than 200 g/day, and urinary sodium excretion lower than 50 mmol/day) to a 50-mmol sodium diet with intensive diuretic therapy (spironolactone 400 mg, with frusemide 160 mg/day for 1 week).

Diuretic-intractable ascites cannot be mobilized or the recurrence cannot be prevented due to the development of diuretic-induced complications that preclude the use of an effective diuretic dosage. Renal impairment, hepatic encephalopathy or electrolyte disturbances may be contraindications to starting diuretic therapy.

The natriuretic response to 80 mg frusemide intravenously is reported to distinguish patients with refractory (< 50 mmol sodium/8 h) from responsive (> 50 mmol/8 h) ascites [74], although the classification of the patient group studied was not as strict as in published criteria [8].

Treatment

The therapeutic options for patients with refractory ascites include repeated therapeutic paracentesis, TIPS, peritoneo-venous (Le Veen) shunting, and liver transplantation.

Therapeutic paracentesis

This has been discussed above for the patient with tense severe ascites as an initial treatment. For refractory ascites large volume paracentesis is the standard therapy. Diuretics are discontinued beforehand and restarted after paracentesis. In this group of patients recurrence of ascites is the rule. Reintroduction of diuretic treatment after paracentesis reduces the recurrence rate at 1 month. Randomized trials comparing large volume paracentesis plus albumin with peritoneo-venous shunts showed them to be equally effective with similar complication rates and survival [23, 25]. Since paracentesis plus albumin is simpler and can be done on a day/outpatient basis, it is the preferred procedure. Because of complications with peritoneo-venous shunting (obstruction, superior vena cava thrombosis, peritoneal fibrosis) use of this technique has declined and in most units has been abandoned in favour of paracentesis.

Transjugular intrahepatic portosystemic shunt (TIPS)

Porta-caval shunts have been largely abandoned for the treatment of refractory ascites because of the high encephalopathy rate.

Early experience with TIPS showed a reduction in diuretic requirements, and a fall in plasma renin and aldosterone activities. However, TIPS may precipitate hepatic encephalopathy and/or liver failure.

Prospective randomized trials comparing TIPS with large volume paracentesis show that TIPS may be more effective, and substantially reduce the need for subsequent paracentesis [41, 64]. In the first study [41],

patients randomized to TIPS had a significantly high mortality due to complications in Child's grade C patients. In the more recent study [64], there was no significant difference in mortality between TIPS and paracentesis-treated patients. The difference between these two studies relates to the number of patients studied and the severity of clinical disease. Further studies are awaited, particularly in patients with non-alcoholic cirrhosis. Currently TIPS remains a second-line choice in the treatment of refractory ascites. Only patients with moderately abnormal liver function and refractory ascites requiring frequent paracentesis should be considered. Factors identifying survival in patients undergoing elective TIPS are serum bilirubin concentration, serum creatinine, prothrombin time (INR) and the cause of underlying liver disease [48]. Patients with alcoholic and cholestatic liver disease had significantly better survival than those with viral and other liver diseases.

Peritoneo-venous (Le Veen) shunt

This allows ascitic fluid to pass from the peritoneal cavity into the general circulation (fig. 9.9). It is inserted under general anaesthesia. The peritoneal cavity is drained through a plastic tube which is connected to a unidirectional pressure-sensitive valve lying extra-peritoneally. From the valve a silicone rubber tube passes subcutaneously from the abdominal wound to the neck and thence the internal jugular vein and superior vena cava (SVC). When the diaphragm descends during inspiration, the intraperitoneal fluid pressure rises while that in the intrathoracic SVC falls.

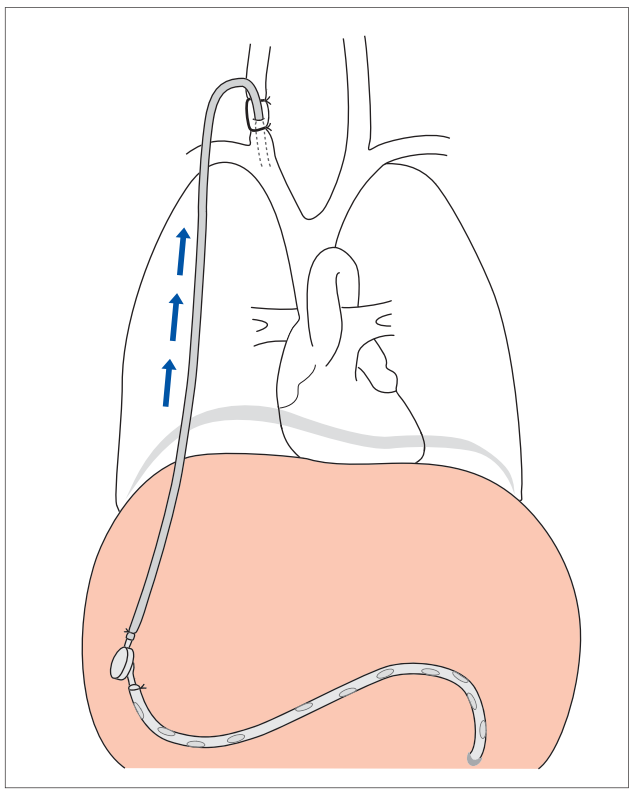


Fig. 9.9. The peritoneo-venous shunt.

Flow of ascites along the shunt depends upon this pressure gradient between peritoneal cavity and SVC.

The peritoneo-venous shunt system may control ascites over many months. It produces sustained expansion of the circulating blood volume and a fall in plasma levels of renin–angiotensin, noradrenaline and antidiuretic hormone. Renal function and nutrition improve.

However, there are complications including disseminated intravascular coagulation, which may be severe and fatal, ascitic leaks, variceal bleeding, pulmonary oedema and sepsis. Peri-operative mortality is around 20% [55] and may be as high as 50% [69]. There is a high readmission rate for shunt dysfunction. Child grade C patients are not suitable for the procedure.

Peritoneo-venous shunting has been virtually abandoned because large volume paracentesis combined with albumen replacement is simpler, equally effective and can be done as an outpatient [23, 25].

Prognosis

The prognosis is always grave after ascites develops in a patient with cirrhosis. It is better if the ascites has accumulated rapidly, especially if there is a well-defined precipitating factor such as gastrointestinal haemorrhage.

A patient with cirrhosis developing ascites has only a 40% chance of being alive 2 years later. Much depends on the major clinical factor leading to fluid retention. If liver cell failure, evidenced by jaundice and hepatic encephalopathy, is severe, the prognosis is poor. If the major factor is a particularly high portal pressure, the patient may respond well to treatment.

Ascites cannot be divorced from the underlying liver disease that caused it and, although it may be controlled, the patient is still liable to die from another complication such as haemorrhage, hepatic coma or primary liver cancer. It is questioned whether control of ascites *per se* increases lifespan. It certainly makes the patient more comfortable.

Because of the poor prognosis, liver transplantation should be considered in all patients with ascites. Early assessment is needed and a decision taken before the clinical decline associated with refractory ascites or hepato-renal syndrome.

An analysis of over 200 cirrhotic patients admitted to hospital for the treatment of ascites showed four variables with independent prognostic value. These were renal water excretion (diuresis after water load),

mean arterial pressure, Child–Pugh class and serum creatinine [17].

Hepato-renal syndrome [13]

Hepato-renal syndrome is the development of renal failure in patients with severe liver disease in the absence of any identifiable renal pathology. It is a functional rather than structural disturbance in renal function. The histology of the kidney is virtually normal. Such kidneys have been successfully transplanted following which they functioned normally. After liver transplantation kidney function also usually returns to normal.

The mechanism is not fully understood, but the renal disturbance is thought to represent the extreme phase of the spectrum of vascular and neurohumoral changes associated with severe liver disease, which in a less severe form result in ascites (figs 9.4, 9.10).

It is a common but severe complication in cirrhotic patients with ascites. About 20% of cirrhotic patients with ascites and normal renal function develop the syndrome after 1 year of follow-up, and 39% at 5 years [21]. Without liver transplantation and prior to the recent studies of treatment using vasocontrictors, recovery of renal function was unusual (< 5% of patients). The prognosis was poor with a median survival after diagnosis of < 2 weeks.

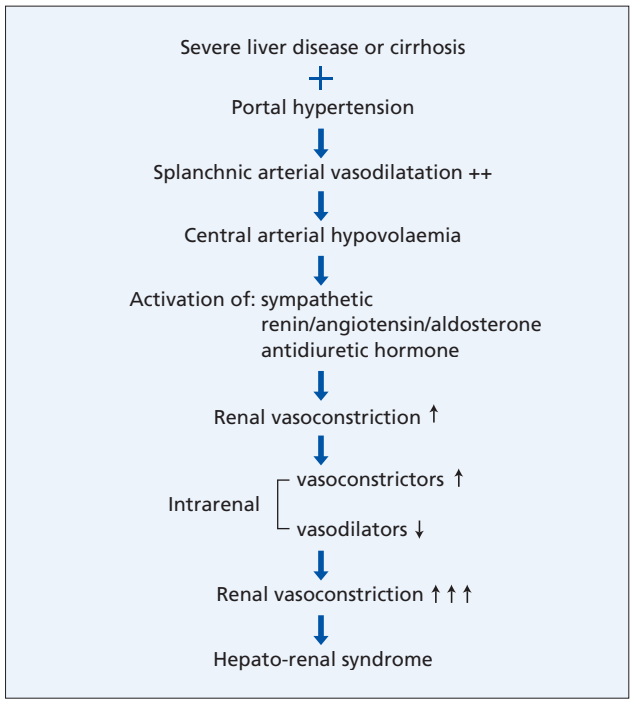


Fig. 9.10. Hypothetical mechanism for hepato-renal syndrome.

Recent therapeutic advances based upon reversal of splanchnic vasodilatation have produced reversal of hepato–renal syndrome in some patients.

Diagnostic criteria (table 9.10)

These are based largely on abnormal renal function tests, the absence of other causes of renal failure, and the absence of sustained improvement in renal function after diuretic withdrawal and fluid challenge. The presence of shock before deterioration of renal function precludes a diagnosis of hepato-renal syndrome.

Additional criteria describe the characteristics of urine flow and content, but since these may be present with other types of renal failure, for example acute tubular necrosis, they are not considered essential for the diagnosis of hepato-renal syndrome.

Classification

Hepato-renal syndrome may be classified into two types:

Type 1. Patients have a rapidly progressive (less than 2 weeks) reduction of renal function with doubling of the initial serum creatinine to greater than 2.5 mg/dl (220 µmol/l) or a 50% reduction in the initial 24-h creatinine clearance to less than 20 ml/min. There is an 80% mortality at 2 weeks in this type, with only 10% surviving more than 3 months [21].

Type 2. Patients satisfy the criteria for the diagnosis but the renal failure does not progress rapidly. These patients usually have relatively preserved hepatic function with refractory ascites. Survival is reduced compared with cirrhotics with ascites but normal renal function.

Table 9.10. Criteria for diagnosis of hepato-renal syndome [8]

Major criteria

1. Low glomerular filtration rate (serum creatinine >1.5 mg/dl (130 µmol/l) *or* creatinine clearance <40 ml/min)
2. Absence of shock, ongoing sepsis, fluid loss, nephrotoxic drugs
3. No sustained improvement in renal function (serum creatinine ≤1.5 mg/dl *or* creatinine clearance ≥40 ml/min) after diuretic therapy stopped and expansion of plasma volume with 1.5 litre of plasma expander
4. Proteinuria <500 mg/day; no ultrasound evidence of renal tract obstruction or renal disease

Additional criteria (not necessary for diagnosis)

1. Urine volume <500 ml/day
2. Urine sodium <10 mmol/day
3. Urine osmolarity > plasma osmolarity
4. Urine red cells <50/high-power field
5. Serum sodium <130 mmol/l

Mechanism

The mechanisms proposed for the formation of ascites in patients with cirrhosis have been discussed at the beginning of this chapter. The peripheral arterial vasodilatation theory proposes initial splanchnic arterial dilatation with consequent stimulation of the sympathetic nervous system (raised noradrenaline) and the renin–angiotensin system. This is the result of activation of volume receptors responding to vascular underfilling. Initially, despite changes in vaso-constrictors and vasodilators, renal function is preserved. For reasons that are not yet established, renal compensatory mechanisms appear to fail. Imbalance between systemic and intra-renal vasodilator and vaso-constrictor mechanisms is likely.

Evidence for this imbalance comes from studies of arachidonic acid derivatives (fig. 9.11). Thromboxane A_2 is a potent vaso-constrictor. Its metabolite thromboxane B_2 is markedly increased in the urine of patients with the hepato-renal syndrome. Urinary excretion of prostaglandin E_2, a vasodilator, is decreased.

Endothelin-1, formed in vascular endothelium, and endothelin-2, formed in tissue, are long-acting vaso-constrictors. Plasma endothelins are increased in the hepato-renal syndrome [54]. This may be related to endotoxaemia.

There is particular sensitivity to the vaso-constrictor effect of endogenous adenosine [36, 43]. Nitric oxide is a potent vasodilator and impaired synthesis may play a role [50].

Clinical features

Many features are associated with an increased risk for hepato-renal syndrome including marked sodium (< 5 mmol/l) and water retention, low mean arterial blood pressure (< 80 mmHg) and marked elevation of the renin–angiotensin–aldosterone system [21]. There is no correlation with the severity of liver failure.

The advanced stage is characterized by progressive azotaemia, usually with hepatic failure and ascites which is difficult to control. The patient complains of anorexia, weakness and fatigue. The blood urea concentration is raised. Hyponatraemia is invariable. Sodium is avidly reabsorbed by the renal tubules and urine osmolarity is increased. In the later stages nausea, vomiting and thirst occur. The patient is drowsy. The picture may be indistinguishable from that of hepatic encephalopathy. Terminally, coma deepens, blood pressure drops and urine volume falls even more. The terminal stages last from a few days to more than 6 weeks.

It may be difficult to distinguish hepatic from renal failure, although patients die from biochemical azotaemia rather than the full clinical picture of kidney failure. Hyperkalaemia is unusual. Death is due to liver failure; survival depends on the reversibility of the liver disease.

Duplex Doppler ultrasonography may be used to evaluate renal arterial resistance. Values are already increased in the non-ascitic cirrhotic without azotaemia and identify patients with a high risk for the hepato-renal syndrome [59]. They are even higher in the ascitic phase and in the hepato-renal syndrome where they predict survival [49].

Differential diagnosis

Iatrogenic renal failure in a cirrhotic patient must be differentiated from genuine hepato-renal syndrome as the management and prognosis are different (table 9.11). Causes include diuretic overdose and severe diarrhoea due, for example, to lactulose. Non-steroidal anti-inflammatory drugs reduce renal prostaglandin production, so reducing the glomerular filtration rate and free water clearance. Nephrotoxic drugs should be identified, including aminoglycosides and X-ray contrast media. Bacterial sepsis, particularly spontaneous bacterial peritonitis, may present with reversible impairment of renal function. Glomerular mesangial IgA deposits, accompanied by complement deposition, complicate cirrhosis, usually in the alcoholic. Hepatitis B and C are associated with immune-related glomerulonephritis. These lesions are diagnosed by finding proteinuria with microscopic haematuria and casts.

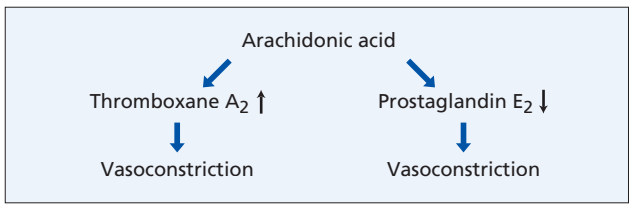


Fig. 9.11. Urinary changes in the hepato-renal syndrome.

Table 9.11. Iatrogenic hepato-renal syndrome

Drugs	Treatment
Diuretics	Volume expansion
Lactulose	Volume expansion
NSAID (prostaglandin inhibition)	Stop drug
Aminoglycosides	Diagnose urine β_2-microglobulins
Cyclosporin	Haemofiltration

NSAID, non-steroidal anti-inflammatory drug.

Prevention

The risk of hepato-renal syndrome is reduced by careful use and monitoring of diuretic therapy, and the early recognition of any complication such as electrolyte imbalance, haemorrhage or infection. Nephrotoxic drugs are avoided. The risk of renal deterioration after large volume paracentesis is reduced by the administration of salt-poor albumin. The risk of further episodes of spontaneous bacterial peritonitis in patients already having had one episode is reduced by prophylactic antibiotic. When spontaneous bacterial peritonitis is treated with antibiotics, the administration of albumin reduces the frequency of renal dysfunction [73].

Treatment

General measures

Since renal dysfunction may be related to hypovolaemia, measurement of the central venous pressure is important. An intravenous fluid challenge is appropriate with up to 1.5 litre of saline or, if available, colloid such as human albumin solution (HAS). Monitoring the patient for fluid overload is necessary although this is not usually a problem because advanced cirrhotics have increased venous compliance [34].

Potentially nephrotoxic drugs are stopped. A search for sepsis is made. Ascites is tapped for white cell count, Gram stain and culture. Blood, urine and cannula tips are cultured. A broad-spectrum antibiotic is started irrespective of proof of infection.

Tense ascites may be drained to improve renal haemodynamics by decreasing inferior vena caval and renal vein pressure.

Haemodialysis, although not formally studied in control trials, is not considered effective. Complications occur including arterial hypotension, coagulopathy, sepsis and gastrointestinal haemorrhage, and most patients die during treatment. Continuous arteriovenous and venovenous haemofiltration have been used but not formally evaluated. Liver transplantation needs to be available rapidly for such therapy to be appropriate, but this is rarely the case in type 1 hepato-renal syndome. The promise of new pharmacological treatments provides a potentially new therapeutic approach which may avoid the need to consider renal support.

Liver transplantation

The survival of patients with type I hepato-renal syndrome is short, from days to a few weeks, and this currently virtually removes liver transplantation as a therapeutic choice. New pharmacological approaches reversing or stabilizing renal dysfunction may allow elective transplantation.

In patients with type 2 hepato-renal syndrome, liver transplantation results in return of acceptable renal function in 90%, and the overall survival rates are similar to those without hepato-renal syndrome [29]. Patients with hepato-renal syndrome have a longer stay in the intensive care unit (21 vs. 4.5 days) and haemodialysis was required more often post-operatively (35 vs. 5%). Since cyclosporin A may contribute to renal deterioration, it has been suggested that azathioprine and steroids be given until a diuresis has started—usually by 48–72 h [29].

These results emphasize the need to identify patients at risk of hepato-renal syndrome and plan transplantation as early as possible.

Pharmacological treatment [13, 16]

Vasodilators. These have been used in an attempt to reverse renal vasoconstriction. Dopamine at renal support doses has a renal vasodilatory effect. Although widely used clinically there is no clear evidence of efficacy. Prostaglandin administration is not associated with significant improvement in renal function.

Vasoconstrictors. The rationale for use of these agents is to reverse the intense splanchnic vasodilatation, which is considered an important factor in ascites formation and hepato-renal syndrome. Renal vasoconstriction reflects systemic and local responses to the reduced effective circulating volume.

Several regimens show promise using agonists of vasopressin V1 receptors. Initially, short-term intravenous ornipressin was shown to improve circulatory dysfunction, suppress the renin–angiotensin–aldosterone and sympathetic nervous system activity, and increase creatinine clearance [42]. With longer term treatment using ornipressin and albumin, renal function improved in four of eight patients with hepato-renal syndrome, but treatment had to be withdrawn in the remainder because of side-effects, including ischaemic events related to ornipressin [30]. Terlipressin (glypressin) is slowly converted into vasopressin *in vivo* and has a longer biological half-life. It has fewer side-effects than ornipressin. Terlipressin given to patients with hepato-renal syndrome type 1 for 2 days improved glomerular filtration rate [33]. Reversal of hepato-renal syndrome has been reported in seven of nine patients treated with terlipressin and intravenous albumin (5–15 days) without side-effects [80].

An alternative pharmacological approach has used long-term midrodine (an α-adrenergic agonist) combined with octreotide (an inhibitor of the release of glucagon) and intravenous albumin [6]. In all eight

patients with type 1 hepato-renal syndrome, treated in this way renal function improved with no side-effects. Survival was long enough in four of the eight to allow successful liver transplantation.

A further study has shown benefit from prolonged (up to 27 days) intravenous ornipressin and dopamine in seven patients with type 1 hepato-renal syndrome which was reversed in four patients [32]. One patient had an ischaemic complication.

These studies represent a major advance in the management of hepato-renal syndrome. Based upon the 'peripheral arterial vasodilatation hypothesis', they suggest that vasoconstrictor drugs can be effective in the treatment of hepato-renal syndrome. Which agent and dose is best and whether albumin infusion is necessary needs randomized studies.

Antioxidant therapy

A preliminary uncontrolled study has suggested improvement in renal function after intravenous *n*-acetylcysteine [35]. Seven of 12 patients survived for 3 months including two patients who underwent successful liver transplantation.

Transjugular intrahepatic portosystemic shunt (TIPS)

Uncontrolled studies have shown that TIPS may improve renal perfusion and reduce the activity of the RAAS. In a prospective study of 31 non-transplantable patients approximately 75% had improvement in renal function after TIPS [12]. The 1-year survival was significantly better in type 2 than type 1 patients (70 vs. 20%). This study excluded patients with a Pugh score > 12, serum bilirubin > 15 mg/dl (250 μmol/l), and severe spontaneous encephalopathy. Controlled trials against other developing modalities would be useful to choose the optimal approach and select appropriate patients.

Extracorporeal albumin dialysis

A small randomized trial of MARS, the molecular absorbent recirculating system, has shown benefit for patients with type 1 hepato-renal syndrome [53]. This modified dialysis method uses an albumin-containing dialysate. Studies are underway to establish whether it has a role in such patients as a bridge to transplantation.

Summary

New approaches offer hope that hepato-renal syndrome, which previously had a dismal outlook, may be improved or reversed. The approaches remain investigational. The optimal approach may become clearer as randomized studies are achieved.

Hyponatraemia [26]

Hyponatraemia is common in cirrhotic patients with ascites, being found in around one-third. The cause is excess body water because of the inability of these patients to adjust the amount of water excreted in urine to that taken in. Serum sodium concentrations of less than 130 mmol/l are treated by fluid restriction, to avoid further falls. Advances in the understanding of the pathogenesis are leading to pharmacological approaches to treatment.

Mechanism

Eighty per cent of the water in the glomerular filtrate is reabsorbed in the proximal tubule and descending limb of Henle. The ascending limb of Henle and distal tubule are impermeable to water. Control of the volume of water passed in urine is dependent on the amount of water reabsorbed in the collecting tubule and collecting duct. This is under the control of vasopressin, which interacts with V2 receptors on the cells of the renal collecting ducts (see fig. 9.2). Vasopressin receptor activation stimulates the translocation of the water channel aquaporin 2 from a cytoplasmic vesicular compartment to the apical membrane. This mechanism may be effected by prostaglandins which inhibit vasopressin-stimulated water reabsorption.

Vasopressin is produced in the hypothalamus. Production is controlled in two ways: by osmoreceptors in the anterior hypothalamus under the influence of plasma osmolarity, and by parasympathetic stimulation as a result of activation of baroreceptors in the atria, ventricles, aortic arch and carotid sinus.

Water retention in cirrhotic patients with ascites is due to excess vasopressin as a result of baroreceptor stimulation. This is thought to be related to the reduced effective circulating volume as a result of splanchnic and other arterial vasodilatation—the same circulatory abnormality which leads to activation of the renin–angiotensin–aldosterone axis and the sympathetic nervous system and sodium retention. However, alterations in sodium and water handling are not synchronous, that for sodium occurring first (see fig. 9.4).

Data show that vasopressin levels are not grossly elevated in cirrhotic patients. The normal inhibition of vasopressin by a water load, however, is blunted or absent. Although there is reduced hepatic metabolism of vasopressin in patients with cirrhosis, related to the severity of disease, this is not thought to be the primary reason for water retention.

Pharmacological treatment

With greater understanding of the mechanisms involved several approaches are being studied to increase free water clearance. These are: (i) blocking secretion of vasopressin by the hypothalamus, or V2 receptors in the collecting ducts; or (ii) perturbing cAMP formation, which acts as the signal between vasopressin and aquaporin in collecting duct cells.

κ-Opioid receptor agonists inhibit vasopressin release. Experimentally and in human studies they increase urine volume [18]. However, because there is no significant decrease in circulating vasopressin levels with the agonist used (niravoline) the mechanism remains unclear [18].

In an experimental model of cirrhosis, the *V2 receptor antagonist*, OPC31260, induced a four-fold increase in water excretion [79].

Demeclocycline, a tetracycline, interferes with the generation and action of cAMP in collecting ducts, and in cirrhotics increases free water clearance and serum sodium. However, in patients with cirrhosis its use is associated with renal impairment.

Summary

Although advances are being made in pharmacological approaches to correct water retention and the associated hyponatraemia, these are not yet clinically applicable. The mainstay of treatment is fluid restriction. Intravenous albumin infusion may be effective in the short term [52]. Whichever approach is used, it should be recognized that hyponatraemia is a predictor of reduced survival in cirrhotic patients with ascites and is a risk factor for the hepato-renal syndrome [21].

References

1 Aalami OO, Allen DB, Organ CH. Chylous ascites; a collective review. *Surgery* 2000; **128**: 761.
2 Ackerman Z, Reynolds TB. Evaluation of pleural fluid in patients with cirrhosis. *J. Clin. Gastroenterol*. 1997; **25**: 619.
3 Albillos A, Cuervas-Mons V, Millan I *et al*. Ascitic fluid polymorphonuclear cell count and serum to ascites albumin gradient in the diagnosis of bacterial peritonitis. *Gastroenterology* 1990; **98**: 134.
4 Andreu M, Sola R, Sitges-Serra A *et al*. Risk factors for spontaneous bacterial peritonitis in cirrhotic patients with ascites. *Gastroenterology* 1993; **104**: 1133.
5 Angeli P, Albino G, Carraro P *et al*. Cirrhosis and muscle cramps: evidence of a causal relationship. *Hepatology* 1996; **23**: 264.
6 Angeli P, Volpin R, Gerunda G *et al*. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. *Hepatology* 1999; **29**: 1690.
7 Arroyo V, Ginès A, Saló J. A European survey on the treatment of ascites in cirrhosis. *J. Hepatol*. 1994; **21**: 667.
8 Arroyo V, Ginès P, Gerbes AL *et al*. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatology* 1996; **23**: 164.
9 Arroyo V, Jimenèz W. Complications of cirrhosis. II. Renal and circulatory dysfunction. Lights and shadows in an important clinical problem. *J. Hepatol*. 2000; **32** (Suppl. 1): 157.
10 Blaise M, Pateron D, Trinchet J-C *et al*. Systemic antibiotic therapy prevents bacterial infection in cirrhotic patients with gastrointestinal haemorrhage. *Hepatology* 1994; **20**: 34.
11 Bories PN, Campillo B, Azaou L *et al*. Long-lasting NO overproduction in cirrhotic patients with spontaneous bacterial peritonitis. *Hepatology* 1997; **25**: 1328.
12 Brensing KA, Textor J, Perz J *et al*. Long-term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. *Gut* 2000; **47**: 288.
13 Cárdenas A, Uriz J, Ginès P *et al*. Hepatorenal syndrome. *Liver Transplant*. 2000; **6**: S63.
14 Casafont F, Sanchez E, Martin L *et al*. Influence of malnutrition on the prevalence of bacterial translocation and spontaneous bacterial peritonitis in experimental cirrhosis in rats. *Hepatology* 1997; **25**: 1334.
15 Chang C-S, Chen G-H, Lien H-C *et al*. Small intestine dysmotility and bacterial overgrowth in cirrhotic patients with spontaneous bacterial peritonitis. *Hepatology* 1998; **28**: 1187.
16 Dagher L, Patch D, Marley R *et al*. Review article: pharmacological treatment of the hepatorenal syndrome in cirrhotic patients. *Aliment. Pharmacol. Ther.* 2000; **14**: 515.
17 Fernández-Esparrach G, Sánchez-Fueyo A, Ginès P *et al*. A prognostic model for predicting survival in cirrhosis with ascites. *J. Hepatol*. 2001; **34**: 46.
18 Gadano A, Moreau R, Pessione F *et al*. Aquaretic effects of niravoline, a kappa-opioid agonist, in patients with cirrhosis. *J. Hepatol*. 2000; **32**: 38.
19 Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal haemorrhage, ascites, and spontaneous bacterial peritonitis. *Gastroenterology* 2001; **120**: 726.
20 Gentilini P, Casini-Raggi V, Di Fiore G *et al*. Albumin improves the response to diuretics in patients with cirrhosis and ascites: results of a randomized, controlled trial. *J. Hepatol*. 1999; **30**: 639.
21 Ginès A, Escorsell A, Ginès P *et al*. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. *Gastroenterology* 1993; **105**: 229.
22 Ginès A, Fernàndez-Esparrach G, Monescillo A *et al*. Randomised trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. *Gastroenterology* 1996; **111**: 1002.
23 Ginès A, Planas R, Angeli P *et al*. Treatment of patients with cirrhosis and refractory ascites by Le Veen shunt with titanium tip: comparison with therapeutic paracentesis. *Hepatology* 1995; **22**: 124.
24 Ginès P, Arroyo V, Quintero E *et al*. Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites. Results of a randomized study. *Gastroenterology* 1987; **93**: 234.
25 Ginès P, Arroyo V, Vargas V *et al*. Paracentesis with intravenous infusion of albumin as compared with peritoneovenous shunting in cirrhosis with refractory ascites. *N. Engl. J. Med*. 1991; **325**: 829.

26 Ginès P, Berl T, Bernardi M *et al*. Hyponatraemia in cirrhosis: from pathogenesis to treatment. *Hepatology* 1998; **28**: 851.

27 Ginès P, Schrier RW. The arterial vasodilation hypothesis of ascites formation in cirrhosis. In Arroyo V, Ginès P, Rodés J, Schrier RW, eds. *Ascites and Renal Dysfunction in Liver Disease. Pathology, Diagnosis and Treatment*. Blackwell Science, Oxford, 1999, p. 411.

28 Girgrah N, Liu P, Collier J, Blendis L, Wong F. Haemodynamic, renal sodium handling, and neurohormonal effects of acute administration of low dose losartan, an angiotensin II receptor antagonist, in preascitic cirrhosis. *Gut* 2000; **46**: 114.

29 Gonwa TA, Morris CA, Goldstein RM *et al*. Long-term survival and renal function following liver transplantation in patients with and without hepatorenal syndrome—experience in 300 patients. *Transplantation* 1991; **51**: 428.

30 Guevara M, Ginès P, Fernández-Esparrach G *et al*. Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansion. *Hepatology* 1998; **27**: 35–41.

31 Guevara M, Ginès P, Jiménez W *et al*. Increased adrenomedullin levels in cirrhosis: relationship with haemodynamic abnormalities and vasoconstrictor systems. *Gastroenterology* 1998; **114**: 336.

32 Gülberg V, Bilzer M, Gerbes AL. Long-term therapy and retreatment of hepatorenal syndrome type 1 with ornipressin and dopamine. *Hepatology* 1999; **30**: 870.

33 Hadengue A, Gadano A, Moreau R *et al*. Beneficial effects of the 2-day administration of terlipressin in patients with cirrhosis and hepatorenal syndrome. *J. Hepatol.* 1998; **29**: 565.

34 Hadengue A, Moreau R, Gaudin C *et al*. Total effective vascular compliance in patients with cirrhosis: a study of the response to acute blood volume expansion. *Hepatology* 1992; **15**: 809.

35 Holt S, Goodier D, Marley R *et al*. Improvement in renal function in hepatorenal syndrome with *N*-acetylcysteine. *Lancet* 1999; **353**: 294.

36 Jacobson ED, Pawlik WW. Adenosine regulation of mesenteric vasodilation. *Gastroenterology* 1994; **107**: 1168.

37 Kakizaki S, Katakai K, Yoshinaga T *et al*. Hepatic hydrothorax in the absence of ascites. *Liver* 1998; **18**: 216.

38 Kao HW, Rakov HE, Savage E *et al*. The effect of large volume paracentesis on plasma volume—a cause of hypovolemia? *Hepatology* 1985; **5**: 403.

39 Kravetz D, Romero G, Argonz J *et al*. Total volume paracentesis decreases variceal pressure, size, and variceal wall tension in cirrhotic patients. *Hepatology* 1997; **25**: 59.

40 Lazaridis KN, Frank JW, Krowka MJ *et al*. Hepatic hydrothorax: pathogenesis, diagnosis, and management. *Am. J. Med.* 1999; **107**: 262.

41 Lebrec K, Giuily N, Hadengue A *et al*. Transjugular intrahepatic portosystemic shunts: comparison with paracentesis in patients with cirrhosis and refractory ascites: a randomised trial. *J. Hepatol.* 1996; **25**: 135.

42 Lenz K, Hörnargl H, Druml W *et al*. Ornipressin in the treatment of functional renal failure in decompensated liver cirrhosis. *Gastroenterology* 1991; **101**: 1060.

43 Llach J, Ginès P, Arroyo V *et al*. Effect of dipyridamole on kidney function in cirrhosis. *Hepatology* 1993; **17**: 59.

44 Llovet JM, Bartoli R, March F *et al*. Translocated intestinal bacteria cause spontaneous bacterial peritonitis in cirrhotic rats: molecular epidemiologic evidence. *J. Hepatol.* 1998; **28**: 307.

45 Llovet JM, Bartoli R, Planas R *et al*. Selective intestinal decontamination with norfloxacin reduces bacterial translocation in ascitic cirrhotic rats exposed to haemorrhagic shock. *Hepatology* 1996; **23**: 781.

46 Llovet JM, Moitinho E, Sala M *et al*. Prevalence and prognostic value of hepatocellular carcinoma in cirrhotic patients presenting with spontaneous bacterial peritonitis. *J. Hepatol.* 2000; **33**: 423.

47 Llovet JM, Planas R, Morillas R *et al*. Short-term prognosis of cirrhosis with spontaneous bacterial peritonitis: multivariate study. *Am. J. Gastroenterol.* 1993; **88**: 388.

48 Malinchoc M, Kamath PS, Gordon FD *et al*. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; **31**: 864.

49 Maroto A, Ginès A, Saló J *et al*. Diagnosis of functional kidney failure of cirrhosis with Doppler sonography: prognostic value of resistive index. *Hepatology* 1994; **20**: 839.

50 Martin P-Y, Ginès P, Schrier RW. Nitric oxide as a mediator of haemodynamic abnormalities and sodium and water retention in cirrhosis. *N. Engl. J. Med.* 1998; **339**: 533.

51 Martin P-Y, Ohara M, Ginès P *et al*. Nitric oxide synthase (NOS) inhibition for one week improves renal sodium and water excretion in cirrhotic rats with ascites. *J. Clin. Invest.* 1998; **101**: 235.

52 McCormick PA, Mistry P, Kaye G *et al*. Intravenous albumin infusion is an effective therapy for hyponatraemia in cirrhotic patients with ascites. *Gut* 1990; **31**: 204.

53 Mitzner SR, Stange J, Klammt S *et al*. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomised, controlled clinical trial. *Liver Transplant.* 2000; **6**: 277.

54 Moore K, Wendon J, Frazer M *et al*. Plasma endothelin immunoreactivity in liver disease and the hepatorenal syndrome. *N. Engl. J. Med*. 1992; **327**: 1774.

55 Moskovitz M. The peritoneovenous shunt: expectations and reality. *Am. J. Gastroenterol*. 1990; **85**: 917.

56 Navasa M, Follo A, Filella X *et al*. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. *Hepatology* 1998; **27**: 1227.

57 Novella M, Sola R, Soriano G *et al*. Continuous vs. inpatient prophylaxis of the first episode of spontaneous bacterial peritonitis with norfloxacin. *Hepatology* 1997; **25**: 532.

58 Perez-Ayuso RM, Arroyo V, Planas R *et al*. Randomised comparative study of efficacy of frusemide vs. spironolactone in nonazotaemic cirrhosis with ascites. *Gastroenterology* 1983; **84**: 961.

59 Platt JF, Ellis JH, Rubin JM *et al*. Renal duplex Doppler ultrasonography: a noninvasive predictor of kidney dysfunction and hepatorenal failure in liver disease. *Hepatology* 1994; **20**: 362.

60 Pockros PJ, Reynolds TB. Rapid diuresis in patients with ascites from chronic liver disease: the importance of peripheral oedema. *Gastroenterology* 1986; **90**: 1827.

61 Ricart E, Soriano G, Novella MT *et al*. Amoxicillin-clavulanic acid vs. cefotaxime in the therapy of bacterial infections in cirrhotic patients. *J. Hepatol.* 2000; **32**: 596.

62 Rimola A, Garcia-Tsao G, Navasa M *et al*. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. *J. Hepatol.* 2000; **32**: 142.

63 Rimola A, Salmerón JM, Clemente G *et al*. Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis: results of a prospective randomized, multicentre study. *Hepatology* 1995; **21**: 674.
64 Rössle M, Ochs A, Gülberg V *et al*. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. *N. Engl. J. Med.* 2000; **342**: 1701.
65 Runyon BA. Management of adult patients with ascites caused by cirrhosis. *Hepatology* 1998; **27**: 264.
66 Runyon BA. Monomicrobial non-neutrocytic bacterascites: a variant of spontaneous bacterial peritonitis. *Hepatology* 1990; **12**: 710.
67 Runyon BA. Patients with deficient ascitic fluid opsonic activity are predisposed to spontaneous bacterial peritonitis. *Hepatology* 1988; **18**: 632.
68 Runyon BA, McHutchinson JG, Antillon MR *et al*. Short-course vs. long-course antibiotic treatment of spontaneous bacterial peritonitis. A randomized controlled study of 100 patients. *Gastroenterology* 1991; **100**: 1737.
69 Scholz DG, Nagorney DM, Lindor KD. Poor outcome from peritoneovenous shunts for refractory ascites. *Am. J. Gastroenterol*. 1989; **84**: 540.
70 Schrier RW, Arroyo V, Bernardi M *et al*. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988; **8**: 1151.
71 Singh N, Gayowski T, Yu VL *et al*. Trimethoprim-sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis: a randomized trial. *Ann. Intern. Med*. 1995; **122**: 595.
72 Solà R, Andreu M, Coll S *et al*. Spontaneous bacterial peritonitis in cirrhotic patients treated using paracentesis or diuretics: results of a randomized study. *Hepatology* 1995; **21**: 340.
73 Sort P, Navasa M, Arroyo V *et al*. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N. Engl. J. Med.* 1999; **341**: 403.
74 Spahr L, Villeneuve J-P, Tran HK *et al*. Furosemide-induced natriuresis as a test to identify cirrhotic patients with refractory ascites. *Hepatology* 2001; **33**: 28.
75 Strauss RM, Martin LG, Kaufman SL *et al*. Transjugular intrahepatic portal systemic shunt for the management of symptomatic cirrhotic hydrothorax. *Am. J. Gastroenterol*. 1994; **89**: 1520.
76 Terg R, Cobas S, Fassio E *et al*. Oral ciprofloxacin after a short course of intravenous ciprofloxacin in the treatment of spontaneous bacterial peritonitis: results of a multicentre, randomised study. *J. Hepatol.* 2000; **33**: 564.
77 Titó L, Ginès P, Arroyo V *et al*. Total paracentesis associated with intravenous albumin management of patients with cirrhosis and ascites. *Gastroenterology* 1990; **98**: 146.
78 Titó L, Rimola A, Ginès P *et al*. Recurrence of spontaneous bacterial peritonitis in cirrhosis: frequency and predictive factors. *Hepatology* 1988; 8: 27.
79 Tsuboi Y, Ishikawa SE, Fujisawa G *et al*. Therapeutic efficacy of the nonpeptide AVP antagonist OPC-31260 in cirrhotic rats. *Kidney Int.* 1994; **46**: 237.
80 Uriz J, Ginès P, Cárdenas A *et al*. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. *J. Hepatol.* 2000; **33**: 43.
81 Van der Merwe S, Dens J, Daenen W *et al*. Pericardial disease is often not recognized as a cause of chronic severe ascites. *J. Hepatol.* 2000; **32**: 164.
82 Wong F, Massie D, Hsu P *et al*. Indomethacin-induced renal dysfunction in patients with well-compensated cirrhosis. *Gastroenterology* 1993; **104**: 869.
83 Xiol X, Castellote J, Baliellas C *et al*. Spontaneous bacterial empyema in cirrhotic patients: analysis of 11 cases. *Hepatology* 1990; **11**: 365.

Chapter 10
The Portal Venous System and Portal Hypertension

The portal system includes all veins that carry blood from the abdominal part of the alimentary tract, the spleen, pancreas and gallbladder. The portal vein enters the liver at the porta hepatis in two main branches, one to each lobe; it is without valves in its larger channels (fig. 10.1) [35].

The *portal vein* is formed by the union of the superior mesenteric vein and the splenic vein just posterior to the head of the pancreas at about the level of the second lumbar vertebra. It extends slightly to the right of the mid-line for a distance of 5.5–8 cm to the porta hepatis. The portal vein has a segmental intra-hepatic distribution, accompanying the hepatic artery.

The *superior mesenteric vein* is formed by tributaries from the small intestine, colon and head of the pancreas, and irregularly from the stomach via the right gastro-epiploic vein.

The *splenic veins* (5–15 channels) originate at the splenic hilum and join near the tail of the pancreas with the short gastric vessels to form the main splenic vein. This proceeds in a transverse direction in the body and head of the pancreas, lying below and in front of the artery. It receives numerous tributaries from the head of the pancreas, and the left gastro-epiploic vein enters it near the spleen. The *inferior mesenteric vein*, bringing blood from the left part of the colon and rectum, usually enters its medial third. Occasionally, however, it enters the junction of the superior mesenteric and splenic veins.

Portal blood flow in man is about 1000–1200 ml/min.

Portal oxygen content. The fasting arterio-portal oxygen difference is only 1.9 volumes per cent (range 0.4–3.3 volumes per cent) and the portal vein contributes 40 ml/min or 72% of the total oxygen supply to the liver.

During digestion, the arterio-portal venous oxygen difference increases due to increased intestinal utilization.

Stream-lines in the portal vein. There is no consistent pattern of hepatic distribution of portal inflow. Sometimes splenic blood goes to the left and sometimes to the right. Crossing-over of the bloodstream can occur in the portal vein. Flow is probably stream-lined rather than turbulent.

Portal pressure is about 7 mmHg (fig. 10.2).

Collateral circulation

When the portal circulation is obstructed, whether it be within or outside the liver, a remarkable collateral circulation develops to carry portal blood into the systemic veins (figs 10.3, 10.29).

Intra-hepatic obstruction (cirrhosis)

Normally 100% of the portal venous blood flow can be recovered from the hepatic veins, whereas in cirrhosis only 13% is obtained [85]. The remainder enters collateral channels which form four main groups.

1 *Group I*: where protective epithelium adjoins absorptive epithelium:

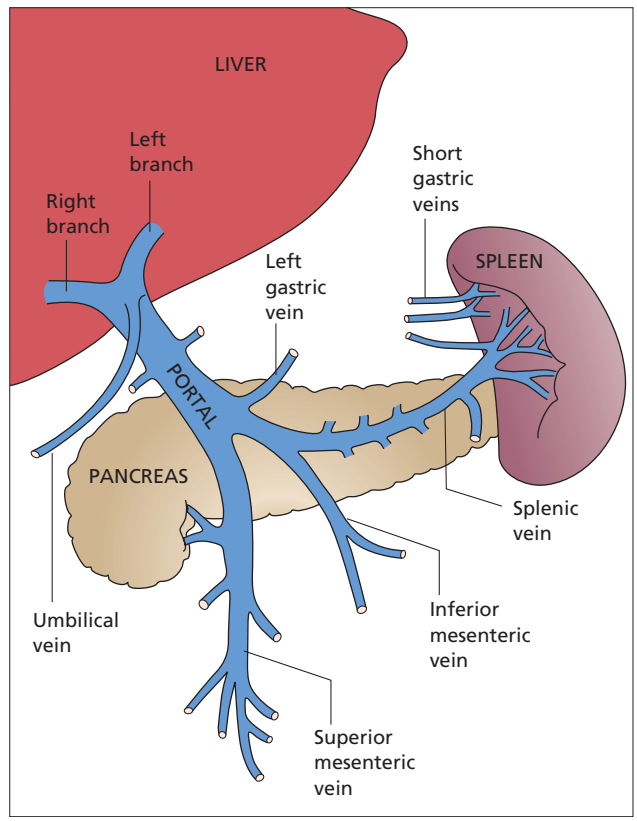


Fig. 10.1. The anatomy of the portal venous system. The portal vein is posterior to the pancreas.

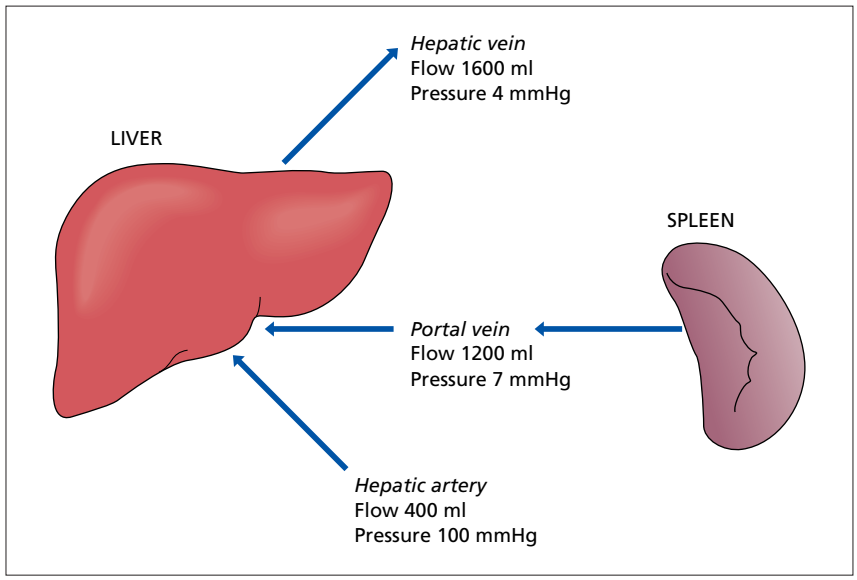


Fig. 10.2. The flow and pressure in the hepatic artery, portal vein and hepatic vein.

(a) At the cardia of the stomach, where the left gastric vein, posterior gastric [66] and short gastric veins of the portal system anastomose with the intercostal, diaphragmo-oesophageal and azygos minor veins of the caval system. Deviation of blood into these channels leads to varicosities in the submucous layer of the lower end of the oesophagus and fundus of the stomach.

(b) At the anus, the superior haemorrhoidal vein of the portal system anastomoses with the middle and inferior haemorrhoidal veins of the caval system. Deviation of blood into these channels may lead to rectal varices.

2 *Group II*: in the falciform ligament through the paraumbilical veins, relics of the umbilical circulation of the fetus (fig. 10.4).

3 *Group III*: where the abdominal organs are in contact with retroperitoneal tissues or adherent to the abdominal wall. These collaterals run from the liver to diaphragm and in the spleno-renal ligament and omentum. They include lumbar veins and veins developing in scars of previous operations or in small or large bowel stomas.

4 *Group IV*: portal venous blood is carried to the left renal vein. This may be through blood entering directly from the splenic vein or via diaphragmatic, pancreatic, left adrenal or gastric veins.

Blood from gastro-oesophageal and other collaterals ultimately reaches the superior vena cava via the azygos or hemiazygos systems. A small volume enters the inferior vena cava. An intra-hepatic shunt may run from the right branch of the portal vein to the inferior vena cava [107]. Collaterals to the pulmonary veins have also been described.

Extra-hepatic obstruction

With extra-hepatic portal venous obstruction, additional collaterals form, attempting to bypass the block and return blood *towards* the liver. These enter the portal vein in the porta hepatis beyond the block. They include the veins at the hilum, venae comitantes of the portal vein and hepatic arteries, veins in the suspensory ligaments of the liver and diaphragmatic and omental veins. Lumbar collaterals may be very large.

Effects

When the liver is cut off from portal blood by the development of the collateral circulation, it depends more on blood from the hepatic artery. It shrinks and shows impaired capacity to regenerate. This might be due to lack of hepatotrophic factors, including insulin and glucagon, which are of pancreatic origin.

Collaterals usually imply portal hypertension, although occasionally if the collateral circulation is very extensive portal pressure may fall. Conversely, portal hypertension of short duration can exist without a demonstrable collateral circulation.

A large portal-systemic shunt may lead to hepatic encephalopathy, septicaemias due to intestinal organisms, and other circulatory and metabolic effects.

Pathology of portal hypertension

Collateral venous circulation is disappointingly insignificant at autopsy. The oesophageal varices collapse.

The spleen is enlarged with a thickened capsule. The

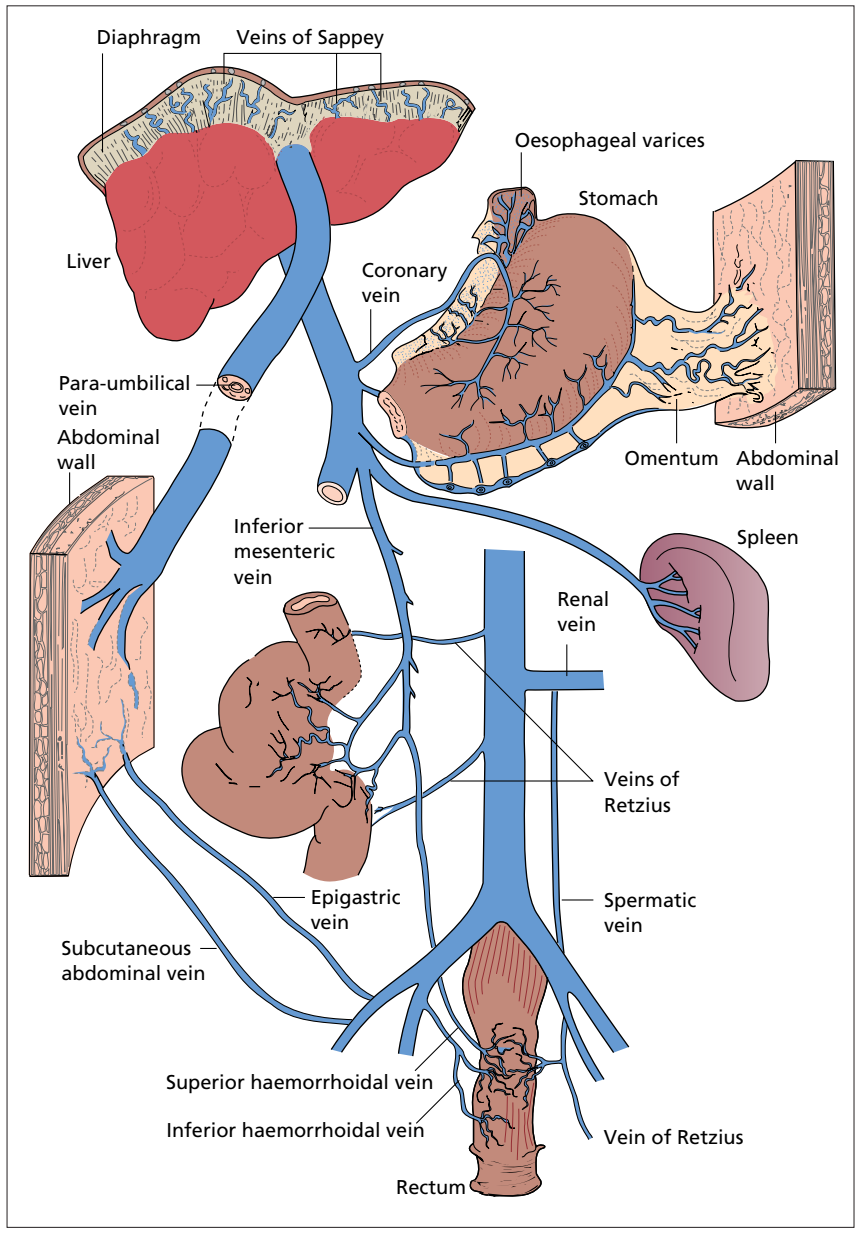


Fig. 10.3. The sites of the portal-systemic collateral circulation in cirrhosis of the liver [85].

surface oozes dark blood (*fibro-congestive splenomegaly*). Malpighian bodies are inconspicuous. Histologically, sinusoids are dilated and lined by thickened epithelium (fig. 10.5). Histiocytes proliferate with occasional erythrophagocytosis. Peri-arterial haemorrhages may progress to siderotic, fibrotic nodules.

Splenic and portal vessels. The splenic artery and portal vein are enlarged and tortuous and may be aneurysmal. The portal and splenic vein may show endothelial haemorrhages, mural thrombi and intimal plaques and may calcify (see fig. 10.13). Such veins are usually unsuitable for portal surgery.

In 50% of cirrhotics small, deeply placed splenic arterial aneurysms are seen [86].

Hepatic changes depend on the cause of the portal hypertension.

The height of the portal venous pressure correlates poorly with the apparent degree of cirrhosis and in particular of fibrosis. There is a much better correlation with the degree of nodularity.

Varices

Oesophageal

If oesophago-gastric varices did not form and bleed, portal hypertension would be of virtually no clinical significance. The major blood supply to oesophageal

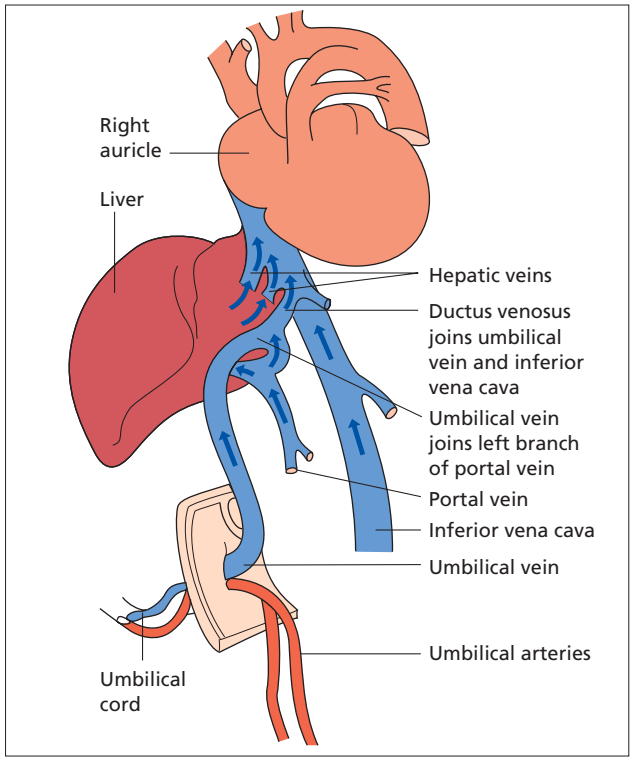


Fig. 10.4. The hepatic circulation at the time of birth.

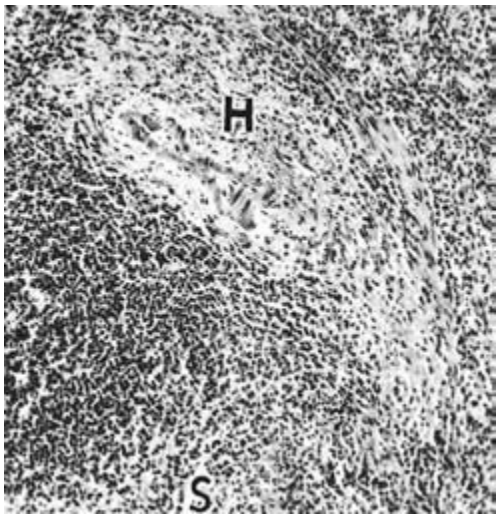


Fig. 10.5. The spleen in portal hypertension. The sinusoids (S) are congested and the sinusoidal wall is thickened. A haemorrhage (H) lies adjacent to an arteriole of a Malpighian corpuscle. (H & E, ×70.)

varices is the left gastric vein. The posterior branch usually drains into the azygos system, whereas the anterior branch communicates with varices just below the oesophageal junction and forms a bundle of thin parallel veins that run in the junction area and continue in large

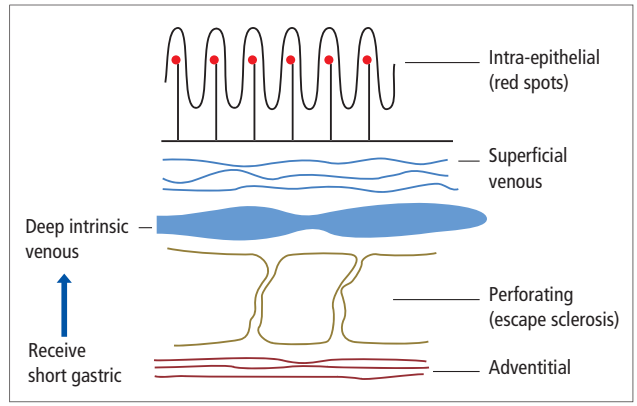


Fig. 10.6. Venous anatomy of the oesophagus.

tortuous veins in the lower oesophagus. There are four layers of veins in the oesophagus (fig. 10.6) [68]. *Intra-epithelial veins* may correlate with the red spots seen on endoscopy and which predict variceal rupture. The *superficial venous plexus* drains into larger, *deep intrinsic veins*. *Perforating veins* connect the deeper veins with the fourth layer which is the adventitial plexus. Typical large varices arise from the main trunks of the deep intrinsic veins and these communicate with gastric varices.

The connection between portal and systemic circulation at the gastro-oesophageal junction is extremely complex [149]. Its adaptation to the cephalad and increased flow of portal hypertension is ill-understood. A palisade zone is seen between the gastric zone and the perforating zone (fig. 10.7). In the palisade zone, flow is bidirectional and this area acts as a water shed between the portal and azygos systems. Turbulent flow in perforating veins between the varices and the peri-oesophageal veins at the lower end of the stomach may explain why rupture is frequent in this region [84]. Recurrence of varices after endoscopic sclerotherapy may be related to the communications between various venous channels or perhaps to enlargement of veins in the superficial venous plexus. Failure of sclerotherapy may also be due to failure to thrombose the perforating veins.

Gastric

These are largely supplied by the short gastric veins and drain into the deep intrinsic veins of the oesophagus. They are particularly prominent in patients with extra-hepatic portal obstruction.

Duodenal varices show as filling defects. Bile duct collaterals may be life-threatening at surgery [31].

Colo-rectal

These develop secondary to inferior mesenteric–internal

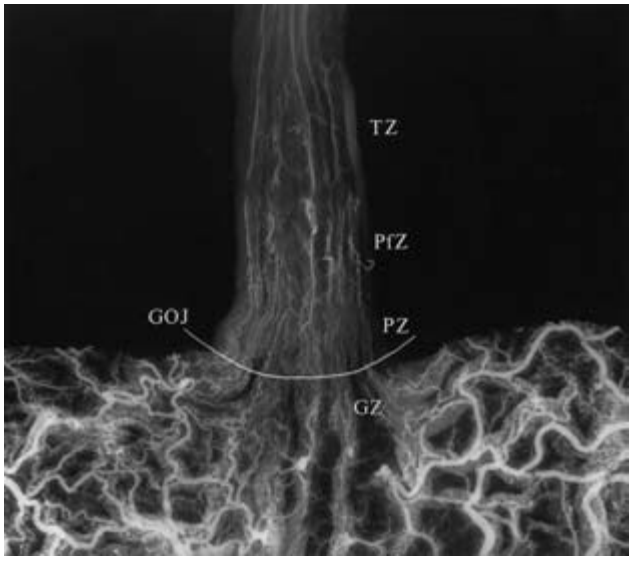


Fig. 10.7. Radiograph of a specimen injected with barium–gelatine, opened along the greater curvature. Four distinct zones of normal venous drainage are identified: the gastric zone (GZ), palisade zone (PZ), perforating zone (PfZ) and truncal zone (TZ). A radio-opaque wire demarcates the transition between the columnar and stratified squamous epithelium. GOJ, gastro-oesophageal junction [149].

iliac venous collaterals [55]. They may present with haemorrhage. They are visualized by colonoscopy. Colonic varices may become more frequent after successful oesophageal sclerotherapy.

Collaterals between the superior haemorrhoidal (portal) veins and the middle and inferior haemorrhoidal (systemic) veins lead to anorectal varices [154].

Portal hypertensive intestinal vasculopathy

Chronic portal hypertension may not only be associated with discrete varices but with a spectrum of intestinal mucosal changes due to abnormalities in the microcirculation [150].

Portal hypertensive gastropathy. This is almost always associated with cirrhosis and is seen in the fundus and body of the stomach. Histology shows vascular ectasia in the mucosa. The risk of bleeding is increased, for instance from non-steroidal anti-inflammatory drugs (NSAIDs). These gastric changes may be increased after sclerotherapy. They are relieved only by reducing the portal pressure [106].

Gastric antral vascular ectasia is marked by increased arteriovenous communications between the muscularis mucosa and dilated precapillaries and veins [112]. Gastric mucosal perfusion is increased. This must be distinguished from portal hypertensive gastropathy. It is not directly related to portal hypertension, but is influenced by liver dysfunction [139].

Congestive jejunopathy and colonopathy. Similar changes are seen in the duodenum and jejunum. Histology shows an increase in size and number of vessels in jejunal villi [93]. The mucosa is oedematous, erythematous and friable [131].

Congestive colonopathy is shown by dilated mucosal capillaries with thickened basement membranes but with no evidence of mucosal inflammation [150].

Others

Portal-systemic collaterals form in relation to bowel–abdominal wall adhesions secondary to previous surgery or pelvic inflammatory disease. Varices also form at mucocutaneous junctions, for instance, at the site of an ileostomy or colostomy.

Haemodynamics of portal hypertension

This has been considerably clarified by the development of animal models such as the rat with a ligated portal vein or bile duct or with carbon tetrachloride-induced cirrhosis. Portal hypertension is related both to vascular resistance and to portal blood flow (fig. 10.8). The fundamental haemodynamic abnormality is an increased resistance to portal flow. This may be mechanical due to the disturbed architecture and nodularity of cirrhosis or due to an obstructed portal vein. Other intra-hepatic factors such as collagenosis of the space of Disse [11], hepatocyte swelling [13, 51] and the resistance offered by portal-systemic collaterals contribute.

There is also a dynamic increase in intra-hepatic vascular resistance.

Stellate (Ito) cells have contractile properties that can be modulated by vaso-active substances [120]. These include nitric oxide (NO) which is vasodilatory [138] (Chapter 6) and endothelin which is a vaso-constrictor [48]. These may modulate intra-hepatic resistance and blood flow especially at a sinusoidal level (fig. 10.9) [155].

As the portal venous pressure is lowered by the development of collaterals deviating portal blood into systemic veins, portal hypertension is maintained by increasing portal flow in the portal system which becomes hyperdynamic. It is uncertain whether the hyperdynamic circulation is the cause or the consequence of the portal hypertension or both. It is related to the severity of liver failure. Cardiac output increases and there is generalized vasodilatation (fig. 10.10). Arterial blood pressure is normal or low (Chapter 6).

Splanchnic vasodilatation is probably the most important factor in maintaining the hyperdynamic circulation. Azygous blood flow is increased. Gastric mucosal blood

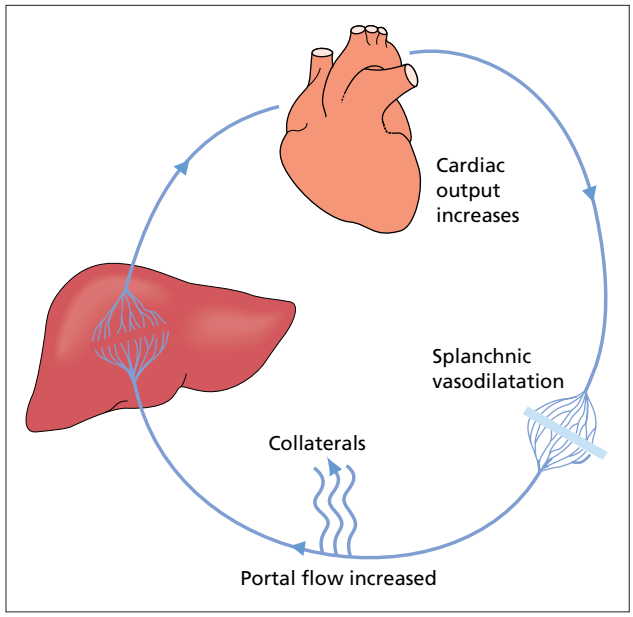


Fig. 10.8. Forward flow theory of portal hypertension.

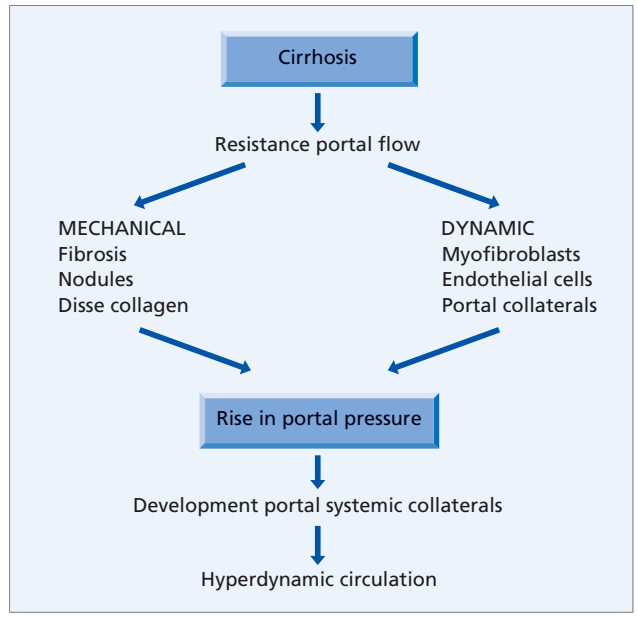


Fig. 10.10. The pathophysiology of portal hypertension in cirrhosis.

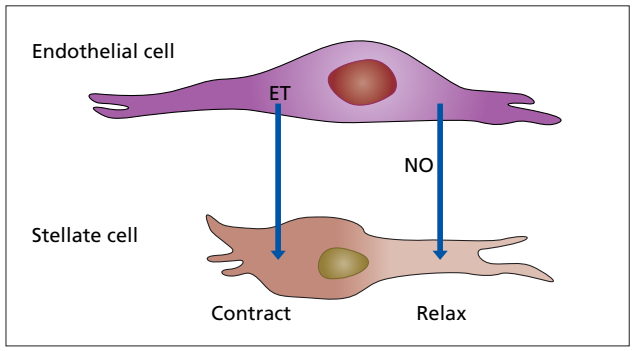


Fig. 10.9. Regulation of sinusoidal blood flow. Endothelial and stellate cells are potential sources of endothelin (ET) which is contractile on stellate cells. Nitric oxide (NO) relaxes stellate cells. NO synthase is the precursor of NO and is produced by endothelial and stellate cells.

flow rises. The increased portal flow raises the oesophageal variceal transmural pressure. The increased flow refers to *total* portal flow (hepatic and collaterals). The actual portal flow reaching the liver is, of course, reduced. The factors maintaining the hyperdynamic splanchnic circulation are multiple. There seems to be an interplay of vasodilators and vaso-constrictors. These might be formed by the hepatocyte, fail to be inactivated by it or be of gut origin and pass through intra-hepatic or extra-hepatic venous shunts.

Endotoxins and cytokines, largely formed in the gut, are important triggers [53]. NO and endothelin-1 are synthesized by vascular endothelium in response to endotoxin. *Prostacyclin* is produced by portal vein endothelium and is a potent vasodilator [98]. It may play a major role in the circulatory changes of portal hypertension due to chronic liver disease.

Glucagon is vasodilatory after pharmacological doses but does not seem to be vaso-active at physiological doses. It is probably not a primary factor in the maintenance of the hyperkinetic circulation in established liver disease [105].

Clinical features of portal hypertension

History and general examination (table 10.1)

Cirrhosis is the commonest cause. Alcoholism or chronic hepatitis should be reported. Past abdominal inflammation, especially neonatal, is important in extra-hepatic portal block. Clotting disease and drugs, such as sex hormones, predispose to portal and hepatic venous thrombosis.

Haematemesis is the commonest presentation. The number and severity of previous haemorrhages should be noted, together with their immediate effects, whether there was associated confusion or coma and whether blood transfusion was required. Melaena, without haematemesis, may result from bleeding varices. The absence of dyspepsia and epigastric tenderness and a previously normal endoscopy help to exclude haemorrhage from peptic ulcer.

The stigmata of cirrhosis include jaundice, vascular

Table 10.1. Investigation of a patient with suspected portal hypertension

History
Relevant to cirrhosis or chronic hepatitis (Chapter 21)
Gastrointestinal bleeding: number, dates, amounts, symptoms, treatment
Results of previous endoscopies
Patient history: alcoholism, blood transfusion, hepatitis B, hepatitis C, intra-abdominal, neonatal or other sepsis, oral contraceptives, myeloproliferative disorder
Examination
Signs of hepato-cellular failure
Abdominal wall veins:
site
direction of blood flow
Splenomegaly
Liver size and consistency
Ascites
Oedema of legs
Rectal examination
Endoscopy of oesophagus, stomach and duodenum
Additional investigations
Liver biopsy
Hepatic vein catheterization
Splanchnic arteriography
Hepatic ultrasound, CT scan or MRI

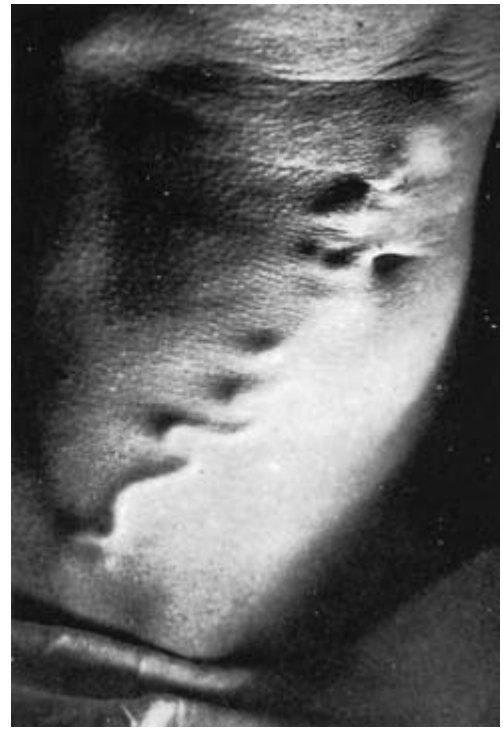


Fig. 10.12. An anterior abdominal wall vein in a patient with cirrhosis of the liver.

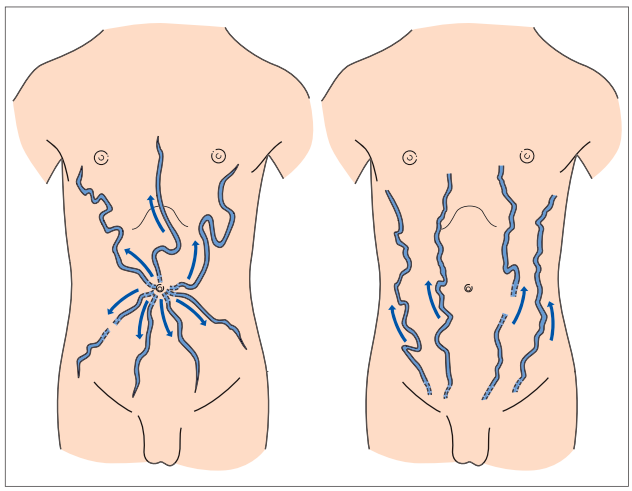


Fig. 10.11. Distribution and direction of blood flow in anterior abdominal wall veins in portal venous obstruction (left) and in inferior vena caval obstruction (right).

spiders and palmar erythema. Anaemia, ascites and pre-coma should be noted.

Abdominal wall veins

In intra-hepatic portal hypertension, some blood from the left branch of the portal vein may be deviated via para-umbilical veins to the umbilicus, whence it reaches veins of the caval system (fig. 10.11). In extra-hepatic portal obstruction, dilated veins may appear in the left flank.

Distribution and direction. Prominent collateral veins radiating from the umbilicus are termed *caput Medusae*. This is rare and usually only one or two veins, frequently epigastric, are seen (figs 10.11, 10.12). The blood flow is away from the umbilicus, whereas in inferior vena caval obstruction the collateral venous channels carry blood upwards to reach the superior vena caval system (fig. 10.11). Tense ascites may lead to functional obstruction of the inferior vena cava and cause difficulty in interpretation.

Murmurs. A venous hum may be heard, usually in the region of the xiphoid process or umbilicus. A thrill, detectable by light pressure, may be felt at the site of maximum intensity and is due to blood rushing through a large umbilical or para-umbilical channel to veins in the abdominal wall. A venous hum may also be heard over other large collaterals such as the inferior mesenteric vein. An arterial systolic murmur usually indicates primary liver cancer or alcoholic hepatitis.

The association of dilated abdominal wall veins and a loud venous murmur at the umbilicus is termed the *Cruveilhier–Baumgarten syndrome* [6, 28]. This may be due

to congenital patency of the umbilical vein, but more usually to a well-compensated cirrhosis [6, 12, 28].

The para-xiphoid umbilical hum and caput Medusae indicate portal obstruction beyond the origin of the umbilical veins from the left branch of the portal vein. They therefore indicate intra-hepatic portal hypertension (cirrhosis).

Spleen

The spleen enlarges progressively. The edge is firm. Size bears little relation to the portal pressure. It is larger in young people and in macronodular rather than micronodular cirrhosis.

An enlarged spleen is the single most important diagnostic sign of portal hypertension. If the spleen cannot be felt or is not enlarged on imaging, the diagnosis of portal hypertension is questionable.

The *peripheral blood* shows a pancytopenia associated with an enlarged spleen (*secondary 'hypersplenism'*). This is related more to reticulo-endothelial hyperplasia than to the portal hypertension and is unaffected by lowering the pressure by a porta-caval shunt.

Liver

A small liver may be as significant as hepatomegaly, and size should be evaluated by careful percussion. It correlates poorly with the height of portal pressure.

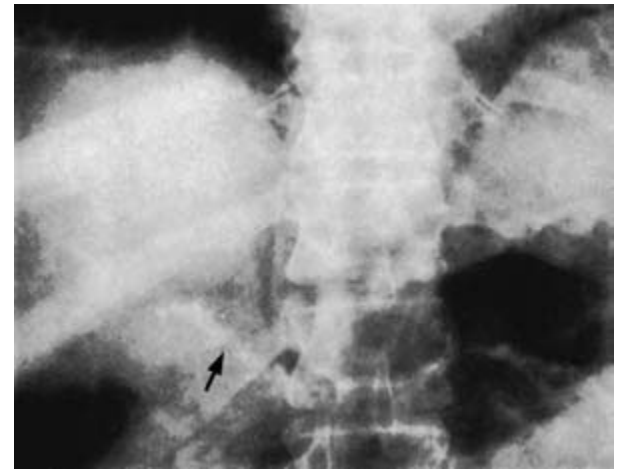
Liver consistency, tenderness or nodularity should be recorded. A soft liver suggests extra-hepatic portal venous obstruction. A firm liver supports cirrhosis.

Ascites

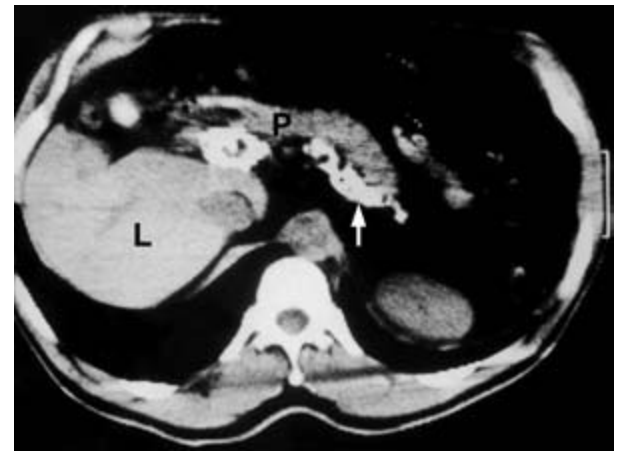
This is rarely due to portal hypertension alone, although a particularly high pressure may be a major factor. The portal hypertension raises the capillary filtration pressure, and determines fluid localization to the peritoneal cavity. Ascites in cirrhosis always indicates liver cell failure in addition to portal hypertension.

Rectum

Anorectal varices are visualized with the sigmoidoscope and may bleed. They are found in 44% of cirrhotic patients, increasing in those who have bled from oesophageal varices [60]. They must be distinguished from simple haemorrhoids which are prolapsed vascular cushions and which do not communicate with the portal system.



(a)



(b)

Fig. 10.13. (a) Plain X-ray of the abdomen. Calcification can be seen in the line of the splenic and portal vein (arrow). (b) CT scan confirms the calcified splenic vein (arrow). L, liver; P, pancreas.

X-ray of the abdomen and chest

This is useful to delineate liver and spleen. Rarely, a calcified portal vein may be shown (fig. 10.13) [4].

Branching, linear gas-shadows in the portal vein radicles, especially near the periphery of the liver and due to gas-forming organisms, may rarely be seen in adults with intestinal infarction or infants with enterocolitis. Portal gas may be associated with disseminated intravascular coagulation. CT and ultrasound (US) may detect portal gas more often, for instance in suppurative cholangitis when the prognosis is not so grave [33].

Tomography of the azygos vein may show enlargement (fig. 10.14) as the collateral flow enters the azygos system.

A widened left paravertebral shadow may be due to lateral displacement of the pleural reflection between the

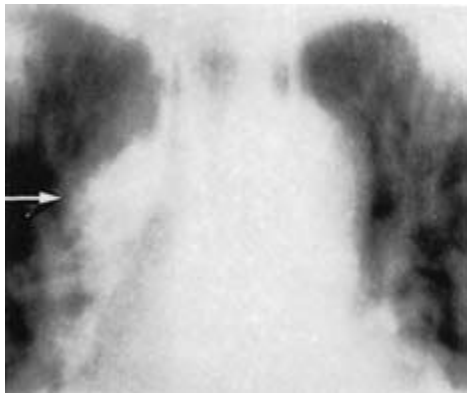


Fig. 10.14. Tomography of the mediastinum of a patient with large porto-systemic collaterals, showing enlargement of the azygos vein (arrow).

aorta and vertebral column by a dilated hemiazygos vein.

Massively dilated para-oesophageal collaterals may be seen on the chest radiograph as a retrocardiac posterior mediastinal mass.

Barium studies

These have largely been replaced by endoscopy.

Oesophageal varices show as filling defects in the regular contour of the oesophagus (fig. 10.15). They are most often in the lower third, but may spread upwards so that the entire oesophagus is involved. Widening and finally gross dilatation are helpful signs.

Gastric varices pass through the cardia, line the fundus in a worm-like fashion and may be difficult to distinguish from mucosal folds.

Occasionally gastric varices show as a lobulated mass in the gastric fundus simulating a carcinoma. Portal venography is useful in differentiation.

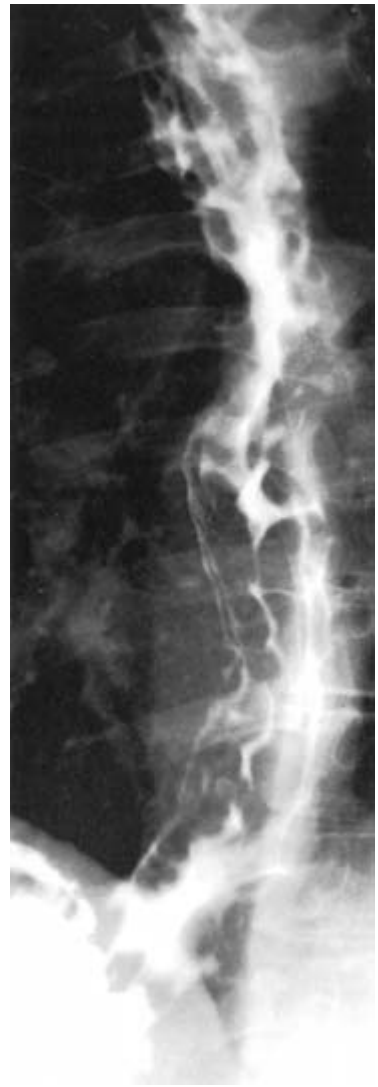


Fig. 10.15. Barium swallow X-ray shows a dilated oesophagus. The margin is irregular. There are multiple filling defects representing oesophageal varices.

Endoscopy

The size of the varix must be graded (figs 10.16, 10.17) [97].

1 *Grade 1* (F1): the varices can be depressed by the endoscope.

2 *Grade 2* (F2): the varices cannot be depressed by the endoscope.

3 *Grade 3* (F3): the varices are confluent around the circumference of the oesophagus.

The larger the varix the more likely it is to bleed. Colour is extremely important. Varices usually appear white and opaque (fig. 10.18). Red colour correlates with blood flow through dilated sub-epithelial and communicating veins. Dilated sub-epithelial veins may appear

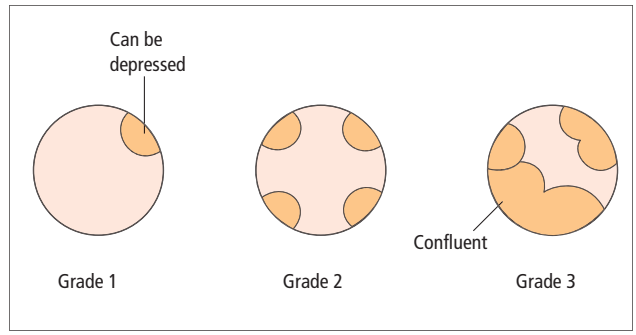


Fig. 10.16. Endoscopic classification of oesophageal varices (adapted from [97]).

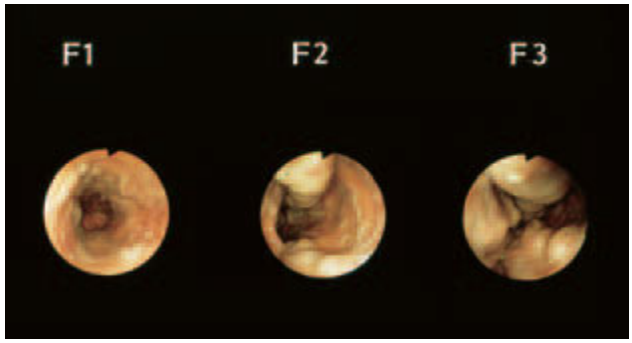


Fig. 10.17. The form (F) of the oesophageal varices (from [97]).

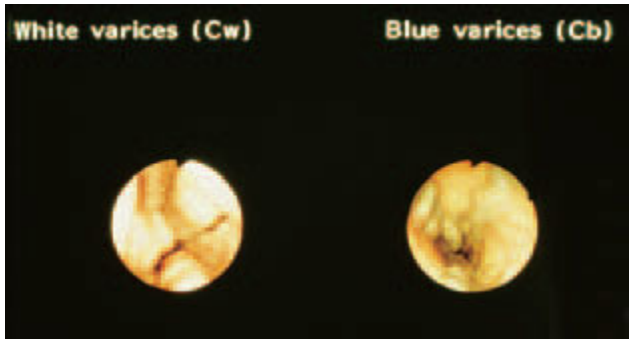


Fig. 10.18. Variceal colour through the endoscope (from [97]).

as raised cherry-red spots (fig. 10.19) and red wheal markings (longitudinal dilated veins resembling whip marks). They lie on top of large sub-epithelial vessels. The haemocystic spot is approximately 4 mm in diameter (fig. 10.20). It represents blood coming from the deeper extrinsic veins of the oesophagus straight out towards the lumen through a communicating vein into the more superficial submucosal veins. Red colour is usually associated with larger varices. All these colour changes, and particularly the red colour sign, predict variceal bleeding. Intra-observer error may depend on the skill and experience of the endoscopist. On the whole, agreement is good for size and red signs [22].

Portal hypertensive gastropathy is seen largely in the fundus, but can extend throughout the stomach (fig. 10.21). It is shown as a mosaic-like pattern with small polygonal areas, surrounded by a whitish-yellow depressed border [140]. Red point lesions and cherry-red spots predict a high risk of bleeding. Black–brown spots are due to intra-mucosal haemorrhage. Sclerotherapy increases the gastropathy [29].

Variceal (azygos) blood flow can be assessed during diagnostic endoscopy by a Doppler US probe passed down the biopsy channel of the standard gastroscope.

Portal hypertensive colopathy is seen in about half the patients with portal hypertension, usually in those with

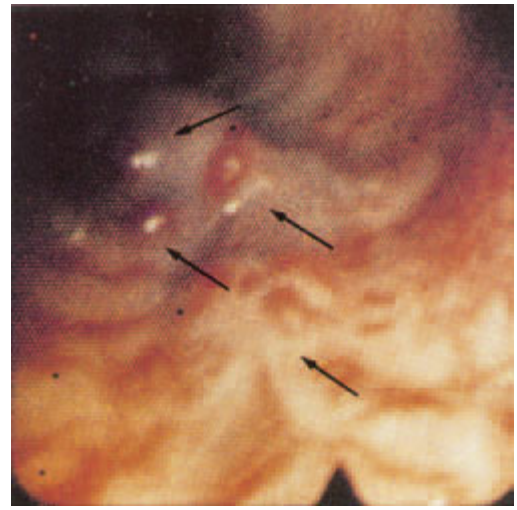


Fig. 10.19. Endoscopic view of cherry-red spots on oesophageal varices (arrows).

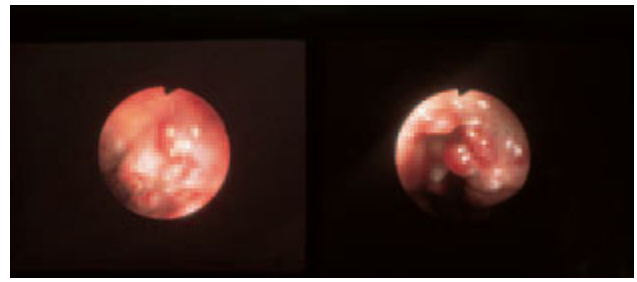


Fig. 10.20. Haemocystic spots on oesophageal varices (from [97]).

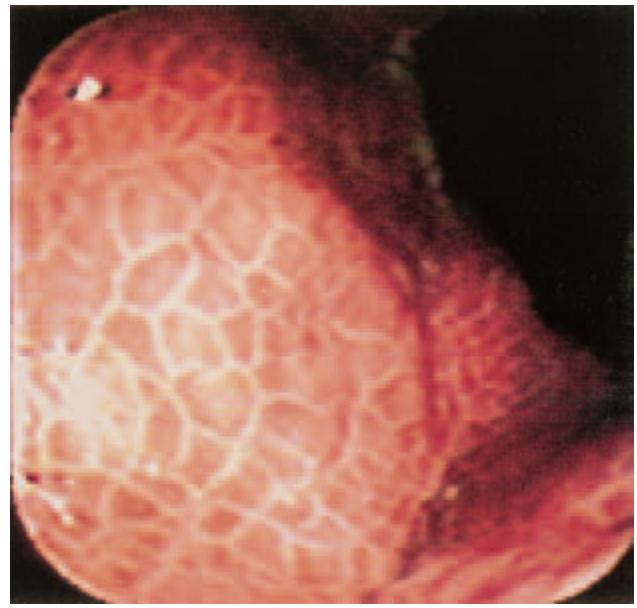


Fig. 10.21. Portal gastropathy. A mosaic of red and yellow is seen together with petechial haemorrhages.

gastropathy. Colonoscopy may be needed to diagnose lower gastrointestinal bleeding in cirrhotic patients [45].

Imaging the portal venous system

Ultrasound

Longitudinal scans at the sub-costal margins and transverse scans at the epigastrium are essential (fig. 10.22). The portal and superior mesenteric veins can always be seen. The normal splenic vein may be more difficult.

A large portal vein suggests portal hypertension, but this is not diagnostic. If collaterals are seen, this confirms portal hypertension. Portal vein thrombosis is accurately diagnosed and echogenic areas can sometimes be seen within the lumen.

Doppler ultrasound

Doppler US demonstrates the anatomy of the portal veins and hepatic artery (table 10.2). Satisfactory results depend on technical expertise. Small cirrhotic livers are difficult to see as are those of the obese. Colour-coded Doppler improves visualization (fig. 10.23). Portal venous obstruction is demonstrated by Doppler US as accurately as by angiography provided the Doppler is technically optimal.

Doppler US shows spontaneous hepato-fugal flow in portal, splenic and superior mesenteric veins in 8.3% of patients with cirrhosis [44]. Its presence correlates with severity of cirrhosis and with encephalopathy. Variceal bleeding is more likely if the flow is hepato-petal.

Table 10.2. Clinical uses of Doppler ultrasound

Portal vein
Patency
Hepato-fugal flow
Anatomical abnormalities
Portal-systemic shunt patency
Acute flow changes
Hepatic artery
Patency (post-transplant)
Anatomical abnormalities
Hepatic veins
Screening Budd–Chiari syndrome

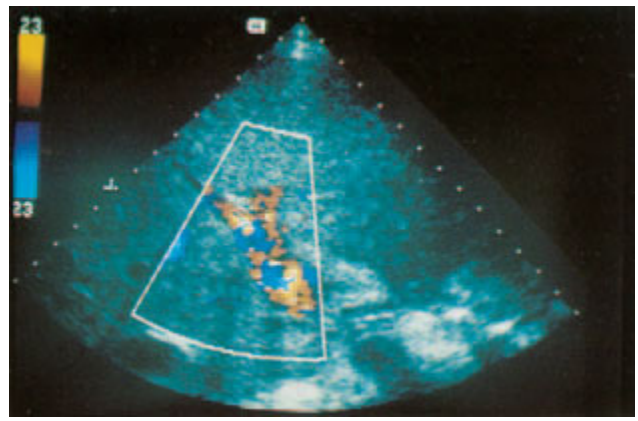


Fig. 10.23. Colour Doppler US of the porta hepatis shows the hepatic artery in red and portal vein in blue.

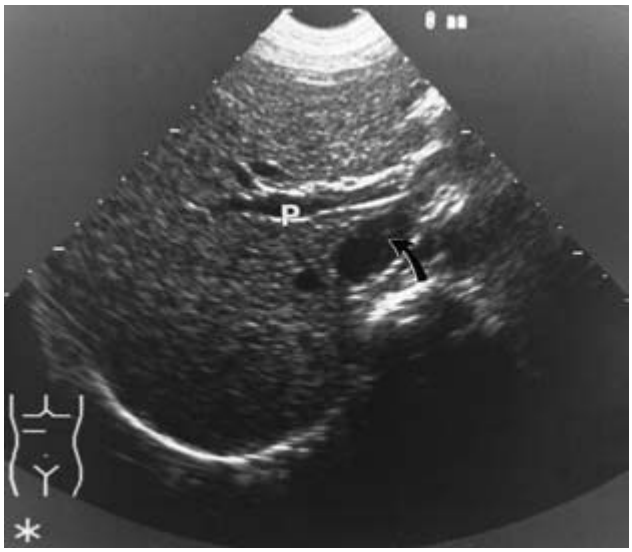


Fig. 10.22. Transverse US shows a patent portal vein (P); the arrow indicates the inferior vena cava.

Abnormalities of the intra-hepatic portal veins can be shown. These are important if surgery is contemplated.

Colour Doppler is a good way of demonstrating portal-systemic shunts and the direction of flow in them. These include surgical shunts but also transjugular intra-hepatic portosystemic shunts (TIPS). Intra-hepatic portal-systemic shunts may be visualized [72].

Colour Doppler screening is useful for patients suspected of the Budd–Chiari syndrome.

The hepatic artery is more difficult than the hepatic vein to locate because of its small size and direction. Nevertheless, duplex Doppler is the primary screening procedure to show a patent hepatic artery after liver transplantation.

Duplex Doppler has been used to measure portal blood flow. The average velocity of blood flowing in the portal vein is multiplied by the cross-sectional area of the vessel (fig. 10.24). There are observer errors in measurement, particularly of velocity. The method is most useful in measuring rapid, large, acute changes in flow

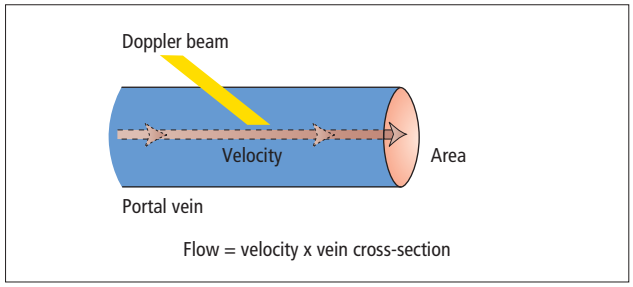


Fig. 10.24. The Doppler real-time US method of measuring portal venous flow.

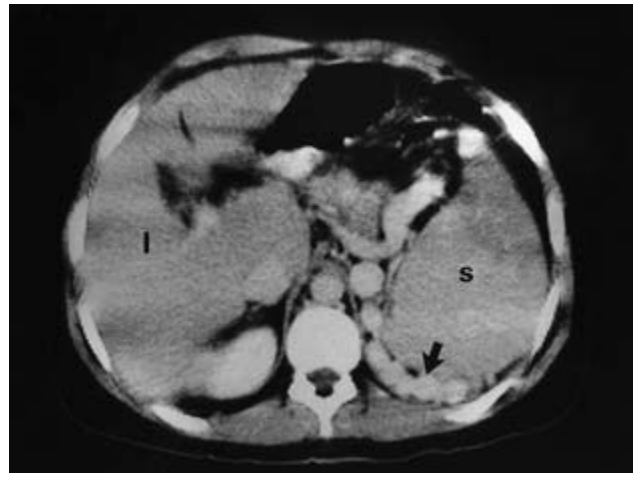


Fig. 10.25. Contrast-enhanced CT scan in a patient with cirrhosis and a large retroperitoneal retrosplenic collateral circulation (arrow). l, liver; s, spleen.

rather than monitoring chronic changes in portal haemodynamics.

Portal blood flow velocity correlates with the presence and size of oesophageal varices. In cirrhosis, the portal vein velocity tends to fall and when less than 16 cm/s portal hypertension is likely.

CT scan

After contrast, portal vein patency can be established and retroperitoneal, perivisceral and para-oesophageal varices may be visualized (fig. 10.25). Oesophageal varices may be shown as intraluminal protusions enhancing after contrast. The umbilical vein can be seen. Gastric varices show as rounded structures, indistinguishable from the gastric wall.

CT arterio-portography is done by rapid CT scanning (preferably helical) during selective injection of contrast into the superior mesenteric vein via a catheter [116]. It is particularly useful in showing focal lesions, the collateral circulation and arteriovenous shunts [141].

Magnetic resonance angiography

Magnetic resonance angiography gives excellent depiction of blood vessels as regions of absent signal (figs 10.26–10.28). Portal patency, morphology and flow of velocity may be demonstrated. Magnetic resonance angiography is more reliable than Doppler [43].

Venography

If the portal vein is patent by scanning, confirmation by venography is not necessary unless portal surgery or hepatic transplantation is being considered.

Patency of the portal vein is important particularly in the diagnosis of splenomegaly in childhood and in excluding invasion by a hepato-cellular carcinoma in a patient with cirrhosis.

Anatomy of the portal venous system must be known before such operations as portal-systemic shunt, hepatic resection or hepatic transplantation. The patency of a surgical shunt may be confirmed.

The demonstration of a large portal collateral circulation is essential for the diagnosis of chronic hepatic encephalopathy (figs 10.25, 10.29).

A filling defect in the portal vein or in the liver due to a space-occupying lesion may be demonstrated.

Venographic appearances

When the portal circulation is normal, the splenic and portal veins are filled but no other vessels are outlined. A filling defect may be seen at the junction of the splenic and superior mesenteric veins due to mixing with non-opacified blood. The size and direction of the splenic and portal veins are very variable. The intra-hepatic branches of the portal vein show a gradual branching and reduction in calibre. Later the liver becomes opaque due to sinusoidal filling. The hepatic veins may rarely be seen in later films.

In cirrhosis, the venogram varies widely. It may be completely normal or may show filling of large numbers of collateral vessels with gross distortion of the intra-hepatic pattern ('tree in winter' appearance) (fig. 10.30).

In extra-hepatic portal or splenic vein obstruction, large numbers of vessels run from the spleen and splenic vein to the diaphragm, thoracic cage and abdominal wall. Intra-hepatic branches are not usually seen, although, if the portal vein block is localized, para-portal vessels may short circuit the lesion (fig. 10.27) and produce a delayed but definite filling of the vein beyond.

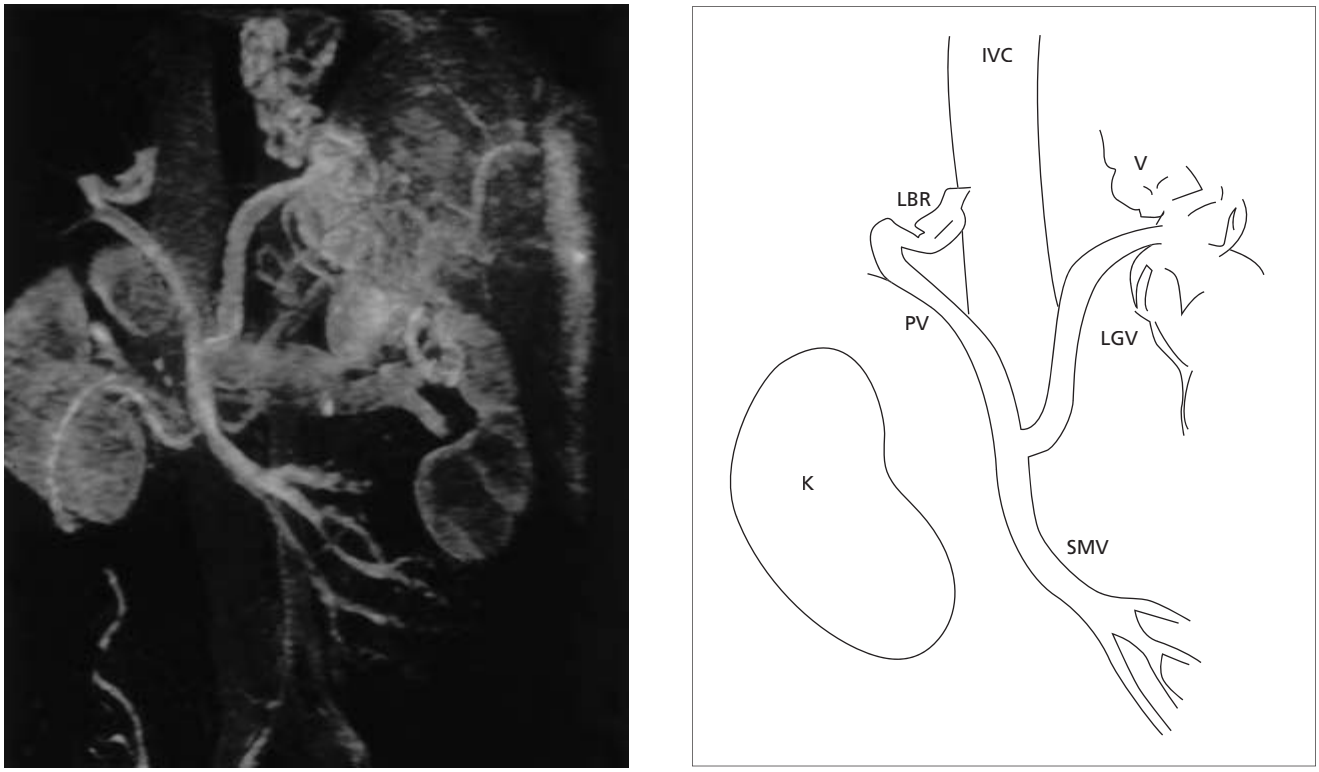


Fig. 10.26. Magnetic resonance angiography of a patient with cirrhosis showing the right kidney (K), superior mesenteric vein (SMV), portal vein (PV), left gastric vein (LGV), left branch of portal vein (LBR), gastro-oesophageal collateral veins (V) and the inferior vena cava (IVC).

Visceral angiography

Safety has increased with the use of smaller (French 5) arterial catheters. New contrast materials are less toxic to kidneys and other tissues and hypersensitivity reactions are rare.

The coeliac axis is catheterized via the femoral artery and contrast is injected. The material that flows into the splenic artery returns through the splenic and portal veins and produces a splenic and portal venogram. Similarly, a bolus of contrast introduced into the superior mesenteric artery returns through the superior mesenteric and portal veins which can be seen in radiographs exposed at the appropriate intervals (figs 10.31, 10.32).

Visceral angiography demonstrates the hepatic arterial system, so allowing space-filling lesions in the liver to be identified. A tumour circulation may diagnose hepato-cellular cancer or another tumour.

Knowledge of splenic and hepatic arterial anatomy is useful if surgery is contemplated. Haemangiomas, other space-occupying lesions and aneurysms may be identified.

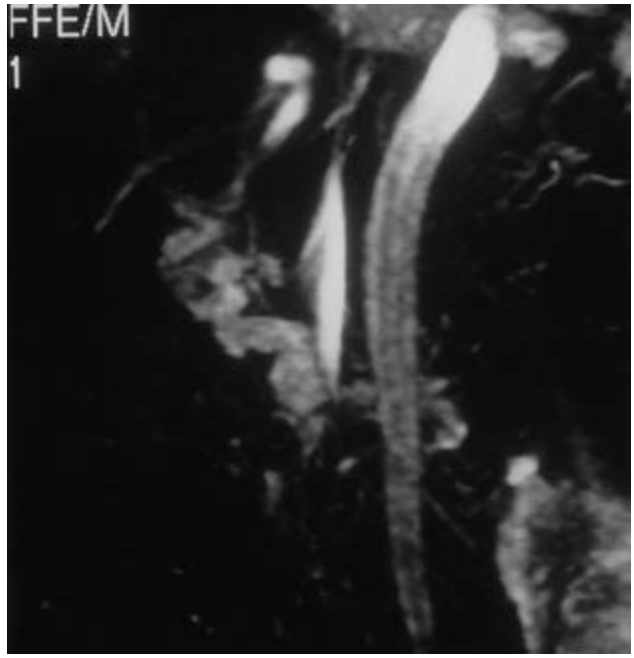
The portal vein may not opacify if flow in it is hepatofugal or if there is 'steal' by the spleen or by large collateral channels. A superior mesenteric angiogram will confirm that the portal vein is in fact patent.

Digital subtraction angiography

The contrast is given by selective arterial injection with immediate subtraction of images. The portal system is very well visualized free of other confusing images (fig. 10.33). Spatial resolution is poorer than with conventional film-based angiography. The technique is particularly valuable for the parenchymal phase of hepatic angiography and for the diagnosis of vascular lesions such as haemangiomas or arteriovenous malformations.

Splenic venography

Contrast material, injected into the pulp of the spleen, flows into the portal venous system with sufficient rapidity to outline splenic and portal veins (fig. 10.30). The collateral circulation is particularly well visualized [2]. Splenic venography has now been replaced by less invasive procedures.



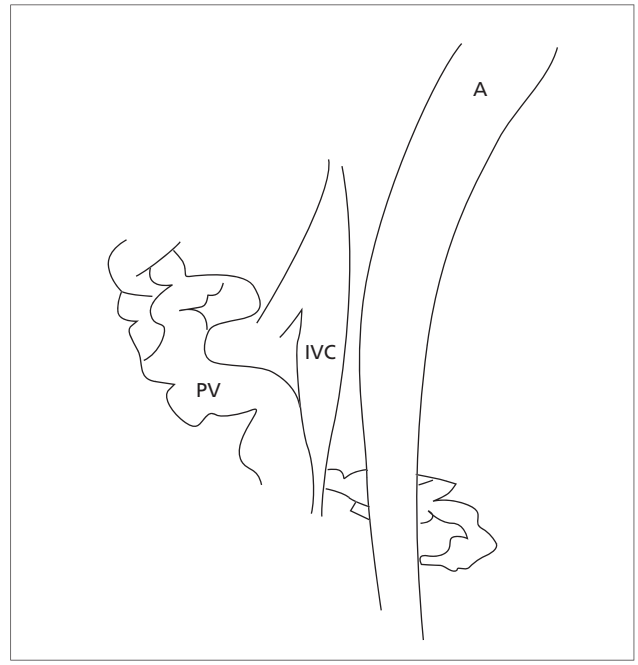


Fig. 10.27. Magnetic resonance angiography in a patient with portal vein thrombosis showing the portal vein replaced by collaterals (PV), the inferior vena cava (IVC) and the aorta (A).

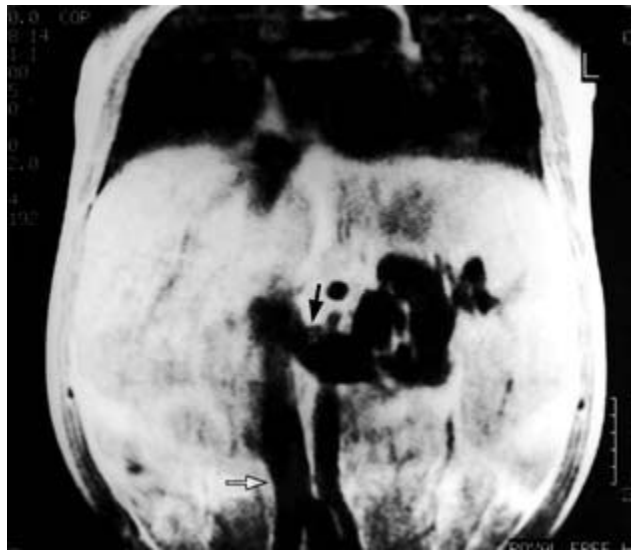


Fig. 10.28. Magnetic resonance angiography showing a spontaneous spleno-renal shunt to the inferior vena cava. Black arrow, renal vein; open arrow, vena cava.

Carbon dioxide wedged venography

Injection of carbon dioxide into a catheter in the wedged hepatic venous position allows an excellent venogram of the hepatic venous and portal venous tree (fig. 10.34) [32].

Portal pressure measurement

A balloon catheter is introduced into the femoral vein and, under fluoroscopic control, into the hepatic vein (fig. 10.35). Measurements are taken in the wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP) positions by inflating and deflating the balloon in the tip of the catheter [32, 111]. The hepatic venous pressure gradient (HVPG) is the difference between WHVP and FHVP. This is the portal (sinusoidal) venous pressure. The relationship of this to portal venous pressure in a cirrhosis which has a large presinusoidal component, such as primary biliary cirrhosis or autoimmune chronic hepatitis, needs further investigation. The normal HVPG is 5–6 mmHg and values of about 20 mmHg are found in patients with cirrhosis. Measurements can be performed at the same time as transjugular liver biopsy.

HVPG may relate to survival [1] and also to prognosis in patients with bleeding oesophageal varices [110]. Its value in the prediction of variceal bleeding is uncertain. The procedure may be used to monitor therapy, for instance the effect of β-blockers such as propranolol, which should maintain the HVPG at less than 12 mmHg.

Variceal pressure

An *endoscopic pressure guage* may be fixed to the end of the endoscope. The level of venous pressure is a major factor predicting variceal haemorrhage [95].

Pressure may be recorded by *direct puncture* of varices

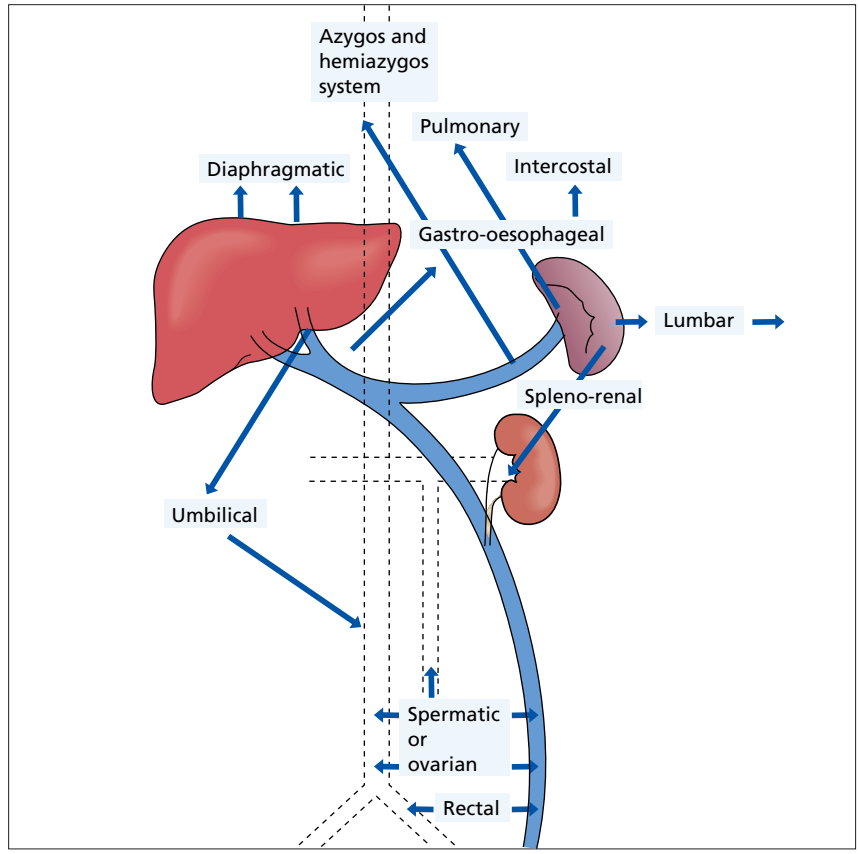


Fig. 10.29. The sites of the collateral circulation in the presence of intra-hepatic portal vein obstruction.

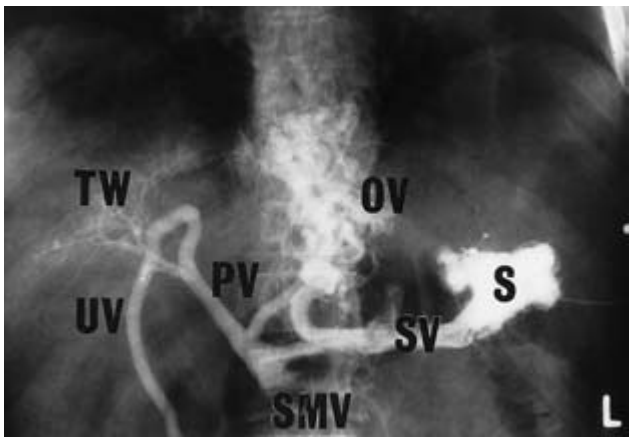


Fig. 10.30. Splenic venogram from a patient with cirrhosis of the liver. The gastro-oesophageal collateral circulation can be seen and the intra-hepatic portal vascular tree is distorted ('tree in winter' appearance). OV, oesophageal veins; PV, portal vein; S, splenic pulp; SMV, superior mesenteric vein; SV, splenic vein; TW, 'tree in winter' appearance; UV, umbilical vein.

at the time of sclerotherapy [61]. It is about 15.5 mmHg in cirrhotic patients, significantly lower than the main portal pressure of about 18.8 mmHg. An *endoscopic balloon* has been developed to measure variceal pressure and this gives comparable results to direct puncture [49].

Estimation of hepatic blood flow

Constant infusion method

Hepatic blood flow may be measured by a constant infusion of indocyanine green (ICG) and catheterization of the hepatic vein [16, 21]. Flow is calculated by the Fick principle.

Plasma disappearance method

Hepatic blood flow can be measured after an intravenous injection of ICG followed by analysis of the disappearance curve in a peripheral artery and hepatic vein.

If the extraction of a substance is about 100%, for instance, using ^{131}I heat-denatured albumin colloidal complex, hepatic blood flow can be determined by peripheral clearance without hepatic vein catheterization.

In patients with cirrhosis, up to 20% of the blood perfusing the liver may not go through normal channels and hepatic extraction is reduced. In these circumstances,

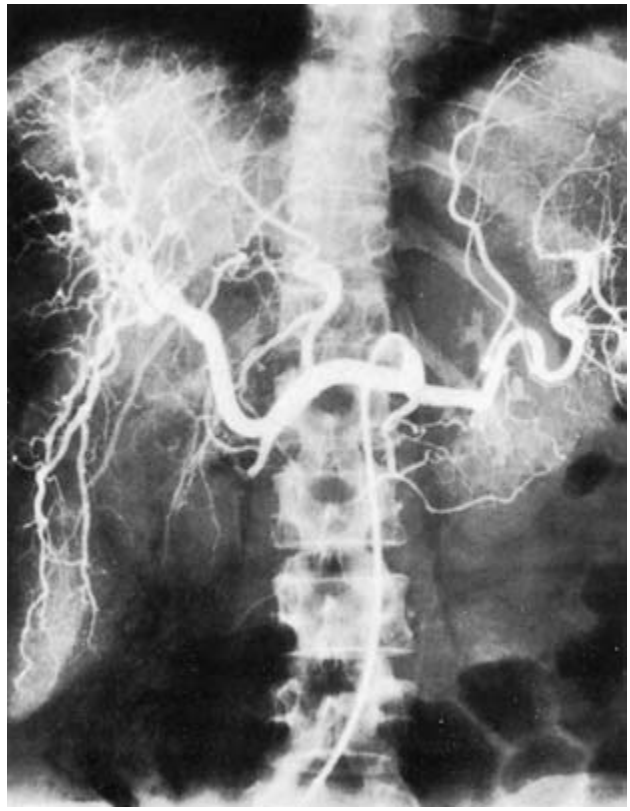


Fig. 10.31. Selective coeliac angiogram showing an intrahepatic arterial pattern. A Riedel's lobe is shown.

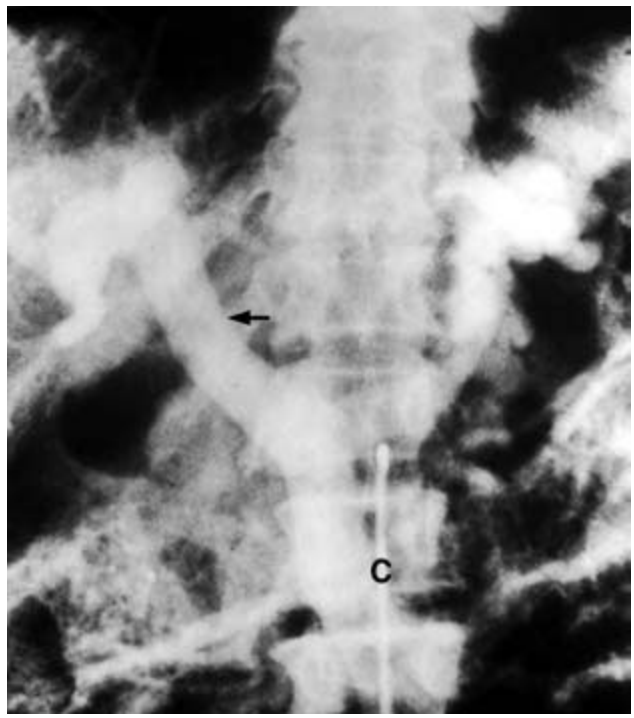


Fig. 10.32. Venous phase of selective coeliac angiogram showing patent portal (arrow) and splenic veins. C, catheter in coeliac axis.

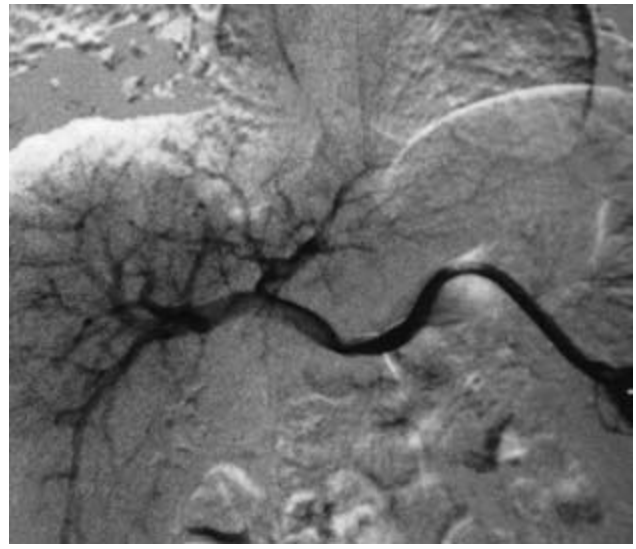


Fig. 10.33. Digital subtraction angiography showing a normal portal venous system.

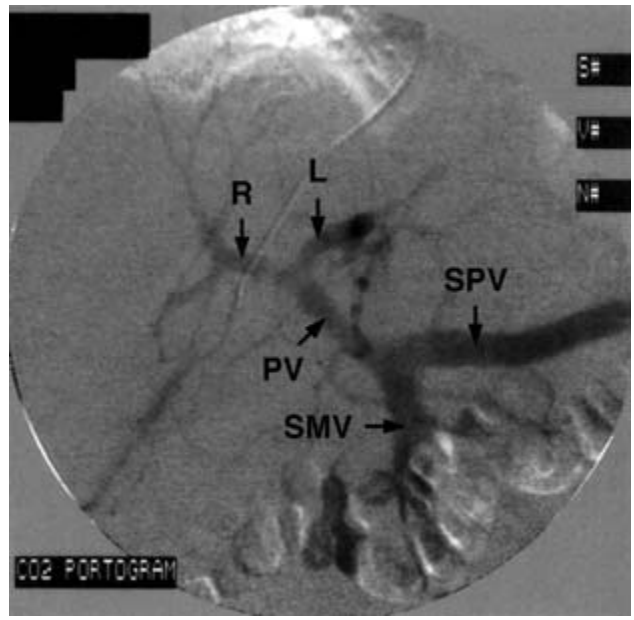


Fig. 10.34. Carbon dioxide portal venography real-time imaging following the injection of carbon dioxide into the wedged hepatic vein. PV, portal vein (L, left branch; R, right branch); SMV, superior mesenteric vein; SPV, splenic vein.

hepatic vein catheterization is necessary to estimate extraction and thus hepatic blood flow.

Azygos blood flow

Most of the blood flowing through gastro-oesophageal varices terminates in the azygos system. Azygos blood

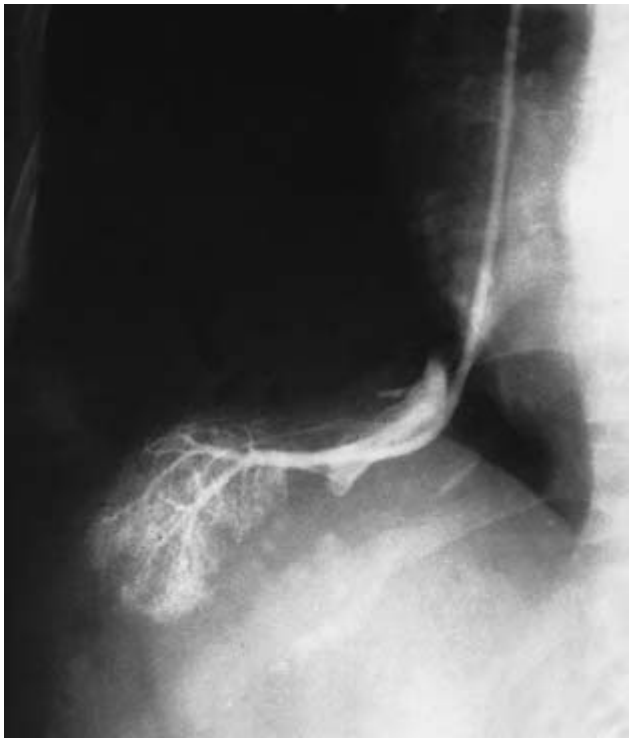


Fig. 10.35. A catheter has been inserted into a hepatic vein via the jugular vein. The wedged position is confirmed by introducing a small amount of contrast, which has entered the sinusoidal bed.

flow can be measured using a double thermo-dilution catheter directed under fluoroscopy into the azygos vein [15]. Alcoholic cirrhotic patients who have bled from varices show a flow of about 600 ml/minute. Azygos flow is markedly reduced by propranolol.

Experimental portal venous occlusion and hypertension

Survival following acute occlusion depends on the development of an adequate collateral circulation. In the rabbit, cat or dog this does not develop and death supervenes rapidly. In the monkey or man, the collateral circulation is adequate and survival is usual.

Acute occlusion of one branch of the portal vein is not fatal. The liver cells of the ischaemic lobe atrophy, but bile ducts, Kupffer cells and connective tissues survive. The unaffected lobe hypertrophies.

Experimentally, portal hypertension can be produced by occluding the portal vein, injecting silica into the portal vein, infecting mice with schistosomiasis, by any experimental type of cirrhosis, or by biliary obstruction. An extensive collateral circulation develops, the spleen enlarges but ascites does not form.

Classification of portal hypertension

Portal hypertension usually follows obstruction to the portal blood flow anywhere along its course. *Portal hypertension* has been classified into two groups: (i) *pre-sinusoidal* (extra-hepatic or intra-hepatic); and (ii) a big general group of *hepatic* causes (fig. 10.36, table 10.3). This distinction is a practical one. The pre-sinusoidal forms, which include obstruction to the sinusoids by Kupffer and other cellular proliferations, are associated with relatively normal hepato-cellular function. Consequently, if patients with this type suffer a haemorrhage from varices, liver failure is rarely a consequence. In contrast, patients with the intra-hepatic type frequently develop liver failure after bleeding.

Extra-hepatic portal venous obstruction

This causes extra-hepatic pre-sinusoidal portal hypertension. The obstruction may be at any point in the course of the portal vein. The *venae comitantes* enlarge in an attempt to deliver portal blood to the liver, so assuming a leash-like cavernous appearance. The portal vein, represented by a fibrous strand, is recognized with difficulty in the multitude of small vessels. This cavernous change follows any block in the main vein (see fig. 10.27).

Aetiology

Infections

Umbilical infection with or without catheterization of the umbilical vein may be responsible in neonates [143]. The infection spreads along the umbilical vein to the left portal vein and hence to the main portal vein. Acute appendicitis and peritonitis are causative in older children.

Portal vein occlusion is particularly common in India, accounting for 20–30% of all variceal bleeding. Neonatal dehydration and infections may be responsible.

Ulcerative colitis and Crohn's disease can be complicated by portal vein block.

Table 10.3. Classification of portal hypertension

Pre-sinusoidal	Extra-hepatic	Blocked portal vein Increased splenic flow
	Intra-hepatic	Portal zone infiltrates Toxic Hepato-portal sclerosis
Hepatic	Intra-hepatic Post-sinusoidal	Cirrhosis Other nodules Blocked hepatic vein

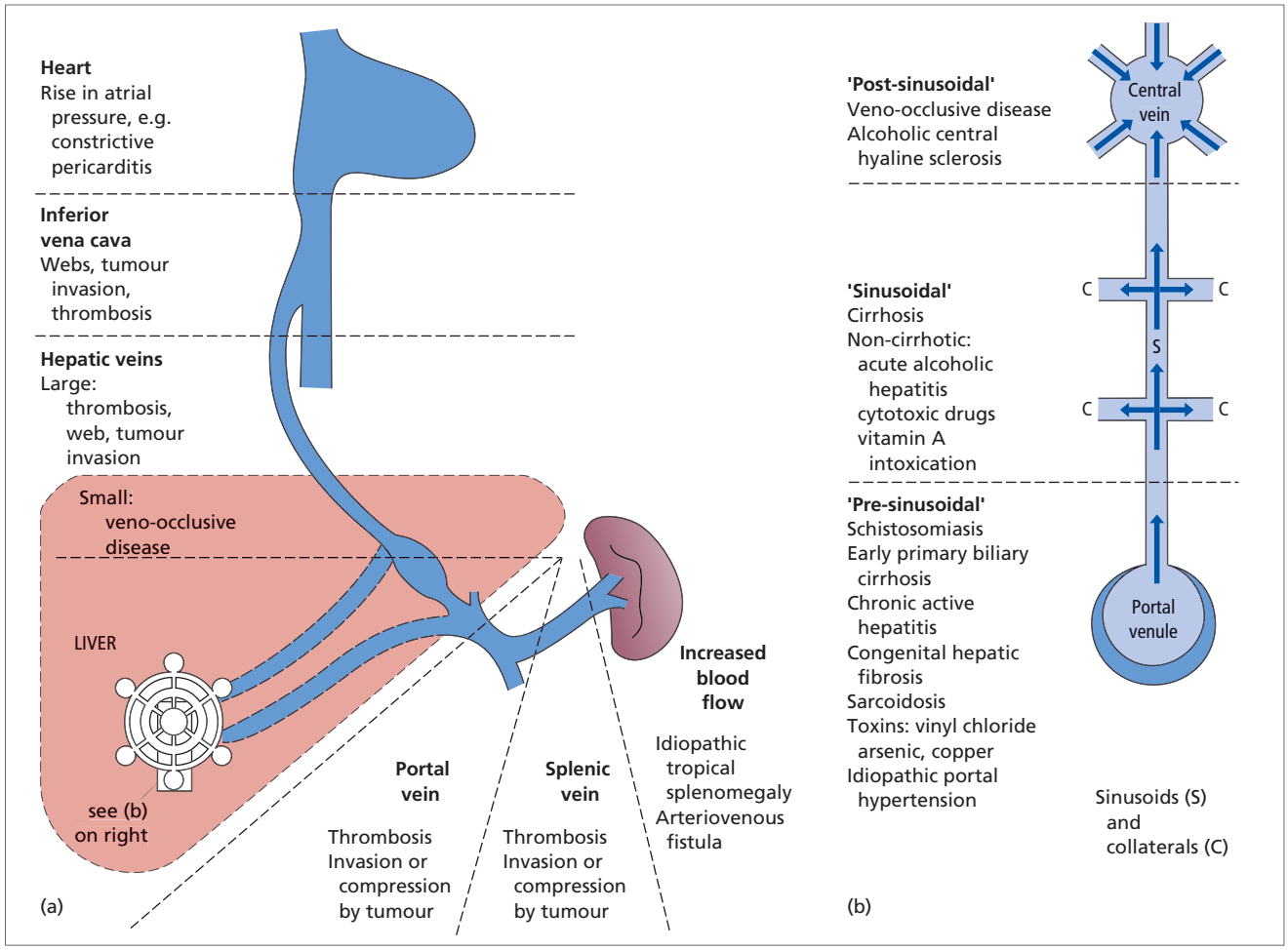


Fig. 10.36. Causes of portal hypertension. (a) Pre- and post-hepatic. (b) Intra-hepatic (NB an overlap exists; wedge hepatic vein pressure may be high in patients with 'pre-sinusoidal' causes, especially as the disease progresses, indicating sinusoidal and/or collateral involvement. Some 'post-sinusoidal' conditions may also have a sinusoidal component) [34].

Portal vein obstruction may be secondary to biliary infections due, for instance, to gallstones or primary sclerosing cholangitis.

Post-operative

The portal and splenic veins commonly block after splenectomy, especially when, pre-operatively, the patient had a normal platelet count. The thrombosis spreads from the splenic vein into the main portal vein. It is especially likely in patients with myeloid metaplasia. A similar sequence follows occluded surgical porto-systemic shunts.

The portal vein may thrombose as a complication of major, difficult hepato-biliary surgery, for instance repair of a stricture or removal of a choledochal cyst.

Trauma

Portal vein injury rarely follows vehicle accidents or stabbing and is rare. Laceration of the portal vein is 50% fatal and ligation may be the only method to control the bleeding.

Hypercoagulable state

This is a frequent cause of portal vein thrombosis in adults. It is commonly due to a myeloproliferative disorder which may be latent [145]. At autopsy, thrombotic lesions are found in macroscopic and microscopic portal veins of patients dying with portal hypertension and myelometaplasia [151]. Ascites and oesophageal varices are associated.

In children, portal vein obstruction has been associated with protein C, protein S and/or antithrombin III deficiency, but it is not likely to be genetic in most instances [38].

Invasion and compression

The classic example is hepato-cellular carcinoma. Carci-

noma of the pancreas, usually of the body, and of other adjacent organs may lead to portal vein block. Chronic pancreatitis is frequently associated with splenic vein obstruction, but involvement of the portal vein is rare (5.6%) [9].

Congenital

Congenital obstruction can be produced anywhere along the line of the right and left vitelline veins from which the portal vein develops. The portal vein may be absent with visceral venous return passing to systemic veins, particularly the inferior vena cava [92]. Hilar venous collaterals are absent.

Congenital abnormalities of the portal vein are usually associated with congenital defects elsewhere [92, 99, 152].

Cirrhosis

The prevalence of portal vein thrombosis complicating cirrhosis is very low [101]. Invasion by a hepato-cellular carcinoma is the most frequent cause. Post-splenectomy thrombocytosis is another aetiological factor. Mural thrombi found at autopsy are probably terminal. It is easy to over-diagnose thrombosis by finding a non-filled portal vein on imaging. This usually represents 'steal' into massive collaterals or into a large spleen.

Miscellaneous

Portal vein thrombosis has very rarely been associated with pregnancy and with oral contraceptives, especially in older women and with long usage [23].

Portal vein block has been associated with general disease of veins and in particular with thrombophlebitis migrans.

In retroperitoneal fibrosis, the portal venous system may be encased by dense fibrous tissue.

Portal vein occlusion with recanalization is a common manifestation of Behçet's disease [8].

Unknown

In about half of patients the aetiology remains obscure. Some of these patients have associated autoimmune disorders such as hypothyroidism, diabetes, pernicious anaemia, dermatomyositis or rheumatoid arthritis [152]. In some instances, the obstruction may have followed undiagnosed intra-abdominal infections such as appendicitis or diverticulitis.

Clinical features

The patient may present with features of the underlying disease, for instance, polycythaemia rubra vera [151] or primary liver cancer.

Bleeding from oesophago-gastric varices is the most common presentation. In those of neonatal origin, the first haemorrhage is at about the age of 4 years (fig. 10.37). The frequency increases between 10 and 15 years and decreases after puberty. However, some patients with portal venous block never bleed and in others haemorrhage may be delayed for as long as 12 years. If blood replacement is adequate, recovery usually ensues in a matter of days. Apart from frank bleeds, intermittent minor blood loss is probably common. This is diagnosed only if the patient is having repeated checks for faecal blood or iron deficiency anaemia.

Especially in children, haemorrhage may be initiated by a minor, intercurrent infection. The mechanism is unclear. Aspirin or a similar drug may be the precipitating factor. Excessive exertion or swallowing a large bolus does not seem to initiate bleeding.

The spleen is always enlarged and symptomless

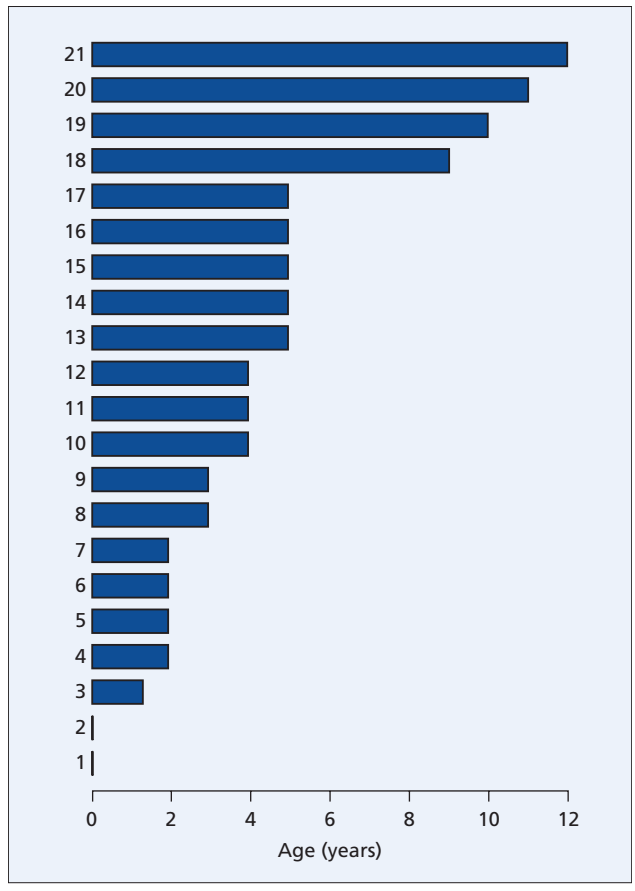


Fig. 10.37. Portal vein occlusion in neonates. Age at time of first haemorrhage in 21 patients in whom the portal vein block occurred in the neonatal period [152].

splenomegaly may be a presentation, particularly in children. Peri-umbilical veins are not seen but there may be dilated abdominal wall veins in the left flank.

The liver is normal in size and consistency. Stigmata of hepato-cellular disease, such as jaundice or vascular spiders, are absent. With acute portal venous thrombosis, ascites is early and transient, subsiding as the collateral circulation develops. Ascites is usually related to an additional factor which has depressed hepatocellular function, such as a haemorrhage or a surgical exploration. It may be seen in the elderly where it is related to the deterioration of liver function with ageing [144].

Hepatic encephalopathy is not uncommon in adults, usually following an additional insult such as haemorrhage, infection or anaesthetic. Chronic encephalopathy may be seen in elderly patients with a particularly large portal-systemic circulation.

Imaging

US shows echogenic thrombus within the portal vein and colour Doppler shows slow flow velocity in the cavernous collaterals and no portal venous signal [70, 108].

CT shows the thrombus as a non-enhancing filling defect within the lumen of the portal vein and dilatation of many small veins at the hilum (fig. 10.38).

MRI shows an area of abnormal signal within the lumen of the portal vein which appears iso-intense on a T_1-weighted image with a more intense signal on a T_2-weighted image (see fig. 5.22).

Angiography in the portal venous phase shows a filling defect or non-opacification of the portal vein. However, the portal vein may not be visualized if blood is diverted away from it into extensive collaterals.

Haematology

Haemoglobin is normal unless there has been blood loss. Leucopenia and thrombocytopenia are related to the enlarged spleen. Circulating platelets and leucocytes, although in short supply, are adequate and function well.

Hypersplenism is not an indication for splenectomy. Blood coagulation is normal.

Serum biochemistry

All the usual tests of 'liver function' are normal. Elevation of serum globulin may be related to intestinal antigens, bypassing the liver through collaterals. Mild pancreatic hypofunction is related to interruption of the venous drainage of the pancreas [153].

Prognosis

This depends on the underlying disease. The outlook is much better than for cirrhosis as liver function is normal. The prognosis is surprisingly good in the child and, with careful management of recurrent bleeding, survival to adult life is expected. The number of bleeds seems to reduce as time passes. Women may bleed in pregnancy but this is unusual; their babies are normal.

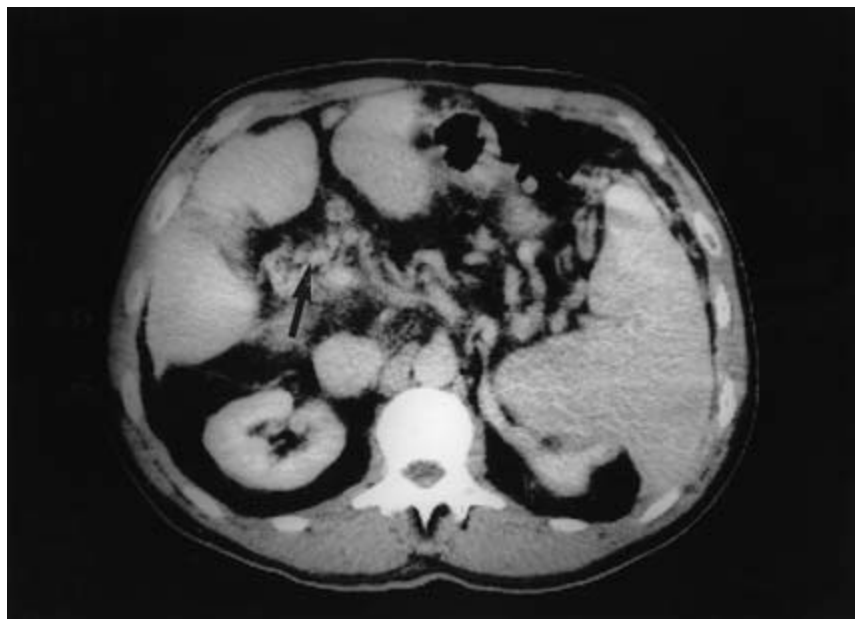


Fig. 10.38. Abdominal CT scan with contrast showing the main portal vein replaced by a leash of small veins (arrow).

Treatment

Any cause must be identified and treated. This may be more important than the portal hypertension. For instance, hepato-cellular carcinoma, invading the portal vein, precludes aggressive therapy for bleeding oesophageal varices. If the variceal bleeding is related to polycythaemia rubra vera, reduction of the platelet count must precede any surgical therapy; anticoagulants may be needed.

Prophylactic treatment of varices is not indicated. They may never rupture and as time passes collaterals open up.

With acute portal vein thrombosis, anticoagulant therapy is usually too late as the clot will have undergone organization. If diagnosed early, anticoagulants may prevent spreading thrombosis.

Children should survive haemorrhage with proper management, including transfusion. Care must be taken to give compatible blood and to preserve peripheral veins. Aspirin ingestion should be avoided. Upper respiratory infections should be treated seriously as they seem to precipitate haemorrhage.

Somatostatin infusions may be needed and, occasionally, the Sengstaken tube.

Endoscopic sclerotherapy is valuable as an emergency procedure.

Major or recurrent bleeds may be treated by later obliterative sclerotherapy. Unfortunately this does not treat the huge gastric fundal varices and the congestive gastropathy continues.

Definitive surgery to reduce portal pressure is usually impossible as there are no suitable veins for a shunt. Even apparently normal-looking veins seen on venography turn out to be in poor condition, presumably related to extension of the original thrombotic process. In children, veins are very small and difficult to anastomose. Myriads of collateral channels add to the technical difficulties.

Results for all forms of surgery are very unsatisfactory. Splenectomy is the least successful.

A shunt (porta-caval, meso-caval or spleno-caval) is the most satisfactory treatment but usually proves impossible.

When the patient is exsanguinating, despite massive blood transfusion, an oesophageal transection may have to be performed. Here again gastric varices are not treated. Post-operative complications are common.

TIPS is usually impossible.

Splenic vein obstruction

Isolated splenic vein obstruction causes sinistral (left-sided) portal hypertension. It may be due to any of the factors causing portal vein obstruction (fig. 10.39). Pancreatic disease such as carcinoma (18%), pancreatitis (65%), pseudocyst and pancreatectomy are particularly important [9].

If the obstruction is distal to the entry of the left gastric vein, a collateral circulation bypasses the obstructed splenic vein through short gastric veins into the gastric fundus and lower oesophagus, so reaching the left gastric vein and portal vein. This leads to very prominent varices in the fundus of the stomach but few in the lower oesophagus.

The selective venous phase of an angiogram, an enhanced CT scan or MRI are diagnostic. Splenectomy, by blocking arterial inflow, is usually curative but unnecessary if the patient has not bled from varices [81].

Hepatic arterio-portal venous fistulae

Portal hypertension results from increased portal venous flow. Increase in intra-hepatic resistance due to a rise in portal flow may also be important. Portal zones show thickening of small portal radicles with accompanying mild fibrosis and lymphocyte infiltration. The increased intra-hepatic resistance may persist after obliteration of the fistula.

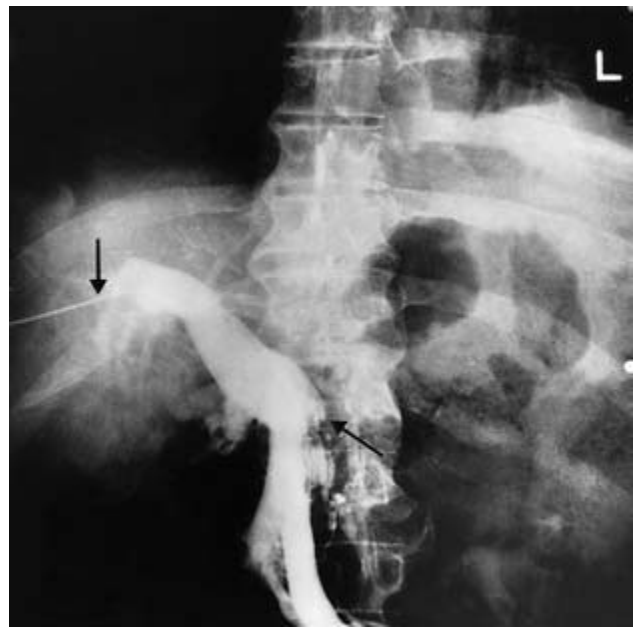


Fig. 10.39. A 64-year-old man with polycythaemia rubra vera. Trans-hepatic portal venogram (transhepatic needle marked by upper arrow) showing a thrombosed splenic vein (marked by the lower arrow) with patent superior mesenteric and portal veins. This patient, after preliminary reduction of red cell and platelet count by radio-active phosphorus, was successfully treated by splenectomy.

These fistulae are usually congenital, traumatic or related to adjacent malignant neoplasm [135]. Inferior mesenteric arteriovenous fistulae may be associated with acute ischaemic colitis.

With large fistulae, a loud arterial bruit is heard in the right upper abdomen. Pain may be pronounced. Others present with portal hypertension.

US and enhanced CT show an enlarged hepatic artery and a dilated intra-hepatic portal vein. The diagnosis is confirmed by arteriography.

Selective non-invasive embolization of the fistula has replaced surgery.

Porto-hepatic venous shunts

These are probably congenital and represent persistence of the omphalomesenteric venous system. They may be between the main portal and hepatic veins or between the right or left portal vein and hepatic veins [26]. They are diagnosed by US, enhanced CT scan, MRI and colour Doppler imaging and confirmed by arteriography.

Intra-hepatic pre-sinusoidal and sinusoidal portal hypertension (fig. 10.40)

Portal tract lesions

In *schistosomiasis*, the portal hypertension results from the ova causing a reaction in the minute portal venous radicles.

In *congenital hepatic fibrosis*, the portal hypertension is probably due to a deficiency of terminal branches of the portal vein in the fibrotic portal zones.

Portal hypertension has been reported with *myeloproliferative diseases* including myelosclerosis, myeloid leukaemia and Hodgkin's disease [37]. The mechanism is complex. In part it is related to infiltration of the portal zones with haemopoietic tissue, but thrombotic lesions in major and minor portal vein radicles and nodular regenerative hyperplasia contribute [151].

In *systemic mastocytosis*, portal hypertension is related to increased intra-hepatic resistance secondary to mast cell infiltration. Increased splenic flow, perhaps with splenic arteriovenous shunting and with histamine release, may contribute.

In *primary biliary cirrhosis*, portal hypertension may be a presenting feature long before the development of the nodular regeneration characteristic of cirrhosis (Chapter 14). The mechanism is uncertain, although portal zone lesions and narrowing of the sinusoids because of cellular infiltration have been incriminated. The portal hypertension of *sarcoidosis* may be similar. Massive fibrosis is usually associated.

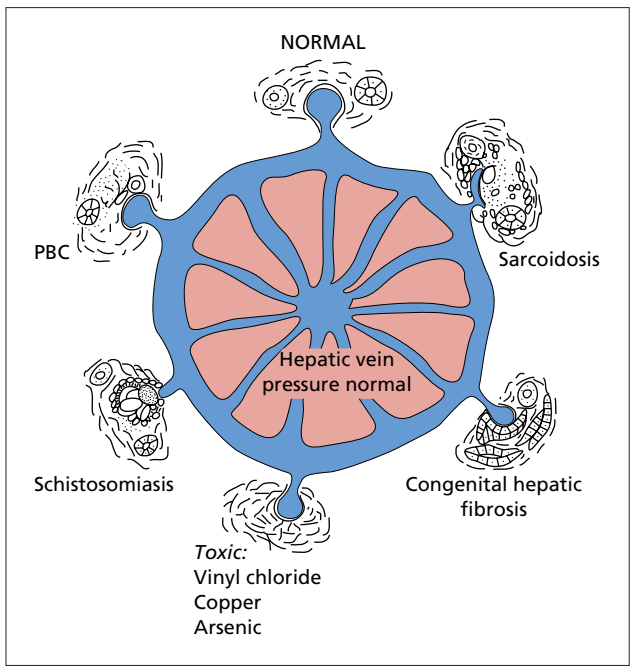


Fig. 10.40. The aetiology of pre-sinusoidal intra-hepatic portal hypertension. PBC, primary biliary cirrhosis.

Toxic causes

The injurious substance is mainly taken up by hepatic stellate cells in Disse's space; these are fibrogenic. Minute portal vein radicles are obstructed and intra-hepatic portal hypertension results.

Inorganic arsenic has caused portal hypertension in patients being treated for psoriasis.

Liver disease in vineyard sprayers in Portugal may be related to exposure to *copper*. Angiosarcoma may be a complication.

Exposure to the vapour of the polymer of *vinyl chloride* leads to sclerosis of portal venules with portal hypertension and angiosarcoma.

Reversible portal hypertension may follow *vitamin A intoxication*—vitamin A being stored in hepatic stellate cells. Prolonged use of *cytotoxic drugs*, such as methotrexate, 6-mercaptopurine and azathioprine, can lead to peri-sinusoidal fibrosis and portal hypertension.

Hepato-portal sclerosis

This is marked by splenomegaly, hypersplenism and portal hypertension without occlusion of portal and splenic veins and with no obvious pathology in the liver [82]. It is a confused entity. It has also been termed non-cirrhotic portal fibrosis, non-cirrhotic portal hypertension and idiopathic portal hypertension. *Banti's*

syndrome, an obsolete term, probably fell into this group. Injury to intra-hepatic portal venous radicles and sinusoidal endothelial cells is the common denominator.

An increase in intra-hepatic resistance indicates an obstruction to hepatic blood flow. Increased lymph flow may help to reduce the high portal pressure [100].

The aetiology may be infectious, toxic or, in many instances, unknown (fig. 10.41). In childhood, intra-hepatic thrombosis of small portal veins could be the primary disorder.

In Japan, it affects largely middle-aged women. A very similar condition in India, called *non-cirrhotic portal fibrosis*, largely affects young males [130]. It has been related to arsenic taken in drinking water and in unorthodox medicines. In both countries, it is probably due to the effects of multiple intestinal infections on the liver. It is therefore decreasing with improved hygiene.

Somewhat similar patients have been reported from the USA [90] and the UK [67].

Liver biopsy shows sclerosis and sometimes obliteration of the intra-hepatic venous bed but the changes, and especially the fibrosis, may be minimal. Large portal veins near the hilum may be thickened and narrow, but this is usually seen only at autopsy. Some of the changes seem to be secondary to partial thrombosis of small portal venous channels with recanalization. Peri-sinusoidal fibrosis is usually present but may be seen only by electron microscopy.

Portal venography shows small portal vein radicles to be narrowed and sparse. The peripheral branches may be irregular with acute-angle division. Some of the large intra-hepatic portal branches may be non-opacified with an increase of very fine vasculature around the large intra-hepatic portal branches. Hepatic venography confirms the vascular abnormalities and vein-to-vein anastomoses are frequent.

Tropical splenomegaly syndrome

This is marked by residence in a malarial area, splenomegaly, hepatic sinusoidal lymphocytosis and Kupffer cell hyperplasia, raised serum IgM and malarial antibody titres and response to prolonged antimalarial chemotherapy. Portal hypertension is not marked and variceal bleeding is rare [130].

Intra-hepatic portal hypertension

Cirrhosis

All forms of cirrhosis lead to portal hypertension and the primary event is obstruction to portal blood flow [85]. Portal venous blood is diverted into collateral channels and some bypasses the liver cells and is shunted directly into the hepatic venous radicles in the fibrous septa. These porto-hepatic anastomoses develop from pre-existing sinusoids enclosed in the septa (fig. 10.42) [114]. The hepatic vein is displaced further and further outwards until it lies in a fibrous septum linked with the portal venous radicle by the original sinusoid. The regenerating nodules become divorced from their portal blood supply and are nourished by the hepatic artery. Even larger porto-hepatic venous anastomoses are found in the cirrhotic liver. About one-third of the total

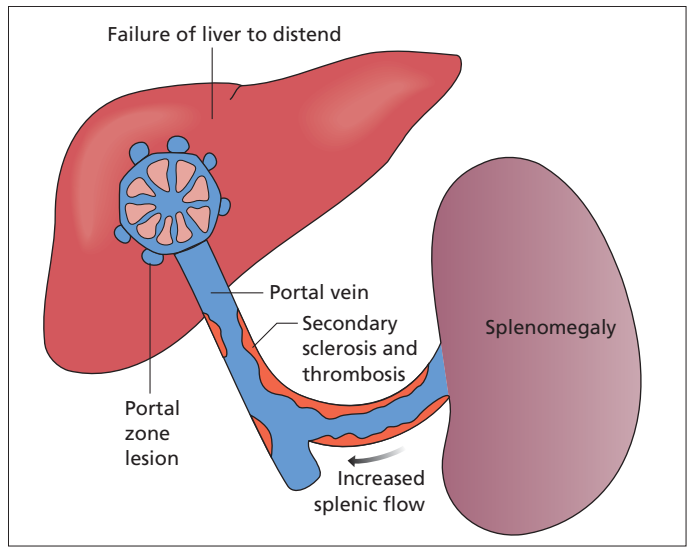


Fig. 10.41. Factors concerned in so-called idiopathic 'primary' portal hypertension.

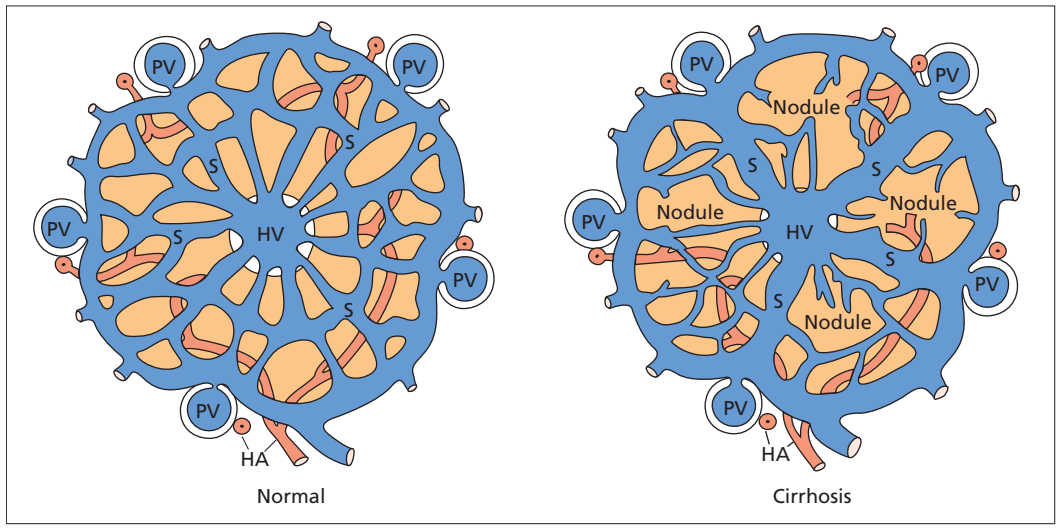


Fig. 10.42. Cirrhosis of the liver showing the formation of portal venous (PV) / hepatic venous (HV) anastomoses or internal Eck fistulae at the site of pre-existing sinusoids (S). Note that the regeneration nodules are supplied by the hepatic artery (HA).

blood flow perfusing the cirrhotic liver may bypass sinusoids, and hence functioning liver tissue, through these channels [134].

The obstruction to portal flow is partially due to nodules which compress hepatic venous radicles (fig. 10.43) [65]. This would lead to a post-sinusoidal portal hypertension. However, in cirrhosis, the wedged hepatic venous (sinusoidal) and main portal pressures are virtually identical and the stasis must extend to the portal inflow vessels. Sinusoids probably provide the greatest resistance to flow. Changes in the space of Disse, particularly collagenization, result in sinusoidal narrowing and this may be particularly important in the alcoholic. Hepatocyte swelling in the alcoholic may also reduce sinusoidal flow [13]. Obstruction is therefore believed to be at all levels from portal zones through the sinusoids to the hepatic venous outflow (fig. 10.44).

The hepatic artery provides the liver with a small volume of blood at a high pressure. The portal vein delivers a large volume at a low pressure (see fig. 10.2). The two systems are equilibrated in sinusoids. In normals, the hepatic artery probably plays little part in maintaining portal venous pressure. In the cirrhotic, more direct arterio-portal shunting has been suspected. Hypertrophy of the hepatic artery and relative increase in flow help to maintain sinusoidal perfusion.

Non-cirrhotic nodules

See Chapter 30.

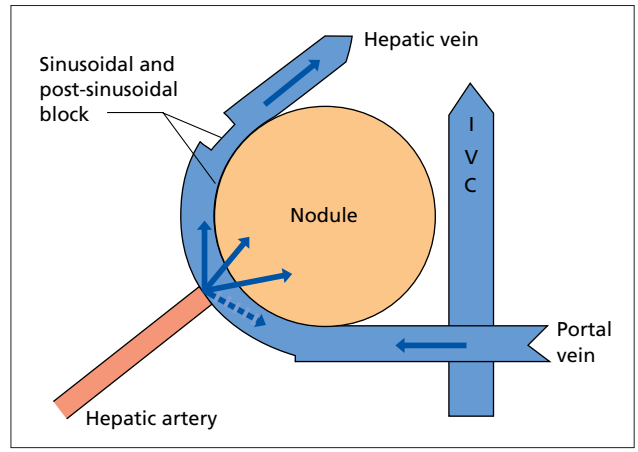


Fig. 10.43. The circulation in hepatic cirrhosis. A nodule obstructs the sinusoids and hepatic veins. The nodule is supplied mainly by the hepatic artery. IVC, inferior vena cava.

Bleeding oesophageal varices

Predicting rupture

Sixty-five per cent of cirrhotic patients with varices will not bleed within 2 years of diagnosis, but 50% will die of the first haemorrhage.

There is a strong correlation between variceal size, assessed endoscopically, and the probability of bleeding [22]. Intravariceal pressure is less important, although a portal pressure above 12 mmHg appears necessary for varices to form and subsequently bleed [76].

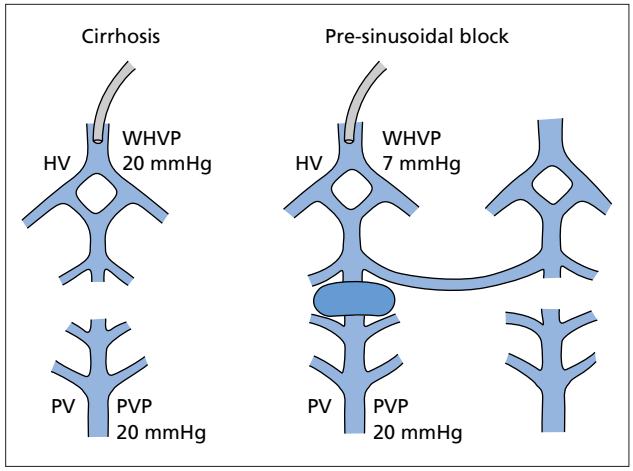


Fig. 10.44. In patients with cirrhosis the wedged hepatic venous pressure (WHVP) (20 mmHg) is equal to the pressure in the main portal vein (PVP) (20 mmHg) (measured via umbilical vein). Resistance to flow extends from the central hepatic vein, through the sinusoids to the portal vein (PV). In pre-sinusoidal portal hypertension normal anastomoses exist between small vascular units and prevent the blocking catheter from producing a large area of stasis. WHVP (7 mmHg) is therefore less than the pressure in the main portal vein (20 mmHg) [117].

'Red spots', danger signs seen at endoscopy, are valuable predictors of imminent haemorrhage.

Child's grade is used to assess hepato-cellular function in cirrhosis (table 10.4). Every patient should be assigned a grade. It is the most important predictor of the likelihood of bleeding. It correlates with variceal size and with the presence of endoscopic red signs and with the response to treatment.

These three variables—size, presence of red signs and hepato-cellular function—are the best predictors of bleeding (fig. 10.45).

Patients with alcoholic cirrhosis may be at most risk [69].

Doppler sonography predicts likelihood of bleeding. This is based on velocity and diameter of the portal vein, spleen size and the presence of collaterals [132].

Prevention of bleeding [18]

Liver function must be improved, for instance, by abstaining from alcohol. Aspirin and NSAIDs should be avoided. No protection comes from avoiding certain foods such as spices or from taking long-term H_2-blockers.

Propranolol is a non-selective β-blocker which reduces portal pressure by splanchnic vaso-constriction and, to a lesser extent, by reducing cardiac output. Hepatic arterial blood flow falls [54, 87]. The drug is given in a dose

Table 10.4. Child's classification of hepato-cellular function in cirrhosis

Group designation	A	B	C
Serum bilirubin (mg/dl)	Below 2.0	2.0–3.0	Over 3.0
Serum albumin (g/dl)	Over 3.5	3.0–3.5	Under 3.0
Ascites	None	Easily controlled	Poorly controlled
Neurological disorder	None	Minimal	Advanced coma
Nutrition	Excellent	Good	Poor: 'wasting'

which reduces the resting pulse rate by 25% 12 h after taking it. There is marked individual variation in the lowering of the portal pressure. Even with large doses, 20–50% of patients do not respond, especially those with advanced cirrhosis [46]. The portal pressure must be maintained at 12 mmHg or lower [54]. If possible, wedged hepatic venous or endoscopic portal pressure should be monitored.

Propranolol should not be given to patients with restrictive airways disease. It may make resuscitation more difficult if the patient bleeds. Encephalopathy can also be induced. Propranolol is a high 'first pass effect' drug and might be expected to have unpredictable results in patients with advanced cirrhosis where hepatic clearance would be delayed. It causes some mental depression.

A meta-analysis of six trials showed a suggestively significant reduction in those bleeding but not in those dying (fig. 10.46) [115]. Further meta-analysis of nine randomized trials showed the incidence of bleeding was significantly reduced by propranolol [104]. It is not easy to select those to treat as 70% of patients with varices will never bleed from them [14]. Propranolol is recommended for those with large varices and with red endoscopic danger signs [18, 104]. Patients with an HVPG greater than 12 mmHg should be treated whatever the size of the varices. *Nadolol* gives equivalent results. Propranolol is the only cost-effective prophylactic therapy for preventing gastrovariceal bleeding in cirrhosis [142]. *Isosorbide-5-mononitrate* is equally effective in prophylaxis of the first bleed, but the probability of death is significantly greater, particularly in those more than 50 years old [52]. The addition of nitrate to β-blocker should be reserved for those failing therapy with the β-blocker alone.

Variceal sclerotherapy or ligation is not so satisfactory or cost-effective as vaso-active drugs.

Meta-analysis of *prophylactic sclerotherapy* showed generally unsatisfactory results [104, 147]. It cannot be recommended.

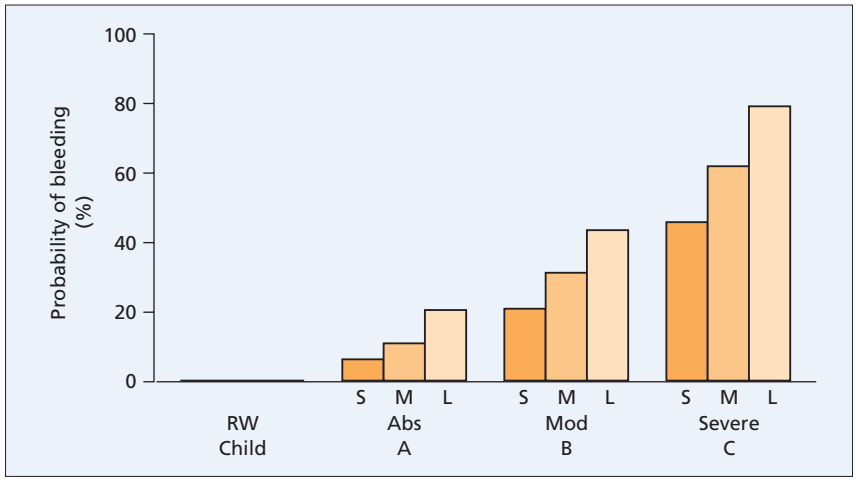


Fig. 10.45. Increasing variceal size (small (S), medium (M) and large (L)) combine with red wheals (RW) on varices (absent, moderate, severe) and Child's grade (A, B, C) to define probability of bleeding at 1 year (adapted from [97]).

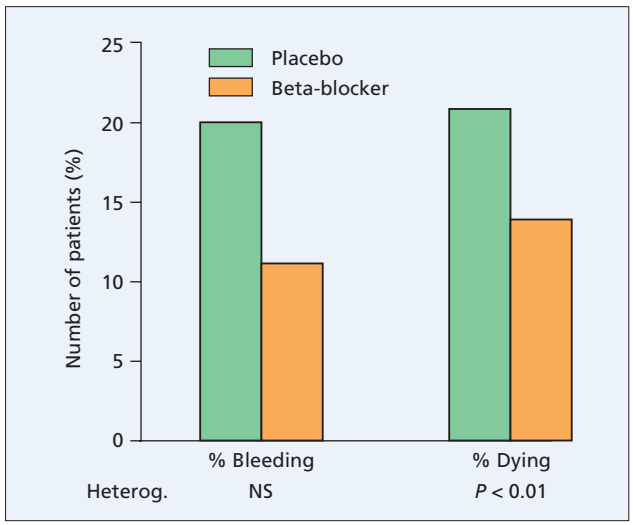


Fig. 10.46. Meta-analysis of six trials of prophylactic propranolol (β-blocker) therapy. Data on dying cannot be relied upon because of significant heterogeneity (Heterog.) in groups. There is, however, a significant reduction in those bleeding [115].

Diagnosis of bleeding

The *clinical features* are those of gastrointestinal bleeding with the added picture of portal hypertension.

Bleeding may be a slow ooze with melaena, rather than a sudden haematemesis. The intestines may be full of blood before the haemorrhage is recognized and bleeding is liable to continue for days.

Bleeding varices in cirrhosis have injurious effects on the liver cells. These may be due to anaemia diminishing hepatic oxygen supply, or to increased metabolic demands resulting from the protein catabolism following haemorrhage. The fall in blood pressure diminishes hepatic arterial flow, on which the regenerating liver nodules depend, and ischaemic hepatitis may ensue. The increased nitrogen absorption from the intestines often leads to hepatic coma (Chapter 7). Deteriorating liver cell function may precipitate jaundice or ascites.

Non-variceal bleeding from duodenal ulcers, gastric erosions and the Mallory–Weiss syndrome is frequent.

Endoscopy is performed routinely to confirm the source of the bleeding (fig. 10.47).

Prognosis

Sixty-five per cent of varices in patients with cirrhosis will not rupture within 2 years of diagnosis. However, between 30 and 50% will die within 6 weeks of the first bleed.

The prognosis is determined by the severity of the hepato-cellular disease. The ominous triad of jaundice, ascites and encephalopathy is associated with an 80% mortality. The 1-year survival in good-risk (Child grade A and B) patients is about 85% and in bad-risk (Child grade C) patients about 30% (table 10.5). The survival score can be based on encephalopathy, prothrombin time and the number of units transfused in the previous 72 h. Alcoholics have a worse prognosis as hepato-cellular disease is greater. Abstention from alcohol considerably improves the prognosis. Patients with continuing chronic hepatitis do poorly. Patients with primary biliary cirrhosis tolerate the haemorrhage reasonably well.

A low portal blood velocity by Doppler predicts shorter survival [157].

The importance of hepato-cellular function is emphasized by the relatively good prognosis for bleeding in patients where hepato-cellular function is relatively well

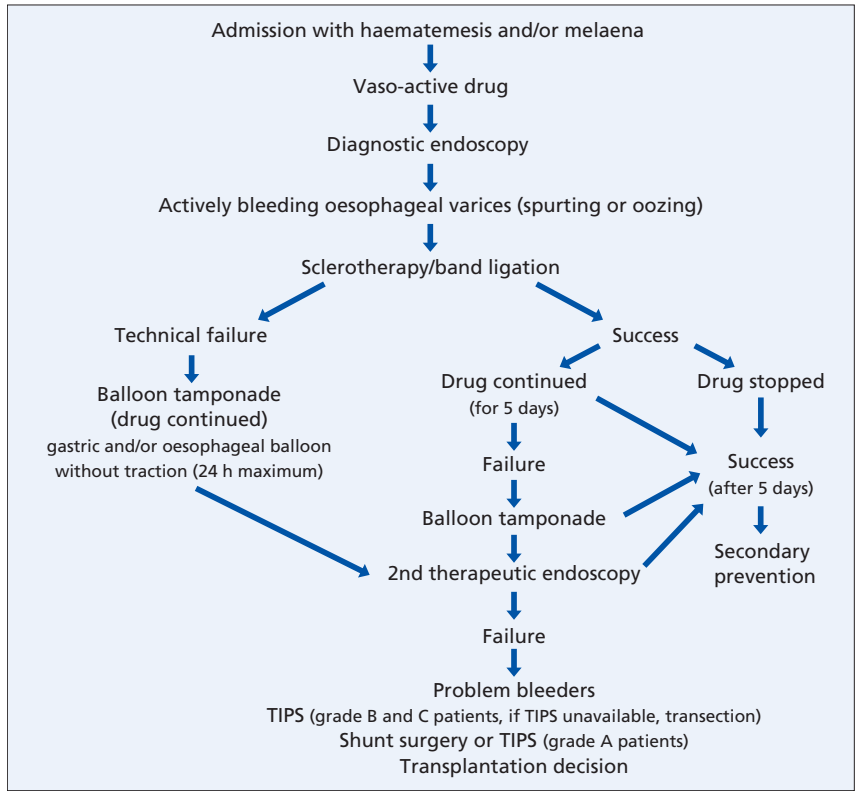


Fig. 10.47. Common practice for the management of oesophageal varices actively bleeding at diagnosis. Acute band ligation should only be performed by an experienced endoscopist [19].

Table 10.5. Pugh's (Child's) grading and hospital deaths at index bleed

Grade	No. patients	Hospital deaths
A	65	3 (5%)
B	68	12 (18%)
C	53	35 (68%)
Total	186	50 (27%)

preserved, as in schistosomiasis, the non-cirrhotic portal hypertension of India and Japan, and portal vein thrombosis.

Management of acute variceal bleeding [19] (fig. 10.47)

Child's grade is recorded (table 10.4). Bleeding is likely to continue and observations must be close. If possible, the patient should be managed by an experienced intensive care team. Haemodynamic monitoring (central venous pressure) and peripheral drip are instigated. The patient is transfused to a 0.3 haematocrit and haemoglobin to less than or equal to 10 g/l. Over-transfusion is avoided. Systolic blood pressure is maintained at equal or greater than 90 mmHg. Saline infusions are avoided.

Clotting defects are corrected and fresh frozen plasma and platelet transfusions may be necessary. Vitamin K_1 intravenously is routine. A proton pump inhibitor, such as omeprazole, is given although there is little controlled evidence of benefit. However, stress-induced mucosal ulcers are frequent.

Liver function is monitored and electrolyte balance maintained.

Bacterial infection is associated with failure to control bleeding [50]. Short-term antibiotic prophylaxis with ciprofloxacin or similar significantly increases the patient's long-term survival [10].

Pneumonia is prevented by special care during endoscopy.

Hepatic encephalopathy is prevented by lactulose and phosphate enemas.

Sedatives should be avoided, and, if essential, oxazepam should be used. Chlordiazepoxide may be required to prevent delirium tremens in alcoholics.

If ascites is very tense, intra-abdominal pressure may be reduced by a cautious paracentesis and the use of spironolactone.

Management requires the availability of many therapeutic options and these may need to be combined in the individual patient (fig. 10.47). They include vaso-active

drugs, endoscopic sclerotherapy and variceal banding, the Sengstaken tube, TIPS and emergency surgery.

Vaso-active drugs

Vaso-active drugs. These lower portal venous pressure and should be started even before diagnostic and therapeutic endoscopy [3, 19, 80]. Treatment should be given even before the patient is admitted to hospital and certainly in the emergency room. Early treatment facilitates the ease with which sclerotherapy can be done as active bleeding has been reduced.

Vasopressin (*pitressin*) lowers portal venous pressure by constriction of the splanchnic arterioles so causing an increase in resistance to the inflow of blood to the gut (fig. 10.48). It controls variceal bleeding by lowering the portal venous pressure.

Vasopressin causes coronary vaso-constriction and an electrocardiogram (ECG) should be taken before it is given. Abdominal colicky discomfort and evacuation of the bowels together with facial pallor are usual during the infusion. Intestinal ischaemia is another possible complication.

Nitroglycerin can be combined with vasopressin in a single sublingual dose.

Glypressin (*terlipressin*) acts in a similar fashion to vasopressin, but is more stable and has a longer half-life. It has fewer side-effects, but is more costly. It gives comparable results to somatostatin, but has more side-effects [42]. Glypressin is given in a dose of 2 mg intravenously every 6 h for 48 h. It may be continued for a further 3 days at 1 mg every 4–6 h.

Somatostatin reduces the portal pressure by increasing splanchnic arterial resistance. It also inhibits a number of vasodilatory peptides including glucagon. It is about equivalent to vasopressin in the control of variceal bleeding, but has less side-effects [71]. An intravenous bolus of 250 µg may be given before emergency endoscopy or sclerotherapy. It is followed by an infusion of 6 mg/24 h for 120 h [3].

Octreotide is a synethetic analogue of somatostatin, sharing four amino acids. It has a much longer half-life (1–2 h). Trials have given conflicting results and data is insufficient to support its use alone in the treatment of acute variceal bleeding [30].

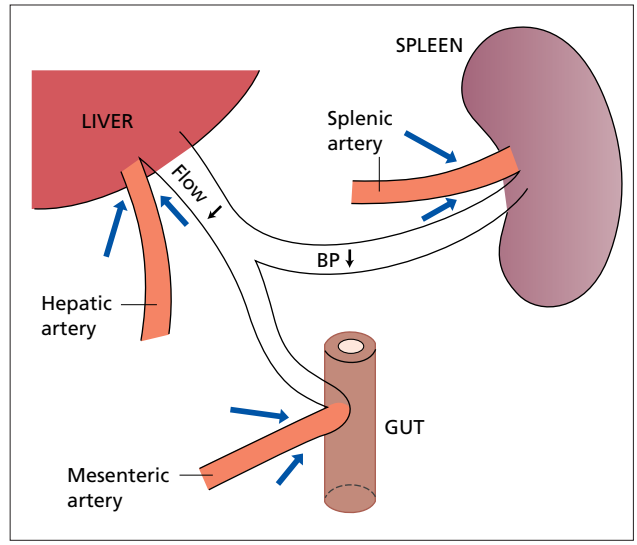


Fig. 10.48. The mode of action of vasopressin on the splanchnic circulation. Hepatic, splenic and mesenteric arteries are shown. Splanchnic blood flow (including hepatic blood flow) and portal venous pressure are reduced by arterial vaso-constriction (blue arrows). BP, blood pressure.

Sengstaken–Blakemore tube (figs 10.49, 10.50)

The use of oesophageal tamponade has decreased markedly with the advent of vaso-active drugs, oesophageal sclerotherapy and TIPS. The four-lumen tube has an oesophageal and a gastric balloon, an aspirating channel for the stomach and a fourth lumen for continuous aspiration above the oesophageal balloon.

Two, but preferably three, assistants are required. The tube is easier to insert if it has been allowed to stiffen in the icebox of a refrigerator. The stomach is emptied. A new, tested and lubricated tube is passed through the mouth into the stomach. The gastric balloon is inflated with 250 ml of air and doubly clamped. The gastric tube is aspirated continuously. The whole tube is pulled back until resistance is encountered and the oesophageal tube is then inflated to a pressure of 40 mmHg, greater than that expected in the portal vein. The tube should be taped securely to the side of the face to provide traction. If necessary, a 500-ml bag of saline, taped to the tube and hung over the side of the bed, may be used for greater traction. Too little traction means that the gastric balloon falls back into the stomach. Too much causes discomfort with retching, and also potentiates gastro-oesophageal ulceration. The position of the tube is checked by X-ray (fig. 10.50). The head of the bed is raised.

The oesophageal tube has continuous low pressure suction and occasional aspiration. Tube traction and oesophageal balloon pressure are checked hourly. After 12 h, traction is released, and the oesophageal balloon deflated leaving the gastric balloon inflated. If bleeding recurs, the traction is reapplied and the oesophageal balloon re-inflated until emergency sclerotherapy, TIPS or surgery is performed.

The compression tubes are successful. Of failures, 10% are due to fundal varices or non-variceal bleeding. In 50%, re-bleeding follows tube withdrawal.

Complications include obstruction to upper airways. If the gastric balloon bursts or deflates, the oesophageal

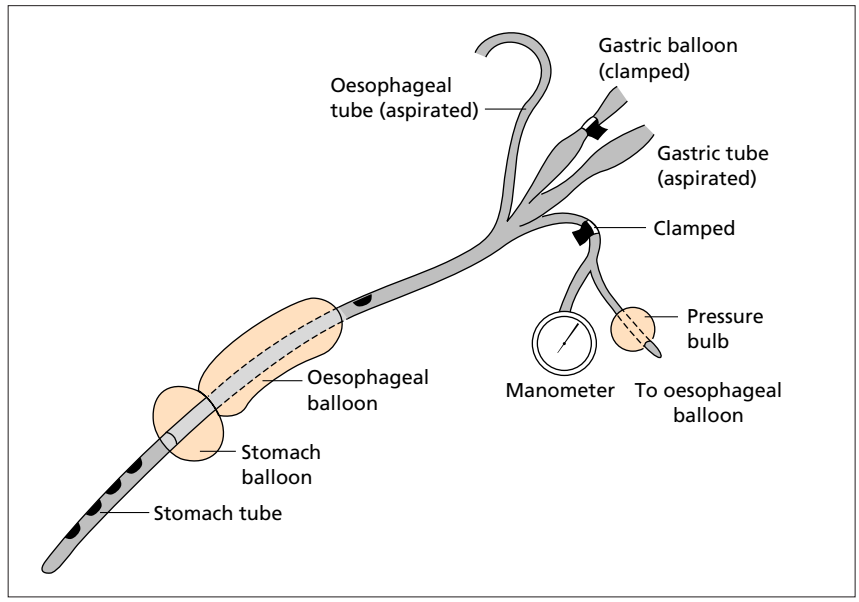


Fig. 10.49. Sengstaken–Blakemore oesophageal compression tube modified by Pitcher [113]. Note the fourth oesophageal tube which aspirates the oesophagus above the oesophageal balloon.

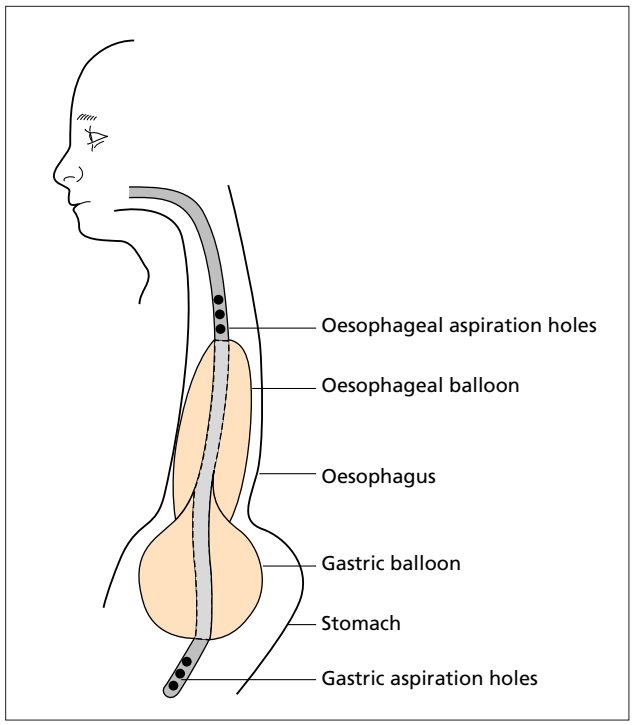


Fig. 10.50. The Sengstaken–Blakemore tube in position.

balloon may migrate into the oropharynx causing asphyxia. The oesophageal balloon must be deflated, and if necessary the tube transected with scissors.

Ulceration of the lower oesophagus complicates prolonged or repeated use. Aspiration of secretions into the lung is prevented by continuous suction above the oesophageal balloon.

The Sengstaken tube is the most certain method for continued control of oesophageal bleeding over hours. Complications are frequent and are in part related to the experience of the operating team. It is unpleasant for the patient. It is useful when transferring patients from one centre to another, when haemorrhage is torrential and when variceal sclerosis, TIPS or surgery are not immediately available. The oesophageal tube should not be kept inflated for more than 24 h and preferably for not more than 10 h.

Endoscopic sclerotherapy and banding

This remains the therapeutic gold standard for the acute treatment of bleeding varices. In 91% of patients the haemorrhage will be controlled [57]. In skilled hands, it can be done while the patient is bleeding although preliminary vaso-active treatment and tamponade may be necessary for clear vision. If the patient re-bleeds, a second emergency sclerotherapy may be given. If more sessions are necessary, the salvage rate is poor and alternative therapy should be considered (fig. 10.47).

Gastric varices are difficult to treat if distant from the cardia.

The failure rate is 6%. In grade C patients, survival is probably unaltered. Good results come from experienced groups. The occasional operator should not attempt to deal with bleeding oesophageal varices using the endoscope. The procedure is done under sedation as necessary. It should be as sterile as possible with mouth washes and careful mouth hygiene. Double-channel endoscopes allow a clear view and safe injection. The sclerosant may be 1% sodium tetradecyl sulphate or 5% ethanolamine oleate. Injection is made just above the gastro-oesophageal junction and should not exceed 4 ml

in any one varix (fig. 10.51). Complications are more likely with chronic, repeated sclerotherapy than with acute injection to stop bleeding. Factors include the volume of sclerosant used and the Child's grade.

Almost every patient will experience transient fever, dysphagia and chest pain.

Endoscopic variceal ligation (*banding*) is an alternative emergency treatment to endoscopic sclerotherapy. It is superior to sclerotherapy, especially when the varix is spurting rather than oozing [79, 80]. It has fewer complications. These include aspiration pneumonia and large oesophageal ulcers. Vaso-constrictor and blood tranfusion needs are reduced [79, 80]. However, it is more difficult to perform while the patient is bleeding and will probably not replace the more general endoscopic sclerotherapy except in specialized centres.

The technique is based on band ligation of haemorrhoids. The varices are ligated and strangulated by the application of small elastic O rings (fig. 10.52) [75]. A standard end-viewing endoscope loaded with a banding device on its tip is inserted into the lower oesophagus. A varix is identified and aspirated into the device, followed by placement of an elastic band around it by pulling the trip wire. The process is repeated until all the varices are ligated.

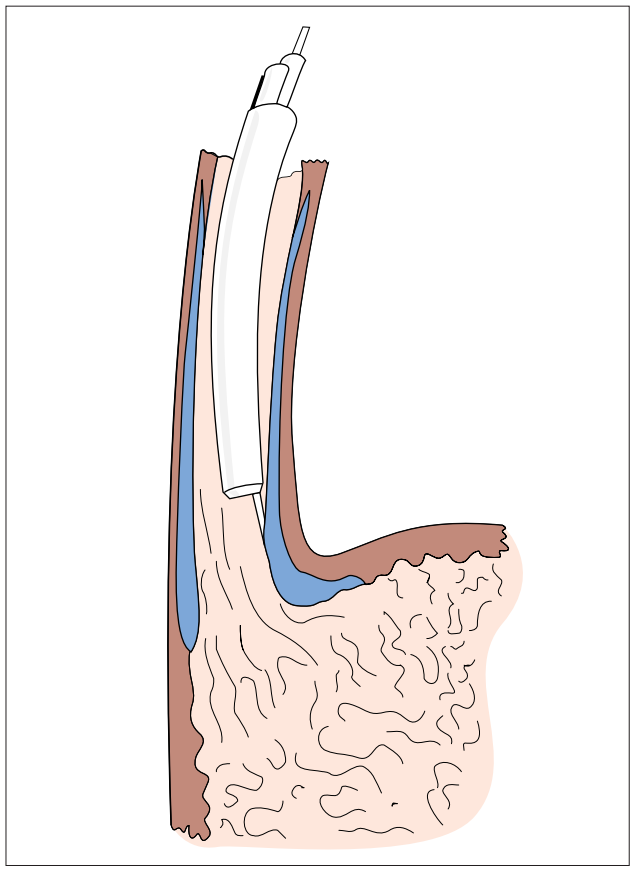


Fig. 10.51. Direct injection of oesophageal varices with an unmodified fibre-optic endoscope.

Emergency surgery

This has been remarkably reduced with the advent of sclerotherapy, vaso-active drugs, balloon tamponade and, in particular, TIPS. When these fail, or are not available, emergency surgery must be considered. An emergency end-to-side porta-caval shunt is effective in stopping bleeding [102]. Mortality is high in grade C patients, and the post-surgical encephalopathy rate is also high. If bleeding is torrential and recurs after two sclerotherapy sessions, TIPS is the best treatment.

Emergency oesophageal transection may be done by the staple gun technique as an emergency, but not as a prophylatic or elective procedure. Within 2 years, varices recurred, enlarged and frequently re-bled [83].

Prevention of re-bleeding

At 1 year, 25% of Child's grade A, 50% of grade B and 75% of grade C patients with cirrhosis will have re-bled from varices. Prevention is difficult and controversial.

Propranolol reduces re-bleeding in patients with large varices who are in good condition [77]. Patients with decompensated cirrhosis do not respond. Propranolol probably has little effect on survival [104]. It is of value in portal gastropathy.

Chronic variceal sclerotherapy is performed at weekly intervals until all varices are thrombosed. Three to five sessions will probably be needed. After eradication,

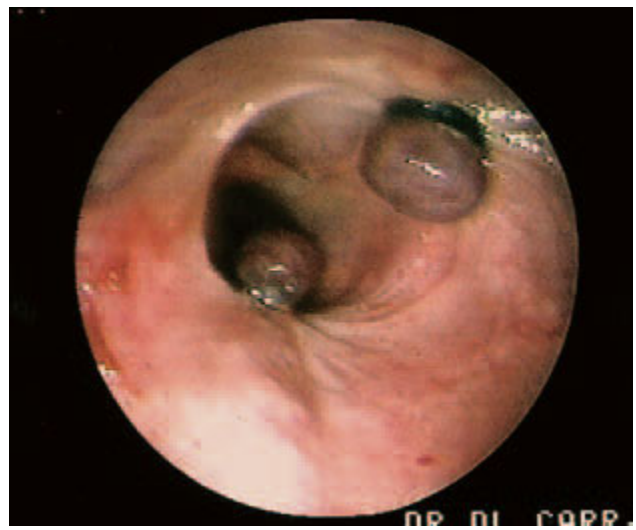


Fig. 10.52. Endoscopic variceal ligation. The varices have been strangulated by an elastic ring introduced via the endoscope.

close endoscopic surveillance and repeated injections to ensure continued eradication are *not* indicated as survival is not increased. Chronic oesophageal sclerotherapy reduces the rate of re-bleeding and the transfusion requirements but has no long-term effect on survival [148]. In good-risk patients, propranolol is as successful as chronic sclerotherapy to obliterate varices [5].

The many complications of chronic sclerotherapy include bleeding from the puncture site, but more usually from remaining varices or deep ulcers that have opened in sub-mucosal channels. Stricture formation is related to chemical oesophagitis, ulceration and acid reflux; impaired swallowing contributes.

Perforation is usually delayed 5–7 days and is probably an extension of the ulcerative process [109].

Pulmonary complications include chest pain, aspiration pneumonia, pleural effusion and mediastinitis [7]. Sclerosant embolizing the lungs may impair respiratory function [123]. Pyrexia and bacteraemia are frequent.

Portal vein thrombosis may affect a subsequent shunt or liver transplantation.

Varices increase at other sites including the stomach, ano-rectal area and percutaneously.

Endoscopic variceal ligation may be the treatment of choice, but variceal recurrence is greater [79, 80].

Chronic sclerotherapy or banding reduces the rate of re-bleeding and transfusion requirements, but has no long-term effect on survival [148]. A shunt, usually porta-caval, or transplant must be considered as rescue when sclerotherapy has failed.

Portal-systemic shunt procedures

(fig. 10.53)

The aim is to reduce portal venous pressure, maintain total hepatic and, particularly, portal blood flow and, above all, not have a high incidence of hepatic encephalopathy. There is no currently available procedure that fulfils all these criteria. Hepatic reserve determines survival. Hepato-cellular function deteriorates after shunting.

Porta-caval

In 1877 Eck [40] first performed a porta-caval shunt in dogs and this remains the most effective way of reducing portal hypertension in man.

The portal vein is joined to the inferior vena cava either end-to-side, with ligation of the portal vein, or side-to-side, maintaining its continuity. The portal blood pressure falls, hepatic venous pressure falls and hepatic arterial flow increases.

Porta-caval shunts are now rare because of the high incidence of post-shunt encephalopathy. Liver function deteriorates due to reduction of portal perfusion. A subsequent hepatic transplantation can be made more difficult. It is still used, after the bleeding episode has been controlled, in patients with good liver reserves who do not have access to tertiary care or who may have bled from gastric varices. It is useful in some patients with early primary biliary cirrhosis, congenital

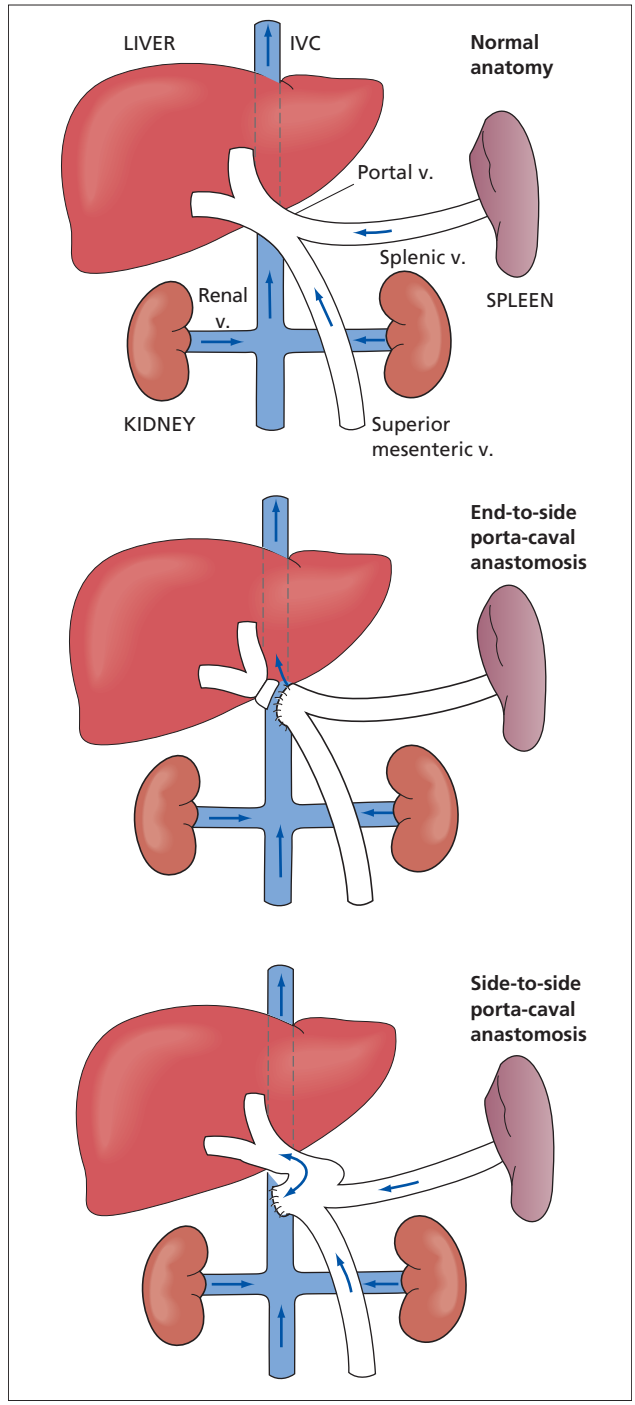


Fig. 10.53. The types of surgical portal-systemic shunt operation performed for the relief of portal hypertension. IVC, inferior vena cava.

hepatic fibrosis with good hepato-cellular function and those with portal vein obstruction at the hilum of the liver.

Patients should have had a haemorrhage from proven oesophageal varices. The portal vein must be good and the patient preferably aged less than 50 years. After the age of 40, survival is reduced and encephalopathy is twice as common.

The patient should not have a history of hepatic encephalopathy, and should be Child's grade A or B.

Meso-caval

This is made between the superior mesenteric vein and the inferior vena cava using a Dacron graft (fig. 10.54) [36]. It is technically easy. Shunt occlusion is usual with time and is followed by re-bleeding [36]. It does not interfere with subsequent hepatic transplantation.

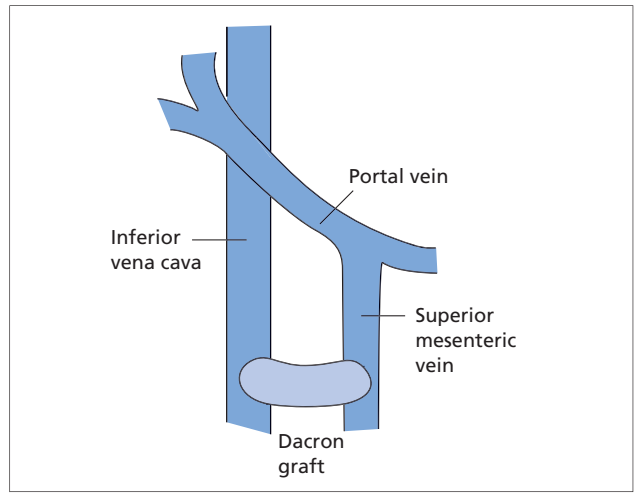


Fig. 10.54. The meso-caval shunt using a Dacron graft.

Selective 'distal' spleno-renal (fig. 10.55)

Veins feeding the dangerous oesophago-gastric collaterals are divided while allowing drainage of portal blood through short gastric-splenic veins through a spleno-renal shunt to the inferior vena cava. It was hoped that portal perfusion would be maintained but this was not so.

The mortality and encephalopathy results are similar to those reported for non-selective shunts. Better results are reported in non-alcoholic patients and where gastric varices are the main problem [91]. The operation does not interfere with a subsequent liver transplant.

Selective spleno-renal shunt is technically difficult and fewer and fewer surgeons are able or willing to perform it.

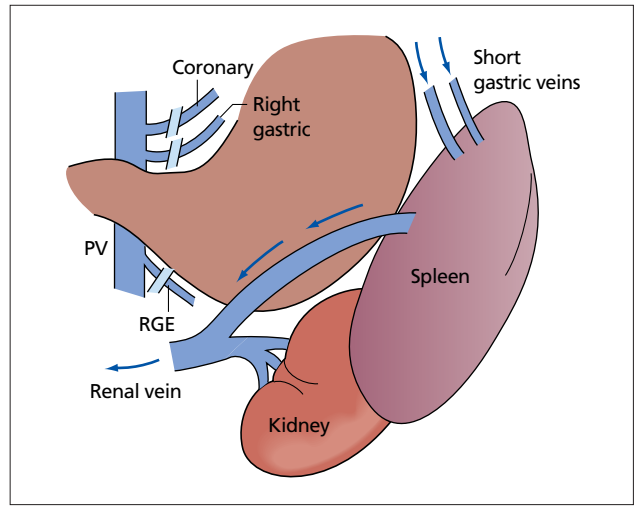


Fig. 10.55. The distal spleno-renal shunt. The veins feeding the varices (coronary, right gastric, right gastro-epiploic—RGE) are ligated. A spleno-renal shunt is made, preserving the spleen; retrograde flow in the short gastric veins is possible. Portal blood flow to the liver is preserved. PV, portal vein.

General results of portal-systemic shunts

The mortality rate in good-risk patients is about 5%. For poor-risk patients the mortality is 50%.

Bleeding from gastro-oesophageal varices is prevented or at least reduced. Size decreases and oesophageal varices disappear within 6 months to 1 year.

Blood pressure and hepatic blood flow fall so that hepatic function deteriorates. Post-operative jaundice is related to this and to haemolysis. Ankle oedema is due to a fall in portal venous pressure while serum albumin level remains low. Increased cardiac output with failure may contribute. Shunt patency is confirmed by US, CT, MRI, Doppler or angiography.

Hepatic encephalopathy may be transient. Chronic changes develop in 20–40% and personality deterioration in about one-third (Chapter 7). The incidence increases with the size of the shunt. Encephalopathy is more common in older patients

Myelopathy with paraplegia and parkinsonian cerebellar syndrome are rare (Chapter 7).

TIPS (transjugular intrahepatic portosystemic shunt)

Early attempts to establish intra-hepatic portal-systemic shunts were unsuccessful because the ballooned tract between the hepatic and portal veins did not remain patent. The use of a Palmaz expandable stent allowed maintenance of shunt patency and so the implantation of a metallic stent between an intra-hepatic branch of the

portal vein and the hepatic vein radicle (figs 10.56, 10.57) [119, 121, 136].

The usual indication is control of bleeding from oesophageal or gastric varices. Full medical treatment including sclerotherapy and vaso-active drugs are given before TIPS is considered. Results are poor if the patient is actively bleeding. The procedure is performed under sedation and with local anaesthesia. Under US control, the portal bifurcation is located. The middle hepatic vein is catheterized by the transjugular route, and a needle introduced through this catheter into a main portal vein branch. A guide-wire is introduced through the needle and the catheter advanced into the portal vein. The needle is removed and portal venous pressure gradient measured. The needle track is balloon-dilated and mesenteric portography performed. A Palmaz metallic balloon expandable stent or a Wallstent self-expanding metal stent is inserted and expanded to 8–12 mm [73]. The diameter is adjusted to achieve a portal pressure gradient of less than 12 mmHg. If portal hypertension persists, a second stent may be placed parallel to the first [58]. US guidance is essential throughout. The time taken is 1–2 h. A subsequent hepatic transplant is not affected by TIPS.

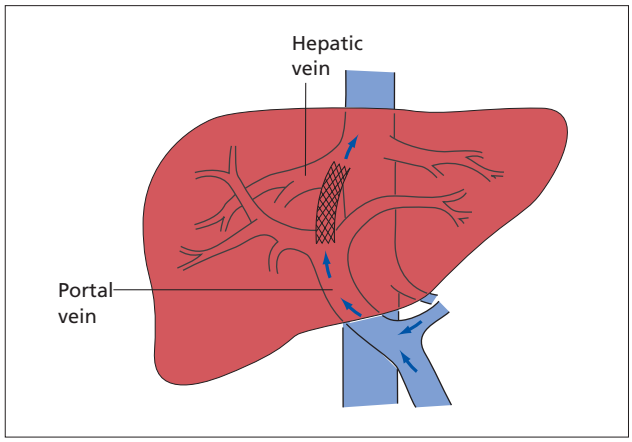


Fig. 10.56. TIPS. An expandable metal stent has been inserted between the portal vein and the hepatic vein producing an intra-hepatic porto-systemic shunt.

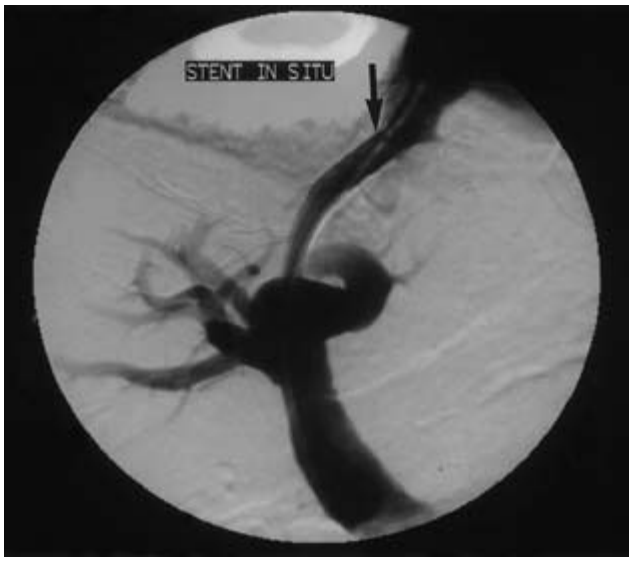


Fig. 10.57. TIPS. A portal venogram showing a porto-hepatic venous shunt; the stent is *in situ* (arrow).

This is a difficult technique and a skilled interventional radiologist must be part of the team. The technical failure rate is about 5–10% (table 10.6). About a third of patients need a second TIPS during the same hospitalization. In 10%, bleeding is uncontrolled by two sessions.

Procedural mortality is less than 1%. Complications include haemorrhage which may be intra-abdominal, biliary or through the liver capsule. The stent may dislocate and have to be retrieved by a looped snare [124].

Infections are prevented by a careful aseptic technique and early removal of central venous lines.

Intravascular haemolysis may be related to damage to erythrocytes by the steel mesh of the stent [128]. Hyperbilirubinaemia developing post-shunt carries a high risk of death or liver transplant [122]. Hypersplenism and, in particular, thrombocytopenia is unaffected [63, 128].

Shunt stenosis and occlusion

The lower pressure gradient between the portal vein and hepatic vein favours occlusion. Early obstruction is due to thrombosis and is related to technical problems [39]. Later stenosis is related to pseudo-intimal hyperplasia and ingrowth of tissue into the shunt lumen [39, 125]. Portal hypertension returns. Cumulative studies show 63% stenosis within the first 6 months and 90% stenosis within 2 years [125]. Prevalence probably depends on the enthusiasm with which shunt patency is investigated.

Follow-up of shunt patency is essential. This may be done by routine portography or Doppler sonography [78]. Duplex sonography may not be sufficiently sensitive to detect patency [103]. Shunt occlusion is treated by

Table 10.6. Reported percentage complications of TIPS

Complication	%
Technical failure	5–10
Portal or splenic vein thrombosis	1–5
Shunt stenosis	33–66
Hepatic encephalopathy	15–30
Worsening liver function	1–5
Chronic haemolysis	1–3

revision of the shunt under local anaesthesia. The shunt may be dilated by percutaneous catheterization or a further stent may be inserted [74]. Stenosed TIPS can be converted to a distal spleno-renal shunt in patients with Child's A and B cirrhosis [133].

Control of bleeding

TIPS reduces portal venous pressure by approximately 50%. It controls bleeding resulting from portal hypertension, whether it be oesophageal, gastric, intestinal, colonic or stomal. It is of particular value as salvage therapy in acute variceal bleeding which cannot be controlled by endoscopy and vaso-active drugs [27, 126]. It is not justified in acute, refractory variceal bleeding in Child's C patients where transplant cannot be offered [111].

The place of TIPS in preventing re-bleeding is less convincing. To be effective, the portal venous gradient must be maintained at less than 12 mmHg, but, because of stenosis, this entails reinvestigation at 1 year and again within the second year [24]. Survival is not increased [88, 89, 126, 127] and health-care costs are not reduced compared with surgical shunts [156]. It is reported as superior [20, 47] or equal [127] to endoscopic sclerotherapy [25], and superior to variceal banding [64].

TIPS encephalopathy

This is a side-to-side portal-systemic shunt and is followed by encephalopathy in about the same percentage (25–30%) as that following surgically performed porta-caval shunts [129]. Encephalopathy is related to the age of the patient, Child's grade and shunt size [118]. It declines after the first 3 months as the stent develops spontaneous closure and perhaps due to cerebral adaptation [96]. It can be treated by placing a smaller stent within the intra-hepatic shunt. Resistant encephalopathy may be an indication for liver transplant.

Circulatory changes

The hyperdynamic circulation of cirrhosis persists [56]. Cardiac output and systemic blood volume increase. Patients with underlying cardiac problems may be projected into heart failure. Pulmonary hypertension may develop [146]. In alcoholic cirrhotic patients, a preclinical cardiomyopathy may be unmasked [62].

Other indications

TIPS effectively controls ascites in Child's grade B patients but survival does not improve (Chapter 9). Hepatic hydrothorax may be treated (Chapter 9).

The hepato-pulmonary syndrome is one indication for TIPS (Chapter 6). Renal function improves in patients with the hepato-renal syndrome (Chapter 9).

Conclusions

TIPS is an effective method of making a side-to-side porta-caval shunt. Skill and experience are necessary. It has all the complications, including encephalopathy, of a standard surgical shunt and, in addition, eventual stenosis is usual. It is used to treat acute oesophageal variceal bleeding refractory to other treatments. It can be used to prevent re-bleeding in Child's A and B patients, ideally in relation to a subsequent liver transplant. Other limited indications include the hepato-renal syndrome, refractory ascites and the Budd–Chiari syndrome.

Hepatic transplantation

Patients with cirrhosis and bleeding varices die because their hepatocytes fail, not from blood loss *per se*. The end-point is death or a liver transplant. Previous sclerotherapy or portal-systemic shunts do not affect post-transplant survival [59]. Liver transplant must be considered for uncontrollable variceal bleeding and end-stage liver disease [41].

Previous surgical shunts make the transplant technically more difficult, particularly if there has been dissection at the hepatic hilum. Spleno-renal and meso-caval shunts and TIPS are not contraindications.

Most of the haemodynamic and humoral changes of cirrhosis are reversed by liver transplant [94].

Pharmacological control of the portal circulation

Portal hypertension is part of a hyperdynamic state with increased cardiac output and reduced peripheral resistance. There are profound changes in autonomic nervous system activity. The various hormonal factors probably involved make pharmacological control possible. Theoretically, portal blood pressure (and flow) could be reduced by lowering cardiac output, by reducing inflow through splanchnic vaso-constriction, by splanchnic venodilatation, by reducing intra-hepatic vascular resistance or, of course, by surgical porta-caval shunting (fig. 10.58). It is preferable to reduce pressure by lowering resistance rather than decreasing flow as hepatic blood flow and function will be maintained.

Conclusions

New treatments of gastro-oesophageal varices are usually variants of the old, such as anatomically different shunts like TIPS, or better methods of variceal oblit-

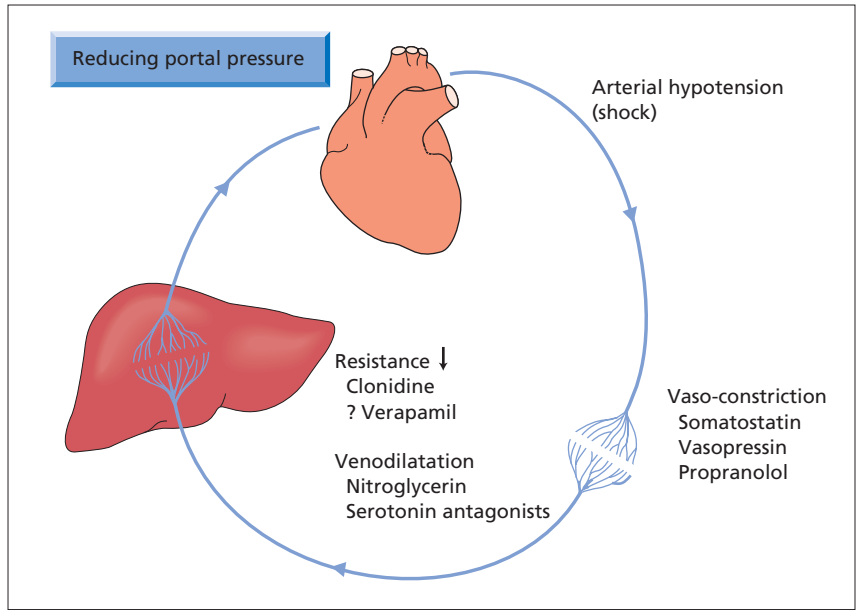


Fig. 10.58. The portal pressure can be reduced by arterial hypotension, splanchnic vaso-constriction, portal venodilatation or reduction in intra-hepatic resistance.

eration. Their proponents are initially enthusiastic, but over the subsequent decade each method takes its place in the background with its forebears. Clinical trials must be interpreted cautiously, and the type of patient being entered, the aetiology of the cirrhosis and of the portal hypertension, together with the degree of hepato-cellular failure (how many Child's grade C?) must be noted. The time of randomization is very important. The risk of further haemorrhage and death rapidly diminishes as the patient survives the first few days after a bleed (fig. 10.59).

Vaso-active drugs, endoscopic sclerotherapy or banding, oesophageal tamponade, TIPS or oesophageal transection will usually stop acute variceal bleeding. Deaths from haemorrhage *per se* should no longer happen. All these procedures have complications and the varices may recur and will probably bleed again.

Long-term control is difficult. All the surgical shunts and TIPS have complications, particularly encephalopathy. They also have their spectacular individual successes, usually in patients with well-compensated cirrhosis where the main problem is the height of the portal pressure or in alcoholics who cease to imbibe.

Long-term propranolol has given varied results. Many patients have a poor response especially those with grade C cirrhosis. Monitoring of portal pressure is essential. Endoscopic sclerotherapy to obliterate varices has many complications, but bleeding episodes are reduced. Both propranolol and sclerotherapy do not prolong survival.

In the group with extra-hepatic portal obstruction, prognosis, even without surgery, is good provided adequate blood transfusion is given.

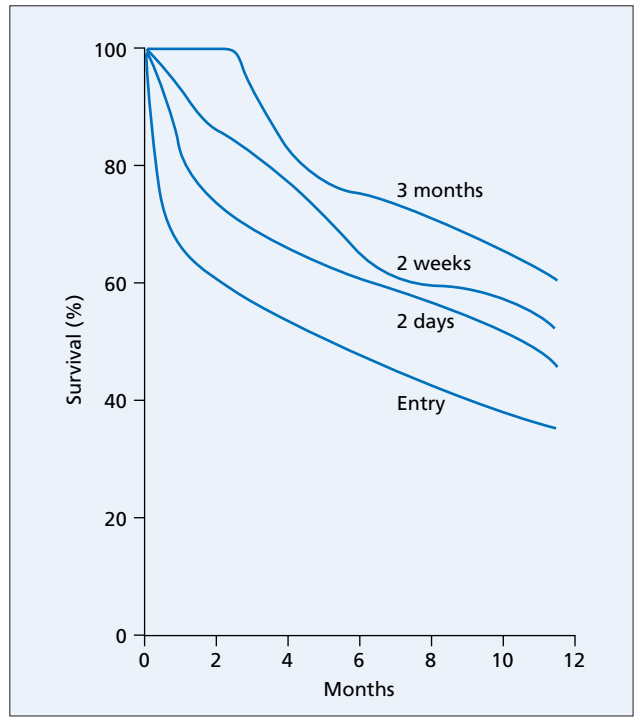


Fig. 10.59. In any trial, survival depends on the time elapsed between the bleed and entry into the trial [137].

Medical measures such as bed rest and a good diet may be followed by a fall in portal pressure, especially in alcoholic subjects who lose fat from the liver. This makes assessment of surgical results even more difficult.

The ultimate treatment is hepatic transplantation [41]. This should be considered in a cirrhotic patient who has

suffered at least two episodes of bleeding varices sufficient to require a blood transfusion.

References

1 Armonis A, Patch D, Burroughs A. Hepatic venous pressure measurement: an old test as a new prognostic marker in cirrhosis. *Hepatology* 1997; **25**: 245.

2 Atkinson M, Sherlock S. Intrasplenic pressure as an index of the portal venous pressure. *Lancet* 1954; **i**: 1325.

3 Avgerinos A, Nevens F, Raptis S *et al*. Early administration of somatostatin and efficacy of sclerotherapy in acute oesophageal variceal bleeds; the European Acute Bleeding Oesophageal Variceal Episodes (ABOVE) randomized trial. *Lancet* 1997; **350**: 1495.

4 Ayuso C, Luburich P, Vilana R *et al*. Calcifications in the portal venous system: comparison of plain films, sonography, and CT. *Am. J. Roentgenol.* 1992; **159**: 321.

5 Barnard B, Lebrec D, Mathurin P *et al*. Propranolol and sclerotherapy in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. *J. Hepatol.* 1997; **26**: 312.

6 Baumgarten P von. Über völlstandiges Offenbleiben der Vena umbilicalis: zugleichein Beitrag zur Frage des Morbus Bantii. *Arb. Path. Anat. Inst. Tübingen* 1907; **6**: 93.

7 Baydur A, Korula J. Cardiorespiratory effects of endoscopic esophageal variceal sclerotherapy. *Am. J. Med.* 1990; **89**: 47.

8 Bayraktar Y, Balkanci F, Kansu E *et al*. Cavernous transformation of the portal vein: a common manifestation of Behçet's disease. *Am. J. Gastroenterol.* 1995; **90**: 1476.

9 Bernades P, Baetz A, Lévy P *et al*. Splenic and portal venous obstruction in chronic pancreatitis. A prospective longitudinal study of a medical-surgical series of 266 patients. *Dig. Dis. Sci.* 1992; **37**: 340.

10 Bernard B, Grange J-D, Khac EN *et al*. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding; a meta-analysis. *Hepatology* 1999; **29**: 1655.

11 Bhathal PS, Grossman HJ. Reduction of the increased portal vascular resistance of the isolated perfused cirrhotic rat liver by vasodilators. *J. Hepatol.* 1985; **1**: 325.

12 Bisseru B, Patel JS. Cruveilhier–Baumgarten disease. *Gut* 1989; **30**: 136.

13 Blendis LM, Orrego H, Crossley IR *et al*. The role of hepatocyte enlargement in hepatic pressure in cirrhotic and non-cirrhotic liver disease. *Hepatology* 1982; **2**: 539.

14 Bornman PC, Krige JEJ, Terblanche J. Management of oesophageal varices. *Lancet* 1994; **343**: 1079.

15 Bosch J, Groszmann RJ. Measurement of azygous venous blood flow by a continuous thermal dilution technique: an index of blood flow through gastroesophageal collaterals in cirrhosis. *Hepatology* 1984; **4**: 424.

16 Bradley SE, Ingelfinger FJ, Bradley GP *et al*. Estimation of hepatic blood flow in man. *J. Clin. Invest.* 1945; **24**: 890.

17 Braun SD, Newman GE, Dunnick NR. Digital splenoportography. *Am. J. Roentgenol.* 1985; **144**: 1003.

18 Burroughs AK, Patch D. Primary prevention of bleeding from esophageal varices. *N. Engl. J. Med.* 1999; **340**: 1033.

19 Burroughs AK, Planas R, Svoboda P. Optimizing emergency care of upper gastrointestinal bleeding in cirrhotic patients. *Scand. J. Gastroenterol.* 1998; 33 (suppl. 226): 14.

20 Cabrera J, Maynar M, Granados R *et al*. Transjugular intrahepatic portosystemic shunt versus sclerotherapy in the elective treatment of variceal hemorrhage. *Gastroenterology* 1996; **110**: 832.

21 Caesar J, Shaldon S, Chiandussi L *et al*. The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. *Clin. Sci.* 1961; **21**: 43.

22 Calès P, Zabotto B, Meskens C *et al*. Gastroesophageal endoscopic features in cirrhosis. Observer variability, interassociations, and relationship to hepatic dysfunction. *Gastroenterology* 1990; **98**: 156.

23 Capron JP, LeMay JL, Muir JF *et al*. Portal vein thrombosis and fatal pulmonary thromboembolism associated with oral contraceptive treatment. *J. Clin. Gastroenterol.* 1981; **3**: 295.

24 Casado M, Bosch J, Garcia-Pagan JC *et al*. Clinical events after transjugular intrahepatic portosystemic shunt: correlation with haemodynamic findings. *Gastroenterology* 1998; **114**: 1256.

25 Cello JP, Ring EJ, Olcott EW *et al*. Endoscopic sclerotherapy compared with percutaneous transjugular intrahepatic portsystemic shunt after initial sclerotherapy in patients with acute variceal haemorrhage. A randomized controlled trial. *Ann. Intern. Med.* 1997; **126**: 858.

26 Chagnon SF, Vallee CA, Barge J *et al*. Aneurysmal portal hepatic venous fistula: report of two cases. *Radiology* 1986; **159**: 693.

27 Chau TN, Patch D, Chan YW *et al*. 'Salvage' transjugular intrahepatic portosystemic shunts: gastric fundal compared with esophageal variceal bleeding. *Gastroenterology* 1998; **114**: 981.

28 Cruveilhier J. Anatomie pathologique du corps humain, vol. I. XVI livr. pl. vi, *Maladies du veines*. J.B. Baillière, Paris, 1829–35.

29 D'Amico G, Montalbano L, Traina M *et al*. Natural history of congestive gastropathy in cirrhosis. *Gastroenterology* 1990; **99**: 1558.

30 D'Amico G, Politi F, Morabito A *et al*. Octreotide compared with placebo in a treatment strategy for early rebleeding in cirrhosis: a double-blind randomized pragmatic trial. *Hepatology* 1998; **28**: 1206.

31 Dan SJ, Train JS, Cohen BA *et al*. Common bile duct varices: cholangiographic demonstration of a hazardous porto-systemic communication. *Am. J. Gastroenterol.* 1983; **78**: 42.

32 Debernardi-Venon W, Bandi J-C *et al*. CO_2 wedged hepatic venography in the evaluation of portal hypertension. *Gut* 2000; **46**: 856.

33 Dennis MA, Pretorius D, Manco-Johnson ML *et al*. CT detection of portal venous gas associated with suppurative cholangitis and cholecystitis. *Am. J. Roentgenol.* 1985; **145**: 1017.

34 Dick R, Dooley JS. Suspected portal hypertension. In Dooley JS, Dick R, Viamonte M *et al*., eds. *Imaging in Hepatobiliary Disease*. Blackwell Scientific Publications, Oxford, 1987; 147.

35 Douglass BE, Baggenstoss AH, Hollinshead WH. Variations in the portal systems of veins. *Proc. Mayo Clin.* 1950; **25**: 26.

36 Dowling JB. Ten years' experience with mesocaval grafts. *Surg. Gynecol. Obstet.* 1979; **149**: 518.

37 Dubois A, Dauzat M, Pignodel C *et al*. Portal hypertension in lymphoproliferative and myeloproliferative disorders:

haemodynamic and histological correlations. *Hepatology* 1993; **17**: 246.
38 Dubuisson C, Boyer-Neumann C, Wolf M *et al*. Protein C, protein S and antithrombin III in children with portal vein obstruction. *J. Hepatol.* 1997; **27**: 132.
39 Ducoin H, El-Khoury J, Rousseau H *et al*. Histopathologic analysis of transjugular intrahepatic portosystemic shunts. *Hepatology* 1997; **25**: 1064.
40 Eck NV. On the question of ligature of the portal vein (trans. title). *Voyenno Med. J. (St Petersburg)* 1877; **130**: Sect. 2.1.
41 Ewaga H, Keeffe EB, Dort J *et al*. Liver transplantation for uncontrollable variceal bleeding. *Am. J. Gastroenterol.* 1994; **89**: 1823.
42 Feu F, Ruiz del Arbol L, Banares R *et al*. Double-blind randomized controlled trial comparing terlipressin and somatostatin for acute variceal haemorrhage. *Gastroenterology* 1996; **111**: 1291.
43 Finn JP, Kane RA, Edelman RR *et al*. Imaging of portal venous system in patients with cirrhosis: MR angiography vs. duplex Doppler sonography. *Am. J. Roentgenol.* 1993; **161**: 989.
44 Gaiani S, Bolondi L, Li Bassi S *et al*. Prevalence of spontaneous hepatofugal portal flow in liver cirrhosis. *Gastroenterology* 1991; **100**: 160.
45 Ganguly S, Sarin SK, Bhatia V *et al*. The prevalence and spectrum of colonic lesions in patients with cirrhotic and noncirrhotic portal hypertension. *Hepatology* 1995; **21**: 1226.
46 Garcia-Tsao G, Grace ND, Groszmann RJ *et al*. Short-term effects of propranolol on portal venous pressure. *Hepatology* 1986; **6**: 101.
47 Garcia-Villarreal L, Martinez-Lagares F, Sierra A *et al*. Transjugular intrahepatic portosystemic shunt versus endoscopic sclerotherapy for the prevention of variceal rebleeding after recent variceal hemorrhage. *Hepatology* 1999; **29**: 27.
48 Gerbes AL, Bilzer M, Gulberg V. Role of endothelins. *Digestion* 1998; **59**: 410.
49 Gertsch P, Fischer G, Kleber G *et al*. Manometry of esophageal varices: comparison of an endoscopic balloon technique with needle puncture. *Gastroenterology* 1993; **105**: 1159.
50 Goulis J, Patch D, Burroughs AK. Bacterial infection in the pathogenesis of variceal bleeding. *Lancet* 1999; **353**: 139.
51 Grossman HJ, Gorssman VL, Bhathal PS. The effect of hepatocyte enlargement on the haemodynamic characteristics of the isolated perfused rat liver preparation. *Hepatology* 1998; **27**: 446.
52 Groszmann RJ. Beta-adrenergic blockers and nitrovasodilators for the treatment of portal hypertension: the good, the bad, the ugly. *Gastroenterology* 1997; **113**: 1794.
53 Groszmann RJ. Hyperdynamic circulation of liver disease 40 years later: pathophysiology and clinical consequences. *Hepatology* 1994; **20**: 1359.
54 Groszmann RJ, Bosch J, Grace ND *et al*. Hemodynamic events in a prospective randomized trial of propranolol vs. placebo in the prevention of a first variceal haemorrhage. *Gastroenterology* 1990; **99**: 1401.
55 Gudjonsson H, Zeiler D, Gamelli RL *et al*. Colonic varices. Report of an unusual case diagnosed by radionuclide scanning, with review of the literature. *Gastroenterology* 1986; **91**: 1543.
56 Guevara M, Gines P, Bandi JC *et al*. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. *Hepatology* 1998; **28**: 416.
57 Hartigan PM, Gebhard RL, Gregory PB. Sclerotherapy for actively bleeding esophageal varices in male alcoholics with cirrhosis. Veterans Affairs Cooperative Variceal Sclerotherapy Group. *Gastrointest. Endosc.* 1997; **46**: 1.
58 Haskal ZJ, Ring EJ, LaBerge JM *et al*. Role of parallel transjugular intrahepatic portosystemic shunts in patients with persistent portal hypertension. *Radiology* 1992; **185**: 813.
59 Ho K-S, Lashner BA, Emond JC *et al*. Prior esophageal variceal bleeding does not adversely affect survival after orthotopic liver transplantation. *Hepatology* 1993; **18**: 66.
60 Hosking SW, Smart HL, Johnson AG *et al*. Anorectal varices, haemorrhoids and portal hypertension. *Lancet* 1989; **i**: 349.
61 Hou MC, Lin HC, Kou BIT *et al*. Sequential variceal pressure measurement by endoscopic needle puncture during maintenance sclerotherapy: the correlation between variceal pressure and variceal rebleeding. *J. Hepatol.* 1998; **29**: 772.
62 Huonker M, Schumacher YO, Ochs A *et al*. Cardiac function and haemodynamics in alcoholic cirrhosis and effects of the transjugular intrahepatic portosystemic stent shunt. *Gut* 1999; **44**: 743.
63 Jabbour N, Zajko A, Orons P *et al*. Does transjugular intrahepatic portosystemic shunt (TIPS) resolve thrombocytopenia associated with cirrhosis? *Dig. Dis. Sci.* 1998; **43**: 2459.
64 Jalan R, Forrest EH, Stanley AJ *et al*. A randomized trial comparing transjugular intrahepatic portosystemic stent-shunt with variceal band ligation in the prevention of rebleeding from esophageal varices. *Hepatology* 1997; **26**: 1115.
65 Kelty RH, Baggenstoss AH, Butt HR. The relation of the regenerated liver nodule to the vascular bed in cirrhosis. *Gastroenterology* 1950; **15**: 285.
66 Kimura K, Ohto M, Matsutani S *et al*. Relative frequencies of portosystemic pathways and renal shunt formation through the 'posterior' gastric vein: portographic study in 460 patients. *Hepatology* 1990; **12**: 725.
67 Kingham JGC, Levinson DA, Stansfeld AG *et al*. Noncirrhotic intrahepatic portal hypertension. A long-term follow-up study. *Q. J. Med.* 1981; **50**: 259.
68 Kitano S, Terblanche J, Kahn D *et al*. Venous anatomy of the lower oesophagus in portal hypertension: practical implications. *Br. J. Surg.* 1986; **73**: 525.
69 Kleber G, Sauerbruch T, Ansari H *et al*. Prediction of variceal hemorrhage in cirrhosis: a prospective follow-up study. *Gastroenterology* 1991; **100**: 1332.
70 Konno K, Ishida H, Uno A *et al*. Cavernous transformation of the portal vein (CTPV): role of colour Doppler sonography in the diagnosis. *Eur. J. Ultrasound* 1996; **3**: 231.
71 Kravetz D, Bosch J, Teres J *et al*. Comparison of intravenous somatostatin and vasopressin infusions in treatment of acute variceal haemorrhage. *Hepatology* 1984; **4**: 442.
72 Kudo M, Tomita S, Tochio H *et al*. Intrahepatic portosystemic venous shunt: diagnosis by colour Doppler imaging. *Am. J. Gastroenterol.* 1993; **88**: 723.
73 La Berge JM, Ring EJ, Gordon RL *et al*. Creation of transjugular intrahepatic portosystemic shunts with the

Wallstent endoprosthesis: results in 100 patients. *Radiology* 1993; **187**: 413.
74 La Berge JM, Somberg KA, Lake JR *et al*. Two-year outcome following transjugular intrahepatic portosystemic shunt for variceal bleeding: results in 90 patients. *Gastroenterology* 1995; **108**: 1143.
75 Laine L, Stein C, Sharma V. Randomized comparison of ligation vs. ligation plus sclerotherapy in patients with bleeding esophageal varices. *Gastroenterology* 1996; **110**: 529.
76 Lebrec D, de Fleury P, Rueff B. Portal hypertension, size of esophageal varices and risk of gastrointestinal bleeding in alcoholic cirrhosis. *Gastroenterology* 1980; **79**: 1139.
77 Lebrec D, Poynard T, Bernuau J *et al*. A randomized controlled study of propranolol for prevention of recurrent gastro-intestinal bleeding in patients with cirrhosis: a final report. *Hepatology* 1984; **4**: 355.
78 Lind CD, Malish TW, Chong WK *et al*. Incidence of shunt occlusion or stenosis following transjugular intrahepatic portosystemic shunt placement. *Gastroenterology* 1994; **106**: 1277.
79 Lo G-H, Lai K-H, Cheng J-S *et al*. Emergency banding ligation vs. sclerotherapy for the control of active bleeding from esophageal varices. *Hepatology* 1997; **25**: 1101.
80 Lo G-H, Lai K-H, Cheng JS *et al*. The additive effect of sclerotherapy to patients receiving repeated endoscopic variceal ligation: a prospective randomized trial. *Hepatology* 1998; **28**: 391.
81 Loftus JP, Nagorney DM, Ilstrup D *et al*. Sinistral portal hypertension. Splenectomy or expectant management. *Ann. Surg*. 1993; **217**: 35.
82 Ludwig J, Hashimoto E, Obata H *et al*. Idiopathic portal hypertension. *Hepatology* 1993; **17**: 1157.
83 McCormick PA, Kaye GL, Greenslade L *et al*. Esophageal staple transection as a salvage procedure after failure of acute injection sclerotherapy. *Hepatology* 1992; **15**: 403.
84 McCormack TT, Rose JD, Smith PM *et al*. Perforating veins and blood flow in oesophageal varices. *Lancet* 1983; **ii**: 1442.
85 McIndoe AH. Vascular lesions of portal cirrhosis. *Arch. Path.* 1928; **5**: 23.
86 Manenti F, Williams R. Injection of the splenic vasculature in portal hypertension. *Gut* 1966; **7**: 175.
87 Mastai R, Bosch J, Bruix J *et al*. β-blockade with propranolol and hepatic artery blood flow in patients with cirrhosis. *Hepatology* 1989; **10**: 269.
88 Merli M, Riggio O, Capocaccia L *et al*. Transjugular intrahepatic portosystemic shunt vs. endoscopic sclerotherapy in preventing variceal rebleeding: preliminary results of a randomized controlled trial. *Hepatology* 1994; **20**: 107A.
89 Merli M, Salerno F, Riggio O *et al*. Transjugular intrahepatic portosystemic shunt vs. endoscopic sclerotherapy for the prevention of variceal bleeding in cirrhosis: a randomized multicentre trial. *Hepatology* 1998; **27**: 40.
90 Mikkelsen WP. Extrahepatic portal hypertension in children. *Am. J. Surg*. 1966; **111**: 333.
91 Millikan WJ, Warren WD, Henderson JM *et al*. The Emory prospective randomized trial: selective vs. non selective shunt to control variceal bleeding. Ten year follow-up. *Ann. Surg*. 1985; **201**: 712.
92 Morse SS, Taylor KJW, Strauss EB *et al*. Congenital absence of the portal vein in oculoauriculo-vertebral dysplasia (Goldenhar syndrome). *Pediatr. Radiol*. 1986; **16**: 437.
93 Nagral AS, Joshi AS, Bhatia SJ *et al*. Congestive jejunopathy in portal hypertension. *Gut* 1993; **34**: 694.
94 Navasa M, Feu F, Garcia-Pagán JC *et al*. Hemodynamic and humoral changes after liver transplantation in patients with cirrhosis. *Hepatology* 1993; **17**: 355.
95 Nevens F, Bustami R, Scheys I *et al*. Variceal pressure is a factor predicting the risk of a first variceal bleeding. A prospective cohort study in cirrhotic patients. *Hepatology* 1998; **27**: 15.
96 Nolte W, Wiltfang J, Schindler C *et al*. Portosystemic hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in patients with cirrhosis: clinical, laboratory, psychometric and electroencephalographic investigations. *Hepatology* 1998; **28**: 1215.
97 North Italian Endoscopic Club for Study and Treatment of Esophageal Varices. Prediction of the first variceal haemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicentre study. *N. Engl. J. Med*. 1988; **319**: 983.
98 Oberti F, Sogni P, Cailmail S *et al*. Role of prostacyclin in haemodynamic alterations in conscious rats with extrahepatic or intrahepatic portal hypertension. *Hepatology* 1993; **18**: 621.
99 Odièvre M, Pigé G, Alagille D. Congenital abnormalities associated with extrahepatic portal hypertension. *Arch. Dis. Child*. 1997; **52**: 383.
100 Oikawa H, Masuda T, Sato S-I *et al*. Changes in lymph vessels and portal veins in the portal tract of patients with idiopathic portal hypertension; a morphometric study. *Hepatology* 1998; **27**: 1607.
101 Okuda K, Ohnishi K, Kimura K *et al*. Incidence of portal vein thrombosis in liver cirrhosis. An angiographic study in 708 patients. *Gastroenterology* 1985; **89**: 279.
102 Orloff MJ, Bell RH Jr, Orloff MS *et al*. Prospective randomized trial of emergency portacaval shunt and emergency medical therapy in unselected cirrhotic patients with bleeding varices. *Hepatology* 1994; **20**: 863.
103 Owens CA, Bartolone C, Warner DL *et al*. The inaccuracy of duplex ultrasonography in predicting patency of transjugular intrahepatic portosystemic shunts. *Gastroenterology* 1998; **114**: 975.
104 Pagliaro L, D'Amico G, Sorensen TIA *et al*. Prevention of first bleeding in cirrhosis. A meta-analysis of randomized trials of nonsurgical treatment. *Ann. Intern. Med*. 1992; **117**: 59.
105 Pak J-M, Lee SS. Glucagon in portal hypertension. *J. Hepatol*. 1994; **20**: 825.
106 Panés J, Piqué JM, Bordas JM *et al*. Reduction of gastric hyperemia by glypressin and vasopressin administration in cirrhotic patients with portal hypertensive gastropathy. *Hepatology* 1994; **19**: 55.
107 Park JH, Cha SH, Han JK *et al*. Intrahepatic portosystemic venous shunt. *Am. J. Roentgenol*. 1990; **155**: 527.
108 Parvey HR, Raval B, Sandler CM. Portal vein thrombosis: imaging findings. *Am. J. Roentgenol*. 1994; **162**: 77.
109 Pasricha PJ, Fleischer DE, Kalloo AN. Endoscopic perforations of the upper digestive tract: a review of their pathogenesis, prevention, and management. *Gastroenterology* 1994; **106**: 787.
110 Patch D, Armonis A, Sabin C *et al*. Single portal pressure measurement predicts survival in cirrhotic patients with recent bleeding. *Gut* 1999; **44**: 264.
111 Patch D, Nikolopoulou V, McCormick A *et al*. Factors

related to early mortality after transjugular intrahepatic portosystemic shunt for failed endoscopic therapy in acute variceal bleeding. *J. Hepatol.* 1998; **28**: 454.
112 Payen J-L, Calès P, Voigt J-J *et al*. Severe portal hypertensive gastropathy and antral vascular ectasia are distinct entities in patients with cirrhosis. *Gastroenterology* 1995; **108**: 138.
113 Pitcher JL. Safety and effectiveness of the modified Sengstaken–Blakemore tube: a prospective study. *Gastroenterology* 1971; **61**: 291.
114 Popper H, Elias H, Petty DE. Vascular pattern of the cirrhotic liver. *Am. J. Clin. Path.* 1952; **22**: 717.
115 Poynard T, Calès P, Pasta L *et al*. Beta-adrenergic antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. An analysis of data and prognostic factors in 589 patients from four randomized clinical trials. Franco Italian Multicentre Study Group. *N. Engl. J. Med.* 1991; **324**: 1532.
116 Redvanly RD, Chezmar JL. CT arterial portography: technique, indications and applications. *Clin. Radiol.* 1997; **52**: 256.
117 Reynolds TB, Ito S, Iwatsuki S. Measurement of portal pressure and its clinical application. *Am. J. Med.* 1970; **49**: 649.
118 Riggio O, Merli M, Pedretti G *et al*. Hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. Incidence and risk factors. *Dig. Dis. Sci.* 1996; **41**: 578.
119 Ring EJ, Lake JR, Roberts JP *et al*. Using transjugular intrahepatic portosystemic shunts to control variceal bleeding before liver transplantation. *Ann. Intern. Med.* 1992; **116**: 304.
120 Rockey D. The cellular pathogenesis of portal hypertension: stellate cell contractility, endothelin and nitric oxide. *Hepatology* 1997; **25**: 2.
121 Rössle M, Haag K, Ochs A *et al*. The transjugular intrahepatic portosystemic stent-shunt procedure for variceal bleeding. *N. Engl. J. Med.* 1994; **330**: 165.
122 Rouillard SS, Bass NM, Roberts JP *et al*. Severe hyperbilirubinemia after creation of transjugular intrahepatic portosystemic shunts: natural history and predictors of outcome. *Ann. Intern. Med.* 1998; **128**: 374.
123 Samuels T, Lovett MC, Campbell IT *et al*. Respiratory function after injection sclerotherapy of oesophageal varices. *Gut* 1994; **35**: 1459.
124 Sanchez RB, Roberts AC, Valji K *et al*. Wallstent misplaced during transjugular placement of an intrahepatic portosystemic shunt: retrieval with a loop snare. *Am. J. Roentgenol.* 1992; **159**: 129.
125 Sanyal AJ, Contos MJ, Yager D *et al*. Development of pseudointima and stenosis after transjugular intrahepatic portosystemic shunts; characterization of cell phenotype and function. *Hepatology* 1998; **28**: 22.
126 Sanyal A, Freedman AM, Luketic VA *et al*. Transjugular intrahepatic portosystemic shunts for patients with active variceal haemorrhage unresponsive to sclerotherapy. *Gastroenterology* 1996; **111**: 138.
127 Sanyal AJ, Freedman AM, Luketic VA *et al*. Transjugular intrahepatic portosystemic shunts compared with endoscopic sclerotherapy for the prevention of recurrent variceal hemorrhage. A randomized controlled trial. *Ann. Intern. Med.* 1997; **126**: 849.
128 Sanyal AJ, Freedman AM, Purdum PP *et al*. The haematologic consequences of transjugular intrahepatic portosystemic shunts. *Hepatology* 1996; **23**: 32.
129 Sanyal AJ, Freedman AM, Shiffman ML *et al*. Portosystemic encephalopathy after transjugular intrahepatic portosystemic shunt: results of a prospective controlled study. *Hepatology* 1994; **20**: 46.
130 Sarin SK. Progress report. Non-cirrhotic portal fibrosis. *Gut* 1989; **30**: 406.
131 Scandalis N, Archimandritis A, Kastanas K *et al*. Colonic findings in cirrhotics with portal hypertension. A prospective colonoscopic and histological study. *J. Clin. Gastroenterol.* 1994; **18**: 325.
132 Schmassmann A, Zuber M, Livers M *et al*. Recurrent bleeding after variceal haemorrhage: predictive value of portal venous duplex sonography. *Am. J. Roentgenol.* 1993; **160**: 41.
133 Selim N, Fendley MJ, Boyer TD *et al*. Conversion of failed transjugular intrahepatic portosystemic shunt to distal splenorenal shunt in patients with Child's A or B cirrhosis. *Ann. Surg.* 1998; **227**: 600.
134 Shaldon S, Chiandussi L, Guevara L *et al*. The measurement of hepatic blood flow and intrahepatic shunted blood flow by colloid heat denatured human serum albumin labelled with I^{131}. *J. Clin. Invest.* 1961; **40**: 1346.
135 Shields SJ, Byse BH, Grace ND. Arterioportal fistula: a role for pre-TIPSS arteriography and hepatic venous pressure measurements. *Am. J. Gastroenterol.* 1992; **87**: 1828.
136 Shiffman ML, Jeffers L, Hoofnagle JH *et al*. The role of transjugular intrahepatic portosystemic shunt for treatment of portal hypertension and its complications: a conference sponsored by the National Digestive Diseases Advisory Board. *Hepatology* 1995; **22**: 1519.
137 Smith JL, Graham D. Variceal haemorrhage—a critical evaluation of survival analysis. *Gastroenterology* 1982; **82**: 968.
138 Sogni P, Moreau R, Gadano A *et al*. The role of nitric oxide in the hyperdynamic circulatory syndrome associated with portal hypertension. *J. Hepatol.* 1995; **23**: 218.
139 Spahr L, Villeneuve J-P, DuFresne MP *et al*. Gastric antral vascular ectasia in cirrhotic patients: absence of relation with portal hypertension. *Gut* 1999; **44**: 739.
140 Spina GP, Arcidiacono R, Bosch J *et al*. Gastric endoscopic features in portal hypertension: final report of a consensus conference, Milan, Italy, 19 September 1992. *J. Hepatol.* 1994; **21**: 461.
141 Taylor CR. Computed tomography in the evaluation of the portal venous system. *J. Clin. Gastroenterol.* 1992; **14**: 167.
142 Teran JC, Imperiale TF, Mullen KD *et al*. Primary prophylaxis of variceal bleeding in cirrhosis: a cost-effectiveness analysis. *Gastroenterology* 1997; **112**: 473.
143 Thompson EN, Sherlock S. The aetiology of portal vein thrombosis with particular reference to the role of infection and exchange transfusion. *Q. J. Med.* 1964; **33**: 465.
144 Thompson EN, Williams R, Sherlock S. Liver function in extra-hepatic portal hypertension. *Lancet* 1964; **ii**: 1352.
145 Valla D, Casadevall N, Huisse MG *et al*. Etiology of portal thrombosis in adults. *Gastroenterology* 1988; **94**: 1063.
146 Van der Linden P, Le Moine O, Ghysels M *et al*. Pulmonary hypertension after transjugular intrahepatic portosystemic shunt: effects on right ventricular function. *Hepatology* 1996; **23**: 982.
147 Van Ruiswyk J, Byrd JC. Efficacy of prophylactic sclerotherapy for prevention of a first variceal haemorrhage. *Gastroenterology* 1992; **102**: 587.
148 Veterans Affairs Cooperative Variceal Sclerotherapy

Group. Sclerotherapy for male alcoholic cirrhotic patients who have bled from esophageal varices: results of a randomized multicentre clinical trial. *Hepatology* 1994; **20**: 618.

149 Vianna A, Hayes PC, Moscoso G *et al*. Normal venous circulation of the gastroesophageal junction. A route to understanding varices. *Gastroenterology* 1987; **93**: 876.

150 Viggiano TR, Gostout CJ. Portal hypertensive intestinal vasculopathy: a review of the clinical, endoscopic, and histopathologic features. *Am. J. Gastroenterol.* 1992; **87**: 944.

151 Wanless IR, Peterson P, Das A *et al*. Hepatic vascular disease and portal hypertension in polycythemia vera and agnogenic myeloid metaplasia: a clinicopathological study of 145 patients examined at autopsy. *Hepatology* 1990; **12**: 1166.

152 Webb LJ, Sherlock S. The aetiology, presentation and natural history of extrahepatic portal venous obstruction *Q. J. Med.* 1979; **48**: 627.

153 Webb L, Smith-Laing G, Lake-Bakaar G *et al*. Pancreatic hypofunction in extrahepatic portal venous obstruction. *Gut* 1980; **21**: 227.

154 Weinshel E, Chen W, Falkenstein DB *et al*. Hemorrhoids or rectal varices: defining the cause of massive rectal hemorrhage in patients with portal hypertension. *Gastroenterology* 1986; **90**: 744.

155 Wheatley AM, Zhang X-Y. Intrahepatic modulation of portal pressure and its role in portal hypertension. *Digestion* 1998; **59**: 424.

156 Zacks SL, Sandler RS, Biddle AK *et al*. Decision analysis of transjugular intrahepatic portosystemic shunt vs. distal splenorenal shunt for portal hypertension. *Hepatology* 1999; **29**: 1399.

157 Zoli M, Iervese T, Merkel C *et al*. Prognostic significance of portal haemodynamics in patients with compensated cirrhosis. *J. Hepatol.* 1993; **17**: 56.

Chapter 11
The Hepatic Artery and Hepatic Veins: the Liver in Circulatory Failure

The hepatic artery

The hepatic artery is a branch of the coeliac axis. It runs along the upper border of the pancreas to the first part of the duodenum where it turns upwards between the layers of the lesser omentum, lying in front of the portal vein and medial to the common bile duct. Reaching the porta hepatis it divides into right and left branches. Its branches include the right gastric artery and the gastroduodenal artery. Aberrant branches are common. Surgical anatomy has been defined in donor livers [6]. The common hepatic artery usually rises from the coeliac axis to form the gastroduodenal and proper hepatic artery which divides into right and left branches. A replaced or accessory right hepatic artery may originate from the superior mesenteric artery. A replaced or accessory left hepatic artery may arise from the left gastric artery. Rarely, the entire common hepatic artery arises as a branch of the superior mesenteric or directly from the aorta. Such anomalies are of great importance in liver transplantation.

Anastomoses occur between the right and left branches, with subcapsular vessels of the liver and with the inferior phrenic artery.

Intra-hepatic anatomy

The hepatic artery enters sinusoids adjacent to the portal tracts [17]. Direct arterio-portal venous anastomoses are not seen in man [17].

The hepatic artery forms a capillary plexus around the bile ducts. Interference with this hepatic arterial supply leads to bile duct injury—surgical and laparoscopic (fig. 11.1) [13]. Diseases of the hepatic artery, such as polyarteritis nodosa, may present as biliary strictures [2].

The connective tissue in the portal zones is supplied by the hepatic artery.

Hepatic arterial flow

In man, during surgery, the hepatic artery supplies 35% of the hepatic blood flow and 50% of the liver's oxygen supply [16]. The hepatic arterial flow serves to hold total hepatic blood flow constant. It regulates blood levels of nutrients and hormones by maintaining blood flow, and thereby hepatic clearance, as steady as possible [10].

The proportion of hepatic arterial flow increases greatly in cirrhosis, related to the extent of portal-systemic venous shunting. It is the main blood supply to tumours. A drop in systemic blood pressure from haemorrhage, or any other cause, lowers the oxygen content of the portal vein and the liver becomes more and more dependent on the hepatic artery for oxygen. The hepatic artery and the portal vein adjust the volume of blood and oxygen they supply to the liver according to demand [10].

Hepatic arteriography

Hepatic arteriography is used for the diagnosis of space-occupying lesions including cysts, abscesses and benign and malignant tumours (Chapter 31), as well as vascular lesions such as aneurysms (fig. 11.2) or arteriovenous fistulae. Embolization via the catheter is used for treating tumours and hepatic trauma, and in the management of hepatic arterial aneurysm or arteriovenous fistulae (figs 11.3, 11.4).

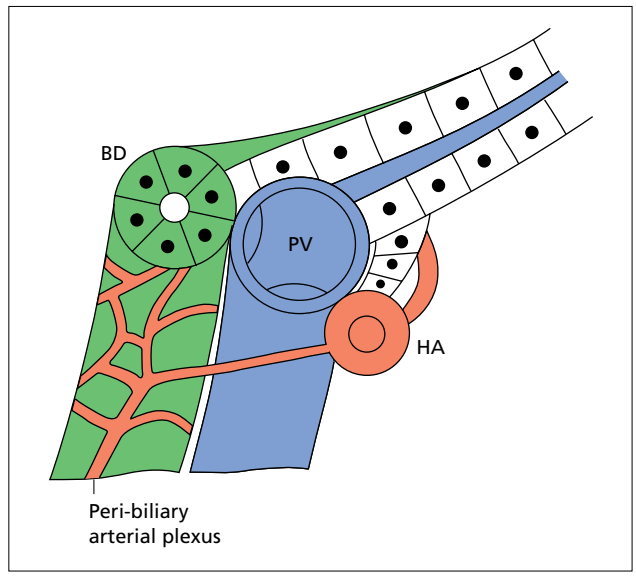


Fig. 11.1. The hepatic artery (HA) forms a peri-biliary plexus supplying the bile duct (BD). PV, portal vein.

Hepatic arterial catheterizaterion is used to introduce cytotoxic drugs into hepato-cellular neoplasms and for pump perfusion in patients with metastases, particularly from colo-rectal cancer (Chapter 31).

Spiral CT is of great value in diagnosing hepatic arterial thrombosis after liver transplant [11] and variations in intra-hepatic anatomy before liver resection [15].

Hepatic artery occlusion

The effects depend on the site and extent of available collateral circulation. If the division is distal to the origins of the gastric and gastroduodenal arteries the patient may die. Survivors develop a collateral circulation. Slow thrombosis is better than sudden block. Simultaneous occlusion of the portal vein is nearly always fatal.

The size of the infarct depends on the extent of the collateral arterial circulation. It rarely exceeds 8 cm in diameter and has a pale centre with a surrounding congested haemorrhagic band. Liver cells in the infarcted area are jumbled together in irregular collections of eosinophilic, granular cytoplasm without glycogen or nuclei. Subcapsular areas escape because they have an alternative arterial blood supply.

Hepatic infarction can develop without arterial occlusion in shock, cardiac failure, diabetic ketosis, toxaemia of pregnancy [9], post-hepatic transplant or systemic lupus erythematosus [7]. If sought by scanning, hepatic infarcts are frequent after percutaneous liver biopsy.

Aetiology

Occlusion of the hepatic artery is very rare. Hitherto it was regarded as a fatal condition. However, hepatic angiography has allowed earlier diagnosis and the prognosis has improved. Some of the causes are polyarteritis nodosa, giant cell arteritis and embolism in patients with acute bacterial endocarditis. A branch of the artery may

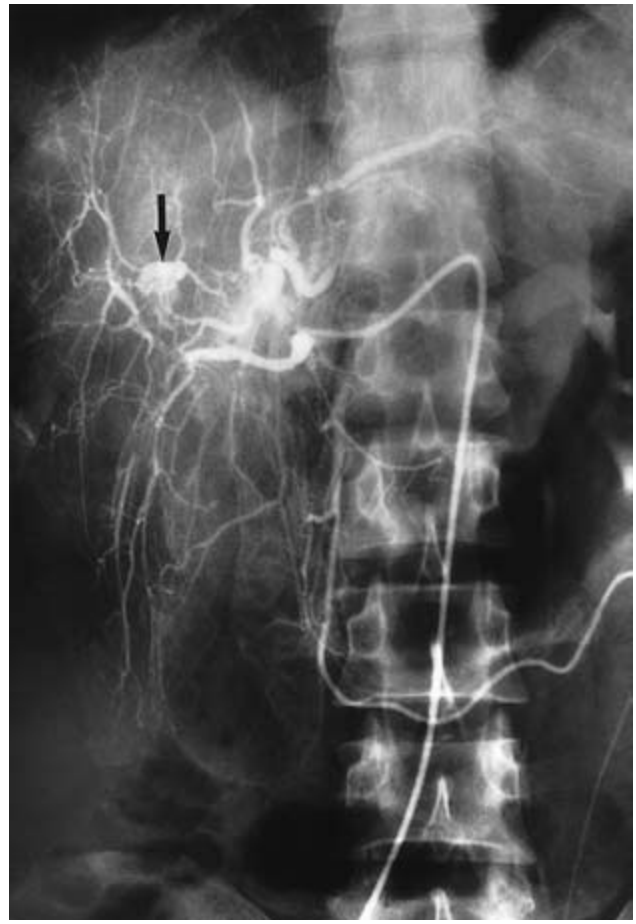
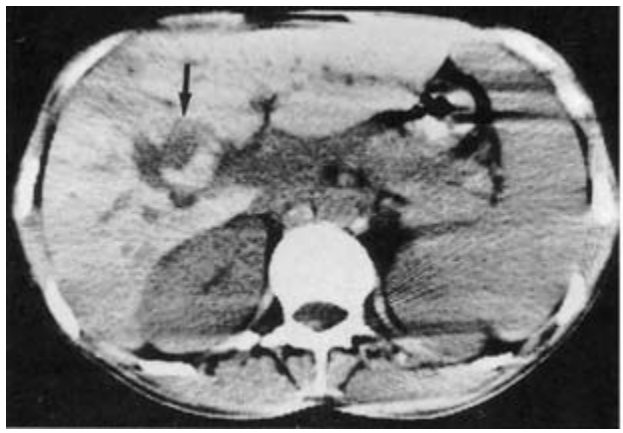
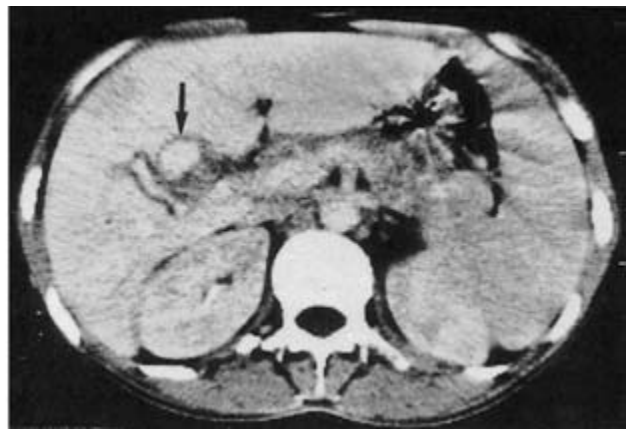


Fig. 11.3. Sub-acute bacterial endocarditis. Coeliac arteriogram showing a 3-cm false aneurysm (arrow) of one of the intra-hepatic branches of the right hepatic artery, 2.5 cm lateral to its major bifurcation.

Fig. 11.2. Hepatic artery aneurysm in a patient with sub-acute bacterial endocarditis. CT scans of the upper abdomen: (a) before and (b) after contrast enhancement. The aneurysm shows as a filling defect (arrow) which highlights following contrast injection.



(a)



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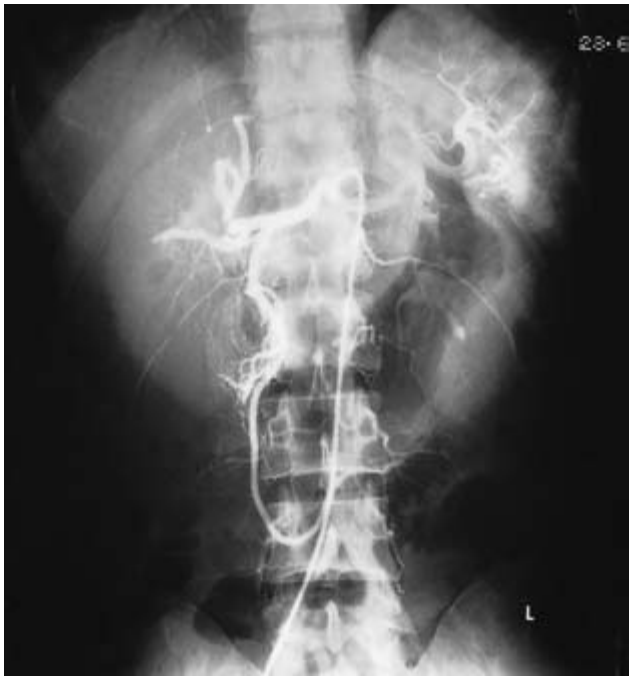


Fig. 11.4. Same patient as in fig. 11.3. Coeliac angiogram immediately post-embolization showing obliteration of the aneurysm and its feeding vessels [8].

be tied during cholecystectomy but recovery is usual. Trauma to the right hepatic or cystic artery may complicate laparoscopic cholecystectomy [1]. Hepatic arterial dissection may follow abdominal trauma or hepatic arterial catheterization. Gangrenous cholecystitis can complicate hepatic artery embolization [14].

Clinical features

The condition is rarely diagnosed ante-mortem. The patient exhibits the features of the cause, such as bacterial endocarditis or polyarteritis nodosa, or has undergone a difficult upper abdominal operation. Sudden pain in the right upper abdomen is followed by collapse and hypotension. Right upper quadrant tenderness develops and the liver edge is tender. Jaundice deepens rapidly. There is usually fever and leucocytosis and liver function tests show hepato-cellular damage. The prothrombin time rises precipitously and haemorrhages develop. With major occlusions the patient passes into coma and is dead within 10 days.

Hepatic arteriography is essential. The obstruction to the hepatic artery may be shown. Intra-hepatic arterial collaterals develop in the portal zones and subcapsular areas. Extra-hepatic collaterals form in the suspensory ligaments and with adjacent structures.

Scanning. The infarcts are round, oval or wedge-shaped and are centrally located. Early lesions are hypoechoic on ultrasound. CT shows infarcts as low attenuation, peripheral wedged-shaped lesions. Occluded arterial vessels may be identified. Later lesions are confluent with distinct margins. MRI shows a lesion of low signal intensity on T_1-weighted images and with high signal intensity on T_2-weighted images [9]. Bile lakes follow large infarcts and these may contain gas.

Treatment. The causative lesion must be treated. Antibotics may prevent secondary infection in the anoxic liver. The general management is that of acute hepatocellular failure. Trauma to the artery is treated by percutaneous arterial embolization.

Hepatic arterial lesions following liver transplantation

The term *ischaemic cholangitis* is used to describe bile duct damage due to ischaemia [12]. It follows post-transplant-associated thrombosis or stenosis of the hepatic artery or occlusion of peri-biliary arteries [5]. Later, thrombosis or stenosis of the hepatic artery or occlusion of peri-biliary arterials leads to segmental hepatic infarction with abscesses and biloma [5]. The picture may be asymptomatic or present as relapsing bacteraemia.

Early diagnosis is made by duplex ultrasound. Spiral CT is highly accurate [11].

Re-transplantation is the only management for lesions of the hepatic artery following transplant.

Ischaemic cholangitis manifesting as segmental strictures and cholangiectases with resultant impared bile flow can also follow hepatic arterial chemotherapy and systemic vasculitis.

Aneurysms of the hepatic artery

These are rare but make up about one-fifth of all visceral aneurysms. The aneurysm may complicate bacterial endocarditis, polyarteritis nodosa or arteriosclerosis. Trauma is becoming increasingly important, including motor vehicle accidents and iatrogenic causes such as biliary tract surgery, liver biopsy and interventional radiological procedures. Pseudo-aneurysms may complicate chronic pancreatitis with pseudo-cyst formation. Bile leaks are significantly associated with pseudo-aneurysm [3]. It may be congenital. The aneurysm may be extra- or intra-hepatic and may vary in size from a pin point to a grapefruit.

Clinical presentation. The classical triad of jaundice [18], abdominal pain and haemobilia is present in only about one-third. Abdominal pain is frequent and may last as long as 5 months before the aneurysm ruptures.

Between 60 and 80% of patients present for the first time with rupture into the peritoneum, biliary tree or

gastrointestinal tract with resultant haemoperitoneum, haemobilia or haematemesis.

The *diagnosis* is suggested by sonography and confirmed by hepatic arteriography and a CT scan after enhancement (fig. 11.2) [8]. Pulsed Doppler ultrasound may show turbulent flow in the aneurysm [4].

Treatment. Intra-hepatic aneurysms are treated by angiographic embolization (figs 11.3, 11.4). Aneurysms of the common hepatic artery are treated surgically by proximal and distal ligation.

Hepatic arteriovenous shunts

These are usually secondary to blunt trauma, liver biopsy or neoplasms, usually primary liver cancer. Multiple shunts may be part of hereditary haemorrhagic telangiectasia, when they can be so extensive that congestive heart failure follows.

Large shunts cause a bruit in the right upper quadrant. The diagnosis is confirmed by hepatic angiography. Embolization with gelfoam is the usual treatment.

References

1 Bacha EA, Stieber AC, Galloway JR *et al*. Non-biliary complication of laparoscopic cholecystectomy. *Lancet* 1994; **344**: 896.
2 Barquist ES, Goldstein N, Zinner MJ. Polyarteritis nodosa presenting as a biliary stricture. *Surgery* 1991; **109**: 16.
3 Croce MA, Fabian TC, Spiers JP *et al*. Traumatic hepatic artery pseudoaneurysm with haemobilia. *Am. J. Surg*. 1994; **168**: 235.
4 Falkoff GE, Taylor KJW, Morse S. Hepatic artery pseudoaneurysm: diagnosis with real-time and pulsed Doppler US. *Radiology* 1986; **158**: 55.
5 Fisher A, Miller CM. Ischemic-type biliary strictures in liver allografts: the Achilles heel revisited? *Hepatology* 1995; **21**: 589.
6 Hiatt JR, Gabbay J, Busuttil RW. Surgical anatomy of the hepatic arteries in 1000 cases. *Ann. Surg*. 1994; **220**: 50.
7 Khoury G, Tobi M, Oren M *et al*. Massive hepatic infarction in systemic lupus erythematosus. *Dig. Dis. Sci*. 1990; **35**: 1557.
8 Kibbler CC, Cohen DL, Cruickshank JK *et al*. Use of CT scanning in the diagnosis and management of hepatic artery aneurysm. *Gut* 1985; **26**: 752.
9 Kronthal AJ, Fishman EK, Kuhlman JE *et al*. Hepatic infarction in pre-eclampsia. *Radiology* 1990; **177**: 726.
10 Lautt WW, Greenaway CV. Conceptual review of the hepatic vascular bed. *Hepatology* 1987; **7**: 952.
11 Legmann P, Costes V, Tudoret L. Hepatic artery thrombosis after liver transplantation: diagnosis with spiral CT. *Am. J. Roentgenol*. 1995; **164**: 97.
12 Ludwig J, Batts KP, MacCarthy RL. Ischemic cholangitis in hepatic allografts. *Mayo Clin. Proc*. 1992; **67**: 519.
13 Sherlock S. The syndrome of disappearing intrahepatic bile ducts. *Lancet* 1987; **ii**: 493.
14 Simons RK, Sinanan MN, Coldwell DM. Gangrenous cholecystitis as a complication of hepatic artery embolization: case report. *Surgery* 1992; **112**: 106.
15 Soyer P, Bluemke DA, Choit MA *et al*. Variations in the intrahepatic portions of the hepatic and portal veins: findings on helical CT scans during arterial portography. *Am. J. Roentgenol*. 1995; **164**: 102.
16 Tygstrup N, Winkler K, Mellengaard K *et al*. Determination of the hepatic arterial blood flow and oxygen supply in man by clamping the hepatic artery during surgery. *J. Clin. Invest*. 1962; **41**: 447.
17 Yamamoto K, Sherman I, Phillips MJ *et al*. Three-dimensional observations of the hepatic arterial terminations in rat, hamster and human liver by scanning electron microscopy of micro vascular casts. *Hepatology* 1985; **5**: 452.
18 Zachary K, Geier S, Pellecchia D *et al*. Jaundice secondary to hepatic artery aneurysm: radiological appearance and clinical features. *Am. J. Gastroenterol*. 1986; **81**: 295.

The hepatic veins

The hepatic veins begin in zone 3. They join the sublobular veins and merge into large hepatic veins which enter the inferior vena cava while it is still partly embedded in the liver. The number, size and pattern of hepatic veins are very variable. Generally, there are three large veins, one draining segments 2, 3 and 4, and the other two draining segments 5, 6, 7 and 8 (fig. 11.5). There are variable numbers of small accessory veins, particularly from the *caudate lobe* [14].

In the normal liver there are no direct anastomoses between the portal vein and hepatic vein, which are linked only by the sinusoids (fig. 11.6). In the cirrhotic liver there are anastomoses between the portal and hepatic veins so that the blood bypasses the regenerating liver cell nodules (see fig. 10.42). There is no evidence, either in the normal or cirrhotic liver, of anastomoses between the hepatic artery and the hepatic vein.

Functions

The pressure in the free hepatic vein is approximately 6 mmHg.

The hepatic venous blood is only about 67% saturated with oxygen.

Dogs have muscular hepatic veins near their caval orifices which form a sluice mechanism. The hepatic veins in man have little muscle.

The hepatic venous blood is usually sterile since the liver is a bacterial filter.

Visualizing the hepatic vein

Hepatic venography is performed by injection of contrast into a wedged hepatic vein radicle. This results in filling of the sinusoidal area draining into the catheter and also in retrograde filling of the portal venous system in that

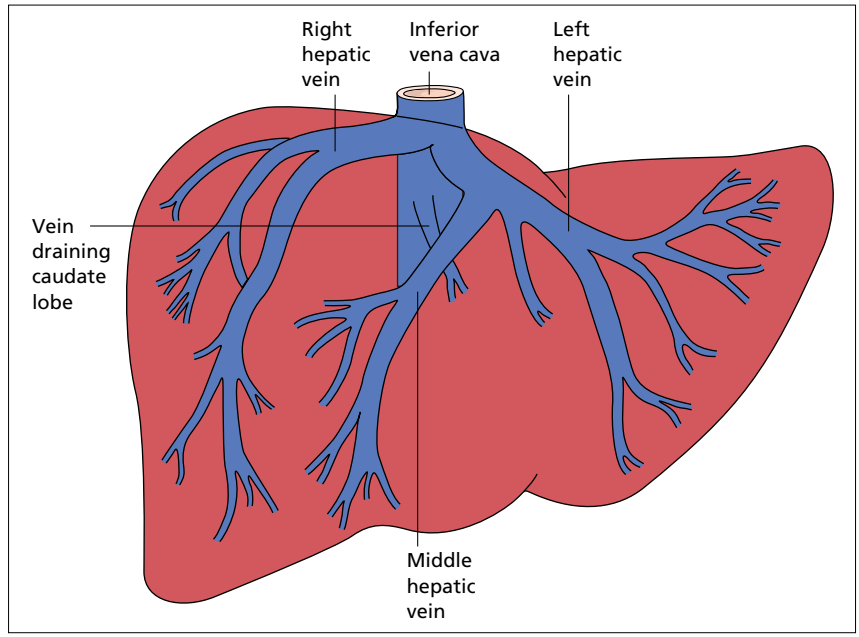


Fig. 11.5. The anatomy of the hepatic venous system. Note the separate vein draining the caudate lobe.

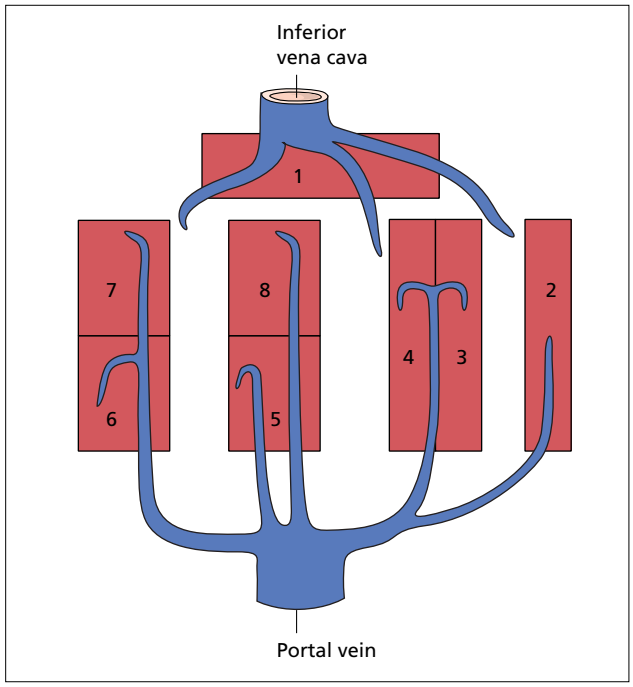


Fig. 11.6. Diagram of the distribution of the four main portal veins to the segments of the liver and the hepatic venous drainage to the inferior vena cava.

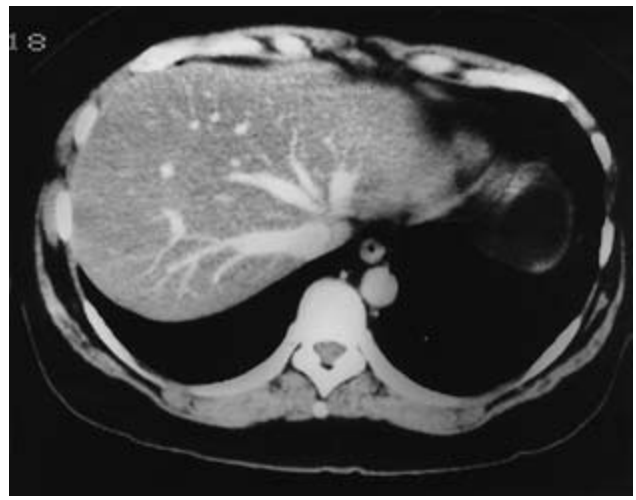


Fig. 11.7. CT scan, without contrast enhancement, in a patient with a fatty liver showing the hepatic venous anatomy well.

area. The portal radicle then carries the contrast medium to other parts of the liver and so other hepatic vein branches become opacified. Cirrhotic nodules and tumour deposits are surrounded by portal vein–hepatic vein anastomoses and may be outlined. In cirrhosis the sinusoidal pattern is coarsened, beady and tortuous, and gnarled hepatic radicles may be seen. The extent of filling of the main portal vein may indicate the extent to which the portal vein has become the outflow tract of the liver.

Scanning. The main hepatic veins may be visualized by ultrasound, colour Doppler imaging, enhanced CT scan and MRI. A CT scan without contrast enhancement in a patient with a fatty liver shows excellent hepatic venous anatomy (fig. 11.7).

Experimental hepatic venous obstruction

The usual method is to constrict the inferior vena cava

by a band placed above the entry of the hepatic veins, and so obstruct the venous return from the liver [5]. Zone 3 haemorrhage and necrosis with fibrosis follow. The hepatic lymphatics dilate and lymph passes through the capsule of the liver forming ascites with a high protein content.

Budd–Chiari (hepatic venous obstruction) syndrome [10, 43, 45]

This condition is usually associated with the names of Budd and Chiari although Budd's description [6] omitted the features, and Chiari's paper [9] was not the first to report the clinical picture. The syndrome comprises hepatomegaly, abdominal pain, ascites and hepatic histology showing zone 3 sinusoidal distension and pooling. It may arise from obstruction to hepatic veins at any site from the efferent vein of the acinus to the entry of the inferior vena cava into the right atrium (fig. 11.8). A similar syndrome may be produced by constrictive pericarditis or right heart failure.

Myeloproliferative diseases, particularly polycythaemia rubra vera are associated in 60% of cases [46]. These may be overt and diagnosed only by the erythroid bone marrow colony test. The patient is often a young female.

The Budd–Chiari syndrome has been associated with systemic lupus erythematosus [45] and with circulating lupus anticoagulant [34], sometimes with disseminated intravascular coagulation. The antiphospholipid syndrome may be primary or secondary to systemic lupus [33]. Idiopathic granulomatous venulitis is another accompaniment which is treated successfully with corticosteroids [49].

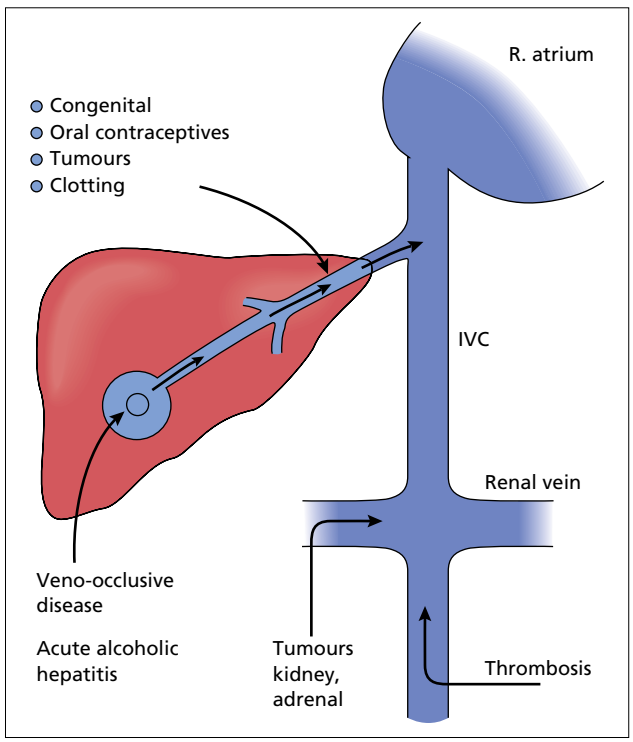


Fig. 11.8. Aetiological factors in the Budd–Chiari syndrome. IVC, inferior vena cava.

Paroxysmal nocturnal haemoglobinuria may be associated, the severity varying from the asymptomatic to a fatal syndrome.

The Budd–Chiari syndrome is associated with deficiency of anticoagulant factors. These include antithrombin III deficiency, whether primary or secondary to proteinuria [11], protein S and protein C deficiency [8]. This may complicate genetically determined resistance to the anticoagulant-activated protein C (factor V Leiden) [12, 40].

Hepatic vein thrombosis complicating Behçet's disease is of sudden event, usually related to extension of a caval thrombosis to the osteum of hepatic veins [2].

The risk in users of oral contraceptives is about the same as other thrombotic complications [47]. Oral contraceptives may act synergistically in those predisposed to clotting.

Hepatic vein thrombosis has been reported in pregnancy (Chapter 27) [21]. Trauma may lead to membranous obstruction to the inferior vena cava in those with a hypercoagulable state [1].

The hepatic veins may be mechanically compressed by severe, polycystic liver disease [44].

Obstruction to the inferior vena cava is secondary to thrombosis in malignant disease, for instance an adrenal or renal carcinoma or invasion by a hepato-cellular cancer [41] or angiosarcoma [36]. Rare tumours include leiomyosarcoma of the hepatic veins [24] and testicular lesions metastatic to the right atrium [15]. Wilms' tumour metastases may involve the inferior vena cava and hepatic veins [37].

Myxoma of the right atrium has caused hepatic venous obstruction. Invasion of hepatic veins by masses of aspergillosis has been reported.

The Budd–Chiari picture also follows central hepatic vein involvement in the alcoholic and in veno-occlusive disease (Chapter 20).

Liver transplantation may be followed by small hepatic vein stenosis with some of the features of veno-occlusive disease. It is usually associated with azathioprine and with cellular rejection [13].

Membranous obstruction of the supra-hepatic segment of the inferior vena cava by a web is usually a sequel to thrombosis. It may be associated with infection or with a hypercoagulable state [3]. The web varies from a thin membrane to a thick fibrous band. It is particularly frequent in Japan and in South Africa and, to a lesser extent, in India [45]. It may affect children.

The clinical picture is milder than for classical

Budd–Chiari syndrome. Markedly enlarged subcutaneous veins over the trunk are conspicuous. The picture has been termed *obliterative hepato-cavopathy* [31].

The Budd–Chiari syndrome is being diagnosed more frequently and in milder forms, probably due to the routine use of imaging, especially ultrasound.

Pathological changes

The hepatic veins show occlusion at points from the ostia to the smaller radicles. Thrombus may have spread from an occluded inferior vena cava. Thrombus may be purulent or may contain malignant cells, depending on the cause. In chronic cases, the vein wall is thickened and there may be some recanalization. In others it is replaced by a fibrous strand; a fibrous web may be seen.

Involvement of large hepatic veins is usually thrombotic. Isolated obstruction to the inferior vena cava or small hepatic veins is usually non-thrombotic [23].

The liver is enlarged, purplish and smooth. Venous congestion is gross and the cut surface shows a 'nutmeg' change. Hepatic veins proximal to the obstruction and, in the acute stage, subcapsular lymphatics, are dilated and prominent.

In the chronic case, the caudate lobe is enlarged and compresses the inferior vena cava as it passes posterior to the liver (fig. 11.9). Areas less affected by obstruction form nodules. The fibrosis and regenerative nodules continue to evolve after the first hepatic vein thrombosis and often progress to involve the portal venous system. The spleen may enlarge and a portal-systemic circulation develops. Mesenteric vessels may thrombose.

Histology shows zone 3 venous dilatation with haemorrhage and necrosis (figs 11.10, 11.11). The parenchymal response depends on the distribution of vascular obstruction [42]. Persisting hepatic venous obstruction results in veno-centric cirrhosis, so-called reverse lobulation. Portal vein involvement leads to veno-portal cirrhosis and mixed forms exist. Large regenerative nodules are usual and are related to a new arterial supply.

Clinical features

These depend on the speed of occlusion and the extent of the hepatic venous involvement. The picture varies all the way from a fulminant course, the patient presenting as encephalopathy and dying within 2–3 weeks, to presentation as chronic hepato-cellular disease, slowly developing and causing confusion with other forms of cirrhosis.

In the most *acute form* the picture is of an ill patient, often suffering from some other condition—for instance renal carcinoma, hepato-cellular cancer, throm-

Fig. 11.9. Vertical section of the liver at autopsy in hepatic venous obstruction. The pale areas represent regeneration and the dark areas are congested. Note the marked hypertrophy of the caudate lobe (C).

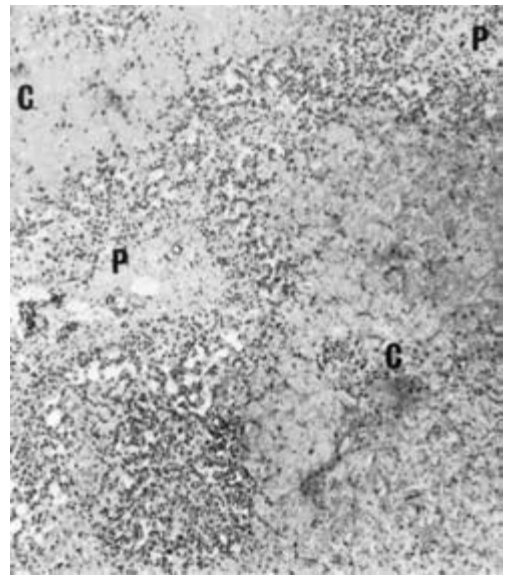


Fig. 11.10. Hepatic venous occlusion (Budd–Chiari syndrome). Hepatic histology showing marked zone 3 haemorrhage (C). The liver cells adjoining the portal zones (P) are spared. (H & E, ×100.)

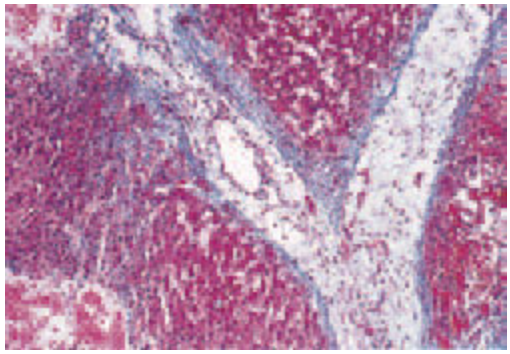


Fig. 11.11. Budd–Chiari syndrome. Longitudinal section of hepatic venules showing fibrosis in the lumen, thickening of the wall and surrounding loss of hepatocytes. (Chromophobe aniline blue.)

bophlebitis migrans or polycythaemia. The presentation is with abdominal pain, vomiting, liver enlargement, ascites and mild icterus. Watery diarrhoea, following mesenteric venous obstruction, is a terminal, inconstant feature. If the hepatic venous occlusion is total, delirium and coma with hepato-cellular failure and death occurs within a few days.

In the more usual *chronic form* the patient presents with pain over an enlarged tender liver and ascites developing over 1–6 months. Jaundice is mild or absent, unless zone 3 necrosis is marked. Pressure over the liver may fail to fill the jugular vein (negative *hepato-jugular reflux*). As portal hypertension increases, the spleen becomes palpable. The enlarged caudate lobe, palpable in the epigastrium, may simulate a tumour.

Asymptomatic patients may have no ascites, hepatomegaly or abdominal pain [18]. Hepatic outflow is diagnosed fortuitously, either by imaging or by the investigation of abnormal liver function tests. It may be explained by remaining patency of one large hepatic vein or development of a large venous collateral.

If the inferior vena cava is blocked, oedema of the legs is gross and veins distend over the abdomen, flanks and back. Albuminuria is found.

The condition may develop over months as ascites and wasting.

Biochemical. Serum bilirubin rarely exceeds 2 mg/100 ml (34 µmol/l). The serum alkaline phosphatase level is raised and the albumin value reduced. Serum transaminase values increase and, if very high, concomitant blockage of the portal vein is suggested. The prothrombin time is markedly increased especially in the acute type. Hypoproteinaemia may be due to protein-losing enteropathy.

The protein content of the ascites should, theoretically, be high, but this is not always so.

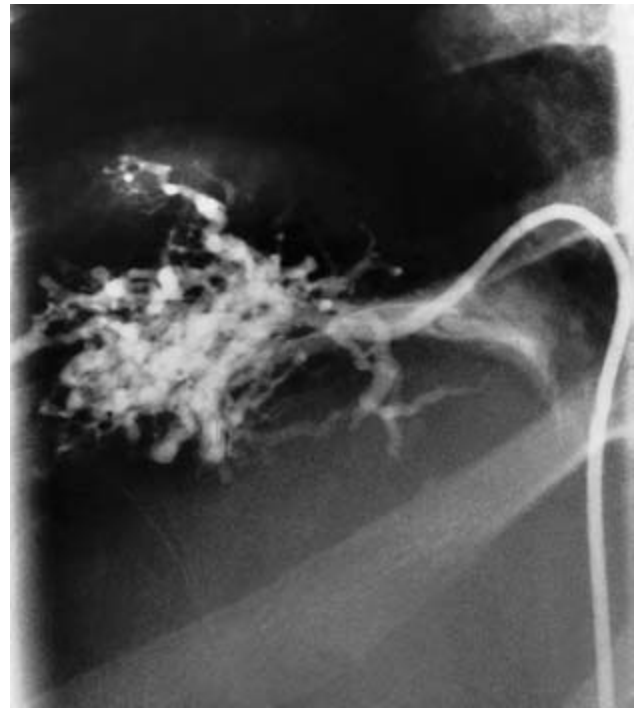


Fig. 11.12. Hepatic venogram in a patient with Budd–Chiari syndrome. Note the lace-like spider-web pattern [10].

Needle liver biopsy. Speckled zone 3 areas can be distinguished from the pale portal areas. Histologically, the picture is of zone 3 congestion (figs 11.10, 11.11). Alcoholic hepatitis or phlebitis of the hepatic veins should be noted.

Hepatic venography may fail or show narrow occluded hepatic veins. Adjacent veins show a tortuous, lace-like spider-web pattern (fig. 11.12) [10]. This probably represents abnormal venous collaterals. The catheter cannot be advanced the usual distance along the hepatic vein and wedges 2–12 cm from the diaphragm.

Inferior vena cavography establishes the patency of the inferior vena cava. The hepatic segment may show side-to-side narrowing due to distortion from the enlarged caudate lobe (fig. 11.13). Pressure measurements should be taken in the inferior vena cava along its length to confirm its patency and to quantify the extent of any membranous or caudate lobe obstruction.

Selective coeliac arteriography. The hepatic artery appears small. Branches appear stretched and displaced, producing the appearance of multiple space-occupying lesions simulating metastases. The venous phase shows delayed emptying of the portal venous bed.

Ultrasound shows hepatic vein abnormalities, caudate lobe hypertrophy, increased reflectivity and compression of the inferior vena cava. The appearances are hypoechogenic in the early stages of acute thrombosis and hyperechogenic with fibrosis in the later stages. Ascites is confirmed.

Doppler ultrasound shows abnormalities in the direction of flow in the hepatic vein and retro-hepatic inferior vena cava. The blood flow in the inferior vena cava and hepatic veins may be absent, reversed, turbulent or continuous. Colour Doppler imaging shows abnormalities in the hepatic veins, portal vein and inferior vena cava and correlates well with venographic appearances [26].

Detection of intra-hepatic collateral vessels is important in the distinction from cirrhosis or where hepatic veins are inconspicuous on ultrasound [26].

CT scan (fig. 11.14) shows enlargement of the liver with diffuse hypodensity before and patchy enhancement after contrast. Heterogeneous hepatic parenchymal patterns are related to regional differences in portal flow. Areas with complete hepatic vein obstruction remain hypodense after contrast probably due to portal flow inversion. Subcapsular areas may enhance.

In the unenhanced scan, the caudate lobe appears dense with surrounding underperfused parenchyma (fig. 11.14).

Thrombi in the inferior vena cava and/or hepatic vein may be seen as intraluminal filling defects that are not changed by contrast [29].

The CT appearances are easily confused with those of hepatic metastases.

MRI shows absence of normal hepatic venous drainage into the inferior vena cava, collateral hepatic veins and signal intensity alterations in the hepatic parenchyma (fig. 11.15). The caudate lobe can be seen deforming the inferior vena cava.

Early diagnosis depends on Doppler ultrasound and MRI [20, 27].

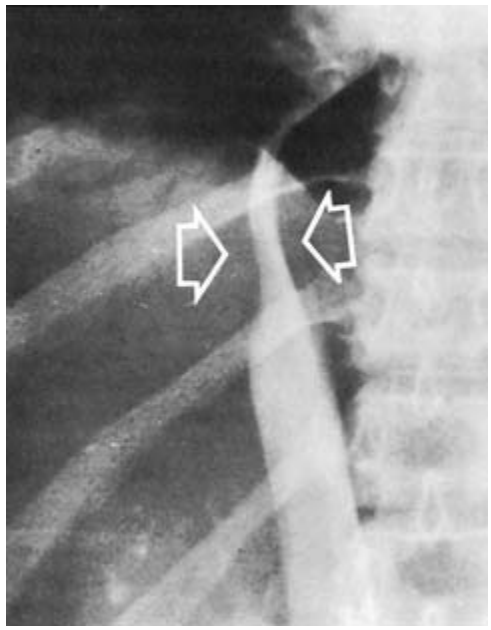


Fig. 11.13. Inferior vena cavogram. Antero-posterior view showing side-to-side narrowing and distortion of the inferior vena cava (arrows). Extrinsic compression from the left is due to an enlarged caudate lobe [43].

Diagnosis

The condition should be suspected if a patient with a tendency to thrombosis, or with malignant disease in or near the liver, or on oral contraceptives, develops tender

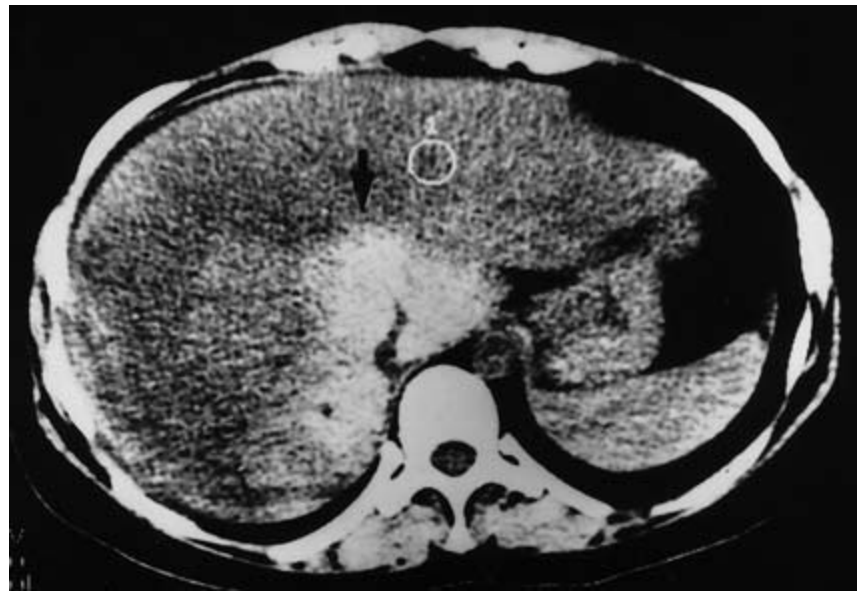


Fig. 11.14. CT scan (unenhanced) showing the caudate lobe (arrow) with surrounding underperfused parenchyma.

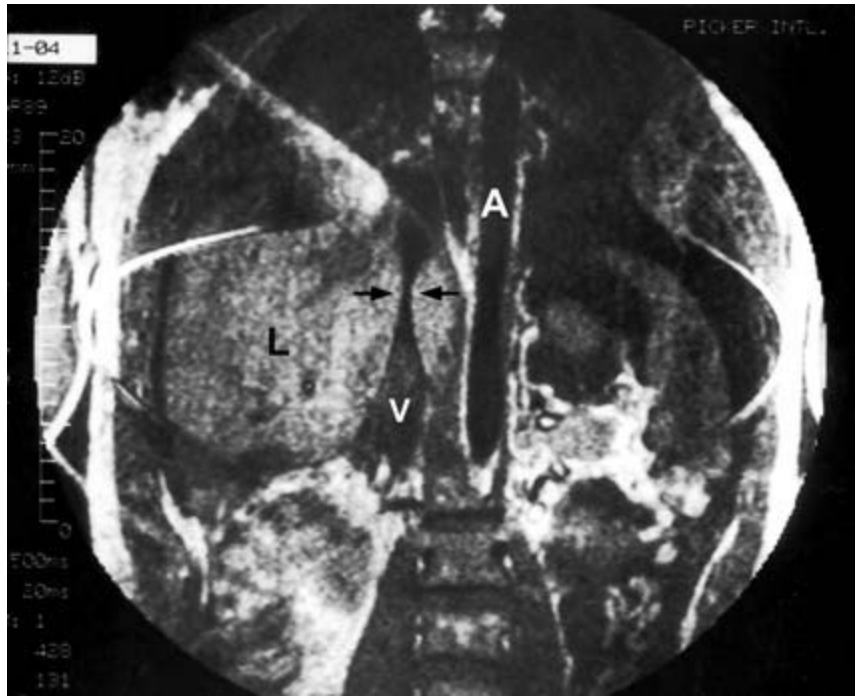


Fig. 11.15. Magnetic resonance scan in a patient with the Budd–Chiari syndrome showing a liver (L) which is dyshomogeneous, the aorta (A) and the inferior vena cava (V). The side-to-side narrowing of the inferior vena cava (arrows) is due to the enlarged caudate lobe.

Table 11.1. Hepatic vein occlusion (Budd–Chiari syndrome)

Presentation
Abdominal pain
Hepatomegaly
Ascites
Liver biopsy
Zone 3 congestion
Imaging
MRI (contrast enhanced)
Doppler ultrasound
Aetiology
Myeloproliferative diseases
Anticoagulant deficiency
Paroxysmal nocturnal haemoglobinuria
Malignant disease
Management
Cause
anticoagulants, venesection
cytotoxic drugs
Ascites (Chapter 9)
Surgical
porta-caval shunt
TIPS
orthotopic transplant

hepatomegaly with ascites (table 11.1). Diagnosis, prognosis and correct treatment are only possible if the block is localized by imaging.

Heart failure and constrictive pericarditis must be excluded. Tense ascites *per se* can elevate the jugular venous pressure and displace the cardiac apex.

Cirrhosis must be distinguished and liver biopsy is helpful. The ascitic protein is usually lower in cirrhosis.

Portal vein thrombosis rarely leads to ascites. Jaundice is absent and the liver is not very large.

Inferior vena caval thrombosis results in distended abdominal wall veins but without ascites. If the renal vein is occluded, albuminuria is gross. Hepatic venous and inferior vena caval thrombosis may, however, coexist.

Hepatic metastases are distinguished clinically and by the liver biopsy.

Prognosis

In the acute form, death in hepatic coma is usual. Thrombosis may spread to the portal and mesenteric veins with infarction of the bowel. In the more chronic and localized instances response to symptomatic therapy may allow prolongation of life for a few years [10].

Prognosis depends on the aetiology, on the extent of the occlusion and whether it can be corrected. Clotting diseases such as polycythaemia are usually found with multiple thrombi of vessels of varying sizes. The inferior vena cava and portal vein may also be involved.

Haemorrhage from oesophageal varices is usually terminal.

Chronic cases may survive many months or even years and up to 22 years has been recorded.

Medical treatment is usually effective only for short periods.

Treatment

Early treatment of an underlying haematological disorder improves long-term survival [17, 28]. This can include anticoagulants in those with hypercoagulation or reduction of haemoglobin and platelets by venesection and cytotoxic drugs in those with polycythaemia and thrombocytosis. Progressive loss of hepatic veins can be halted as large intra-hepatic and portal-systemic collaterals develop [18]. Long-term anticoagulation is given for patients with the antiphospholipid syndrome [33].

Ascites is treated with a low sodium diet, diuretics and paracentesis. Severe cases demand ever increasing doses of potent diuretics and eventually the patient is overtaken by inanition and renal failure. Some milder cases, however, respond slowly and require less treatment with time.

The timing of *surgery* is difficult. On the one hand, some revascularization may continue. On the other hand, the long-term results of medical therapy are so poor that as time passes, surgical treatment becomes mandatory.

Portal-systemic shunts

The aim is to decompress the congested liver and reverse portal venous flow so allowing the portal vein to serve as an outflow channel [19]. Shunt is indicated only if hepatic synthetic function is preserved [38]. Results on the whole are unsatisfactory due to thrombosis of the shunt, especially in those with haematological disorders or where stents have been used. If the shunt remains patent, 5-year survival is 87%, falling to 38% if the shunt thromboses [32]. Life-long anticoagulation is essential.

Liver function usually deteriorates slowly and the patient becomes a candidate for transplant [38]. Morbidity for transplantation is greater with a previous shunt.

The enlarged caudate lobe increases pressure in the infra-hepatic inferior vena cava so that it may exceed the portal venous pressure. If it exceeds 20 mmHg shunting is precluded [22]. The anatomical bulk of the caudate lobe makes a technical approach to the portal vein difficult.

If the portal vein is also occluded, shunts will not function. Transplantation becomes possible only if the mesenteric vein is patent.

Clinically, shunts such as side-to-side porta-caval or meso-caval are technically difficult. Grafts are often needed, increasing the likelihood of thrombosis [35]. A meso-caval interposition shunt has given good results and does not affect the subsequent hepatic transplantation. Meso-atrial shunt is used rarely when the inferior vena cava is obstructed [22].

TIPS

This is technically feasible if the hepatic vein can be entered [30]. It is useful where the patient is a candidate for transplant or if the pressure difference between the hepatic vein and inferior vena cava gradient is less than 10 mmHg [16]. Long-term patency is poor [4]. TIPS may be useful in fulminant liver failure due to the Budd–Chiari syndrome where it is a bridge to transplant [39].

Percutaneous transluminal angioplasty

This has been used to dilate webs (fig. 11.16) and also for hepatic vein obstruction after liver transplant [50]. It is particularly useful if the supra-hepatic portion of the inferior vena cava is involved. As in webs, multiple dilatations are usually necessary [25]. Intravascular metallic stents may be introduced after the dilatation [48]. Stents are usually reserved for those in whom angioplasty has failed.

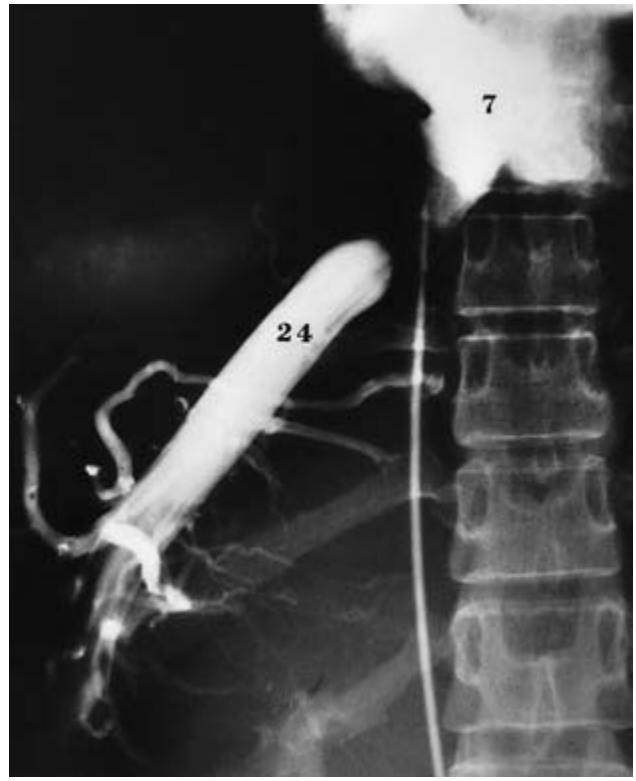


Fig. 11.16. Hepatic venogram in a patient with the Budd–Chiari syndrome due to obstruction of the right main hepatic vein. The right hepatic venous pressure is 24 mmHg distal to the obstruction and 7 mmHg proximal to it. (Courtesy of D.S. Zimmon.)

Orthotopic liver transplantation

This is indicated when the patient deteriorates despite aggressive medical therapy. The patient has usually progressed to cirrhosis with hepato-cellular failure [35]. The transplant may have been preceded by a TIPS so allowing more time to procure the donor liver. Surgical shunt may have failed. The 1-year survival is 85% [38] and the 10-year survival is 69% [35]. Post-transplant thrombosis remains a problem and early anticoagulation is essential [7]. In the case of an underlying thrombotic condition, this must be life long. Hepatic transplant cures protein C, S and antithrombin III deficiency.

Veno-occlusive disease

See Chapter 20.

Spread of disease by the hepatic veins

The hepatic veins link the portal and systemic venous systems. Malignant disease of the liver is spread by the hepatic veins to the lungs and hence to other parts. Liver abscesses can burst into the hepatic vein and metastatic abscesses may result. Parasitic disease, including amoebiasis, hydatid disease and schistosomiasis, is spread by this route. The porto-hepatic venous anastomoses developing in cirrhosis may allow intestinal organisms to cause septicaemia.

References

1 Balian A, Valla D, Naveau S *et al*. Post-traumatic membranous obstruction of the inferior vena cava associated with a hypercoagulable state. *J. Hepatol*. 1998; **28**: 723.
2 Bayraktar Y, Balkanci F, Bayraktar M *et al*. Budd–Chiari syndrome: a common complication of Behçet's disease. *Am. J. Gastroenterol*. 1997; **92**: 858.
3 Blanshard C, Dodge G, Pasi J *et al*. Membranous obstruction of the inferior vena cava in a patient with factor V Leiden: evidence for post-thrombotic aetiology. *J. Hepatol.* 1997; **26**: 731.
4 Blum U, Rossle M, Haag K *et al*. Budd–Chiari syndrome: technical, haemodynamic and clinical results of treatment with transjugular intrahepatic portosystemic shunt. *Radiology* 1995; **197**: 805.
5 Bolton C, Barnard WG. The pathological occurrences in the liver in experimental venous stagnation. *J. Path. Bact*. 1931; **34**: 701.
6 Budd G. *On Diseases of the Liver*, 3rd edn. Blanchard & Lea, Philadelphia, 1857.
7 Campbell DA Jr, Rolles K, Jamieson N *et al*. Hepatic transplantation with perioperative and long-term anticoagulation as treatment for Budd–Chiari syndrome. *Surg. Gynecol. Obstet*. 1988; **166**: 511.
8 Casella JF, Bontempo FA, Markel H *et al*. Successful treatment of homozygous protein C deficiency by hepatic transplantation. *Lancet* 1988; **i**: 435.
9 Chiari H. Ueber die selbständige Phlebitis obliterans der Hauptstämme der Venae hepaticae als Todesurache. *Beitr. Path. Anat*. 1899; **26**: 1.
10 Clain D, Freston J, Kreel L *et al*. Clinical diagnosis of the Budd–Chiari syndrome. *Am. J. Med*. 1967; **43**: 544.
11 Das M, Carroll SF. Antithrombin III deficiency: an aetiology of Budd–Chiari syndrome. *Surgery* 1985; **97**: 242.
12 Denninger MH, Beldjord K, Durand F *et al*. Budd–Chiari syndrome and factor V Leiden mutation. *Lancet* 1995; **345**: 525 (letter).
13 Dhillon AP, Burroughs AK, Hudson M *et al*. Hepatic venular stenosis after orthotopic liver transplantation. *Hepatology* 1994; **19**: 106.
14 Dodds WJ, Erickson SJ, Taylor AJ *et al*. Caudate lobe of the liver: anatomy, embryology, and pathology. *Am. J. Roentgenol*. 1990; **154**: 87.
15 Feingold ML, Litwak RL, Geller SS *et al*. Budd–Chiari syndrome caused by a right atrial tumour. *Arch. Intern. Med*. 1971; **127**: 292.
16 Ganger GB, Klapman JB, McDonald V *et al*. Transjugular intrahepatic portosystemic shunt (TIPS) for Budd–Chiari syndrome or portal vein thrombosis. Review of indications and problems. *Am. J. Gastroenterol*. 1999; **94**: 603.
17 Ganguli SC, Ramzan NN, McKusick MA *et al*. Budd–Chiari syndrome in patients with haematological disease: a therapeutic challenge. *Hepatology* 1998; **27**: 1157.
18 Hadengue A, Poliquin M, Vilgrain V *et al*. The changing scene of hepatic vein thrombosis: recognition of asymptomatic cases. *Gastroenterology* 1994; **106**: 1042.
19 Hemming AW, Langer B, Greig P *et al*. Treatment of Budd–Chiari syndrome with portosystemic shunt or liver transplantation. *Am. J. Surg*. 1996; **171**: 176.
20 Kane RJ, Eustace S. Diagnosis of Budd–Chiari syndrome: comparison between sonography and magnetic resonance angiography. *Radiology* 1995; **195**: 117.
21 Khuroo MS, Datta DV. Budd–Chiari syndrome following pregnancy. Report of 16 cases with roentgenologic, haemodynamic and histological studies of the hepatic outflow tract. *Am. J. Med*. 1980; **68**: 113.
22 Klein AS, Sitzmann JV, Coleman J *et al*. Current management of the Budd–Chiari syndrome. *Ann. Surg*. 1990; **212**: 144.
23 Ludwig J, Hashimoto E, McGill DB *et al*. Classification of hepatic venous outflow obstruction: ambiguous terminology of the Budd–Chiari syndrome. *Mayo Clin. Proc*. 1990; **65**: 51.
24 McMahon HE, Ball HG III. Leiomyosarcoma of hepatic vein and the Budd–Chiari syndrome. *Gastroenterology* 1971; **61**: 239.
25 Martin LG, Henderson JM, Millikan WJ Jr *et al*. Angioplasty for long-term treatment of patients with Budd–Chiari syndrome. *Am. J. Roentgenol*. 1990; **154**: 1007.
26 Millener P, Grant EG, Rose S *et al*. Color Doppler imaging findings in patients with Budd–Chiari syndrome: correlation with venographic findings. *Am. J. Roentgenol*. 1993; **161**: 307.
27 Miller WJ, Federle MP, Straub EH *et al*. Budd–Chiari syndrome: imaging with pathologic correlation. *Abdom. Imaging* 1993; **18**: 329.
28 Min AD, Atillasoy EO, Schwartz ME *et al*. Reassessing the role of medical therapy in the management of hepatic vein thrombosis. *Liver Transplant Surg*. 1997; **3**: 423.
29 Mori H, Maeda H, Fukuda T *et al*. Acute thrombosis of the inferior vena cava and hepatic veins in patients

with Budd–Chiari syndrome: CT demonstration. *Am. J. Roentgenol*. 1989; **153**: 987.
30 Ochs A, Sellinger M, Haag K *et al*. Transjugular intrahepatic portosystemic stent-shunt in the treatment of Budd–Chiari syndrome. *J. Hepatol*. 1993; **18**: 217.
31 Okuda K, Kate M, Shrestha SM. Proposal of a new nomenclature for Budd–Chiari syndrome: hepatic vein thrombosis vs. thrombosis of the inferior vena cava at its hepatic portion. *Hepatology* 1998; **28**: 1191.
32 Panis Y, Belghiti J, Valla D *et al*. Portosystemic shunt in Budd–Chiari syndrome: long-term survival and factors affecting shunt patency in 25 patients in Western countries. *Surgery* 1994; **115**: 276.
33 Pelletier S, Landi B, Piette J-C *et al*. Antiphospholipid syndrome as the second cause of non-tumorous Budd–Chiari syndrome. *J. Hepatol*. 1994; **21**: 76.
34 Pomeroy C, Knodell RG, Swaim WR *et al*. Budd–Chiari syndrome in a patient with the lupus anticoagulant. *Gastroenterology* 1984; **86**: 158.
35 Ringe B, Lang H, Oldhafer K-J *et al*. Which is the best surgery for Budd–Chiari syndrome: venous decompression or liver transplantation? A single-centre experience with 50 patients. *Hepatology* 1995; **21**: 1337.
36 Schluger LK, Cubukcu O, Klion F *et al*. Unexplained Budd–Chiari syndrome in a young man. *Hepatology* 1995; **21**: 584.
37 Schraut WH, Chilcote RR. Metastatic Wilms' tumour causing acute hepatic-vein occlusion (Budd–Chiari syndrome). *Gastroenterology* 1985; **88**: 576.
38 Shaked A, Goldstein RM, Klintmalm GB *et al*. Portosystemic shunt vs. orthotopic liver transplantation for the Budd–Chiari syndrome. *Surg. Gynecol. Obstet*. 1992; **174**: 453.
39 Shrestha R, Durham HD, Wachs M *et al*. Use of transjugular intrahepatic portosystemic shunt as a bridge to transplantation in fulminant hepatic failure due to Budd–Chiari syndrome. *Am. J. Gastroenterol*. 1997; **92**: 2304.
40 Svensson PJ, Dahlback B. Resistance to activated protein C as a basis for venous thrombosis. *N. Engl. J. Med*. 1994; **330**: 517.
41 Takayasu K, Muramatsu Y, Moriyama N *et al*. Radiological study of idiopathic Budd–Chiari syndrome complicated by hepatocellular carcinoma. A report of four cases. *Am. J. Gastroenterol*. 1994; **88**: 249.
42 Tanaka M, Wanless IR, Pathology of the liver in Budd–Chiari syndrome: portal vein thrombosis and the histogenesis of veno-centric cirrhosis, veno-portal cirrhosis, and large regenerative nodules. *Hepatology* 1998; **27**: 488.
43 Tavill AS, Wood EJ, Kreel L *et al*. The Budd–Chiari syndrome: correlation between hepatic scintigraphy and the clinical, radiological and pathological findings in 19 cases of hepatic venous outflow obstruction. *Gastroenterology* 1975; **68**: 509.
44 Uddin W, Ramage JK, Portmann B *et al*. Hepatic venous outflow obstruction in patients with polycystic liver disease: pathogenesis and treatment. *Gut* 1995; **36**: 142.
45 Valla D, Benhamou J-P. Obstruction of the hepatic veins or supra-hepatic inferior vena cava. *Dig. Dis*. 1996; **14**: 99.
46 Valla D, Casadevall N, Lacombe C *et al*. Primary myeloproliferative disorder and hepatic vein thrombosis: a prospective study of erythroid colony formation *in vitro* in 20 patients with Budd–Chiari syndrome. *Ann. Intern. Med*. 1985; **103**: 329.
47 Valla D, Le MG, Poynard T *et al*. Risk of hepatic vein thrombosis in relation to recent use of oral contraceptives: a case–control study. *Gastroenterology* 1986; **90**: 807.
48 Venbrux AC, Savader SJ, Mitchell SE *et al*. Interventional management of Budd–Chiari syndrome. *Semin. Intervent. Radiol*. 1994; **11**: 312.
49 Young ID, Clark RN, Manley PN *et al*. Response to steroids in Budd–Chiari syndrome caused by idiopathic granulomatous venulitis. *Gastroenterology* 1988; **94**: 503.
50 Zajko AB, Claus D, Clapuyt P *et al*. Obstruction to hepatic venous drainage after liver transplantation: treatment with balloon angioplasty. *Radiology* 1989; **170**: 763.

Circulatory failure

A rise in pressure in the right atrium is readily transmitted to the hepatic veins. Liver cells are particularly vulnerable to diminished oxygen supply, so that a failing heart, lowered blood pressure or reduced hepatic blood flow are reflected in impaired hepatic function. The left lobe of the liver may suffer more than the right.

Hepatic changes in acute heart failure and shock

Hepatic changes are common in acute heart failure and in shock. Ischaemic changes follow cessation of hepatic blood flow during the course of hepatic transplantation or tumour resection.

Some patients show mild icterus. Jaundice has been recorded in severely traumatized patients. Serum transaminase levels increase markedly and the prothrombin time rises.

Light microscopy shows a congested zone 3 with local haemorrhage (fig. 11.17). Focal necrosis with eosinophilic hepatocytes, hydropic change and polymorph infiltration is usual. The reticulin framework is preserved within the necrotic zone. With recovery,

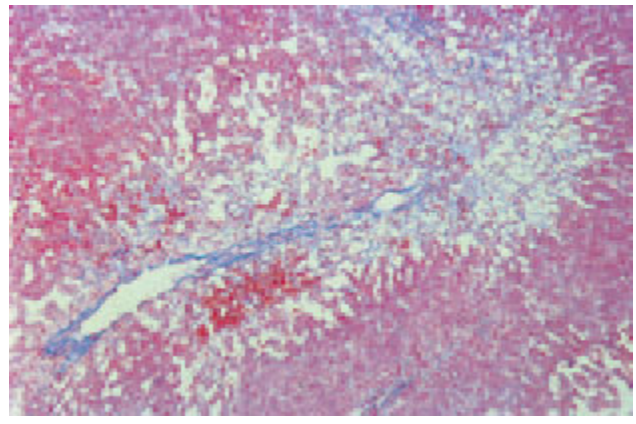


Fig. 11.17. Acute heart failure due to coronary thrombosis with prolonged hypotension. Zone 3 (stained blue) shows disappearance and necrosis of liver cells. The sinusoids are dilated with areas of haemorrhage. (Picro–Mallory stain, ×25.)

particularly after trauma, mitoses may be prominent. Diffuse hepatic calcification can follow shock [28]. This might be related to the disturbance of intra-cellular Ca^{2+} homeostasis as a result of ischaemia.

Mechanisms of the hepatic changes

The changes can be related to duration. The fall in blood pressure leads to reduction in liver blood flow and hepatic arterial vaso-constriction. The oxygen content of the blood is reduced. The cells in zone 3 receive blood at a lower oxygen tension than zone 1 cells and therefore more readily become anoxic and necrotic. Intense selective splanchnic vaso-constriction follows.

The hepatocyte injury is largely hypoxic. Insufficient substrates and accumulation of metabolites contribute. The mechanisms are multiple. The absence of available oxygen results in loss of mitochondrial oxidative phosphorylation. Impaired membrane function and reduced protein synthesis contribute. There are alterations in hepato-cellular ion homeostasis [3].

Hypoxia can induce hydrogen peroxide in hepatocytes and this induces apoptosis in sinusoidal endothelial cells [21]. Much of the tissue damage develops during re-perfusion, when there is a large flux of oxygen-derived 'free' radicles [31]. These initiate lipid peroxidation with disruption of membrane integrity. Experimentally, superoxide, formed during re-perfusion, may combine with nitric oxide (NO) to cause hepato-cellular injury [18]. Free radical peroxynitrate may be responsible. Lysosomal membranes may be peroxidized with the release of enzymes into the cytoplasm. Treatment is unsatisfactory. 'Free' radicle trapping agents such as vitamin E, glutathione and ascorbic acid are being evaluated.

Ischaemic hepatitis

This term is defined as marked and rapid elevation of serum transaminases in the setting of an acute fall in cardiac output. *Acute hepatic infarction* or *hypoxic hepatitis* are alternative definitions. The picture simulates acute viral hepatitis.

The patient usually suffers from cardiac disease, often ischaemic or a cardiomyopathy. It is particularly frequent in patients in coronary care units where it affects 22% of those with a low cardiac output, a decreased hepatic blood flow and passive venous congestion [11]. Zone 3 necrosis, without inflammation, results. Clinical evidence of hepatic failure is absent. Congestive cardiac failure is inconspicuous. It may be associated with renal impairment and hyperglycaemia [10].

Ischaemic hepatitis may complicate variceal haemorrhage in cirrhotic patients [14].

Severe arterial hypoxaemia due to obstructive sleep apnoea may be causative [20].

Serum bilirubin and alkaline phosphatase values increase slightly, but serum transaminases and lactic dehydrogenase values rise rapidly and strikingly [12]. Values return speedily towards recovery in less than 1 week. Mortality is high (58.6%) and depends on the underlying cause and not the liver injury [12]. If the liver has been previously damaged by chronic congestive heart failure, acute circulatory failure may lead to the picture of fulminant hepatic failure [23].

Post-operative jaundice

Jaundice developing *soon* after surgery may have multiple causes. Increased serum bilirubin follows blood transfusion, particularly of stored blood. Extravasated blood in the tissues gives an additional bilirubin load.

Impaired hepato-cellular function follows operation, anaesthetics and shock. Severe jaundice develops in approximately 2% of patients with shock resulting from major trauma [24]. Hepatic perfusion is reduced particularly if the patient is in incipient circulatory failure and the cardiac output is already reduced. Renal blood flow also falls.

Anaesthetics and other drugs used in the operative period must be considered. Sepsis, *per se*, can produce deep jaundice which may be cholestatic.

Rarely, a *cholestatic jaundice* may be noted on the first or second post-operative day. It reaches its height between the fourth and tenth day, and disappears by 14–18 days. Serum biochemical changes are variable. Sometimes, but not always, the alkaline phosphatase and transaminase levels are increased. Serum bilirubin can rise to levels of 23–39 mg/100 ml. The picture simulates extra-hepatic biliary obstruction. Patients have all had an episode of shock, and have been transfused. Hepatic histology shows only minor abnormalities. The mechanism of the cholestasis is uncertain. This picture must be recognized and, if necessary, needle biopsy of the liver performed.

Severely ill patients in intensive care following severe trauma or post-operative intra-abdominal sepsis may develop jaundice, which reflects severe multiple organ failure and a poor prognosis [29]. The jaundice is usually of cholestatic type with raised conjugated serum bilirubin and alkaline phosphatase levels and only slightly increased transaminases.

Endotoxaemia and sepsis may activate inflammatory mediators leading to vascular damage, increased permeability and oedema and impaired oxygen transport [5].

Bile flow falls following the reduction in hepatic arterial perfusion (*ischaemic cholangitis*) [2].

Ischaemia in the rat liver is followed by ATP depletion in the cholangiocytes with changes in membrane and membrane–skeletal structures [9].

Jaundice after cardiac surgery

Jaundice develops in 20% of patients having cardiopulmonary bypass surgery [6, 7]. It carries a bad prognosis. The jaundice is detected by the second post-operative day. Serum bilirubin is conjugated and the level returns to normal in 2–4 weeks in those who survive. Serum alkaline phosphatase may be normal or only slightly increased and transaminases are raised, often to very high levels. Older patients are particularly at risk. Jaundice is significantly associated with multiple valve replacement, high blood transfusion requirements and a longer bypass time.

Many factors contribute. The liver may have already suffered from prolonged heart failure. Operative hypotension, shock and hypothermia contribute. Infections, drugs (including anticoagulants) and anaesthetics must be considered.

Liver blood flow falls. The serum bilirubin load is increased by blood transfusion. The pump may contribute by decreasing erythrocyte survival and by adding gaseous micro-emboli and platelet aggregates and debris to the circulation.

Virus B and C hepatitis are rare nowadays. Cytomegalovirus hepatitis may develop.

The liver in congestive heart failure

***Pathological changes* [16]**

Hepatic autolysis is particularly rapid in the patient dying with heart failure [26]. Autopsy material is therefore unreliable for assessment.

Macroscopic changes. The liver is enlarged, and purplish with rounded edges. Nodularity is inconspicuous but nodular masses of hepatocytes (*nodular regenerative hyperplasia*) may be seen. The cut surface (fig. 11.18) shows prominent hepatic veins which may be thickened. The liver drips blood. Zone 3 is prominent with alternation of yellow (fatty change) and red (haemorrhage) areas.

Histological changes. The hepatic venule is dilated, and the sinusoids entering it are engorged for a variable distance towards the periphery. In severe cases, there is frank haemorrhage with focal necrosis of liver cells. The liver cells show a variety of degenerative changes but each zone 1 is surrounded by relatively normal cells to a depth that varies inversely with the extent of the zone 3 atrophy. Biopsy sections show significant fatty change in only about a third of cases. This contrasts with the usual post-mortem picture. Cellular infiltration is inconspicuous.

Zone 3 degenerating cells are often packed with brown lipochrome pigment. As they disintegrate, pigment lies free. Bile thrombi, particularly in zone 1, may be seen in the deeply jaundiced. Zone 3 PAS-positive, diastase-resistant hyaline globules may be seen [15].

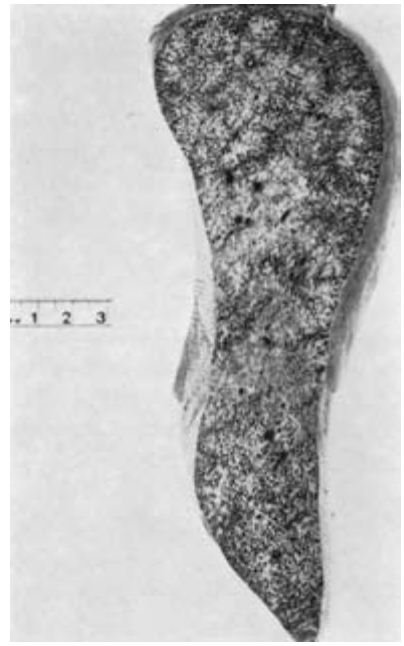


Fig. 11.18. Cut surface of the liver from a patient dying with congestive heart failure. Note the dilated hepatic veins. Light areas corresponding to peripheral fatty zones alternate with dark areas corresponding to zone 3 congestion and haemorrhage.

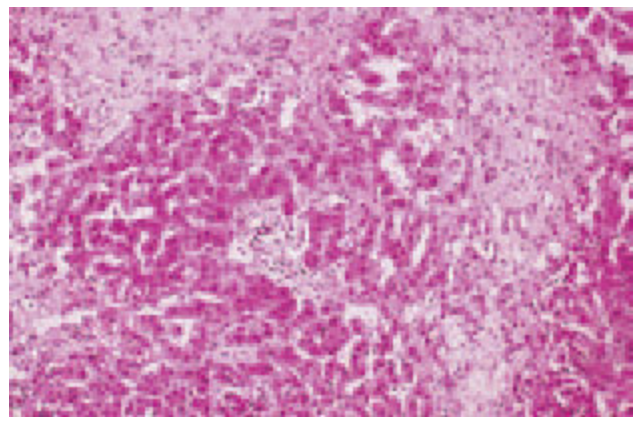


Fig. 11.19. Cardiac cirrhosis. Zone 3 fibrosis is increased and septa extend to link other central veins isolating nodules of liver cells. (H & E.)

Zone 3 reticulin condenses. Collagen increases and the central vein shows phlebosclerosis. Eccentric thickening or occlusion of the walls of zone 3 veins and peri-venular scars extends into the lobule [16]. If the heart failure continues or relapses, bridges develop between central veins so that the unaffected portal zone is surrounded by a ring of fibrous tissue (*reversed lobulation*) (fig. 11.19). Later the portal zones are involved and a

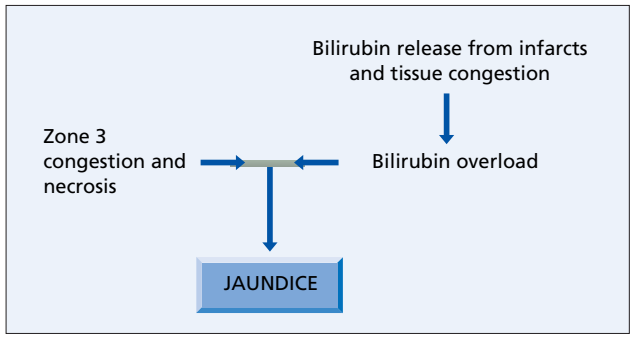


Fig. 11.20. Mechanisms of hepatic jaundice developing in patients with cardiac failure.

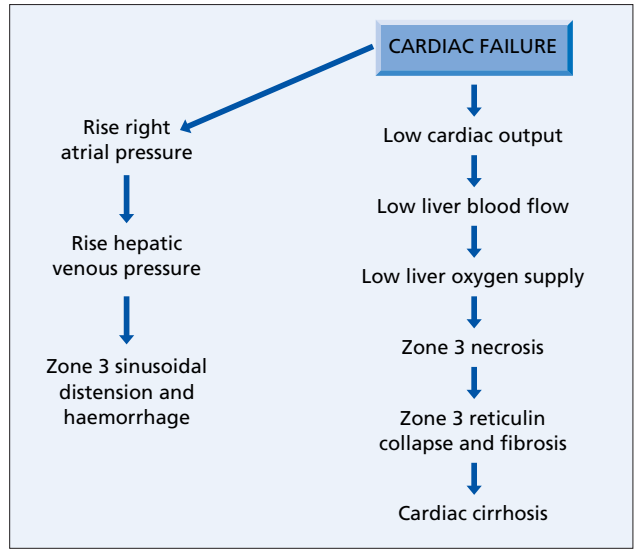


Fig. 11.21. Possible mechanisms of the hepatic histological changes in heart failure.

complex cirrhosis results. A true cardiac cirrhosis is extremely rare.

Mechanism (fig. 11.20)

Hypoxia causes degeneration of the zone 3 liver cells, dilatation of sinusoids and slowing of bile secretion. Endotoxins diffusing through the intestinal wall into the portal blood may augment this effect [27]. The liver attempts to compensate by increasing the oxygen extracted as the blood flows across the sinusoidal bed. Collagenosis of Disse's space may play a minor role in impairing oxygen diffusion.

Necrosis correlates with a low cardiac output [1]. The hepatic venous pressure increases and this correlates with zone 3 congestion [1].

Thrombosis begins in the sinusoids and may propagate to the hepatic veins with secondary local, portal vein thrombosis, ischaemia, parenchymal loss and fibrosis [30].

Clinical features

Mild jaundice is common but deeper icterus is rare and associated with chronic congestive failure. In hospital inpatients, cardio-respiratory disease is the commonest cause of a raised serum bilirubin level. Oedematous areas escape, for bilirubin is protein-bound and does not enter oedema fluid with a low protein content.

Jaundice is partly hepatic, for the greater the extent of zone 3 necrosis the deeper the icterus (fig. 11.21) [26].

Bilirubin released from infarcts or simply from pulmonary congestion, provides an overload on the anoxic liver. Patients in cardiac failure who become jaundiced with minimal hepato-cellular damage usually have pulmonary infarction [26]. The serum shows unconjugated bilirubinaemia.

The patient may complain of right abdominal pain, probably due to stretching of the capsule of the enlarged liver. The firm, smooth, tender lower edge may reach the umbilicus.

A rise in right atrial pressure is readily transmitted to the hepatic veins. This is particularly so in tricuspid incompetence when the hepatic vein pressure tracing resembles that obtained from the right atrium. Palpable systolic pulsation of the liver can be related to this transmission of pressure. Pre-systolic hepatic pulsation occurs in tricuspid stenosis. The expansion may be felt bimanually. This expansibility distinguishes it from the palpable epigastric pulsation due to the aorta or a hypertrophied right ventricle. Correct timing of the pulsation is important.

In heart failure, pressure applied over the liver increases the venous return and the jugular venous pressure rises due to the inability of the failing right heart to handle the increased blood flow. The *hepato-jugular reflux* is of value for identifying the jugular venous pulse and to establish that venous channels between the hepatic and jugular veins are patent. The reflux is absent if the hepatic veins are occluded or if the main mediastinal or jugular veins are blocked. It is useful for diagnosing tricuspid regurgitation [19].

Atrial pressure is reflected all the way to the portal system. Doppler sonography shows increased pulsatility in the portal vein depending on the severity of the heart failure [13].

Ascites is associated with a particularly high venous pressure, a low cardiac output and severe zone 3 necrosis. In patients with mitral stenosis and tricuspid incompetence or constrictive pericarditis, the ascites may be out of proportion to the oedema and symptoms of congestive heart failure. The ascitic fluid protein content is

raised to 2.5 g/dl or more, similar to that observed in the Budd–Chiari syndrome [25].

Confusion, lethargy and coma are related to cerebral anoxia. Occasionally the whole picture of impending hepatic coma may be seen. Splenomegaly is frequent. Other features of portal hypertension are usually absent except in very severe cardiac cirrhosis associated with constrictive pericarditis.

Contrast-enhanced CT shows retrograde hepatic venous opacification on the early scans and a diffusely mottled pattern of hepatic enhancement during the vascular phase [22].

Cardiac cirrhosis should be suspected in patients with prolonged, decompensated mitral valve disease with tricuspid incompetence or in patients with constrictive pericarditis. The prevalence has fallen since both these conditions are relieved surgically.

Biochemical changes

The biochemical changes are small and proportional to the severity of the heart failure.

In congestive failure the serum bilirubin level usually exceeds 1 mg/dl and in about one-third it is more than 2 mg/dl [26]. The jaundice may be deep, exceeding 5 mg/dl and even up to 26.9 mg/dl. Patients with advanced mitral valve disease and a normal serum bilirubin concentration have a normal hepatic bilirubin uptake but diminished capacity to eliminate conjugated bilirubin related to reduced liver blood flow [4]; this contributes to post-operative jaundice.

Serum alkaline phosphatase is usually normal or slightly increased. Serum albumin values may be mildly reduced. Protein loss from the intestine may contribute.

Serum transaminases are higher in acute than chronic failure and are proportional to the degree of shock and the extent of zone 3 necrosis. The association of very high values with jaundice may simulate acute viral hepatitis.

Prognosis

The prognosis is that of the underlying heart disease. Cardiac jaundice, particularly if deep, is always a bad omen.

Cardiac cirrhosis *per se* does not carry a bad prognosis. If the heart failure responds to treatment, the cirrhosis compensates.

The liver in constrictive pericarditis

The clinical picture and hepatic changes are those of the Budd–Chiari syndrome.

Marked thickening of the liver capsule simulates sugar icing (*zuckergussleber*). Microscopically, the picture is of cardiac cirrhosis.

Jaundice is absent. The liver is enlarged and hard and may pulsate [8]. Ascites is gross.

Diagnosis must be made from ascites due to cirrhosis or to hepatic venous obstruction [17]. This is done by the paradoxical pulse, the venous pulse, the calcified pericardium, the echocardiogram, the electrocardiogram and by cardiac catheterization.

Treatment is that of the cardiac condition. If pericardectomy is possible, prognosis as regards the liver is good although recovery may be slow. Within 6 months of a successful operation, liver function tests improve and the liver shrinks. The cardiac cirrhosis will not resolve completely, but fibrous bands become narrower and avascular.

References

1 Arcidi JM Jr, Moore GM, Hutchins GM. Hepatic morphology in cardiac dysfunction. A clinicopathologic study of 1000 subjects at autopsy. *Am. J. Pathol*. 1981; **104**: 159.

2 Batts KP. Ischemic cholangitis. *Mayo Clin. Proc*. 1998; **73**: 380.

3 Berger ML, Reynolds RC, Hagler HK *et al*. Anoxic hepatocyte injury: role of reversible changes in elemental content and distribution. *Hepatology* 1989; **9**: 219.

4 Bohmer T, Kjekshus E, Nitter-Hauge S. Studies on the elevation of bilirubin preoperatively in patients with mitral valve disease. *Eur. Heart J*. 1994; **15**: 10.

5 Carrico JC, Meakins JL, Marshall JC *et al*. Multiple-organ failure syndrome. *Arch. Surg*. 1986; **121**: 196.

6 Chu C-M, Chang C-H, Liaw Y-F *et al*. Jaundice after open heart surgery: a prospective study. *Thorax* 1984; **39**: 52.

7 Collins JD, Bassendine MF, Ferner R *et al*. Incidence and prognostic importance of jaundice after cardiopulmonary bypass surgery. *Lancet* 1983; **i**: 1119.

8 Coralli RJ, Crawley IS. Hepatic pulsations in constrictive pericarditis. *Am. J. Cardiol*. 1986; **58**: 370.

9 Doctor RB, Dahl RH, Salter KD *et al*. Reorganization of cholangiocyte membrane domains represents an early event in rat liver ischaemia. *Hepatology* 1999; **29**: 1364.

10 Gitlin N, Serio KM. Ischemic hepatitis: widening horizons. *Am. J. Gastroenterol*. 1992; **87**: 831.

11 Henrion J, Descamps O, Luwaert R *et al*. Hypoxic hepatitis in patients with cardiac failure: incidence in a coronary care unit and measurement of hepatic blood flow. *J. Hepatol*. 1994; **21**: 696.

12 Hickman PE, Potter JM. Mortality associated with ischaemic hepatitis. *Aust. NZ J. Med*. 1990; **20**: 32.

13 Hosoki T, Arisawa J, Marukawa T *et al*. Portal blood flow in congestive heart failure: pulsed duplex sonographic findings. *Radiology* 1990; **174**: 733.

14 Kamiyama T, Miyakawa H, Tajiri K. Ischemic hepatitis in cirrhosis. Clinical features and prognostic implications. *J. Clin. Gastroenterol*. 1996; **22**: 126.

15 Klatt EC, Koss MN, Young TS *et al*. Hepatic hyaline globules associated with passive congestion. *Arch. Pathol. Lab. Med*. 1988; **112**: 510.

16 Lefkowitch JH, Mendez L. Morphologic features of hepatic injury in cardiac disease and shock. *J. Hepatol*. 1986; **2**: 313.

17 Lowe MD, Harcombe AA, Grace AA *et al*. Restrictive-constrictive heart failure masquerading as liver disease. *Br. Med. J.* 1998; **318**: 585.
18 Ma TT, Ischiropoulos H, Brass CA. Endotoxin-stimulated nitric oxide production increases injury and reduces rat liver chemiluminescence during reperfusion. *Gastroenterology* 1995; **108**: 463.
19 Maisel AS, Atwood JE, Goldberger AL. Hepatojugular reflux: useful in the bedside diagnosis of tricuspid regurgitation. *Ann. Intern. Med*. 1984; **101**: 781.
20 Mathurin P, Durand F, Ganne N *et al*. Ischemic hepatitis due to obstructive sleep apnea. *Gastroenterology* 1995; **109**: 1682.
21 Motoyama S, Minamiya Y, Saito S *et al*. Hydrogen peroxide derived from hepatocytes induces sinusoidal cell apoptosis in perfused hypoxic rat liver. *Gastroenterology* 1998; **114**: 153.
22 Moulton JS, Miller BL, Dodd GD III *et al*. Passive hepatic congestion in heart failure: CT abnormalities. *Am. J. Roentgenol*. 1988; **151**: 939.
23 Nouel O, Henrion J, Bernuau J *et al*. Fulminant hepatic failure due to transient circulatory failure in patients with chronic heart disease. *Dig. Dis. Sci*. 1980; **25**: 49.
24 Nunes G, Blaisdell FW, Margaretten W. Mechanism of hepatic dysfunction following shock and trauma. *Arch. Surg*. 1970; **100**: 646.
25 Runyon BA. Cardiac ascites: a characterization. *J. Clin. Gastroenterol*. 1988; **10**: 410.
26 Sherlock S. The liver in heart failure; relation of anatomical, functional and circulatory changes. *Br. Heart J.* 1951; **13**: 273.
27 Shibayama Y. The role of hepatic venous congestion and endotoxaemia in the production of fulminant hepatic failure secondary to congestive heart failure. *J. Pathol.* 1987; **151**: 133.
28 Shibuya A, Unuma T, Sugimoto M *et al*. Diffuse hepatic calcification as a sequela to shock liver. *Gastroenterology* 1985; **89**: 196.
29 te Boekhorst T, Urlus M, Doesburg W *et al*. Etiologic factors of jaundice in severely ill patients: a retrospective study in patients admitted to an intensive care unit with severe trauma or with septic intra-abdominal complications following surgery and without evidence of bile duct obstruction. *J. Hepatol*. 1988; **7**: 111.
30 Wanless IR, Liu JJ, Butany J. Role of thrombosis in the pathogenesis of congestive hepatic fibrosis (cardiac cirrhosis). *Hepatology* 1995; **21**: 1232.
31 Weisiger RA. Oxygen radicals and ischemic tissue injury. *Gastroenterology* 1986; **90**: 494.

Chapter 12
Jaundice

Bilirubin metabolism [37]

Bilirubin is the end product of haem, the majority (80–85%) coming from haemoglobin with only a small fraction derived from other haem-containing proteins such as cytochrome P450 (fig. 12.1). Approximately 300 mg bilirubin is formed daily. Production from haemoglobin takes place in reticulo-endothelial cells.

The enzyme that converts haem to bilirubin is microsomal haem oxygenase (fig. 12.2). Cleavage of the porphyrin ring occurs selectively at the α-methane bridge. The α-bridge carbon atom is converted to carbon monoxide and the original bridge function is replaced by two oxygen atoms which are derived from molecular oxygen. The resulting linear tetrapyrrole has the structure of the IX α-biliverdin. This is converted further to IX α-bilirubin by a cytosolic enzyme, biliverdin reductase. Such a linear tetrapyrrole should be water soluble, whereas bilirubin is lipid soluble. The lipid solubility is explained by realignment of the pyrrole ring such that internal hydrogen bonding masks the propionic acid side chains making bilirubin poorly soluble in aqueous solvents. This bonding can be broken by alcohol in the diazo (van den Bergh) reaction converting unconjugated, indirect, bilirubin to direct reacting bilirubin. *In vivo* the stable hydrogen bonds are altered by esterification of the propionic groups by glucuronic acid.

About 20% of circulating bilirubin is not formed from the haem of mature erythrocytes. A small proportion comes from immature cells in the spleen and bone marrow. This component is increased in haemolytic states. The remainder is formed in the liver from haem proteins such as myoglobin, cytochromes and unknown sources.

Hepatic transport and conjugation of bilirubin (fig. 12.3)

Unconjugated bilirubin is transported in the plasma tightly bound to albumin. A very small amount is dialysable, but this can be increased by substances such as fatty acids and organic anions which compete with bilirubin for albumin binding. This is important in the neonate where such drugs as sulphonamides and salicylates facilitate diffusion of bilirubin into the brain and so increase the risk of kernicterus.

The liver extracts organic anions including fatty acids and bile acid and non-bile-acid cholephils, such as bilirubin, despite tight albumin binding. Studies suggest that bilirubin dissociating from albumin in the sinusoid diffuses across the unstirred water layer at the surface of the hepatocyte [42]. A previously proposed albumin receptor has not been substantiated. The mechanism for

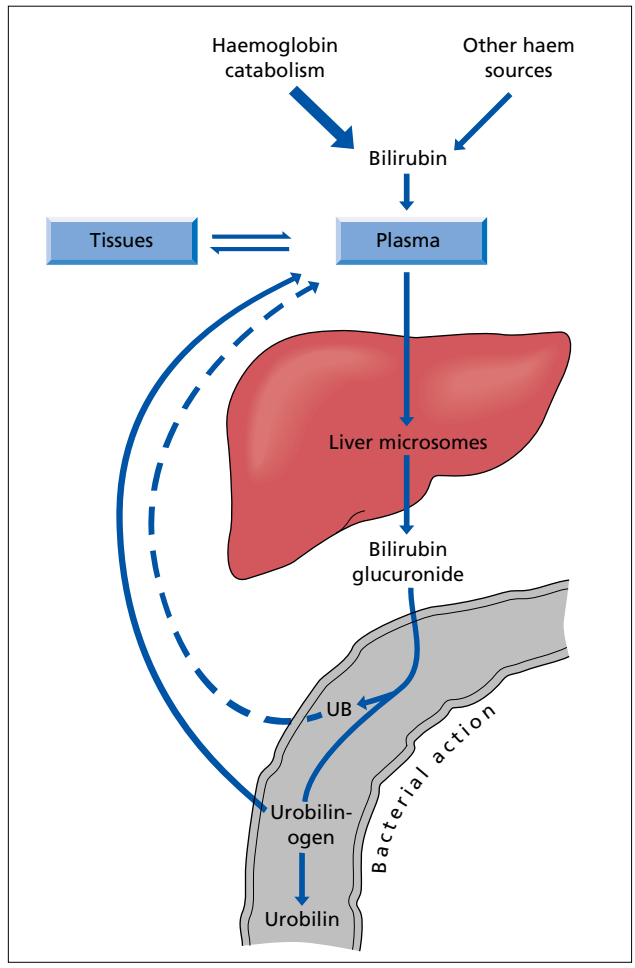


Fig. 12.1. The metabolism of bilirubin. UB, unconjugated bilirubin.

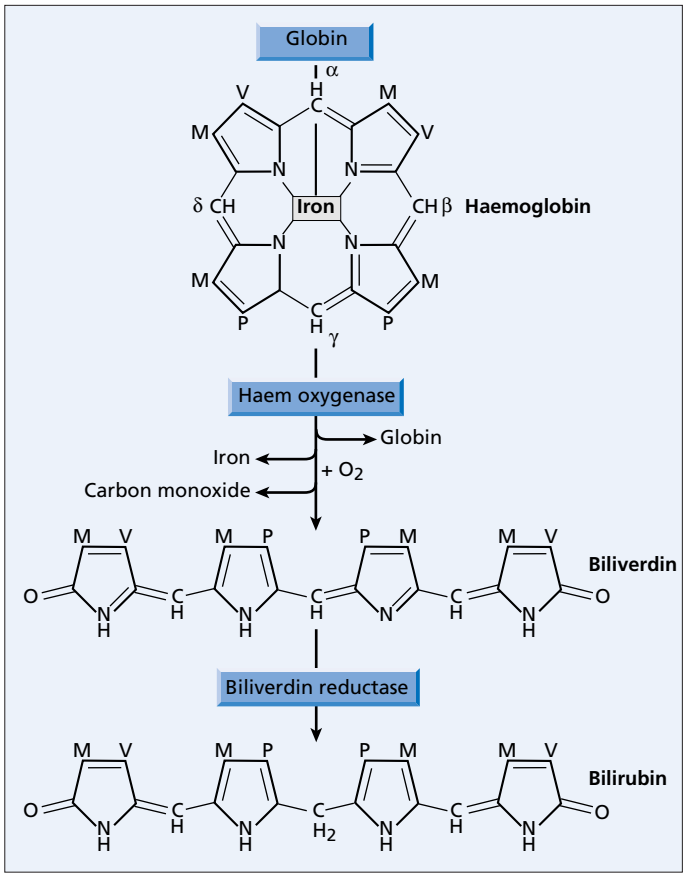


Fig. 12.2. The metabolism of haemoglobin to bilirubin. M, methyl; P, propionate; V, vinyl.

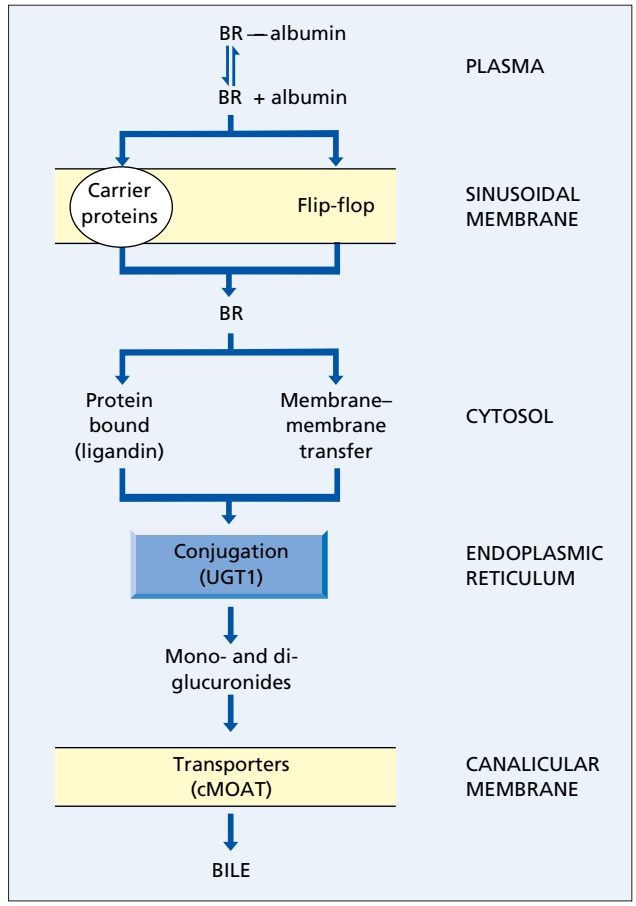


Fig. 12.3. Bilirubin (BR) uptake, metabolism and secretion by the hepatocyte. MOAT, multi-specific organic anion transporter; UGT1, uridine diphosphate glucuronosyl transferase 1.

passage of bilirubin across the plasma membrane into the hepatocyte involves either transport proteins, such as the organic anion transporter [37], and/or bilirubin flip-flop across the membrane [42]. Uptake is highly effective because of the rapid hepatic metabolism by glucuronidization and excretion into bile, and also because of binding by carrier proteins in the cytosol such as glutathione-*S*-transferase (ligandin).

Unconjugated bilirubin is non-polar (lipid soluble). It is converted to a polar (water soluble) compound by conjugation and this allows its excretion into the bile. The microsomal enzyme responsible, bilirubin uridine diphosphate glucuronosyl transferase (UGT), converts unconjugated bilirubin to conjugated bilirubin mono- and diglucuronide. Bilirubin UGT is a one of several UGT enzyme isoforms that are responsible for the conjugation of many endogenous metabolites, hormones and neurotransmitters.

The gene expressing bilirubin UGT is on chromosome 2. The structure of the gene is complex (fig. 12.4) [5, 11, 36]. Exons 2–5 at the 3′ end are constant components of all isoforms of UGT. To complete the gene, one of several first exons can be employed. Exon 1*1 encodes the variable region for bilirubin UGT1*1, responsible for virtually all bilirubin conjugation. Another first exon, 1*4, encodes the variable region for another bilirubin UGT but although mRNA can be detected this appears to play no role in bilirubin conjugation even in the absence of bilirubin 1*1 activity [3, 5, 36]. Other first exons (exon 1*6

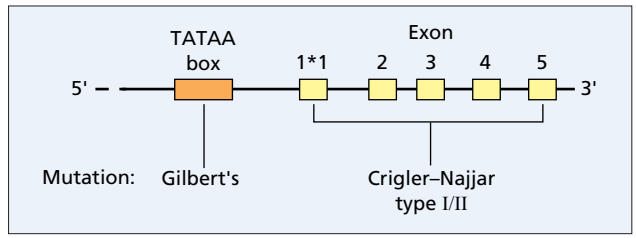


Fig. 12.4. Structure of gene for bilirubin UGT1*1 with five exons and the promoter region (TATAA box). There are several other possible first exons (not shown) that can be spliced to exons 2–5, and have other substrate specificities.

and 1*7) encode the enzyme isoforms for phenol UGTs. Thus selection of one of the exon 1 sequences gives different substrate specificity and enzyme characteristics.

Expression of UGT1*1 depends further on a promoter region containing a TATAA box in a 5′ position relative to exon 1*1.

Detail of the gene structure is relevant to the pathogenesis of the unconjugated hyperbilirubinaemias (Gilbert's and Crigler–Najjar syndromes; see below), where conjugating enzyme in the liver is reduced or absent.

Levels of UGT are well maintained in hepato-cellular jaundice and even increased in cholestasis. They are reduced in the neonate.

The major bilirubin conjugate in human bile is the diglucuronide. A single microsomal glucuronyl system catalyses both the conversion of bilirubin to the monoglucuronide and on diglucuronide. With a high bilirubin load, as in haemolysis, monoglucuronide formation is favoured, whereas if the bilirubin load is low or there is enzyme induction the diglucuronide increases.

Although conjugation as a glucuronide remains the most important mechanism, sulphate, xylose and glucose conjugation also occur to a small extent and may be increased in cholestasis.

In the late stages of cholestatic or hepato-cellular jaundice, despite high serum bilirubin levels, none can be detected in the urine. This is due to a third type of bilirubin, a bilirubin monoconjugate, covalently bound to albumin. This would not be filtered by the glomerulus and hence would not reach the urine.

Biliary canalicular excretion of bilirubin is mediated by the ATP-dependent multi-specific organic anion transporter (cMOAT) also called multi-drug resistance protein-2 (MRP-2) [23]. Biliary excretion of glucuronide is the rate-limiting factor in the transport of bilirubin from plasma to bile.

Bile acids are secreted into bile by the bile salt export pump (BSEP). The separate mechanism for bilirubin and bile acid is exemplified by the Dubin–Johnson syndrome where there is a defect in the excretion of conjugated bilirubin, while bile salt excretion is usually normal. A high proportion of the conjugated bilirubin in bile is incorporated into mixed micelles with cholesterol, phospholipids and bile salts.

Bilirubin diglucuronide in bile is polar (water soluble) and hence is not absorbed from the small intestine. In the colon, bacterial β-glucuronidases hydrolyse the conjugated bilirubin, which is then reduced to urobilinogens and urobilin which are excreted in the stool (fig. 12.1). Neonates who lack an intestinal flora are at increased risk of absorption of unconjugated bilirubin formed from conjugated bilirubin by intestinal β-glucuronidase. In the presence of bacterial cholangitis some hydrolysis of the bilirubin glucuronide is possible in the biliary tree and unconjugated bilirubin is precipitated. This may be important in the production of bilirubin gallstones.

Urobilinogen is non-polar and is well absorbed from the small intestine, but only minimally from the colon. The little that is normally absorbed is re-excreted by the liver (*entero-hepatic circulation*) and kidneys. With hepato-cellular dysfunction, re-excretion by the liver is impaired and more is excreted in the urine. This accounts for the urobilinogenuria of alcoholic liver disease, pyrexia, heart failure and the early stages of viral hepatitis.

Distribution of jaundice in the tissues

Circulating protein-bound bilirubin does not easily enter protein-low tissue fluids. If protein levels are higher, jaundice becomes more evident. Thus exudates tend to be more icteric than transudates.

Cerebrospinal fluid from jaundiced subjects contains a small amount of bilirubin, the level being one-tenth to one-hundredth of that found in the serum. The cerebrospinal fluid is more likely to be xanthochromic when meningitis is present, the classical example being Weil's disease with both jaundice and meningitis.

In deep jaundice, the ocular fluids are yellow, and this is considered to explain the extremely rare symptom of xanthopsia (seeing yellow).

The basal ganglia may be stained yellow in the newborn (kernicterus). This is due to the high concentration of circulating, unconjugated bilirubin having an affinity for neural tissue.

Urine, sweat, semen and milk contain bile pigment in the deeply jaundiced patient. Bilirubin is a normal constituent of synovial fluid.

Paralysed parts and oedematous areas tend to remain uncoloured.

Bilirubin is readily bound to elastic tissue. Skin, ocular sclera and blood vessels have a high elastic tissue content, and easily become icteric. This also accounts for the disparity between the depth of skin jaundice and serum bilirubin levels during recovery from hepatitis and cholestasis.

Factors determining the depth of jaundice

Even with complete bile duct obstruction, the depth of jaundice is very variable. After an initial rapid increase, the serum bilirubin levels off after about 3 weeks although the obstruction persists. The level of jaundice depends on both bile pigment production and the capacity of the kidney for its excretion. Rates of bilirubin production may vary and products other than bilirubin, which do not give the diazo reaction, may be formed from haem catabolism. The intestinal mucosa may allow the passage of bilirubin, presumably unconjugated, from the blood.

In prolonged cholestasis the skin is greenish, possibly due to biliverdin, which does not give the diazo reaction for bilirubin.

Conjugated bilirubin, because of its water solubility and penetration of body fluids, produces more jaundice than unconjugated pigment. This accounts for the more intense colour of hepato-cellular and cholestatic rather than haemolytic jaundice.

Classification of jaundice

Classification is into three types (figs 12.5, 12.6): pre-hepatic, hepatic and cholestatic. There is much overlap, particularly between the hepatic and cholestatic varieties.

Pre-hepatic. There is an increased bilirubin load on the liver cell most usually due to haemolysis. The circulating serum bilirubin is largely unconjugated and the serum transaminase and alkaline phosphatase are normal. Bilirubin cannot be detected in urine. This picture of unconjugated hyperbilirubinaemia is also seen when there is failure of bilirubin conjugation as in Gilbert's and Crigler–Najjar syndrome.

Hepatic. This is related to failure of the hepatocyte to excrete conjugated bilirubin into bile, presumably as a result of the failure of transport systems across the hepatocyte and the canalicular membrane. Conjugation is intact and therefore there is reflux of conjugated bilirubin into

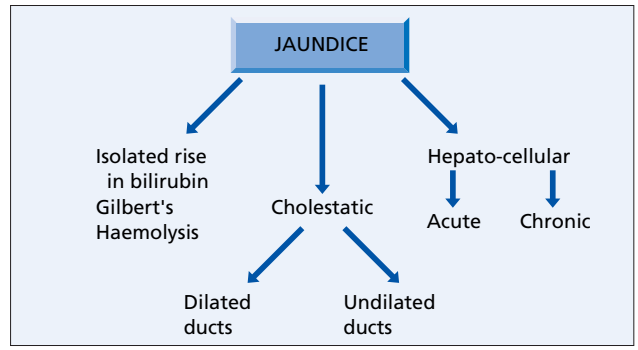


Fig. 12.5. Classification of jaundice.

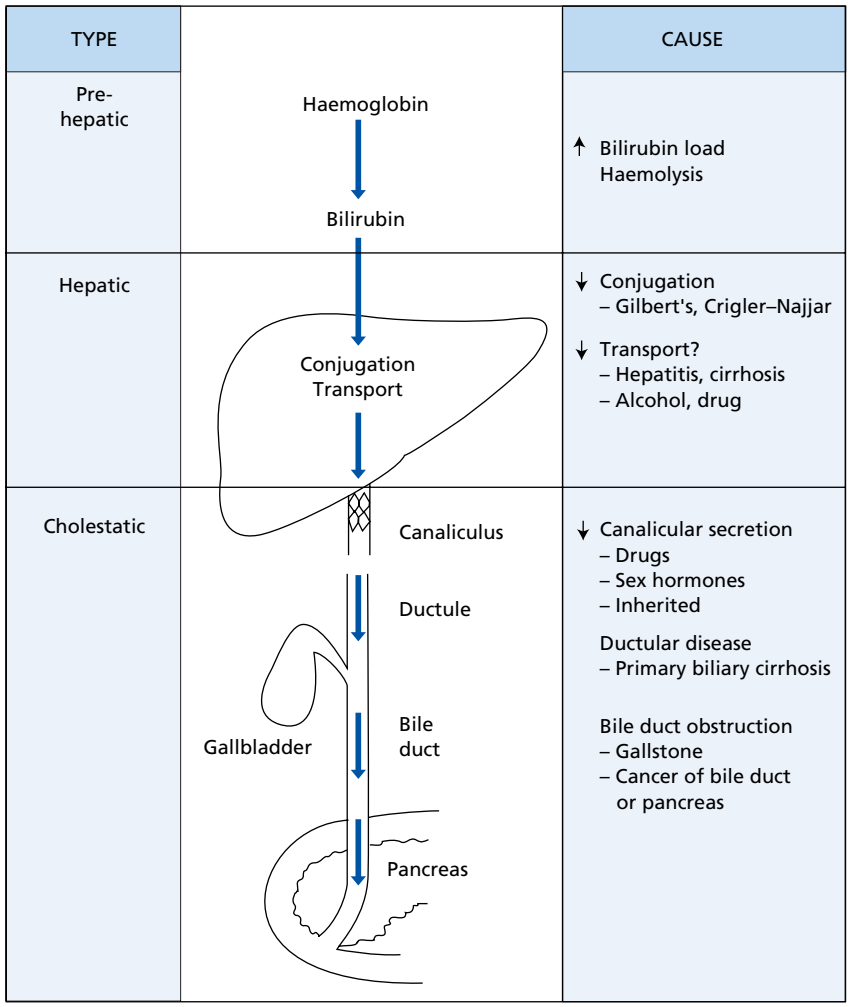


Fig. 12.6. Classification and causes of jaundice.

the circulation. Serum biochemistry shows an increase in liver enzymes according to the underlying cause; being predominantly transaminases in viral and drug hepatitis. The jaundice usually comes on rapidly. Fatigue and malaise are conspicuous. If liver damage is severe there may be evidence of liver failure with encephalopathy, fluid retention with oedema and ascites, and bruising both spontaneous and related to venepunctures due to reduced hepatic synthesis of coagulation factors. In the long-standing case, serum albumin levels are reduced.

Cholestatic (Chapter 13). This is due to failure of adequate amounts of bile to reach the duodenum, either through failure of canalicular secretion of bile or physical obstruction to the bile duct at any level. The patient is relatively well, apart from the causative condition, and pruritus is characteristic. The patient becomes increasingly pigmented. The serum shows increases in conjugated bilirubin, biliary alkaline phosphatase, γ-glutamyl transpeptidase (γ-GT), total cholesterol and conjugated bile acids. Steatorrhoea is responsible for weight loss and malabsorption of fat-soluble vitamins A, D, E and K, and calcium.

Diagnosis of jaundice (tables 12.1, 12.2; fig. 12.7)

A careful history and physical examination with routine biochemical and haematological tests are essential. The stool should be inspected and occult blood examination performed. The urine is tested for bilirubin and urobilinogen excess. The place of special tests such as ultrasound, liver biopsy and cholangiography will depend on the category of jaundice.

Clinical history

Occupation should be noted; particularly employment involving alcohol or contact with rats carrying Weil's disease.

Table 12.1. First steps in the diagnosis of the jaundiced patient

Clinical history and examination
Urine, stools
Serum biochemical tests
bilirubin
transaminase (AST, ALT)
alkaline phosphatase, γ-GT
albumin
quantitative immunoglobulins
Haematology
haemoglobin, white cells, platelets
Blood film
Prothrombin time (before and after i.v. vitamin K)
X-ray of chest

ALT, alanine transaminase; AST, aspartate transaminase; γ-GT, γ-glutamyl transpeptidase.

Place of origin (Mediterranean, African or Far East) may suggest carriage of hepatitis B or C.

Family history is important with respect to jaundice, hepatitis and anaemia. Positive histories are helpful in diagnosing haemolytic jaundice, congenital hyperbilirubinaemia and hepatitis.

Contact with jaundiced persons, particularly in nurseries, camps, hospitals and schools, is noted. Close contact with patients on renal units or with drug abusers is recorded, as is any *injection* in the preceding 6 months. 'Injections' include blood tests, drug abuse, tuberculin testing, dental treatment and tattooing as well as blood or plasma transfusions. The patient is asked about previous *drug treatment* with possible hepato-toxic agents. Consumption of *shellfish* and previous *travel* to areas where hepatitis is endemic should be noted.

Previous dyspepsia, fat intolerance and biliary colic suggest choledocholithiasis.

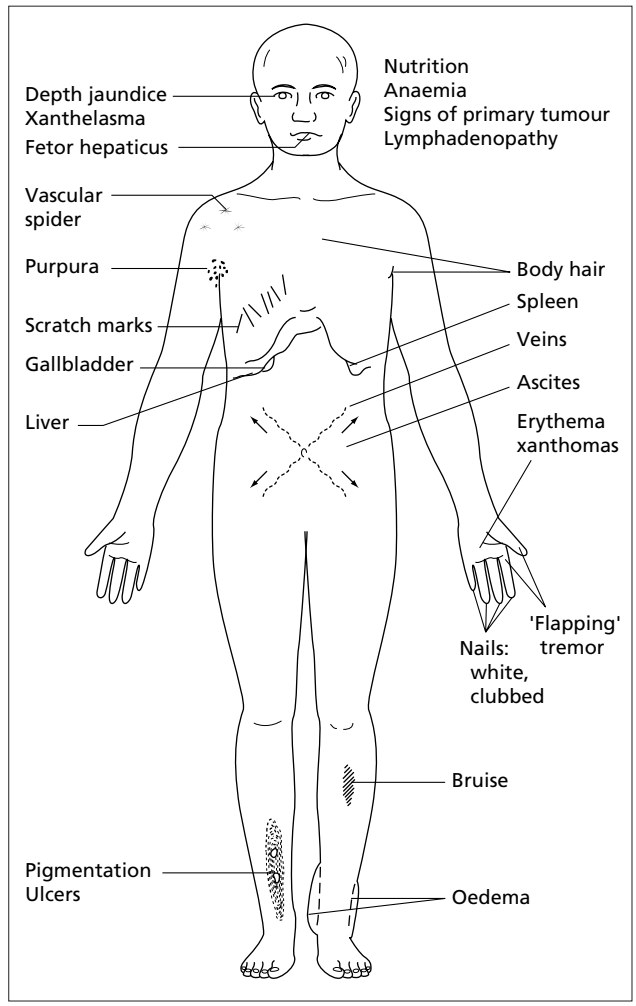


Fig. 12.7. Physical signs in jaundice.

Table 12.2. General features of the common types of acute jaundice

	Gallstones in common bile duct	Carcinoma in peri-ampullary region	Acute viral hepatitis	Cholestatic drug jaundice
Antecedent history	Dyspepsia, previous attack	Nil	Contacts, injections, transfusion or nil	Taking drug
Pain	Constant epigastric, biliary colic or none	Constant epigastric, back or none	Ache over liver or none	None
Pruritus	±	+	Transient	+
Rate of development of jaundice	Slow	Slow	Rapid	Rapid
Type of jaundice	Fluctuates or persistent	Usual but not always	Rapid onset, slow fall with recovery	Variable, usually mild
Weight loss	Slight to moderate	Progressive	Slight	Slight
Examination				
Diathesis	Frequently female, obese	Over 40 years old	Young usually	Often older female, psychotic
Depth of jaundice	Moderate	Deep	Variable	Variable, rash sometimes
Ascites	0	Rarely with metastases	If severe and prolonged	0
Liver	Enlarged, slightly tender	Enlarged, not tender	Enlarged and tender	Slightly enlarged
Palpable gallbladder	0	+ (sometimes)	0	0
Tender gallbladder area	+	0	0	0
Palpable spleen	0	Occasionally	About 20%	0
Temperature	↑	Not usually	↑ onset only	↑ onset
Investigations				
Leucocyte count	↑ or normal	↑ or normal	↓	Normal
Differential leucocytes	Polymorphs ↑	—	Lymphocytes ↑	Eosinophilia at onset
Faeces				
colour	Intermittently pale	Pale	Variable, light to dark	Pale
occult blood	0	±	0	0
Urine: urobilin(ogen)	+	Absent	– Early + Late	– Early
Serum bilirubin (μmol/l)	Usually 50–170	Steady rise to 250–500	Varies with severity	Variable
Serum alkaline phosphatase (times normal)	>3×	>3×	<3×	>3×
Serum aspartate transaminase (times normal)	<5×	<5×	>10×	>5×
Ultrasound and CT	Gallstones ± dilated duct	Dilated ducts ± mass	Splenomegaly	Normal

Jaundice after biliary tract surgery suggests residual calculus, traumatic stricture of the bile duct or hepatitis. Jaundice following the removal of a malignant growth may be due to hepatic metastases. Jaundice due to sepsis and/or shock is common in hospital practice and is often assumed due to viral or drug liver injury [41].

Alcoholics usually have associated features such as anorexia, morning nausea, diarrhoea and mild pyrexia. They may complain of pain over the enlarged liver.

Progressive failure of health and weight loss favour an underlying carcinoma.

The onset is extremely important. Preceding nausea, anorexia and an aversion to smoking (in smokers), followed by jaundice a few days later, suggest viral hepatitis or drug jaundice. Cholestatic jaundice develops

more slowly, often with persistent pruritus. Pyrexia with rigors suggests cholangitis associated with gallstones or biliary stricture.

Dark urine and pale stools precede hepato-cellular or cholestatic jaundice by a few days. In haemolytic jaundice the stools have a normal colour.

In hepato-cellular jaundice the patient feels ill; in cholestatic jaundice he may be inconvenienced only by the itching or jaundice, any other symptoms being due to the cause of the obstruction.

Persistent mild jaundice of varying intensity suggests haemolysis. The jaundice of compensated cirrhosis is usually mild and variable and is associated with normal stools, although patients with superimposed acute 'alcoholic hepatitis' may be deeply jaundiced and pass pale stools.

Biliary colic may be continuous for hours rather than being intermittent. Back or epigastric pain may be associated with pancreatic carcinoma.

Examination (fig. 12.7)

Age and sex. A parous, middle-aged, obese female may have gallstones. The incidence of type A hepatitis decreases as age advances but no age is exempt from type B and C. The probability of malignant biliary obstruction increases with age. Drug jaundice is very rare in childhood.

General examination. Anaemia may indicate haemolysis, cancer or cirrhosis. Gross weight loss suggests cancer. The patient with haemolytic jaundice is a mild yellow colour, with hepato-cellular jaundice is orange, and with prolonged biliary obstruction has a deep greenish hue. A hunched-up position suggests pancreatic carcinoma. In alcoholics, the skin signs of cirrhosis should be noted. Sites to be examined for a primary tumour include breasts, thyroid, stomach, colon, rectum and lung. Lymphadenopathy is noted.

Mental state. Slight intellectual deterioration with minimal personality change suggests hepato-cellular jaundice. Fetor and 'flapping' tremor indicate impending hepatic coma.

Skin changes. Bruising may indicate a clotting defect. Purpuric spots on forearms, axillae or shins may be related to the thrombocytopenia of cirrhosis. Other cutaneous manifestations of cirrhosis include vascular spiders, palmar erythema, white nails and loss of secondary sexual hair.

In chronic cholestasis, scratch marks, melanin pigmentation, finger clubbing, xanthomas on the eyelids (xanthelasmas), extensor surfaces and palmar creases, and hyperkeratosis may be found.

Pigmentation of the shins and ulcers may be seen in some forms of congenital haemolytic anaemia.

Malignant nodules should be sought in the skin. Multiple venous thromboses suggest carcinoma of the body of the pancreas. Ankle oedema may indicate cirrhosis, or obstruction of the inferior vena cava due to hepatic or pancreatic malignancy.

Abdominal examination. Dilated peri-umbilical veins indicate a portal collateral circulation and cirrhosis. Ascites may be due to cirrhosis or to malignant disease. A very large nodular liver suggests cancer. A small liver may indicate severe hepatitis or cirrhosis, and excludes extra-hepatic cholestasis in which the liver is enlarged and smooth. In the alcoholic, fatty change and cirrhosis may produce a uniform enlargement of the liver. The edge is tender in hepatitis, in congestive heart failure, with alcoholism, in bacterial cholangitis and occasionally in malignant disease. An arterial murmur over the liver indicates acute alcoholic hepatitis or primary liver cancer.

In choledocholithiasis the gallbladder may be tender and Murphy's sign positive. A palpable, and sometimes visibly enlarged, gallbladder suggests pancreatic cancer.

The abdomen is carefully examined for any primary tumour. Rectal examination is essential.

Urine and faeces. Bilirubinuria is an early sign of viral hepatitis and drug jaundice. Persistent absence of urobilinogen suggests total obstruction of the common bile duct. Persistent excess of urobilinogen with negative bilirubin supports haemolytic jaundice.

Persistent pale stools suggest biliary obstruction. Positive occult blood favours a diagnosis of ampullary, pancreatic or alimentary carcinoma or of portal hypertension.

Serum biochemical tests

Serum bilirubin confirms jaundice, indicates depth and is used to follow progress. Serum alkaline phosphatase values more than three times normal strongly suggest cholestasis if bone disease is absent and γ-GT is elevated; high values may also be found in patients with non-biliary cirrhosis.

Serum albumin and globulin levels are little changed in jaundice of short duration. In more chronic hepato-cellular jaundice the albumin is depressed and globulin increased. Electrophoretic analysis shows raised α_2- and β-globulins in cholestatic jaundice, in contrast to γ-globulin elevation in hepato-cellular jaundice.

Serum transaminases increase in hepatitis compared with variable but lower levels in cholestatic jaundice. High values may sometimes be found transiently with acute bile duct obstruction due to a stone.

Haematology

A low total leucocyte count with a relative lymphocytosis suggests hepato-cellular jaundice. A polymorph leucocytosis may be found in alcoholic and severe viral hepatitis. Increased leucocyte counts are found with acute cholangitis or underlying malignant disease. If

haemolysis is suspected, investigations should include a reticulocyte count, examination of the blood film, erythrocyte fragility, Coombs' test and examination of the bone marrow.

If the prothrombin time is prolonged, vitamin K_1 10 mg intravenously for 3 days leads to a return to normal in cholestasis, whereas patients with hepato-cellular jaundice show little change.

Diagnostic routine

Clinical evaluation allows the patient to be categorized into hepato-cellular, infiltrative, possible extra-hepatic biliary obstruction and likely extra-hepatic biliary obstruction [10]. Various algorithms are possible (fig. 12.8). The sequence employed depends on the clinical evaluation, the facilities available and the risk of each investigation. Cost plays a part.

A small proportion of patients with extra-hepatic biliary obstruction are incorrectly diagnosed as having intra-hepatic cholestasis, whereas a larger proportion of patients with intra-hepatic disease are initially thought to have extra-hepatic obstruction.

Computer models are based on clinical history and examination with haematological and biochemical observations made during the first 6 h in hospital [29]. These have a performance equalling that of the hepatologist and better than some non-specialist internists. One computer-based system had an overall diagnostic accuracy of 70%, which was the same as experienced hepatologists who, however, reached a correct diagnosis with fewer questions per consultation [7].

Radiology

A chest film is taken to show primary and secondary tumours and any irregularity and elevation of the right diaphragm due to an enlarged or nodular liver.

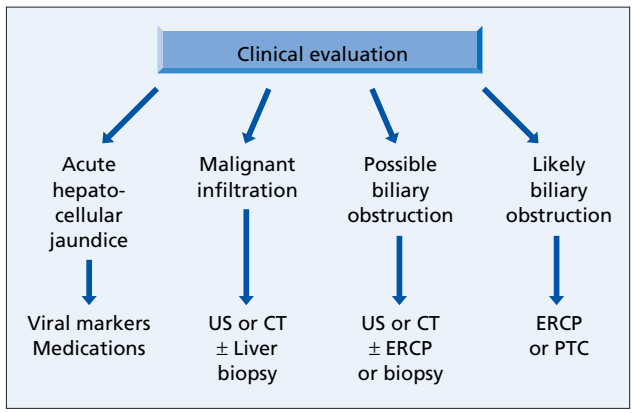


Fig. 12.8. An algorithm for diagnosing jaundice. CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; PTC, percutaneous transhepatic cholangiography; US, ultrasound.

Visualization of the bile ducts

This is indicated if the patient is cholestatic (Chapter 13). The first procedure in distinguishing hepato-cellular from surgical, main duct 'obstructive' jaundice is ultrasound to show whether or not the intra-hepatic bile ducts are dilated (figs 12.8, 13.18). This is usually followed by endoscopic examination (ERCP) although the advances in MRI make non-invasive MRCP an alternative, particularly where there is a relative contraindication to the endoscopic approach (Chapter 32). If direct cholangiography is necessary and ERCP has failed or there has been previous biliary bypass surgery, percutaneous cholangiography is indicated.

Viral markers

These are indicated for hepatitis A and B, cytomegalovirus and Epstein–Barr infections (Chapters 16 and 17). The serum antibody to hepatitis C virus becomes positive only 2–4 months after infection (Chapter 18).

Needle liver biopsy

Acute jaundice rarely merits liver biopsy, which is reserved for the patient who presents diagnostic difficulty and where an intra-hepatic cause is suspected. Deep jaundice is not a contraindication. If dilated bile ducts are shown on imaging, cholangiography is indicated and liver biopsy is inappropriate.

Transjugular or CT- or ultrasound-guided biopsy with plugging of the puncture site in the liver is useful if clotting defects preclude the routine percutaneous technique (Chapter 3).

Acute viral hepatitis is usually diagnosed easily. The greatest difficulty arises in the cholestatic group. However, in most instances an experienced histopathologist can distinguish appearances of intra-hepatic cholestasis, for instance due to drugs or to primary biliary cirrhosis, from the appearances of a block to the main bile ducts.

Laparoscopy

The appearance of a dark green liver with an enormous gallbladder favours extra-hepatic biliary obstruction. Tumour nodules may be seen and needle biopsy may be made under direct vision. A pale yellow–green liver suggests hepatitis and cirrhosis is obvious. The method cannot be relied upon to distinguish extra-hepatic biliary obstruction, especially due to a carcinoma of the main hepatic ducts, from intra-hepatic cholestasis due to drugs.

A photographic record should be taken of the appearances. In the presence of jaundice, peritoneoscopy is safer than needle biopsy but, if necessary, the two procedures may be combined.

Laparotomy

Before the many scanning techniques became available, patients occasionally underwent laparotomy in order to establish the cause of jaundice, with the risk of precipitating acute liver or renal failure. With all the scanning and other diagnostic approaches available laparotomy is inappropriate as a diagnostic approach.

Familial non-haemolytic hyperbilirubinaemias (table 12.3)

Although the upper limit of serum bilirubin is usually taken to be 17 µmol/l (0.8 mg/dl), in some 5% of healthy blood donors higher values (20–50 µmol/l) may be found. When those suffering from haemolysis or from liver disease have been excluded there remain the patients with familial abnormalities of bilirubin metabolism. The commonest is Gilbert's syndrome. Other syndromes can also be identified. The prognosis is excellent. Accurate diagnosis, particularly from chronic liver disease, is important for it enables the patient to be reassured. It is based on family history, duration, absence of stigmata of hepato-cellular disease and of splenomegaly, exclusion of haemolysis, normal serum transaminases and, if necessary, liver biopsy.

Table 12.3. Isolated rise in serum bilirubin

Type	Diagnostic points
Unconjugated	
Haemolysis	Splenomegaly. Blood film. Reticulocytosis. Coombs' test
Gilbert's syndrome	Familial. Serum bilirubin increases with fasting and falls on phenobarbitone administration. Liver biopsy normal but conjugating enzyme reduced. Normal serum transaminases. DNA analysis
Crigler–Najjar syndrome	
type I	No conjugating enzyme in liver No response to phenobarbitone Analysis of gene expression Risk of kernicterus Liver transplantation effective
type II	Absent or deficient conjugating enzyme in liver Response to phenobarbitone
Conjugated	
Dubin–Johnson syndrome	Black-liver biopsy. No concentration of cholecystographic media. Secondary rise in BSP test
Rotor type	Normal liver biopsy. Cholecystography normal BSP test no uptake

BSP, bromsulphalein.

Primary hyperbilirubinaemia

This very rare condition is due to increased production of 'early labelled' bilirubin in the bone marrow. The cause is probably the premature destruction of abnormal red cell precursors (ineffective erythrocyte synthesis). The clinical picture is of compensated haemolysis. Peripheral erythrocyte destruction is normal. The condition is probably familial [1].

Gilbert's syndrome

This is named after Augustin Gilbert (1858–1927), a Parisian physician [40]. It is defined as benign, familial, mild, unconjugated hyperbilirubinaemia (serum bilirubin 17–85 µmol/l [1–5 mg/dl]) not due to haemolysis and with normal routine tests of liver function and hepatic histology. It affects some 2–5% of the population.

It may be diagnosed by chance at a routine medical examination or when the blood is being examined for another reason, for instance after viral hepatitis. It has an excellent prognosis. Jaundice is mild and intermittent. Deepening may follow an intercurrent infection or fasting and is associated with malaise, nausea and often discomfort over the liver. These symptoms are probably no greater than in normal controls [21]. There are no other abnormal physical signs; the spleen is not palpable.

Patients with Gilbert's syndrome have a deficiency in hepatic bilirubin glucuronidation—about 30% of normal. The bile contains an excess of bilirubin monoglucuronide over the diglucuronide. The Bolivian squirrel monkey is an animal model for this disorder [26].

The genetic basis for Gilbert's syndrome has been clarified by the finding that the promoter region ($A(TA)_6TAA$) of the gene encoding UGT1*1 (see fig. 12.4) has an additional TA dinucleotide, resulting in a change to ($A(TA)_7TAA$) [3, 19]. It is inherited as autosomal recessive; that is, patients are homozygous for this abnormality.

There is a close relationship between the promoter region genotype and the expression of hepatic bilirubin UGT enzyme activity [27]. Individuals with the 7/7 genotype have the lowest enzyme activity. Heterozygotes (6/7 genotype) have an enzyme activity intermediate between 7/7 and normal wild-type 6/6.

A survey of individuals from eastern Scotland and Canadian Inuit populations have shown homozygosity

for the genotype A(TA)$_7$TAA allele in 12–17% of those tested [5]. This genotype may not always correlate with the serum bilirubin because environmental factors, such as alcohol ingestion, influence hepatic bilirubin UGT activity.

Patients with other variations of the A(TA)$_n$TAA allele have also shown elevated serum total bilirubin levels, including the alleles 5/6, 5/7 and 7/8 [5].

In Asians and the Japanese, the frequency of the TATAA box mutations is low, at around 3%. Studies suggest that heterozygosity for mutations in the UGT1*1 gene itself may have a mild hyperbilirubinaemia and appear clinically similar to patients with Gilbert's syndrome [15].

The lengthening of this promoter sequence is thought to interfere with the binding of the transcription factor IID, resulting in reduced UGT1*1 gene expression. However, although a reduced enzyme level is necessary for Gilbert's syndrome, it is not sufficient alone, and other factors such as reduced hepatic intake of bilirubin [24] and occult haemolysis may play a role in the development of hyperbilirubinaemia. Thus there may be a mild impairment of bromsulphalein (BSP) [24] and tolbutamide clearance (a drug that does not need conjugation).

The variant of the TATAA box found in Gilbert's syndrome is a major factor determining the unconjugated hyperbilirubinemia in ABO-incompatible neonates and also neonates with prolonged unconjugated hyperbilirubinaemia [13, 18]. It has also been implicated in persistent unconjugated hyperbilirubinaemia after liver transplantation, due to an abnormal TATAA box in the donor liver [12]. The same variant promoter also appears to influence the level of hyperbilirubinaemia in individuals with inherited haemolytic diseases [30] including β thalassemia where there is also an association with gallstone formation [26].

Specialist diagnostic tests include the increase in serum bilirubin on fasting (fig. 12.9) [22], the fall on taking phenobarbitone which induces the hepatic conjugating enzyme (fig. 12.10), and the increase following intravenous nicotinic acid which raises the osmotic fragility of red blood cells.

Thin layer chromatography shows a significantly higher proportion of unconjugated bilirubin than in normals, chronic haemolysis or chronic hepatitis; this is diagnostic. The fasting serum bile acids are normal or even low. Low values for bilirubin conjugating enzyme are found in liver biopsies. However, Gilbert's syndrome is usually diagnosed with ease without recourse to these specialist methods. The demonstration of a raised bilirubin level that is predominantly unconjugated, with normal liver enzymes and no evidence of haemolysis, is usually sufficient to reassure the patient who is otherwise asymptomatic without abnormal physical signs.

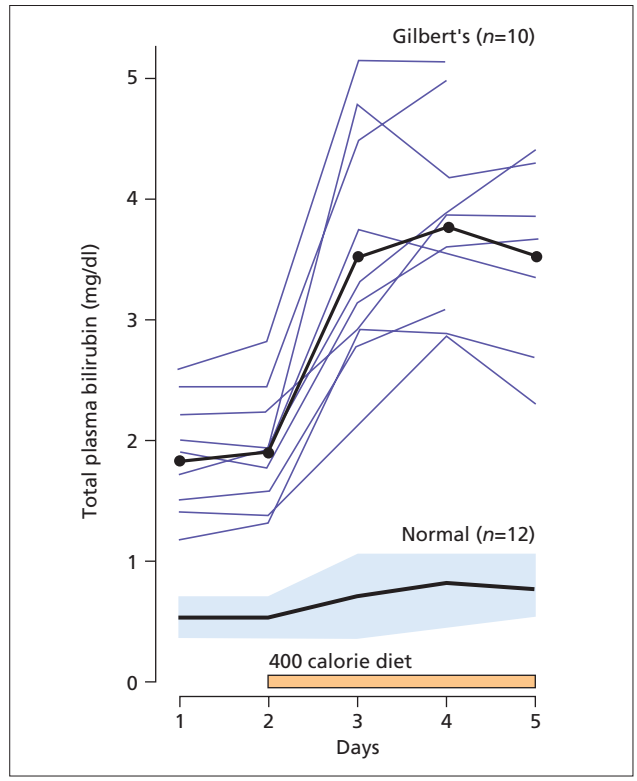


Fig. 12.9. Gilbert's syndrome. The serum unconjugated bilirubin level increases during a 400 calorie diet [22].

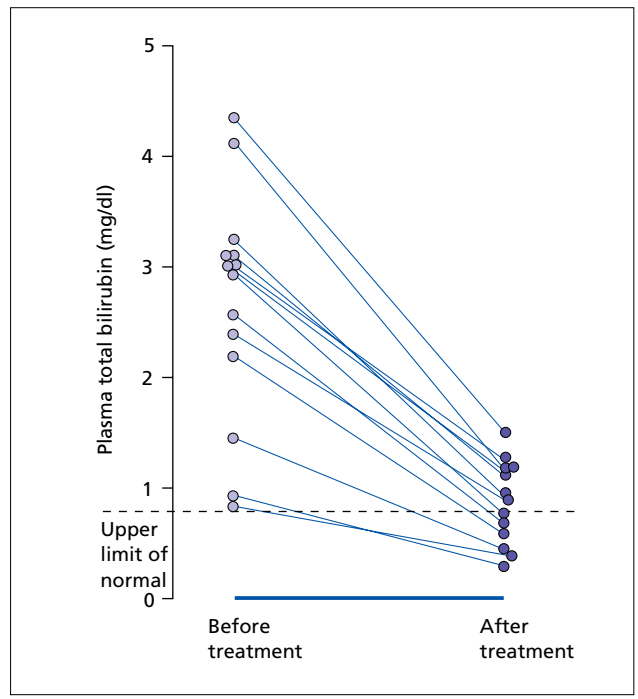


Fig. 12.10. Gilbert's syndrome. The effect of phenobarbitone (60 mg, three times a day) on the serum bilirubin level [2].

Patients with Gilbert's syndrome have a normal life expectancy and reassurance is the only necessary treatment. Hyperbilirubinaemia is life long and not associated with increased morbidity [21].

Serum bilirubin may be reduced by phenobarbitone [2] but, as icterus is rarely obvious, few patients will gain cosmetic benefit from this treatment. 'Sufferers' should be warned that jaundice can follow an intercurrent infection, repeated vomiting or missed meals. The 'sufferer' is a normal risk for life insurance.

Crigler–Najjar syndrome [11, 20]

This extreme form of familial non-haemolytic jaundice is associated with very high serum unconjugated bilirubin values. Inheritance is autosomal recessive. Deficiency of conjugating enzyme can be demonstrated in the liver. Total pigment in the bile is minimal.

Type I

In untreated patients the serum bilirubin is in excess of 350 μmol/l. No bilirubin conjugating enzyme can be detected in the liver. Bile contains only traces of bilirubin conjugates [11]. Since the serum bilirubin levels eventually stabilize, the patient must have some alternative pathway of bilirubin metabolism.

The molecular defect is in one of the five exons (1*1–5) of the bilirubin UGT1*1 gene (see fig. 12.4). Analysis of the Crigler–Najjar type I mutations by expression in COS cells or fibroblasts shows no bilirubin conjugating activity [33].

Around 170 cases of Crigler–Najjar type I have been reported in the world literature [11]. The overall prevalence is unknown. Before phototherapy was used, patients died at between 1 and 2 years of age from kernicterus. In this complication, due to high levels of unconjugated bilirubin, there is staining of basal ganglia and cranial nerve nuclei. Unconjugated bilirubin *in vitro* damages neurons and astrocytes through increased apoptosis [34]. The bilirubin encephalopathy may lead to central deafness, oculomotor palsy, ataxia, choreoathetosis, mental retardation, seizures, spasticity and death. This complication of the Crigler–Najjar syndrome is usually seen in the very young patient but may occur later.

Treatment is by daily phototherapy to keep the serum bilirubin level below 350 μmol/l. Oral calcium phosphate makes phototherapy more effective [38]. There is no response to phenobarbitone. Phlebotomy and plasmapheresis have been used to reduce the serum bilirubin, but with only temporary success. Phototherapy degrades unconjugated bilirubin into products including lumibilirubin, which is water soluble and can be secreted into the bile. Some of the photodegradation products may spontaneously revert to natural isomers of unconjugated bilirubin and the oral administration of calcium salts prevents their reabsorption. An alternative approach to reduce serum bilirubin levels is to inhibit the breakdown of haemoglobin to bilirubin by the enzyme haem oxygenase. Tin protoporphyrin, a haem oxygenase inhibitor, has been demonstrated to give a temporary (5–7 weeks) decrease in plasma unconjugated bilirubin of around 30% [28].

Orthotopic or orthotopic-auxiliary liver transplantation is the only definitive therapy for Crigler–Najjar type I. It has been recommended that this should be performed at a young age, particularly where reliable phototherapy cannot be guaranteed [39]. Phototherapy, although initially successful, becomes less efficient after puberty. There is always a risk of kernicterus because of lack of compliance and/or events that precipitate hyperbilirubinaemia, including infection, drug interactions, trauma and surgical procedures.

In a survey of 57 patients with Crigler–Najjar type I, 37% had received a liver transplant [39]. Twenty-six per cent had suffered brain damage but in half of these damage was mild and liver transplantation was still deemed appropriate.

Experimental treatment using percutaneous, transhepatic intra-portal administration of normal hepatocytes successfully reduced the serum bilirubin and the duration of phototherapy in a case report [9].

In *Gunn rats*, a mutant strain of the Wistar rat, bilirubin UGT is absent and there is unconjugated hyperbilirubinaemia. The genetic defect corresponds to that in Crigler–Najjar type I, with a deletion in the exon common to all UGT enzymes resulting in a premature stop codon which leads to the synthesis of truncated, inactive UGT isoforms. Experimentally, several approaches to gene therapy have been attempted in Gunn rats [37] with varying success. The metabolic defect has been corrected experimentally by site-specific repair using a chimeric oligonucleotide [16].

Type II

Bilirubin conjugating enzyme is reduced to less than 10% of normal in the liver and, although present, is undetectable by the usual methods of analysis. The serum bilirubin usually does not exceed 350 μmol/l. Jaundice is present of about half of patients within the first year of life, but can occur as late as 30 years of age. Acute exacerbations of hyperbilirubinaemia may occur during fasting or intercurrent illnesses and bilirubin encephalopathy can develop [20]. The patients respond dramatically to phenobarbitone and survive into adult life.

DNA analysis of the bilirubin UGT1*1 gene (see fig. 12.4) has shown mutations in exons 1*1–5 [4, 11].

However, expression analysis of these mutants has shown residual enzyme activity—explaining the lower serum bilirubin concentration than found in Crigler–Najjar type I—the presence of glucuronides in bile and the beneficial effect of phenobarbitone.

Some relatives of patients with Crigler–Najjar syndrome have an elevated serum bilirubin concentration, below that of true Crigler–Najjar but higher than that of Gilbert's syndrome [19]. Analysis of the UGT1*1 gene has suggested that these patients are compound heterozygotes, one allele having the Gilbert's TATAA box mutation, and the other having a Crigler–Najjar mutation [3, 36].

Type II is not always benign and phototherapy and phenobarbitone should be given to keep the serum bilirubin level less than 340 µmol/l (26 mg/dl).

The distinction between type I and type II Crigler–Najjar syndrome is made by observing the response to phenobarbitone treatment. There is no response in patients with type I. In patients with type II, the serum bilirubin level falls by more than 25%. There are exceptions to this rule. Some patients with type II do not respond to phenobarbitone. Definitive diagnosis in these patients could be done by *in vitro* expression of mutant DNA from patients in COS cells or fibroblasts, but this is too elaborate and expensive for routine use [33]. An alternative approach is to analyse duodenal bile after phenobarbitone. In type II there is an increase in biliary mono- and diconjugates. In type I only minimal traces of monoconjugate bilirubin are found [35].

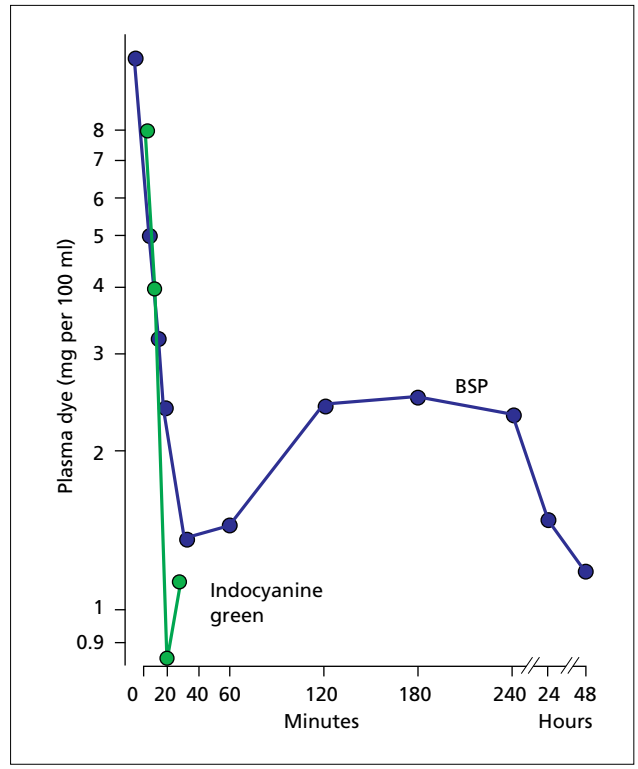


Fig. 12.11. Bromsulphalein (BSP) tolerance test (5 mg/kg i.v.) in a patient with Dubin–Johnson syndrome. At 40 min, the BSP level has almost returned to normal. An increase is then seen at 120, 180 and 240 min. Dye can still be detected in the blood at 48 h. The indocyanine green test is also shown and is normal at 20 min, but also has a tendency to increase at 30 min.

Dubin–Johnson syndrome

This is a chronic, benign, intermittent jaundice with conjugated and some unconjugated hyperbilirubinaemia and with bilirubinuria. It is autosomal recessive, and is most frequent in the Middle East among Iranian Jews. The mutation responsible is in the gene encoding cMOAT [23]. The defect in this transporter explains the diagnostic pattern seen in the prolonged BSP test [17]. After intravenous injection of BSP there is an initial fall in serum level which then rises so that the value at 120 min exceeds that seen at 45 min (fig. 12.11) due to regurgitation into the circulation of the glutathione conjugate, which is normally excreted into bile via cMOAT. The defect in this transporter also explains the increased urinary excretion of coproporphyrin I. Studies in the TR$^-$ rat, which has a mutation in the homologous canalicular transporter, has allowed characterization of these and other biochemical defects.

The liver, macroscopically, is greenish-black (black-liver jaundice) (fig. 12.12). In sections the liver cells show a brown pigment which is neither iron nor bile (fig. 12.13). There is no correlation between liver pigment and

Fig. 12.12. This needle liver biopsy from a patient with Dubin–Johnson syndrome is blackish-brown.

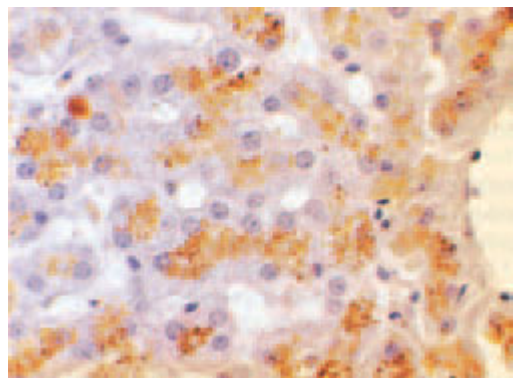


Fig. 12.13. Dubin–Johnson hyperbilirubinaemia. The liver cells and Kupffer cells are packed with a dark pigment which gives the staining reactions of lipofuscin. (H & E, ×275.)

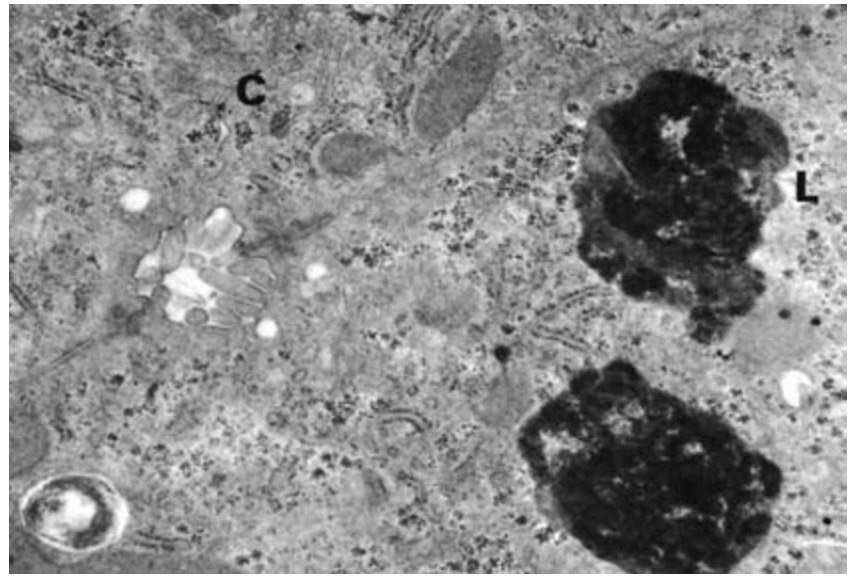


Fig. 12.14. Dubin–Johnson syndrome. Electron microscopy showing normal bile canaliculi with intact microvilli (C). Lysosomes (L) are enlarged, irregularly shaped and contain granular material and often membrane-bound lipid droplets.

serum bilirubin levels. The chemical nature of the pigment is not certain. Previously thought due to melanin, recent data support the proposal that impaired secretion of anionic metabolites of tyrosine, phenylalanine and tryptophan is responsible [14].

Electron microscopy shows the pigment in dense bodies related to lysosomes (fig. 12.14).

Pruritus is absent and the serum alkaline phosphatase and bile acid levels are normal.

The contrast media used in intravenous cholangiography are not transported into bile but ^{99m}Tc-HIDA excretion shows a normal liver, biliary tree and gallbladder.

Rotor type

This is a similar form of chronic familial conjugated hyperbilirubinaemia. It resembles the Dubin–Johnson syndrome, the main difference being the absence of brown pigment in the liver cell [32]. Electron microscopy may show abnormalities of mitochondria and peroxisomes [8].

The condition also differs from the Dubin–Johnson type in that the gallbladder opacifies on cholecystography and there is no secondary rise in the BSP test. The abnormality causing BSP retention appears to be related to a defect in hepatic uptake rather than excretion as originally demonstrated in the Dubin–Johnson syndrome. ^{99m}Tc-HIDA excretion gives no visualization of the liver, gallbladder or biliary tree.

Total urinary coproporphyrins are raised, as in cholestasis.

Family studies make an autosomal inheritance probable. The Rotor type has an excellent prognosis.

The group of familial non-haemolytic hyperbilirubinaemias

There is much overlap between the various syndromes of congenital hyperbilirubinaemia. Patients are found in the same family with conjugated hyperbilirubinaemia, with or without pigment in the liver cells. Pigmented livers have been found in patients with unconjugated hyperbilirubinaemia [6]. In one large family the propositi had the classic Dubin–Johnson picture, but the commonest abnormality in the family was unconjugated hyperbilirubinaemia [6]. In another family, conjugated and unconjugated hyperbilirubinaemia alternated in the same patient [31]. Such observations add to the confusion in separating the groups and in deciding the inheritance.

References

1 Arias IM. Chronic unconjugated hyperbilirubinaemia (CUH) with increased production of bile pigment not derived from the haemoglobin of mature, circulating erythrocytes. *J. Clin. Invest.* 1962; **41**: 1341.
2 Black M, Sherlock S. Treatment of Gilbert's syndrome with phenobarbitone. *Lancet* 1970; **i**: 1359.
3 Bosma PJ, Chowdhury JR, Bakker C *et al*. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. *N. Engl. J. Med.* 1995; **333**: 1171.
4 Bosma PJ, Goldhoorn B, Elferink RPJO *et al*. A mutation in bilirubin uridine 5′-diphosphate-glucuronosyltransferase isoform 1 causing Crigler–Najjar syndrome Type II. *Gastroenterology* 1993; **105**: 216.
5 Burchell B, Hume R. Molecular genetic basis of Gilbert's syndrome. *J. Gastroenterol. Hepatol.* 1999; **14**: 960.
6 Butt HR, Anderson VE, Foulk WT *et al*. Studies of chronic idiopathic jaundice (Dubin–Johnson syndrome). II. Evalua-

tion of a large family with the trait. *Gastroenterology* 1966; **51**: 619.
7 Camma C, Garofalo G, Almasio P *et al*. A performance evaluation of the expert system 'jaundice' in comparison with that of three hepatologists. *J. Hepatol.* 1991; **13**: 279.
8 Evans J, Lefkowitch J, Lim CK *et al*. Fecal porphyrin abnormalities in a patient with features of Rotor's syndrome. *Gastroenterology* 1981; **81**: 1125.
9 Fox, IJ, Chowdhury JR, Kaufman SS *et al*. Treatment of the Crigler–Najjar syndrome type I with hepatocyte transplantation. *N. Engl. J. Med.* 1998; **338**: 1422.
10 Frank BB. Clinical evaluation of jaundice. A guideline of the patient care committee of the American Gastroenterological Association. *JAMA* 1989; **262**: 3031.
11 Jansen PLM. Diagnosis and management of Crigler–Najjar syndrome. *Eur. J. Paediatr.* 1999; **158** (Suppl. 2): S89.
12 Jansen PLM, Bosma PJ, Bakker C *et al*. Persistent unconjugated hyperbilirubinemia after liver transplantation due to an abnormal bilirubin UDP-glucuronosyltransferase gene promotor sequence in the donor. *J. Hepatol.* 1997; **27**: 1.
13 Kaplan M, Hammerman C, Renbaum P *et al*. Gilbert's syndrome and hyperbilirubinaemia in ABO-incompatible neonates. *Lancet* 2000; **356**: 652.
14 Kitamura T, Alroy J, Gatmaitan Z *et al*. Defective biliary excretion of epinephrine metabolites in mutant (TR^-) rats: relation to the pathogenesis of black liver in the Dubin–Johnson syndrome and Corriedale sheep with an analogous excretory defect. *Hepatology* 1992; **15**: 1154.
15 Koiwai O, Nishizawa M, Hasada K *et al*. Gilbert's syndrome is caused by heterozygous missense mutation in the gene for bilirubin UDP-glucuronosyltransferase. *Hum. Mol. Gen.* 1995; **4**:1183.
16 Kren BT, Parashar B, Bandyopadhyay P *et al*. Correction of the UDP-glucuronosyltransferase gene defect in the Gunn rat model of Crigler–Najjar syndrome type I with a chimeric oligonucleotide. *Proc. Natl. Acad. Sci. USA* 1999; **96**: 10349.
17 Mandema E, De Fraiture WH, Nieweg HO *et al*. Familial chronic idiopathic jaundice (Dubin–Sprinz disease) with a note on bromsulphalein metabolism in this disease. *Am. J. Med.* 1960; **28**: 42.
18 Monaghan G, McLellan A, McGeehan A *et al*. Gilbert's syndrome is a contributory factor in prolonged unconjugated hyperbilirubinemia of the newborn. *J. Paediatr.* 1999; **134**: 441.
19 Monaghan G, Ryan M, Seddon R *et al*. Genetic variation in bilirubin UDP-glucuronosyltransferase gene promoter and Gilbert's syndrome. *Lancet* 1996; **347**: 578.
20 Nowicki MJ, Poley JR *et al*. The hereditary hyperbilirubinaemias. *Bailliere's Clin. Gastroenterol.* 1998; **12**: 355.
21 Olsson R, Stigendal L. Clinical experience with isolated hyperbilirubinemia. *Scand. J. Gastroenterol.* 1989; **24**: 617.
22 Owens D, Sherlock S. The diagnosis of Gilbert's syndrome: role of the reduced caloric intake test. *Br. Med. J.* 1973; **iii**: 559.
23 Paulusma CC, Kool M, Bosma PJ *et al*. A mutation in the human canalicular multispecific organic anion transporter gene causes the Dublin–Johnson syndrome. *Hepatology* 1997; **25**: 1539.
24 Persico M, Persico, E, Bakker CTM *et al*. Hepatic uptake of organic anions affects the plasma bilirubin level in subjects with Gilbert's syndrome mutations in UGT1A1. *Hepatology* 2001; **33**: 627.
25 Portman OW, Chowdhury JR, Chowdhury NR *et al*. A nonhuman primate model of Gilbert's syndrome. *Hepatology* 1984; **4**: 175.
26 Premawardhena A, Fisher CA, Fathiu F *et al*. Genetic determinants of jaundice and gallstones in haemoglobin E β thalassaemia. *Lancet* 2001; **357**: 1945.
27 Raijmakers MTM, Jansen PLM, Steegers EAP *et al*. Association of human liver bilirubin UDP-glucuronyltransferase activity with a polymorphism in the promoter region of the UGT1A1 gene. *J. Hepatol.* 2000; **33**: 348.
28 Rubaltelli FF, Guerrini P, Reddie E *et al*. Tin-protoporphyrin in the management of children with Crigler–Najjar disease. *Paediatrics* 1989; **84**: 728.
29 Saint-Marc Girardin M-F, Le Minor M, Alperovitch A *et al*. Computer-aided selection of diagnostic tests in jaundiced patients. *Gut* 1985; **26**: 961.
30 Sampietro M, Iolascon A. Molecular pathology of Crigler–Najjar type I and II and Gilbert's syndromes. *Haematologica* 1999; **84**: 150.
31 Satler J. Another variant of constitutional familial hepatic dysfunction with permanent jaundice and with alternating serum bilirubin relations. *Acta Hepatosplen*. 1966; **13**: 38.
32 Schiff L, Billing BH, Oikawa Y. Familial nonhemolytic jaundice with conjugated bilirubin in the serum. A case study. *N. Engl. J. Med.* 1959; **260**: 1314.
33 Seppen J, Bosma PJ, Goldhoorn, BG *et al*. Discrimination between Crigler–Najjar type I and II by expression of mutant bilirubin uridine diphosphate glucuronosyl transferase. *J. Clin. Invest.* 1994; **94**: 2385.
34 Silva RFM, Rodrigues CMP, Brites D. Bilirubin-induced apoptosis in cultured rat neural cells is aggravated by chenodeoxycholic acid but prevented by ursodeoxycholic acid. *J. Hepatol.* 2001; **34**: 402.
35 Sinaasappel M, Jansen PLM. The differential diagnosis of Crigler–Najjar disease, types 1 and 2, by bile pigment analysis. *Gastroenterology* 1991; **100**: 783.
36 Strassburg CP, Manns MP. Jaundice, genes and promoters. *J. Hepatol.* 2000; **33**: 476.
37 Tiribelli C, Ostrow JD. New concepts in bilirubin and jaundice: report of the Third International Bilirubin Workshop, April 6–8, 1995, Trieste, Italy. *Hepatology* 1996; **24**: 1296.
38 van der Veere CN, Jansen PLM, Sinaasappel M *et al*. Oral calcium phosphate: a new therapy for Crigler–Najjar disease? *Gastroenterology* 1997; **112**: 455.
39 van der Veere CN, Sinaasappel M, McDonagh AF *et al*. Current therapy of Crigler–Najjar syndrome type I: report of a world registry. *Hepatology* 1996; **24**: 311.
40 Watson KJR, Gollan JL. Gilbert's syndrome. *Clin. Gastroenterol.* 1989; **3**: 337.
41 Whitehead MW, Hainsworth I, Kingham JGC. The causes of obvious jaundice in South West Wales: perceptions versus reality. *Gut* 2001; **48**: 409.
42 Zucker SD, Goessling W, Gollan JL. Kinetics of bilirubin transfer between serum albumin and membrane vesicles. *J. Biol. Chem.* 1995; **270**: 1974.

Chapter 13
Cholestasis

Cholestasis is defined as the failure of normal bile to reach the duodenum. This may be due to pathology anywhere between the hepatocyte and the ampulla of Vater. The term 'obstructive jaundice' is not used, as in many instances no mechanical block can be shown in the biliary tract.

Prolonged cholestasis produces biliary cirrhosis; the time taken for its development varies from months to years. The transition is not reflected in a sudden change in the clinical picture. The term 'biliary cirrhosis' is reserved for a pathological picture. It is diagnosed when there are features of cirrhosis such as nodule formation, encephalopathy or fluid retention.

Fig. 13.1. Scanning electron micrograph of the canalicular biliary system.

Anatomy of the biliary system

Bile salts, conjugated bilirubin, cholesterol, phospholipids, proteins, electrolytes and water are secreted by the liver cell into the canaliculus (fig. 13.1). The bile secretory apparatus comprises the *canalicular membrane* with its carrier proteins, the *intra-cellular organelles* and the *cytoskeleton* of the hepatocyte (fig. 13.2). *Tight junctions* between hepatocytes seal the biliary space from the blood compartment.

The canalicular membrane contains carrier proteins which transport bile acids, bilirubin, cations and anions. The microvilli increase the surface area. The organelles include the Golgi apparatus and lysosomes. Vesicles carry proteins such as IgA from the sinusoid to the canaliculus, and newly synthesized cholesterol and phospholipid, and possibly bile acid membrane transporters, from the microsomes to the bile canalicular membrane.

The peri-canalicular cytoplasm contains elements of the *cytoskeleton* of the hepatocyte: *microtubules*, *microfilaments* and *intermediate filaments* [84]. Microtubules are

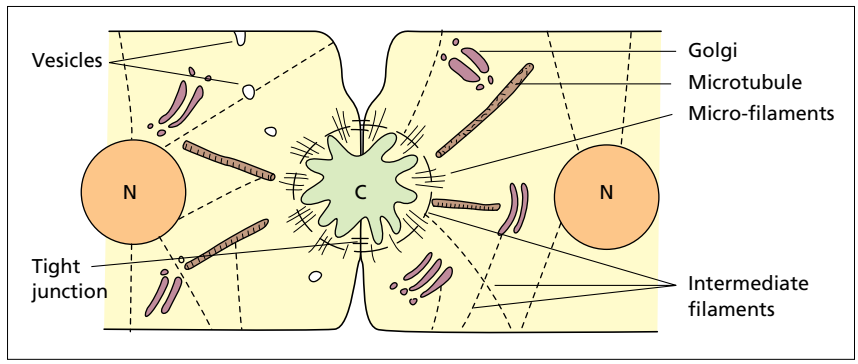


Fig. 13.2. The biliary secretory apparatus. Diagram of the ultrastructure of the bile canaliculus (C), cytoskeleton, and organelles (N, nucleus).

formed by the polymerization of tubulin and provide a network within the cell, particularly near the basolateral membrane and Golgi apparatus. They participate in receptor-mediated vesicular transcytosis, in the secretion of lipids, and under some conditions the secretion of bile acids. Their formation is inhibited by colchicine.

Micro-filament formation involves the interaction between polymerized (F) and free (G) actin. Canalicular motility and contraction depend upon micro-filaments which are clustered around the canalicular membrane. Phalloidin increases, and cytochalasin B reduces the polymerization of actin. Both inhibit canalicular motility and produce cholestasis.

Intermediate filaments are composed of cytokeratin. They form a network between the plasma membrane, nucleus, intra-cellular organelles and other elements of the cytoskeleton. The disruption of intermediate filaments affects intra-cellular transport processes and obliterates the canalicular space.

The canalicular secretion is modified by water and electrolytes passing between hepatocytes across the tight junction (*paracellular flow*). This transfer is due to the osmotic gradient between the canalicular secretion and the intra-cellular fluid in continuity with the space of Disse. Disruption of the tight junction leads to free passage of solute and larger molecules into the canaliculus with loss of the osmotic gradient and cholestasis. Canalicular bile may also regurgitate into the sinusoid.

The bile canaliculi empty into ductules sometimes called cholangioles or canals of Hering (fig. 13.3). These are found largely in the portal zones of the liver. The ductule passes into the interlobular bile duct which is the first bile channel to be accompanied by a branch of the hepatic artery and portal vein. These are also found in the portal triad. These channels unite with one another to form septal bile ducts and so on until the two main hepatic ducts emerge from the right and left lobes of the liver at the porta hepatis.

Small bile ducts distal to the canals of Hering are lined by four to five cholangiocytes. There are tight junctions between the cholangiocytes, which lie on a basement membrane. Microvilli project into the bile duct lumen [5]. In larger bile duct radicals the cholangiocytes are larger and more columnar in shape. The properties of cholangiocytes differ between the small and large ducts [5, 49].

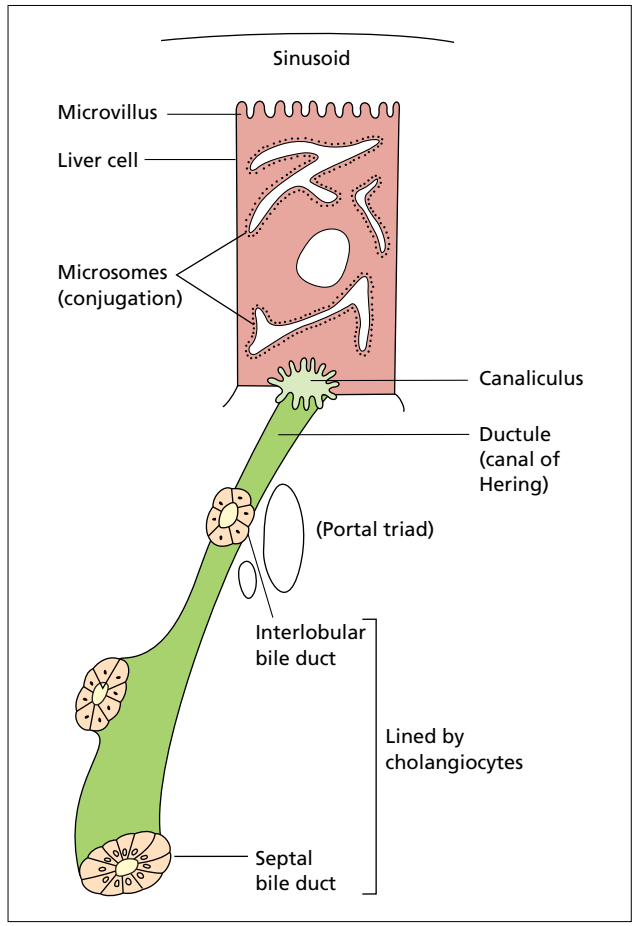


Fig. 13.3. The anatomy of the intra-hepatic biliary system.

Secretion of bile

Secretion is relatively independent of perfusion pressure. Bile is produced by hepatocytes and modified by cholangiocytes lining the bile ducts. Bile formation is dependent on energy-dependent transport processes in the basolateral and canalicular membranes of the hepatocyte, and the basolateral and apical membranes of cholangiocytes. There is transepithelial movement of organic molecules, electrolytes and water, as well as passage of solutes between adjacent cells (paracellular route) [58, 83]. The total bile flow in man is about 600 ml/day (fig. 13.4). The hepatocyte provides two components: bile salt dependent (≈225 ml/day) and bile salt independent (≈225 ml/day). Cholangiocytes contribute a further 150 ml/day.

The passage of conjugated bile salts into the biliary canaliculus is the most important factor promoting bile formation. This is the *bile salt dependent fraction*. Water follows the osmotically active bile salts and there is a tight relationship between bile flow and bile salt secretion. The entero-hepatic cycling of conjugated bile salts depends upon their reabsorption by the ileal Na^+-dependent bile salt transporter into the circulation and then their transfer from the sinusoidal to the canalicular membrane of the hepatocyte.

Bile salt independent flow is shown by extrapolation of bile salt excretion versus bile flow data to zero bile salt secretion when a positive intercept is shown. This indicates that flow would continue at zero bile salt excretion, presumably by a bile salt independent process. In this case osmotically active solutes, such as glutathione and bicarbonate, generate water flow.

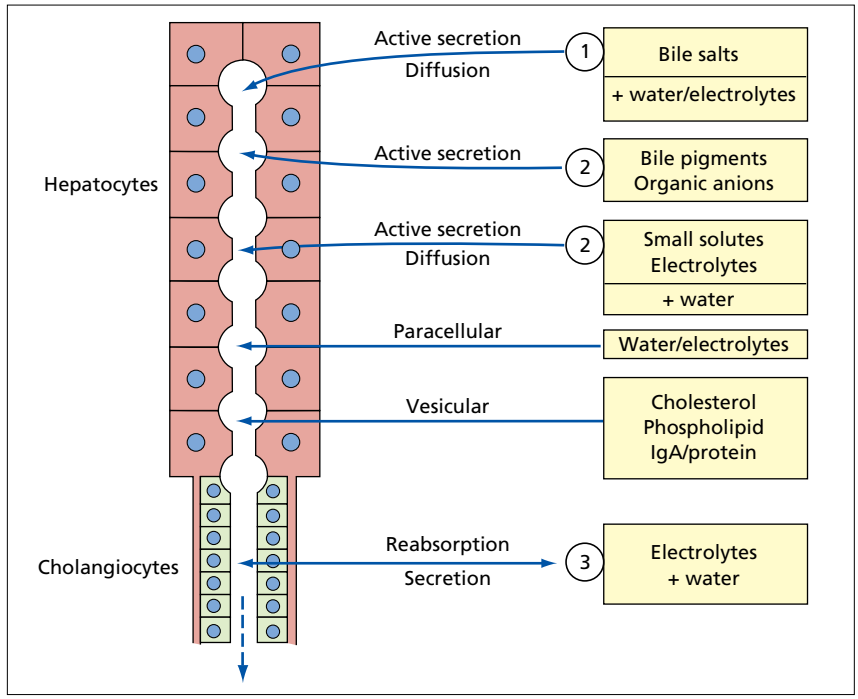


Fig. 13.4. Mechanisms of bile formation. (1) Bile salt dependent (≈225 ml/day). (2) Bile salt independent (≈225 ml/day). (3) Ductular flow (≈150 ml/day) stimulated by secretin.

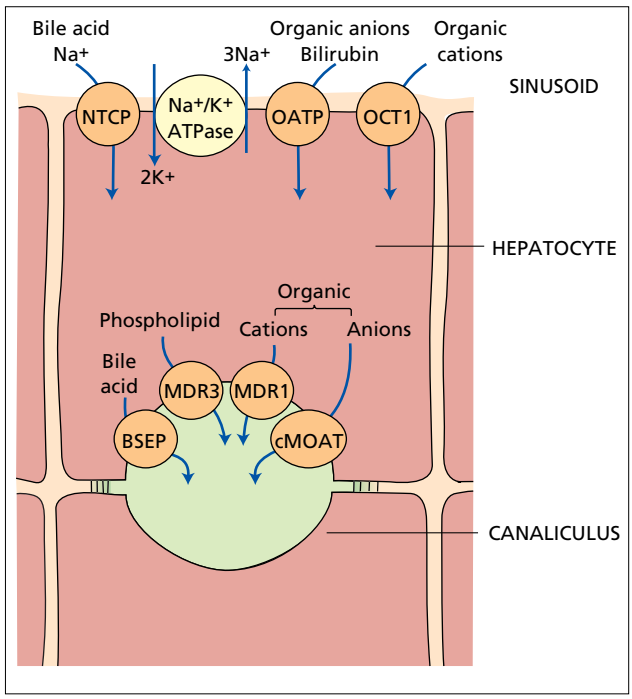


Fig. 13.5. Major transport systems in bile formation. Note the Na^+/K^+–ATPase or sodium pump (centre top), the sinusoidal Na^+ taurocholate co-transporting protein (NCTP), the sinusoidal multi-specific organic anion transporter (OATP) and the organic cation transport 1 (OCT1). The canalicular membrane transporters are: BSEP, the bile salt export pump; cMOAT, the multi-specific organic anion transporter; MDR1, the ATP-dependent transporter of organic cations; and MDR3, an ATP-dependent phospholipid transporter (flippase). Other transport systems include a sinusoidal Na^+–H^+ exchanger, and canalicular bicarbonate transport.

Cellular mechanisms

The hepatocyte is a polarized secretory epithelial cell with a basolateral (sinusoidal and lateral) and apical (canalicular) membrane (fig. 13.5).

Bile formation requires the uptake of bile acids and other organic and inorganic ions across the basolateral (sinusoidal) membrane, transport through the hepatocyte and excretion across the canalicular membrane. This is followed by osmotic filtration of water from the hepatocyte and along the paracellular pathway.

The secretory process depends upon the presence of one set of carrier proteins in the basolateral membrane and another in the canalicular membrane (fig. 13.5). Driving the whole process is the Na^+/K^+–ATPase in the basolateral membrane which maintains a chemical gradient and potential difference between the hepatocyte and its surroundings. This transporter exchanges three intra-cellular sodium ions for two extra-cellular potassium ions, thus maintaining the sodium (high outside : low inside) and potassium (low outside : high inside) gradient. In addition, because of the imbalance of electrical exchange, the cell interior is negatively charged (–35 mV) compared with the exterior, favouring uptake of positively charged ions and excretion of those with a negative charge. The Na^+/K^+–ATPase is present on the basolateral membrane; it is not found on the canalicular membrane. This carrier, among others, is influenced by changes in membrane fluidity.

Sinusoidal uptake

In the basolateral (sinusoidal) membrane of the hepato-

cyte there are multiple transport systems for organic anion uptake with partially overlapping substrate specificities (fig. 13.5). The Na^+-dependent taurocholate co-transporter protein (NTCP) transports bile acids conjugated with taurine or glycine. The organic anion transporter protein (OATP) is sodium independent and carries several molecules including bile acids, bromsulphthalein and other organic anions. There is also an organic cation transporter (OCT1) [43, 58, 83]. Less well-defined carriers are thought to transport bilirubin into the hepatocyte [66].

Other ion transporters on the basolateral surface are the Na^+–H^+ exchanger involved in control of intracellular pH. An Na^+–HCO_3–co-transporter also serves this function. The basolateral membrane also contains uptake processes for sulphate, non-esterified fatty acids and organic cations.

Intra-cellular transport

Transport of bile acids across the cell involves cytosolic proteins. The major protein is 3-α-hydroxysteroid dehydrogenase. Glutathione-*S*-transferase and fatty acid binding proteins are less important. The endoplasmic reticulum and Golgi apparatus are implicated in the transfer of bile acid. Vesicular transport of bile salts only seems relevant at high, supraphysiological flux rates.

The transcytotic vesicular pathway transports fluid phase proteins and ligands such as IgA and low density lipoprotein (LDL). Transfer from basolateral membrane to the region of the canaliculus takes about 10 min. This mechanism accounts for only a small percentage of total bile flow. It is microtubule dependent.

Canalicular secretion

The canalicular membrane is a special part of the hepatocyte plasma membrane which contains transporters responsible for carrying molecules into bile against steep concentration gradients. It also contains enzymes such as alkaline phosphatase and γ-glutamyl-transpeptidase.

These transporters mainly belong to the family of ATP-binding cassette proteins of which several hundred have been identified across many organisms including prokaryotes, plants, insects and mammals. They are by definition ATPase dependent. The canalicular multispecific organic anion transporter (cMOAT also known as MRP-2, a member of the multi-drug resistance protein family) carries glucuronide and glutathione-*S*-conjugates, e.g. bilirubin diglucuronide. The canalicular bile salt export pump (BSEP) carries bile acids and is in part driven by the negative intra-cellular electric potential. Bile acid independent flow probably depends upon glutathione transport as well as the canalicular secretion of bicarbonate, possibly by a Cl^-/HCO_3–exchanger.

Two members of the P-glycoprotein family are important in canalicular transport; both are ATP dependent [64]. Multiple drug resistance 1 (MDR1) is a transporter of hydrophobic organic cations, and derives its name from being responsible for transporting cytotoxic drugs out of cancer cells, rendering them resistant to these drugs. The endogenous substrate is not known. MDR3 is a phospholipid translocator that acts as a flippase for phosphatidylcholine, and is important in the secretion of phospholipid into bile. The function and importance of this and other canalicular transporters has been clarified by experimental knockout models and also the recognition of human cholestatic syndromes where mutations in transporter genes have been found (see below).

Water and inorganic ions (in particular sodium) enter canalicular bile by diffusion across the tight junctions because of the osmotic gradient. The tight junction is a negatively charged semi-permeable barrier.

Bile secretion is influenced by many hormones and second messengers including cyclic AMP and protein kinase C. Passage of bile from the canaliculus involves micro-filaments which are responsible for canalicular motility and contraction.

Ductular modification of bile

Although both small and larger bile ducts are lined by cholangiocytes, the function of these cells differs according to their position along the biliary system. Smaller cholangiocytes lining the small bile ducts adjacent to the canals of Hering and canaliculi provide a passive lining, taking little or no part in modifying bile. These cells may play a role as poorly differentiated primordial cells which can proliferate and acquire functional features of large cholangiocytes when these have been damaged. There may be passive absorption of lipophilic molecules including unconjugated bile acids and unconjugated bilirubin across these cells but currently this is speculation [49].

The cholangiocytes lining the larger bile ducts participate in hormone-regulated ductal secretion of a bicarbonate-rich solution—so-called *ductular bile flow*. They express secretin receptors, the cystic fibrosis transmembrane conductance regulator (CFTR), the chloride–bicarbonate exchanger and somatostatin receptors. After secretin binds to its basolateral receptor, intracellular cyclic AMP synthesis increases. This activates protein kinase A (PKA) which subsequently activates the chloride channel (CFTR). Function of the chloride–bicarbonate exchanger depends upon the transport of chloride ions by CFTR into the bile duct. Chloride within the bile duct lumen is reabsorbed into cholangiocytes in exchange for bicarbonate.

Interaction of somatostatin with its receptor (SSTR2) on the basolateral surface of large cholangiocytes

depresses cyclic AMP synthesis so that there is a reversal of the mechanism described above; there is a decrease in chloride channel opening and chloride–bicarbonate exchanger activity [5, 49].

Several other gastrointestinal hormones, peptides and nerve pathways influence ductular bile secretion. Bombesin and vaso-active intestinal peptide (VIP) increase bile flow through stimulation of the chloride–bicarbonate exchanger. Gastrin, insulin and endothelin inhibit secretin-induced bicarbonate-rich choleresis. Acetyl choline increases basal- and secretin-stimulated bicarbonate secretion.

Cholangiocytes may also play a role in the reabsorption of taurocholate via an apical carrier similar to the ileal bile acid transporter [79].

There are also water channels (aquaporins) in the apical and basolateral membrane of the cholangiocyte. Secretin triggers the insertion of aquaporin 1 into the apical membrane of the cholangiocyte and this facilitates transport of water into bile [56]. Aquaporin 4, in the basolateral membrane subserves entry of water into the cell [57]. Thus ductular bile formation depends upon the regulation of both ion transporters and water channels in the cholangiocyte.

Ursodeoxycholic acid and other dehydroxy bile acids cross the biliary epithelium by non-ionic diffusion. The bile acid recirculates to the liver ('cholehepatic shunting') for further excretion. This explains the choleretic effect of ursodeoxycholic acid associated with high biliary bicarbonate secretion [79].

Bile is normally secreted at a pressure of about 15–25 cmH_2O. A rise to about 35 cmH_2O results in suppression of bile flow and so to jaundice. Bilirubin and bile acid secretion may stop, resulting in *white bile* which appears like a clear mucus-containing fluid.

Genetic defects in transporters

The discovery of mutations in some of the transporters described above has added to the understanding of their function. The syndrome of progressive familial intra-hepatic cholestasis (PFIC) comprises subgroups for which genetic defects have been found or mapped.

Mutation of the BSEP gene and absence of canalicular BSEP have been shown in patients with type 2 PFIC.

Mutations in the MDR3 gene cause type 3 PFIC. There is no cholestasis since bile flow is not impaired. Hepatobiliary damage is thought to be caused by the lack of phospholipid in bile so that bile acids are toxic to cholangiocytes and hepatocytes.

The genetic abnormality in type 1 PFIC and benign recurrent intra-hepatic cholestasis has been mapped to chromosome 18q21 in some but not all families [59]. The gene involved (FIC1) is a P-type ATPase but neither its function in the liver nor the pathogenetic mechanism causing cholestasis is known.

Mutations in cMOAT/MRP-2 which transports bilirubin and bilirubin glucuronide across the canalicular membrane are responsible for the Dubin–Johnson syndrome [44].

Syndrome of cholestasis

Definition

Cholestasis is interference with bile flow or formation. This can occur anywhere between the basolateral (sinusoidal) membrane of the hepatocyte and the ampulla of Vater.

Functionally, cholestasis is defined as a decrease in canalicular bile flow. There is a decreased hepatic secretion of water and/or organic anions (bilirubin, bile acid).

Morphologically, cholestasis is defined as the accumulation of bile in liver cells and biliary passages.

Clinically, cholestasis is the retention in the blood of all substances normally excreted in the bile. Serum bile acids are increased. Clinical features are itching (not always present) and raised serum alkaline phosphatase (biliary isoenzyme) and γ-glutamyl-transpeptidase.

Classification

Cholestasis may be classified as extra- or intra-hepatic, and acute or chronic.

Extra-hepatic cholestasis encompasses conditions where there is physical obstruction to the bile ducts. Usually this is outside the liver, but a hilar cholangiocarcinoma growing up main intra-hepatic ducts would be included. The most common cause is a stone in the common duct (Chapter 34); other causes are carcinoma of the pancreas and ampulla (Chapter 36), benign bile duct stricture (Chapter 35) and cholangiocarcinoma (Chapter 37). Usually this group causes acute cholestasis.

Intra-hepatic cholestasis includes those conditions where there is no demonstrable obstruction (on cholangiography) to the major bile ducts. Causes are drug-induced cholestasis, cholestatic hepatitis (Chapter 16), hormones, primary biliary cirrhosis (Chapter 14) and septicaemia. Primary sclerosing cholangitis (Chapter 15) may produce both intra- and extra-hepatic cholestasis, depending on the size of duct involved and whether there is a 'dominant' stricture in the common duct. Rare causes of intra-hepatic cholestasis include Byler's disease (PFIC type 1), benign recurrent cholestasis, Hodgkin's disease and amyloid. Intra-hepatic cholestasis may be acute, e.g. drug related, or chronic as in primary biliary cirrhosis and primary sclerosing cholangitis.

The importance of the distinction between extra- and intra-hepatic cholestasis is that symptoms and

biochemistry may not separate them. There is a need for a diagnostic algorithm to differentiate between the two.

Patients with both acute and chronic cholestasis may itch, malabsorb fat and be vitamin K deficient. Chronic cholestatic patients may have in addition hyperlipidaemia and bone disease.

Pathogenesis

Physical obstruction to the bile duct by stone or stricture is straightforward. The pathogenesis of primary biliary cirrhosis and primary sclerosing cholangitis is described elsewhere (Chapters 14 and 15). Drugs, hormones and sepsis affect hepatocyte cytoskeleton and membrane (table 13.1).

Membrane fluidity. Ethinyl oestradiol is known to decrease fluidity of the sinusoidal plasma membrane. This can be prevented experimentally by the methyl donor S-adenosyl-L-methionine (SAME).

Membrane transporters. Endotoxin decreases Na^+/K^+–ATPase activity. Cyclosporin A inhibits ATP-dependent bile acid transport across the canalicular membrane. In an experimental model of the cholestasis associated with colitis, there is decreased expression of the canalicular multi-specific organic anion transporter (cMOAT) possibly due to increased endotoxin levels [50]. Bile acid uptake and secretion by the liver are reduced [87].

Cytoskeleton. Integrity of the canalicular membrane may be altered by disruption of either the *micro-filaments* responsible for canalicular tone and contraction, or the *tight junctions*. Cholestasis due to phalloidin is related to depolymerization of the actin of micro-filaments. Chlorpromazine also affects polymerization of actin. Cytochalasin B and androgens disrupt micro-filaments and canaliculi become less contractile. Oestrogens and phalloidin disrupt tight junctions and this leads to loss of the normal barrier between the intracellular fluid in the space of Disse and canalicular bile, with passage of solutes directly from canaliculus into blood, and vice versa.

Vesicular transport. This depends upon the integrity of microtubules and these can be disrupted by colchicine and chlorpromazine.

Ductular abnormalities. Inflammation and epithelial changes interfere with bile flow but are probably secondary rather than primary.

Table 13.1. Possible cellular mechanisms of cholestasis

Membrane lipid/fluidity	Modified
Na^+/K^+–ATPase/other carriers	Inhibited
Cytoskeleton	Disrupted
Canalicular integrity (membrane, tight junction)	Lost

Effects of retained bile acids

The mechanism of hepato-cellular damage in cholestasis is not fully understood but seems related to the retention of toxic substances, particularly hydrophobic bile acids, which have many effects including the production of oxygen free radicals by mitochondria. Thus although the initial cellular insult may be immunological, toxic or genetic, injury may be exacerbated by bile acids. These not only produce cell necrosis but also trigger apoptosis [74] depending on the concentration of toxic bile acid. Thus, at low concentrations there is apoptosis; at higher concentrations, necrosis. Mitochondrial dysfunction and damage appears involved in both. Ursodeoxycholic acid prevents apoptosis during cholestasis by inhibiting mitochondrial membrane depolarization and channel formation [74]. Aside from cell death, cholestasis impairs enzyme activity. Bile duct ligation decreases mitochondrial respiratory chain enzyme activity and β-oxidation. This does not recover completely after obstruction is relieved [51].

Pathology

Some changes are related to cholestasis itself and depend on its duration. Characteristic changes of specific diseases are not covered here but in the appropriate chapters.

Macroscopically the cholestatic liver is enlarged, green, swollen and with a rounded edge. Nodularity develops late.

Light microscopy. Zone 3 shows marked bilirubin stasis in hepatocytes, Kupffer cells and canaliculi (fig. 13.6). Hepatocytes may show feathery degeneration, possibly due to retention of bile salts, with foamy cells and surrounding mononuclear cells. Cellular necrosis, regeneration and nodular hyperplasia are minimal.

Portal zones (zone 1) show ductular proliferation (fig. 13.7) due to the mitogenic effect of bile salts. Hepatocytes

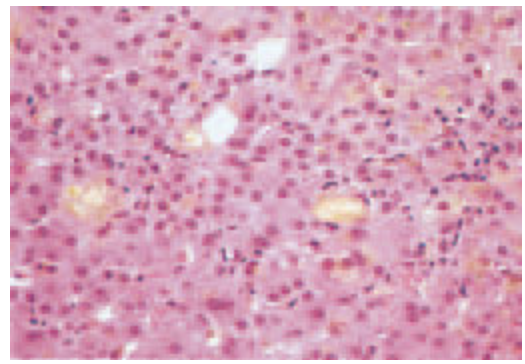


Fig. 13.6. Cholestasis: bile is seen in dilated canaliculi and hepatocytes.

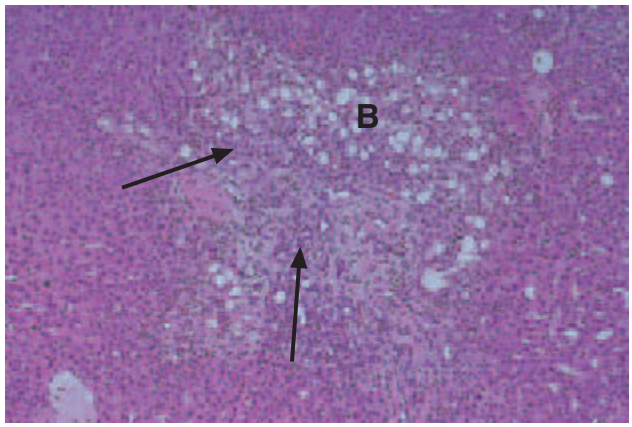


Fig. 13.7. Bile duct obstruction. There is portal tract expansion and ductular proliferation (arrows) with balloon ('feathery') degeneration of surrounding hepatocytes (B). (H & E,×40.)

transform into bile duct cells and form basement membranes. Reabsorption of bile constituents by ductular cells can result in microlith formation.

Following bile duct obstruction the hepatic changes develop very rapidly. Cholestasis is seen within 36 h. Bile duct proliferation is early; portal fibrosis develops later. After about 2 weeks, duration cannot be related to the extent of hepatic change. *Bile lakes* represent ruptured interlobular ducts.

With ascending cholangitis, histology shows accumulations of polymorphonuclear leucocytes related to bile ducts. The sinusoids also contain numerous polymorphs.

Fibrosis can be seen in zone 1. This is reversible if the cholestasis is relieved. The zone 1 fibrosis extends to meet bands from adjacent zones (fig. 13.8) so that eventually zone 3 is enclosed by a ring of connective tissue (fig. 13.9). In the early stages, the relationship of hepatic vein to portal vein is normal and this distinguishes the picture from biliary cirrhosis. Continuing peri-ductular fibrosis may lead to disappearance of bile ducts and this is irreversible.

Zone 1 oedema and inflammation are related to reflux of bile into lymphatics and to leucotrienes. Mallory bodies can accompany the inflammation and fibrosis in zone 1. Copper-associated protein, demonstrated by orcein staining, is seen in peri-portal hepatocytes.

Class I HLA antigens are normally expressed on hepatocytes. Reports on the pattern of class II expression are conflicting. This HLA antigen seems to be absent on hepatocytes of normal children and present in some patients with autoimmune liver disease and primary sclerosing cholangitis [55].

Biliary cirrhosis follows prolonged cholestasis. Fibrous tissue bands in the portal zones coalesce and the lobules are correspondingly reduced in size. Fibrous bridges join

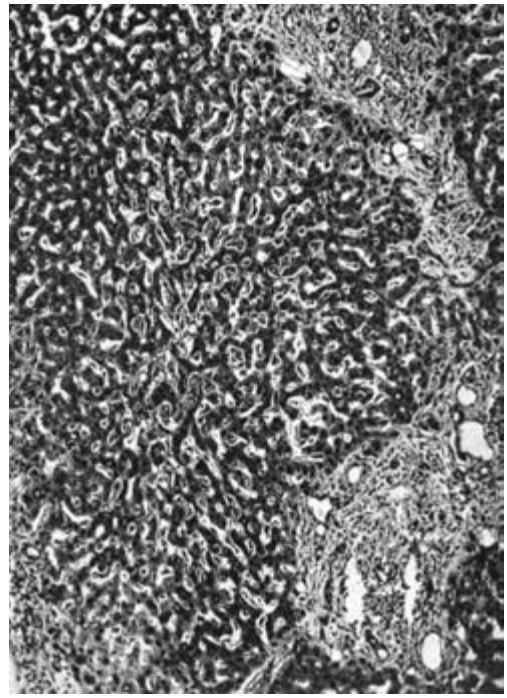


Fig. 13.8. Unrelieved common bile duct obstruction showing bile duct proliferation and fibrosis in the portal tracts, which are becoming joined together. Bile pigment accumulations can be seen in the centrizonal areas. The hepatic lobular architecture is normal. (H & E,×67.)

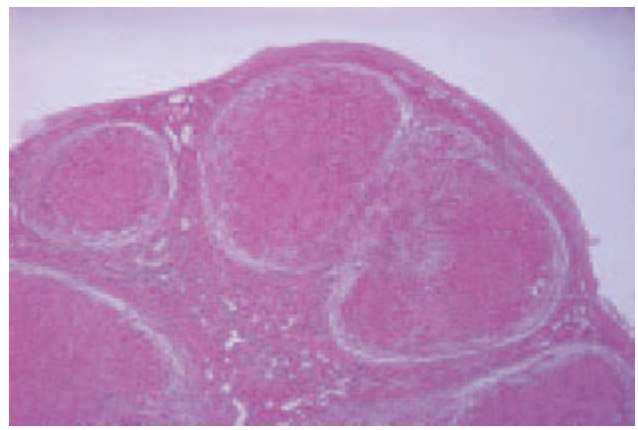


Fig. 13.9. Biliary cirrhosis. Low power view showing marked peri-nodular oedema and partly coalescent nodules—features typical of this condition. (H & E,×15.)

portal and centrizonal areas (fig. 13.9). Nodular regeneration of liver cells follows, but a true cirrhosis rarely follows biliary obstruction. In total biliary obstruction due to cancer of the head of the pancreas, death ensues before nodular regeneration has had time to develop. Biliary cirrhosis is associated with partial biliary obstruction due, for instance, to benign biliary stricture or primary sclerosing cholangitis.

In biliary cirrhosis the liver is larger and greener than in non-biliary cirrhosis. Margins of nodules are clear-cut rather than moth-eaten. If the cholestasis is relieved the portal zone fibrosis and bile retention disappear slowly.

Electron microscopy. The biliary canaliculi show changes irrespective of the cause. These include dilatation and oedema, blunting, distortion and sparsity of the microvilli. The Golgi apparatus shows vacuolization. Peri-canalicular bile-containing vesicles appear and these represent the 'feathery' hepatocytes seen on light microscopy. Lysosomes proliferate and contain copper bound as a metalloprotein.

The endoplasmic reticulum is hypertrophied; all these changes are non-specific for the aetiology of the cholestasis.

Changes in other organs. The spleen is enlarged and firm due to reticulo-endothelial hyperplasia and increase in mononuclear cells. Later, cirrhosis results in portal hypertension and splenomegaly.

The intestinal contents are bulky and greasy; the more complete the cholestasis, the paler the stools.

The kidneys are swollen and bile stained. Casts containing bilirubin are found in the distal convoluted tubules and collecting tubules. The casts may be heavily infiltrated with cells and the tubular epithelium is disrupted. The surrounding connective tissue may then show oedema and inflammatory infiltration. Scar formation is absent.

Clinical features

Prominent features of cholestasis, both acute and chronic, are itching and malabsorption. Bone disease (hepatic osteodystrophy) and cholesterol deposition (xanthomas, xanthelasmas) are seen with chronic cholestasis, which is also associated with skin pigmentation due to melanin. In contrast to the patient with hepato-cellular disease where there is malaise and physical deterioration, the cholestatic patient feels well. On examination, the *liver* is usually enlarged with a firm smooth non-tender edge. *Splenomegaly* is unusual except in biliary cirrhosis where portal hypertension has developed. Stools are pale.

Pruritus has been attributed to retained bile acids. However, even with the most sophisticated biochemical methods, pruritus did not correlate with the concentration of any naturally occurring bile acid in serum or in skin [29]. Moreover, in terminal liver failure, when pruritus is lost, serum bile acids may still be increased.

The association of pruritus with cholestasis suggests that it is due to some substance normally excreted in the bile. Disappearance of itching when liver cells fail indicates that the agent responsible may be manufactured by the liver. Cholestyramine binds many compounds and thus its success in treating the pruritus of cholestasis does not incriminate one particular agent.

Attention has turned towards agents that may produce itching by a central neurotransmitter mechanism [9, 46].

There is evidence from experimental studies and therapeutic trials that endogenous opioid peptides may be responsible by increasing central opioidergic neurotransmission. Opiate agonists induce opioid receptor mediated scratching activity of central origin. Cholestatic animals in which endogenous opioids accumulate have evidence of increased opioidergic tone, reversible by naloxone. Opiate antagonists reduce scratching in cholestatic patients [6, 89] and may produce opioid withdrawal-like reactions [47].

Opiates are not the only neurotransmitter implicated in itching, however. Ondansetron, a 5-HT_3 serotonin receptor antagonist, may also improve itching [60, 75] although not all trials have found significant benefit [61].

Further studies are awaited to unravel the mechanism of this troublesome and occasionally devastating complication of cholestasis, and to find an oral, effective, reliable treatment without side-effects.

Fatigue is a troublesome symptom in 70–80% of patients with chronic cholestatic liver disease, although to what extent this is due to cholestasis as opposed to chronic liver disease *per se* is not clear. It has an impact on quality of life. Experimental data do show behavioural changes in cholestasis and suggest a central mechanism involving serotoninergic neurotransmission and/or neuroendocrine defects in the corticotrophin-releasing hormone axis [9, 80–82]. However, the mechanisms responsible for fatigue in patients with cholestatic liver disease remain speculative [48].

Steatorrhoea is proportional to the degree of jaundice. It is due to the lack of sufficient intestinal bile salts for the absorption of dietary fat and fat-soluble vitamins (A, D, K and E) (figs 13.10, 13.11). Micellar solution of lipid is inadequate. Stools are loose, pale, bulky and offensive. The colour gives a good indication of whether cholestasis is total, intermittent or decreasing.

Fat-soluble vitamins. In short-term cholestasis which requires invasive techniques for investigation and treatment, vitamin K replacement may be necessary to correct the prolonged prothrombin time.

In prolonged cholestasis, plasma vitamin A levels fall. Hepatic storage is normal and the deficiency is due to poor absorption. If cholestasis is sufficiently long standing, hepatic reserves become exhausted and failure of dark adaption follows (night blindness) [86]. Vitamin D deficiency may also occur leading to osteomalacia.

Vitamin E deficiency has been reported in children with cholestasis [77]. The picture is of cerebellar ataxia, posterior column dysfunction, peripheral neuropathy and

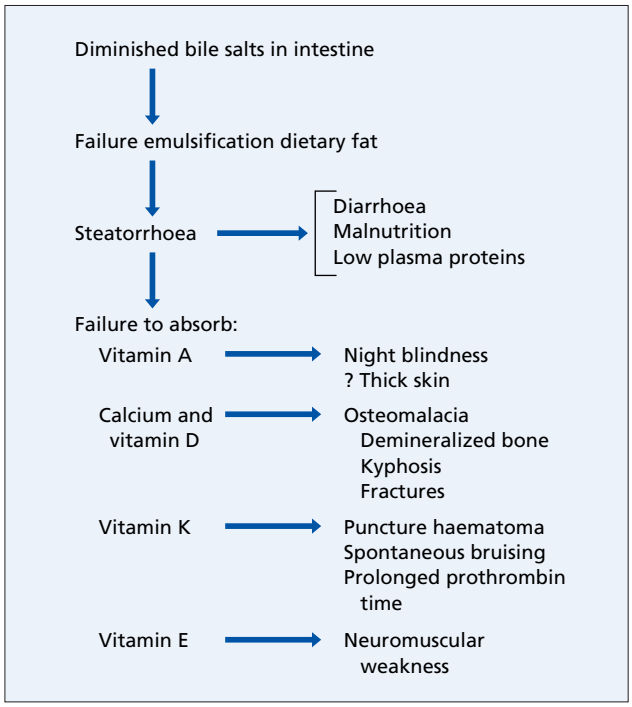


Fig. 13.10. The effects of lack of intestinal bile in chronic cholestatic jaundice.

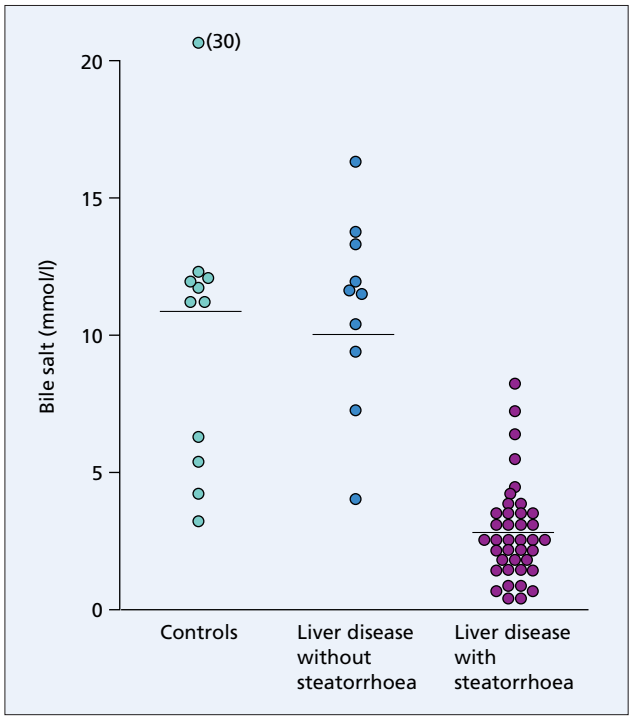


Fig. 13.11. Bile salt concentration of aspirated intestinal contents in patients with non-alcoholic liver disease with and without steatorrhoea [4].

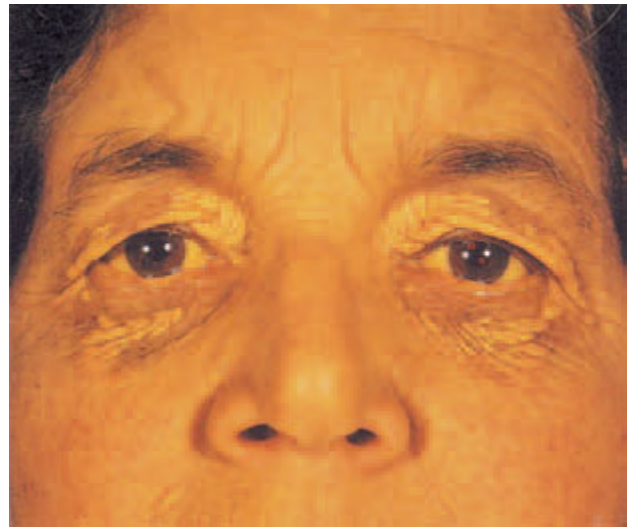


Fig. 13.12. Primary biliary cirrhosis. The patient shows xanthelasma and pigmentation.

retinal degeneration. If the serum bilirubin level exceeds 100 µmol/l (6 mg/dl) almost all adult patients with cholestasis will have subnormal vitamin E levels [45]. However, a specific neurological syndrome does not seem to develop in adults.

Xanthomas. These occur in chronic cholestasis but are seen less frequently than before because of treatment at an earlier stage with liver transplantation. The planous varieties (xanthelasma) are flat or slightly raised, yellow and soft and are usually noted around the eyes (fig. 13.12). They may also be seen in the palmar creases, below the breast and on the neck (fig. 13.13), chest or back. The tuberous lesions, also rarely seen now, appear later and are found on extensor surfaces, on pressure points and in scars. They disappear if serum cholesterol levels fall after cholestasis is relieved or in the late stage of hepatocellular failure.

Hepatic osteodystrophy [36, 90]

Bone disease is a complication of chronic liver disease and in particular chronic cholestasis where it has been studied in most detail. Bone pain and fractures occur. Possible mechanisms are *osteomalacia* and *osteoporosis*. Studies show that osteoporosis is responsible for the bone changes in the majority of patients with primary biliary cirrhosis and primary sclerosing cholangitis, although the potential for osteomalacia exists. A recent study has suggested that risk factors for osteoporosis are low body mass index, steroid treatment, increasing age and female sex rather than cholestasis *per se* [63].

Bone disease manifests as loss of height, back pain (usually mid-thoracic or lumbar), collapsed vertebrae and fractures particularly of ribs with minimal trauma.

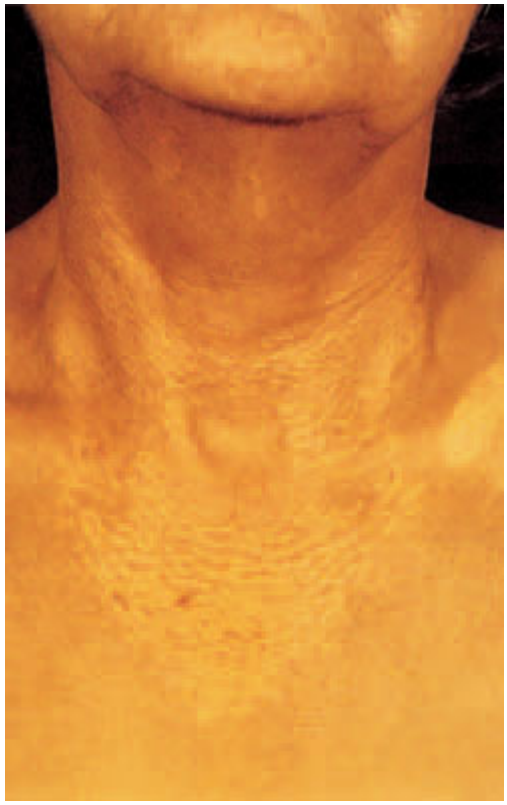


Fig. 13.13. Primary biliary cirrhosis. Xanthomatous skin lesions in the necklace area.

Spinal X-rays may show vertebrae of low density, as well as compression (fig. 13.14).

Bone mineral density may be measured by dual photon absorptiometry. One-third of patients with primary biliary cirrhosis and approximately 10% of those with primary sclerosing cholangitis have a bone density value below the fracture threshold [2, 53]. In patients with primary sclerosing cholangitis, osteoporosis is associated with advanced disease (fig. 13.15) [37].

The pathogenetic mechanism of the bone disease is uncertain, but is likely to be multifactorial. Normal bone homoeostasis depends on the correct balance between bone removal by osteoclasts and bone formation by osteoblasts. Remodelling begins with the retraction of the lining cells (terminally differentiated osteoblasts) from a quiescent area of bone. Osteoclasts attach and resorb bone, forming lacunae. These cells are then replaced by osteoblasts which fill the lacunae with new bone (osteoid), a matrix of collagen and other proteins. The osteoid is then 'mineralized', a process dependent on calcium, and therefore vitamin D. The two main forms of metabolic bone disease are osteoporosis and osteomalacia. In osteoporosis there is loss of bone (both matrix and its mineral). In osteomalacia there is defective mineralization of osteoid. To establish the process leading to bone disease in chronic cholestasis, bone biopsy with special analytical techniques has been necessary.

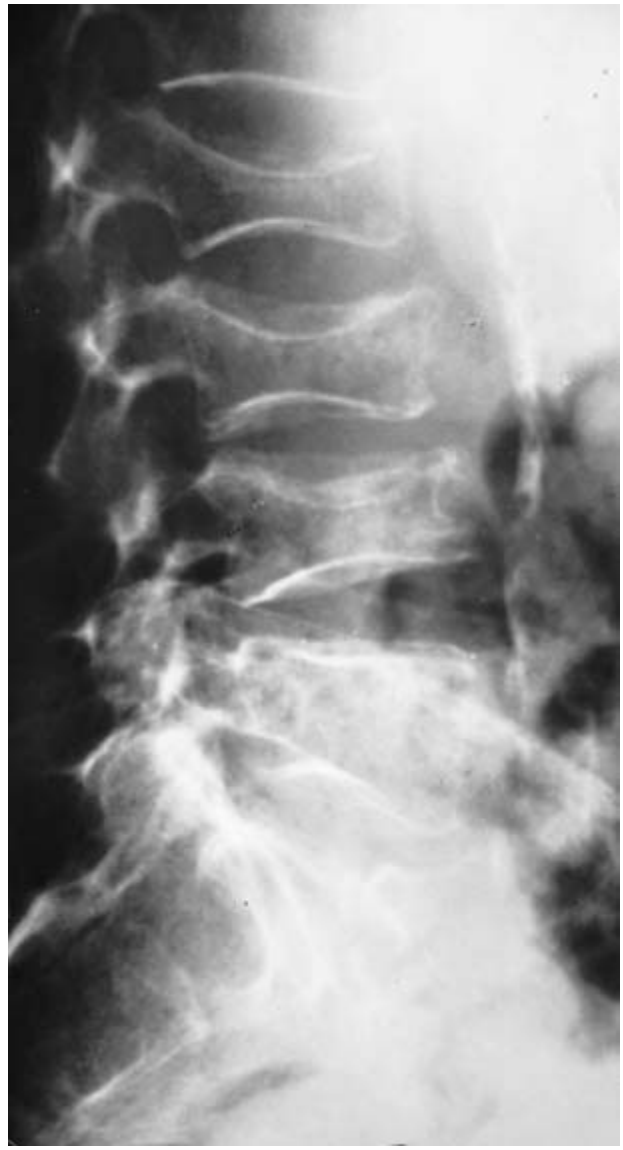


Fig. 13.14. Primary biliary cirrhosis jaundiced for 3 years. Lumbar spine showing very severe biconcave deformities and vertebral compression.

Studies have shown that the majority of patients with hepatic osteodystrophy have *osteoporosis*. Both reduced bone formation and increased resorption have been found in chronic cholestatic liver disease. It has been suggested that reduced formation occurs in pre-cirrhotic patients, with increased resorption in those with advanced disease [36]. In post-menopausal women without liver disease both bone resorption and bone formation are increased, with resorption exceeding formation. This will play a part in patients with primary biliary cirrhosis after the menopause.

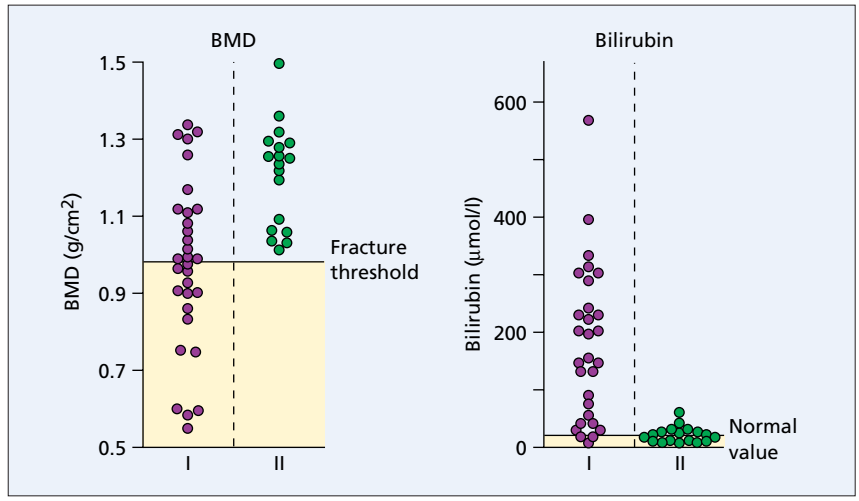


Fig. 13.15. Bone mineral density (BMD) and serum bilirubin concentration in patients with advanced sclerosing cholangitis (group I) and newly diagnosed primary sclerosing cholangitis (group II) [37].

Table 13.2. Factors increasing risk of bone disease in chronic cholestasis

General	Reduced physical activity Low body mass index Increasing age Female sex Reduced sunlight exposure
Cholestasis	Vitamin D and K deficiency Reduced calcium availability Increased serum bilirubin
Genetic	Vitamin D receptor genotype
Hormonal	Menopause/hypogonadism Steroid therapy

The cause of osteoporosis in chronic cholestatic liver disease is multifactorial (table 13.2) and not well understood. Factors involved in normal bone metabolism may play a role including vitamin D, calcitonin, parathyroid hormone, growth hormone and sex steroids. External influences in cholestatic patients include immobility, poor nutrition and reduced muscle mass. Vitamin D levels may be reduced due to malabsorption, inadequate diet and reduced exposure to the sun. Treatment with vitamin D, however, does not correct the bone disease. Activation of vitamin D, by 25-hydroxylation in liver and 1-hydroxylation in the kidney, is normal.

In normal individuals and those with primary osteoporosis, allelic polymorphisms of the vitamin D receptor (VDR) gene are related to bone mineral density. VDR genotypes also correlate with the degree of osteoporosis and vertebral fracture in patients with primary biliary cirrhosis [78].

Plasma from patients with jaundice inhibits osteoblast proliferation; unconjugated bilirubin but not bile salts had an inhibitory effect [42].

Treatment with ursodeoxycholic acid does not reduce the rate of bone loss in primary biliary cirrhosis [53]. Liver transplantation results in an improved bone density but this is delayed until 1–5 years after transplant [3]. Before recovery, spontaneous bone fractures are common [23], occurring in 35% of patients with primary biliary cirrhosis in the first year. Corticosteroids used for immunosuppression probably play a part in this increased fracture rate. Vitamin D levels may not return to normal for several months after transplantation and supplementation has been recommended [3].

It is important to measure vitamin D levels in patients with chronic cholestasis since although *osteomalacia* is unusual it may be present and is easily corrected. Isoenzyme analysis of serum alkaline phosphatase will show whether excess bone isoenzyme is present as well as the biliary/liver form. Bone changes cannot be predicted by serum calcium and phosphate values. X-rays may show changes of osteomalacia such as pseudo-fractures and Looser's zones. The hands show rarefaction. Bone biopsy shows wide, uncalcified osteoid seams surrounding the trabeculae. The cause of vitamin D deficiency is probably multiple. Cholestatic patients fail to go out in the sun or take an adequate diet. Absorption is poor due to steatorrhoea. Long-term cholestyramine use may exacerbate the deficiency.

Another manifestation of bone disease is painful *osteoarthropathy* in the wrists and ankles (fig. 13.16) [24]. This is a non-specific complication of chronic liver disease.

Changes in copper metabolism

Approximately 80% of absorbed copper is normally excreted in the bile and lost in the faeces. In all forms of cholestasis, but particularly if it is chronic (as in primary biliary cirrhosis, biliary atresia or sclerosing cholangitis),

copper accumulates in the liver to levels equal to or exceeding those found in Wilson's disease. Pigmented corneal rings resembling the Kayser–Fleischer ring are seen rarely [27].

Hepatic copper may be measured in biopsies or demonstrated histochemically by rhodamine staining. Copper-associated protein may be shown by orcein staining. These methods give circumstantial support to a diagnosis of cholestasis. In cholestasis the retained copper is probably not hepato-toxic. Electron microscopy shows it in electron-dense lysosomes. The organelle changes and oxidative-phosphylation defects associated with cytosolic and mitochondrial copper in Wilson's disease are not observed [31].

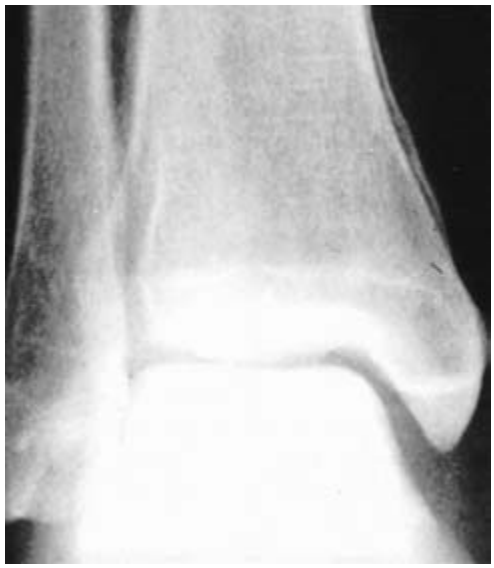


Fig. 13.16. Osteoarthropathy in chronic cholestasis. New subperiosteal bone is seen at the lower end of the tibia.

Development of hepato-cellular failure

This is slow, and it is remarkable how well the liver cells function in the presence of cholestasis. After 3–5 years of chronic jaundice, liver cell failure is indicated by rapidly deepening jaundice, ascites, oedema and a lowered serum albumin level. Pruritus lessens and the bleeding tendency is not controlled by parenteral vitamin K. Hepatic encephalopathy is terminal.

Extra-hepatic effects (fig. 13.17) [22]

Itching and jaundice are self-evident, but there are numerous other less obvious effects of cholestasis. These have been studied mainly in the context of bile duct obstruction. They may result in serious complications when the patient is stressed by dehydration, blood loss or surgical or non-surgical procedures. Cardio-vascular responses are abnormal and peripheral vaso-constriction in response to hypotension is impaired. The kidneys have an increased susceptibility to hypotension and hypoxic damage [28]. The processes involved in responding to sepsis and in wound healing are impaired. The prolonged prothrombin time is correctable with vitamin K but coagulation may still be abnormal due to platelet dysfunction. The gastric mucosa is more suscep-

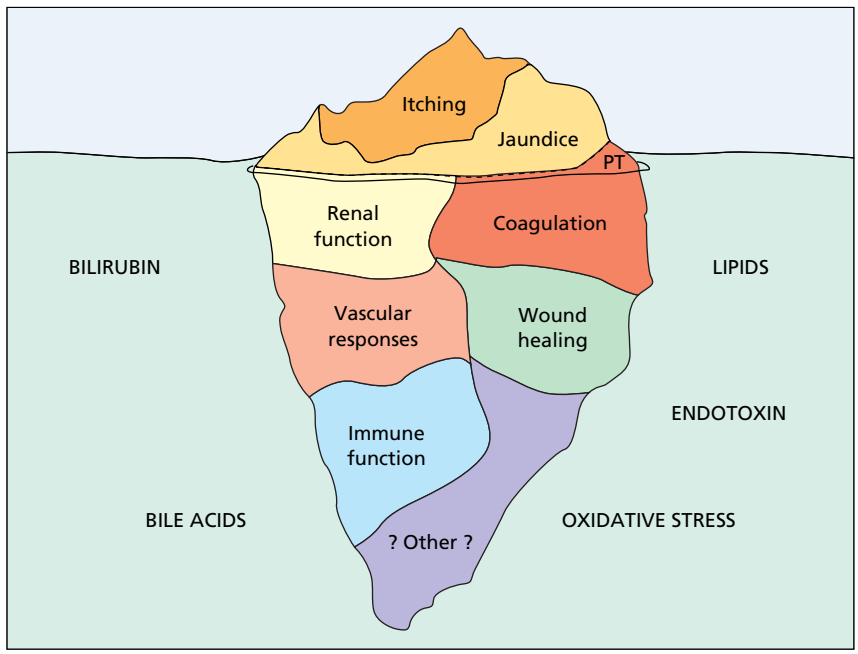


Fig. 13.17. Extra-hepatic effects of cholestasis. Itching and jaundice are obvious (the tip of the iceberg) but there are many other effects for which the clinician should make allowance. Pathogenic factors include bilirubin, bile acids, lipid changes, endotoxaemia and oxidative stress. (PT, prothrombin time.)

tible to ulceration. The cause of these changes is multifactorial. Bile acids and bilirubin have been shown to alter cellular metabolism and function. Changes in serum lipids affect membrane structure and function.

Experimental cholestatic liver disease is associated with increased lipid peroxidation in the kidney, brain and heart [54]. Cholestasis impairs hepatic sinusoidal endothelial cell function [92]. This may be caused by endotoxaemia and release of TNF and IL1 by activated Kupffer cells. Chronic bile duct ligation leads to an increased sensitivity to lipopolysaccharide—a component of the outer membrane of Gram-negative bacteria [35]. *N*-acetylcysteine may give protection through anti-oxidant pathways [69]. The same agent gives partial protection against renal dysfunction in experimental cholestasis [39].

Thus although deeply jaundiced patients with cholestasis may appear well apart from itching, there are metabolic and functional changes that under the stress of surgical and non-surgical procedures may result in acute renal failure, haemorrhage, wound dehiscence and an increased risk of sepsis.

Haematology

Changes in cholestasis include the appearance of target cells on blood film related to an accumulation of cholesterol in the red cell membrane. This increases red cell surface area and leads to target cell formation.

In extra-hepatic cholestasis, anaemia implies infection, blood loss or malignant disease. A polymorphonuclear leucocytosis suggests cholangitis or underlying neoplastic disease.

Biochemistry

All the constituents of the bile show an increased level in the serum. Conjugation of biliary substances is intact but excretion defective.

The *serum conjugated bilirubin level* is raised. In unrelieved cholestasis the level rises slowly for the first 3 weeks and then fluctuates, always tending to increase. When the cholestasis is relieved, serum bilirubin values fall slowly to normal. This is in part due to the formation of bili-albumin, in which bilirubin and albumin are covalently bound.

The *serum alkaline phosphatase level* is raised, usually to more than three times the upper limit of normal. *Serum γ-glutamyl-transpeptidase levels* are raised. The rises are due to increased synthesis or release of enzymes from liver and biliary plasma membranes.

The total *serum cholesterol* increases but not in all cases. In chronic cholestasis the total serum lipids are greatly increased and this involves particularly phospholipid and total cholesterol. These changes probably reflect increased hepatic synthesis, regurgitation of biliary cholesterol and lecithin into the circulation, and reduced plasma lecithin cholesterol acyl transferase (LCAT) activity. Triglycerides are very slightly increased. In spite of the high lipid content, the serum is characteristically clear and not milky. This may be due to the surface action effect of phospholipid, which keeps the other lipids in solution. Serum cholesterol values fall terminally.

Serum lipoproteins are increased, due to a rise in the low density (α_2, β) fraction. The high density lipoproteins are decreased.

The cholestatic liver secretes a variety of unusual lipoproteins and these can be related to low plasma LCAT levels. The lipoproteins of cholestasis differ from those found in atherosclerosis. Atheroma is not a complication of prolonged cholestasis. The abnormal lipoproteins appear by electron microscopy as disc-shaped particles.

Lipoprotein-X (*LP-X*) is a spherical particle, 70 nm in diameter, associated with the low density lipoprotein fraction. It is increased in both intra- and extra-hepatic cholestasis but is of no practical diagnostic value.

Bile salts accumulate in the blood in cholestasis.

Serum albumin and globulin concentrations are normal in acute cholestasis. With the development of biliary cirrhosis the serum albumin tends to fall.

The *serum aspartate transaminase* is usually less than 100 iu/l.

Urine. Conjugated bilirubin is present. Urinary urobilinogen is excreted in proportion to the amount of bile reaching the duodenum.

Bacteriology

In the febrile patient with bile duct obstruction or primary sclerosing cholangitis, blood cultures should be performed. Septicaemia, especially due to Gram-negative organisms, complicates patients with duct stones, and those with malignant obstruction or sclerosing cholangitis after invasive procedures. Patients with partial biliary obstruction and cholangitis have a high bacterial population in the bile, rivalling that in the colon. Whether this causes systemic sepsis depends on the biliary pressure and thus the degree of obstruction.

Diagnostic approach

Clinical features from an accurate history and physical examination often suggest the cause of the cholestasis. *Pain* can be related to duct stones, tumour or gallbladder disease. *Fever* and *rigors* may indicate cholangitis due to duct stone or traumatic stricture (*Charcot's intermittent biliary fever*). The patient may have taken *drug treatment* that coincides with the development of cholestasis.

Ulcerative colitis raises the possibility of primary sclerosing cholangitis. On examination, hepatic nodularity may indicate metastatic *malignancy*. Other abdominal masses may indicate a primary lesion such as carcinoma of the stomach or colon. Endoscopy, rectal examination and sigmoidoscopy may indicate carcinoma. An enlarged gallbladder suggests non-calculous biliary obstruction.

However, clinical and biochemical evaluation is not infallible. A small proportion of patients with extra-hepatic obstruction are incorrectly diagnosed as having intra-hepatic cholestasis, whereas a larger proportion of patients with intra-hepatic disease are thought to have extra-hepatic obstruction. A diagnostic algorithm is important (fig. 13.18). The first procedure should be real-time ultrasound, which allows the distinction between cholestasis with dilated bile ducts and cholestasis without duct dilatation. If ultrasound shows dilated ducts, cholangiography (Chapter 32) is necessary.

Non-invasive imaging of the bile duct using magnetic resonance cholangiopancreatography (MRCP) has a diagnostic accuracy similar to direct cholangiography (ERCP, PTC). MRCP is chosen when the evidence for bile duct disease is equivocal. MRCP is also of value in the elderly patient where a more invasive procedure is not appropriate without the support of further imaging.

If direct cholangiography is required then ERCP is the first choice unless access to the duodenal papilla is impossible because of duodenal stenosis or previous hepatico-jejunostomy. If ERCP is not possible or fails and a therapeutic procedure is likely to be needed, PTC should be undertaken. Drainage of an obstructed biliary system is possible both by endoscopic and percutaneous approaches although there are more complications with the latter.

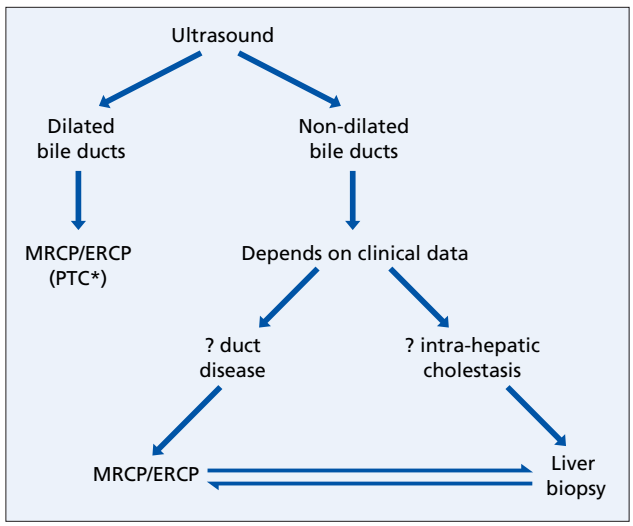


Fig. 13.18. Diagnosis of cholestasis. ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; PTC, percutaneous transhepatic cholangiography; *, if ERCP fails.

If ultrasound does not show dilated ducts the next step depends upon the clinical data. If duct disease such as stone or primary sclerosing cholangitis is suspected, MRCP or ERCP is chosen. If the cholangiogram is normal then liver biopsy should be considered. If an intra-hepatic cholestasis due to a drug or infiltration is likely from clinical data then liver biopsy is performed as the first approach. If this shows evidence of large bile duct disease, MRCP or ERCP is necessary.

Liver biopsy can be performed safely in patients with cholestatic jaundice, however deep, after correction of the prothrombin time with vitamin K. However, with the advent of scanning and cholangiography it is unusual for a patient with duct obstruction to have a biopsy with the risk of bile leakage. In such patients biopsy should not be necessary to make the diagnosis.

Diagnostic possibilities

Extra-hepatic cholestasis

Causes include common bile duct stone (Chapter 34), pancreatic and ampullary carcinoma (Chapter 36), cholangiocarcinoma (Chapter 37), benign bile duct stricture (Chapter 35) and bile duct infections (Chapter 29). Dominant benign strictures and cholangiocarcinoma can cause duct obstruction in primary sclerosing cholangitis (Chapter 15).

Large bile duct disease with undilated intra-hepatic ducts

Occasionally diseases that involve the main bile ducts do not result in intra-hepatic biliary dilatation and *simulate* intra-hepatic cholestasis. A common duct stone may be present without dilated intra-hepatic ducts if the stone is only causing intermittent obstruction. Ultrasound may mislead, but the history should indicate this possibility. There are also conditions that affect both intra- and extra-hepatic ducts and cross the diagnostic classification of intra- and extra-hepatic cholestasis. These include primary sclerosing cholangitis, sclerosing cholangitis complicating long-standing duct stones with sepsis, and rarely duct changes seen with sarcoidosis (Chapter 28).

Intra-hepatic cholestasis (fig. 13.19, table 13.3)

The cause of intra-hepatic cholestasis lies within the liver, somewhere distal to the hepato-cellular microsomes but above the major bile ducts. The general clinical and biochemical picture is the same as for

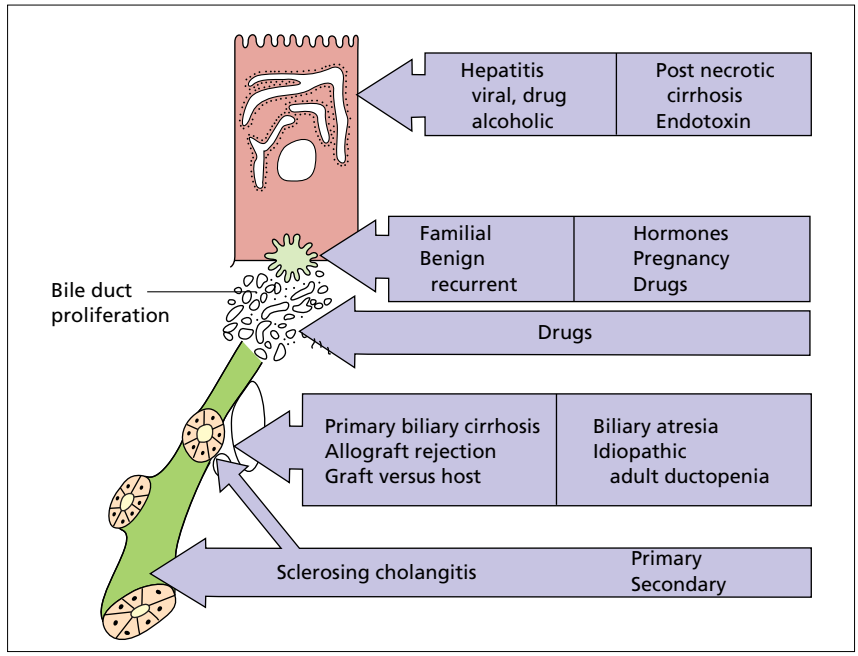


Fig. 13.19. Classification of intra-hepatic cholestasis according to possible major sites of involvement of the biliary tree.

Table 13.3. Intra-hepatic cholestasis

Type	Diagnostic points
Hepato-cellular	
viral hepatitis	History; onset typical; viral A, B and C markers
alcoholic hepatitis	History; large tender liver; spiders; liver biopsy
drugs	History; onset 6 weeks of starting; liver biopsy
sex hormones (canalicular)	Hormone therapy; remit on stopping; liver biopsy
Benign recurrent cholestasis	Repeated; cholangiography normal; normal liver between attacks
Progressive familial cholestasis	Onset in infancy
Bile acids	All rare; often familial
Biliary	
intra-hepatic atresia	History; age; liver biopsy
primary biliary cirrhosis	Female; onset pruritus; positive mitochondrial antibody; raised serum IgM; liver biopsy
primary sclerosing cholangitis	Association ulcerative colitis; ERCP

extra-hepatic cholestasis. Febrile cholangitis is absent. The liver is not necessarily enlarged and is not tender. Bile ducts are not dilated within the liver. The three main types are discussed here.

Hepato-cellular

The cholestasis is complex. There is primary injury to intra-cellular membranes. Leakage of bile salts through defective canaliculi leads to a reduction of bile salt dependent bile flow. Inhibition of canalicular ATPase interferes with bile salt independent secretion. Impaired hydroxylation of cholesterol to bile acids in the endoplasmic reticulum reduces bile salt dependent flow.

Cholestatic viral hepatitis (Chapter 16). The history of exposure and the nature of the prodromal symptoms may be helpful. The liver biopsy appearances are those of acute viral hepatitis. Cholangiography may be necessary to rule out duct disease.

Acute alcoholic hepatitis (Chapter 22) can be cholestatic. The history of alcohol abuse, the large tender liver and, often, vascular spiders on the skin are helpful points. Liver biopsy appearances are diagnostic. Chronic pancreatitis may be associated.

In some patients with *cryptogenic macronodular cirrhosis* cholestasis may be prominent.

Canalicular membrane changes

Cholestatic reactions to oral contraceptives (Chapter 20) and in the last trimester of pregnancy (Chapter 27) fall into this group.

Drugs include the promazine group, long-acting sulphonamides, antibiotics and anti-thyroid drugs (Chapter 20). The history is important and liver biopsy appearances are usually diagnostic.

Benign recurrent intra-hepatic cholestasis

This rare condition presents as multiple episodes of cholestatic jaundice [12, 88]. It has recently been proposed that *benign* be omitted from the title of this condition, and the term recurrent familial intra-hepatic cholestasis be used since in some patients the cholestatic episodes reduce the quality of life to such an extent that transplantation is warranted [85]. Main bile duct obstruction must be excluded by endoscopic or percutaneous cholangiography. Other causes known to produce cholestasis, such as drugs, should be ruled out. There should be symptom-free intervals of several months or years. The first patient described survived 22 episodes and three laparotomies [88]. Another patient had 27 attacks over 38 years.

The onset is with itching, occasionally with influenza-type illness and vomiting. Twenty-five to 50% of patients suffer abdominal pain [12]. There is often fatigue, anorexia and weight loss. Serum alkaline phosphatase levels increase but transaminases are virtually normal. Jaundice appears and persists for 3–4 months.

Hepatic histology shows cholestasis with bile plugs, portal zone expansion, mononuclear cells and some liver cell degeneration, mainly in zone 1. Hepatic histology and liver function are normal in remission [88].

Aetiology. The disease is autosomal recessive and the gene locus involved has been mapped to the FIC1 locus as for PFIC1 [15]. The role of the proposed candidate gene is not known.

Environmental factors are suggested by the allergic diathesis; some patients have rashes. The condition may recur at particular times of the year.

Treatment. The attacks are self-limiting and vary in duration. Corticosteroid treatment is probably of little benefit. *S*-adenosylmethionine is ineffective. Results with ursodeoxycholic acid are conflicting.

Progressive familial intra-hepatic cholestasis [44]

This is a group of rare autosomal recessive diseases characterized by cholestasis in infancy (see also Chapter 26, table 26.6). Three types are recognized.

PFIC type 1 (Byler's disease) is an autosomal recessive disease present in the Amish population (descendants of Jacob and Nancy Byler). Recurrent episodes of intra-hepatic cholestasis lead to permanent cholestasis, fibrosis, cirrhosis and liver failure. Liver transplantation may be necessary in the first decade of life. Characteristically serum γ-glutamyl-transferase is not or only slightly increased. Genetic studies have mapped the PFIC1 locus in Amish descendants to chromosome 18q21–q22. This region contains the gene FIC1 which encodes a P-type ATPase and in Amish patients with PFIC a single specific mutation is found [14]. The pathogenetic mechanism causing this condition is not clear. In some non-Amish families the genetic defect is in the same FIC1 locus. However, other non-Amish individuals with the PFIC syndrome (Byler's syndrome) have different histological appearances and the condition is not linked to the FIC locus [59].

PFIC type 2 is due to mutations in the BSEP. In contrast to PFIC1, PFIC2 often begins as a non-specific giant cell hepatitis which may not be distinguish-able from intra-hepatic neonatal giant cell hepatitis. Affected individuals are usually permanently jaundiced. There is progressive cholestasis requiring liver transplantation.

PFIC type 3 is due to mutations in the MDR3 gene (phosphoflippase). Bile salt enters the canaliculus and bile ducts but without protective phospholipid. Serum γ-glutamyl-transferase is usually markedly elevated. There is extensive bile duct proliferation on biopsy. In this group symptoms appear later in life than in PFIC types 1 and 2 and presentation in adult life is reported [41]. Liver transplantation is often necessary. A high incidence of intra-hepatic cholestasis in pregnancy has been reported in a family with PFIC type 3 [40] although this can also be seen in other PFIC subtypes.

Miscellaneous

Cholestasis in *severe bacterial infections*, particularly in childhood or post-operatively, is presumably hepato-cellular. It can also be related to the cholestatic effect of endotoxin on Na^+/K^+–ATPase.

Cholestasis develops with *prolonged parenteral nutrition* especially in neonates (Chapter 26) but also in adults [72]. It may be due to lithocholate formed by bacterial 7-α-dehydroxylation of chenodeoxycholic acid in the intestinal tract.

Hodgkin's disease may be complicated by deep cholestasis. This is not necessarily related to excess haemolysis, hepatic infiltration or invasion of major bile ducts. There may be loss of intra-hepatic bile ducts which resolves after successful treatment [18].

Biliary precipitation of insoluble solutes. Unconjugated bilirubin may precipitate as intra-hepatic pigment stones or as inspissated bile in *cystic fibrosis*.

Protoporphyrins in *erythrocytic protoporphyria* may precipitate in the biliary canaliculi.

The cholestasis of *intrahepatic atresia* (infantile cholangiopathy) (Chapter 26) may be related to viral injury to intra-hepatic bile ducts. Adults and adolescents with *paucity of intra-hepatic bile ducts* are being increasingly described [13, 25]. The condition may be familial [16] or drug-induced [20, 73], or a late onset form of the non-syndromic type seen in children [13].

Zellweger's syndrome [26]. This is very rare and presents before 6 months of age with progressive cholestasis and hepatomegaly. There is associated mental retardation, a characteristic facies, hypotonia and renal cysts. It is caused by a defect in hepatic peroxisomes and bile acid oxidation is abnormal with the appearance of C27 bile acids appearing in serum and bile. Affected individuals have a short survival of only a few years. Oral bile acid therapy should be considered [76].

Primary biliary cirrhosis—see Chapter 14.

Primary sclerosing cholangitis—see Chapter 15.

Treatment

Biliary decompression: resection (fig. 13.20)

The choice between non-surgical and surgical treatment will depend upon the cause of obstruction and the clinical state of the patient. Common duct stones are treated by endoscopic sphincterotomy and removal (Chapter 34). In malignant obstruction the resectability of the tumour should be assessed in the operable patient. If judged inoperable or irresectable, an endoscopic stent is inserted to drain the bile duct; the percutaneous route is taken if the endoscopic attempt fails. Surgical bypass is the alternative. Which approach is employed will depend upon the patient, the facilities, and the expertise available.

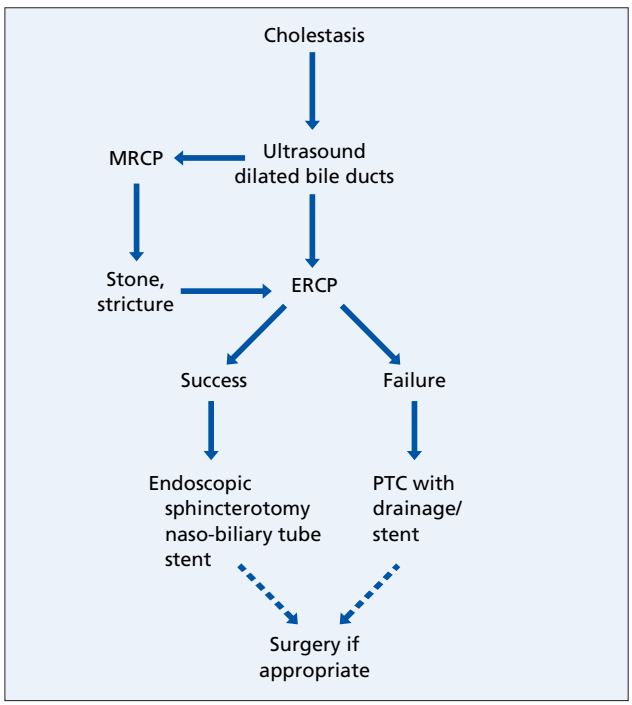


Fig. 13.20. Therapeutic options for bile duct obstruction.

The preparation of the patient for any of these procedures is critical in order to avoid complications that include renal failure, which may occur in 5–10% of patients [28], and sepsis. *Coagulation* is corrected with parenteral vitamin K. *Dehydration* and *hypotension*, which can lead to acute tubular necrosis, are prevented by intravenous hydration, usually with 0.9% NaCl, and close monitoring of fluid balance. *Mannitol* is given to protect renal function but patients must be well hydrated before its use. A trial has questioned its benefit [34]. Post-operative renal dysfunction may in part be caused by circulating endotoxin derived from increased intestinal absorption. To reduce absorption of endotoxin, oral deoxycholate or lactulose have been given and appear to protect against renal impairment after surgery [67]. There is no post-operative benefit if renal failure is already abnormal before surgery.

To reduce the risk of septic complications after both non-surgical and surgical intervention, antibiotic is given beforehand. The duration of treatment after the procedure will depend upon whether or not there is evidence of sepsis, and how successful biliary decompression has been.

The important factors associated with increased post-operative morbidity and mortality are an initial haematocrit of 30% or less, a serum bilirubin value exceeding 200 µmol/l (12 mg/dl) and a malignant lesion [21]. Deep jaundice can be relieved pre-operatively by percutaneous external drainage or endoscopy stenting but randomized controlled studies have not shown benefit [52].

Medical

Pruritus (table 13.4)

Biliary drainage. Pruritus is relieved in patients with biliary obstruction by external or internal biliary

Table 13.4. Drug treatment of pruritus

Routine	Cholestyramine
Variable effect	Anti-histamine; ursodeoxycholic acid; phenobarbitone
Careful use	Rifampicin
Experimental	Naloxone, nalmefene; ondansetron; *S*-adenosyl-L-methionine; propofol

drainage. Itching disappears or is much improved after 24–48 h.

Cholestyramine. This resin will stop itching in 4–5 days in patients with partial biliary obstruction. It is known to bind bile salts in the intestines so eliminating them in the faeces but until the pathogenesis of itching is better understood, its actual mechanism of action will remain speculative. One sachet (4 g) should be given before and one after breakfast so that the arrival of the drug in the duodenum coincides with gallbladder contraction. If necessary, a further dose may be taken before the midday and evening meals. The maintenance dose is usually about 12 g/day. The drug causes nausea and there is a reluctance to take it. It is particularly valuable for itching associated with primary biliary cirrhosis, primary sclerosing cholangitis, biliary atresia and biliary stricture. Serum bile acid levels fall. Serum cholesterol drops and skin xanthomas diminish or disappear.

Cholestyramine increases faecal fat even in normal subjects. The dose should be the smallest one that controls pruritus. Hypoprothrombinaemia has developed due to failure to absorb vitamin K.

Cholestyramine may bind calcium, other fat-soluble vitamins and drugs having an entero-hepatic circulation, particularly digoxin. Care must be taken that the cholestyramine and other drugs are given at separate times.

Ursodeoxycholic acid (13–15 mg/kg per day) can reduce itching in patients with primary biliary cirrhosis perhaps by a choleretic effect or by reducing toxic bile salts [71]. Although its use has been associated with biochemical resolution of drug-induced cholestasis [70], it is unproven as an anti-pruritic agent in this and other cholestatic syndromes.

Anti-histamines. These are of value only for their sedative action.

Phenobarbitone may relieve itching in patients resistant to other therapy.

Naloxone, an opiate antagonist given as an intravenous infusion, reduced itching in a randomized controlled trial [6], but is not appropriate for long-term use. An oral opiate antagonist, nalmefene, is also effective [7, 10] and clinical trials of another orally active opiate antagonist, naltrexone, have also shown benefit [89]. Both oral agents are experimental and not yet in clinical use.

Ondansetron reduced itching in small placebo-controlled trials [75] but subsequent studies have questioned its benefit [60, 61].

Propofol, an hypnotic agent given intravenously, has improved itching in 80% of patients [11]. Only short-term benefit has been studied.

S-adenosyl-L-methionine, which among many effects improves membrane fluidity and acts as an antioxidant, has been used to treat cholestatic syndromes [65]. Results are inconsistent and currently this agent remains experimental.

Rifampicin (300–450 mg daily) relieves pruritus within 7 days [19, 30]. This may be by enzyme induction or by inhibition of bile acid uptake. Potential side-effects include increased risk of gallstone formation, reduction in 25-OH-cholecalciferol levels, drug interactions, hepato-toxicity and emergence of resistant organisms, although successful longer term use (mean 18 months) is reported in children without clinical or biochemical toxicity [91]. Patients treated with this agent should be carefully selected and frequently monitored.

Steroids. Glucocorticoids will relieve itching, but at the expense of severe bone thinning particularly in post-menopausal women.

Bright light therapy (10 000 lux) has been studied and found beneficial in a pilot study [8]. Its use is based on the circadian pattern of cholestatic pruritus.

Ileal diversion decreases pruritus and improves quality of life in children with cholestasis and intractable itching [38].

Plasmapheresis. This has been used to treat intractable pruritus associated with hypercholesterolaemia and xanthomatous neuropathy. The procedure is temporarily effective but is costly and labour intensive.

Hepatic transplantation The wide range of partially effective and experimental therapies underlines the difficulty in treating some patients with long-standing cholestasis. Intractable itching may be an indication for liver transplantation.

Nutrition (table 13.5)

The problem is that of intestinal bile salt deficiency. Dietetic advice if available should be taken. Calorie intake should be maintained and protein must be ade-

Table 13.5. Management of chronic cholestasis

Dietary fat (if steatorrhoea)			
reduce neutral fat (40 g daily)			
add medium chain triglycerides (up to 40 g daily)			
Fat-soluble vitamins*	Oral	K	10 mg/day
		A	25 000 U/day
		D	400–4 000 U/day
	i.v.	K	10 mg/month
	i.m.	A	100 000 U/3-monthly
	i.m.	D	100 000 U/month
Calcium			
extra low fat milk			
oral calcium			

*Initial dose and route depend on severity of deficiency and cholestasis, and compliance; maintenance dose depends on response. See text for vitamin E.

quate. In patients with clinically overt steatorrhoea, neutral fat will be poorly tolerated and badly absorbed with reduced calcium absorption. It should be restricted if steatorrhoea is exacerbated and is a clinical problem. Additional fat is supplied by medium chain triglycerides (MCT) as an emulsion, e.g. in a milk shake. In the absence of luminal bile acids, MCT are digested and absorbed quite well into the portal vein as free fatty acids. They can be given as Liquigen (Scientific Hospital Supplies Ltd, UK) or as MCT (coconut) oil for cooking or in salads. Calcium supplements should also be given.

In acute cholestasis, vitamin K deficiency may be shown by prolongation of the prothrombin time. Parenteral vitamin K (10 mg) should be given daily for 2–3 days; the prothrombin time characteristically corrects within a day or two.

In the chronic case, prothrombin time and serum vitamin A and D levels should be monitored, and vitamins A, D and K replaced as necessary. Replacement may be done orally or parenterally depending on the severity of depletion, jaundice and steatorrhoea, and whether the deficiency is corrected. If testing of vitamin levels is not available, empirical replacement is appropriate particularly once the patient becomes jaundiced. Easy bruising suggests prothrombin and thus vitamin K deficiency.

Patients with night blindness may improve with oral rather than intramuscular vitamin A [86]. Vitamin E is not absorbed [1] and dl tocopherol, as the acetate 10 mg daily, is given by injection to children with chronic cholestasis. Others may take 200 mg daily by mouth.

Bone changes [90]

The osteopenia of cholestatic liver disease is predominantly osteoporosis. Malabsorption of vitamin D with subsequent osteomalacia occurs but is less common. Monitoring of serum 25-hydroxyvitamin D levels is necessary; bone densitometry scans will show the degree of osteopenia.

When vitamin D deficiency is detected, treatment is with vitamin D, either 50 000 units orally three times a week [36], or 100 000 units intramuscularly monthly. If serum levels do not become normal on oral therapy, the dose should be increased, or the parenteral route used. Prophylaxis against vitamin D deficiency when vitamin D levels cannot be monitored is empirical but appropriate for the patient with jaundice or long-standing cholestasis without jaundice. Unless serum levels can be monitored, parenteral replacement of vitamin D is more appropriate than the oral route.

In patients with symptomatic osteomalacia, oral or parenteral 1,25-dihydroxyvitamin D_3 appears to be the vitamin D metabolite of choice, but carries a risk of hypercalcaemia. It is biologically very active and has a short half-life. An alternative would be 1α-vitamin D_3 but full metabolic activity only follows hepatic 25-hydroxylation.

Measures should be taken to prevent osteoporosis. These have been little studied in chronic cholestasis. A balanced diet is encouraged with calcium supplements. A daily oral intake of at least 1.5 g elemental calcium should be achieved using effervescent calcium (Sandoz) or calcium gluconate. Patients should be encouraged to take extra skimmed (fat-free) milk and expose themselves to safe levels of sunlight or ultraviolet light. They are also encouraged to be mobile and active, though if osteopenia is severe this may have to be moderated or an exercise programme planned under supervision.

Corticosteroids worsen the process of osteoporosis and should be avoided.

In post-menopausal patients oestrogen replacement therapy is indicated. Such treatment in patients with primary biliary cirrhosis showed no increase in cholestasis while there was a trend towards a reduction in bone loss [17, 62].

Bisphosphonates may be beneficial in cholestatic bone disease. A comparative study between editronate and sodium fluoride (with calcium and vitamin D supplements) favoured editronate, which increased vertebral bone density [33]. Arendronate may be better than editronate in primary biliary cirrhosis patients with osteopenia [68]. Although a limited study of fluoride treatment showed improved bone density in patients with primary biliary cirrhosis [32], larger studies in postmenopausal osteoporosis show no reduction in fractures. Calcitonin has not been shown to be beneficial.

Hepatic bone disease worsens after liver transplantation and calcium and vitamin D supplementation should be continued.

No specific treatment is available for the painful periosteal reactions. Simple analgesics may be of use, and, if arthropathy is present, physiotherapy may be helpful.

References

1 Alvarez F, Landrieu P, Laget P *et al*. Nervous and ocular disorders in children with cholestasis and vitamin A and E deficiencies. *Hepatology* 1983; **3**: 410.

2 Angulo P, Therneau TM, Jorgensen RA *et al*. Bone disease in patients with primary sclerosing cholangitis: prevalence, severity and prediction of progression. *J. Hepatol.* 1998; **29**: 729

3 Argao EA, Balistreri WF, Hollis BW *et al*. Effect of orthotopic liver transplantation on bone mineral content and serum vitamin D metabolites in infants and children with chronic cholestasis. *Hepatology* 1994; **20**: 598.

4 Badley BWD, Murphy GM, Bouchier IAD *et al*. Diminished micellar phase lipid in patients with chronic nonalcoholic liver disease and steatorrhea. *Gastroenterology* 1970; **58**: 781.

5 Baiocchi L, LeSage G, Glaser S *et al*. Regulation of cholangiocyte bile secretion. *J. Hepatol.* 1999; **31**: 179.
6 Bergasa NV, Alling DW, Talbot TL *et al*. Effects of naloxone infusions in patients with pruritus of cholestasis: a double-blind randomized controlled trial. *Ann. Intern. Med.* 1995; **123**: 161.
7 Bergasa NV, Alling DW, Talbot TL *et al*. Oral nalmefene therapy reduces scratching activity due to the pruritus of cholestasis: a controlled study. *J. Am. Acad. Dermatol.* 1999; **41**: 431.
8 Bergasa NV, Link MJ Keogh M *et al*. Pilot study of bright-light therapy reflected towards the eyes for pruritus of chronic liver disease. *Am. J. Gastroenterol*. 2001; **96**: 1563.
9 Bergasa NV, Mehlman JK, Jones EA. Pruritus and fatigue in primary biliary cirrhosis. *Bailliere's Clin. Gastroenterol.* 2000; **14**: 643.
10 Bergasa NV, Schmitt JM, Talbot TL *et al*. Open-label trial of oral nalmefene therapy for the pruritus of cholestasis. *Hepatology* 1998; **27**: 679.
11 Borgeat A, Wilder-Smith OHG, Mentha G. Subhypnotic doses of propofol relieve pruritus associated with liver disease. *Gastroenterology* 1993; **104**: 244.
12 Brenard R, Geubel AP, Benhamou J-P. Benign recurrent intrahepatic cholestasis. *J. Clin. Gastroenterol.* 1989; **11**: 546.
13 Bruguera M, Llach J, Rodes J. Non-syndromic paucity of intrahepatic bile ducts in infancy and idiopathic ductopenia in adulthood: the same syndrome? *Hepatology* 1992; **15**: 830.
14 Bull LN, Juijn JA, Liao M *et al*. Fine-resolution mapping by haplotype evaluation: the examples of PFIC1 and BRIC. *Human Genet.* 1999; **104**: 241.
15 Bull LN, van-Eijk MJ, Pawlikowska L *et al*. A gene encoding a P-type ATPase mutated in two forms of hereditary cholestasis. *Nature Genet.* 1998; **18**: 219.
16 Burak KW, Pearson DC, Swain MG *et al*. Familial idiopathic adulthood ductopenia: a report of five cases in three generations. *J. Hepatol.* 2000; **32**: 159.
17 Crippin JS, Jorgensen RA, Dickson ER *et al*. Hepatic osteodystrophy in primary biliary cirrhosis: effects of medical treatment. *Am. J. Gastroenterol.* 1994; **89**: 47.
18 Crosbie OM, Crown JP, Nolan NPM *et al*. Resolution of paraneoplastic bile duct paucity following successful treatment of Hodgkin's disease. *Hepatology* 1997; **26**: 5.
19 Cynamon HA, Andres JM, Iafrate RP. Rifampin relieves pruritus in children with cholestatic liver disease. *Gastroenterology* 1990; **98**: 1013.
20 Degott C, Feldmann G, Larrey D *et al*. Drug-induced prolonged cholestasis in adults: a histological semiquantitative study demonstrating progressive ductopenia. *Hepatology* 1992; **15**: 244.
21 Dixon JM, Armstrong CP, Duffey SW *et al*. Factors affecting morbidity and mortality after surgery for obstructive jaundice: a review of 373 patients. *Gut* 1983; **24**: 845.
22 Dooley JS. Extrahepatic biliary obstruction: systemic effects, diagnosis, management. In Benhamou J-P, Bircher J, McIntre N, Rizzetto M, Rodes J, eds. *Oxford Textbook of Clinical Hepatology*. Oxford University Press, Oxford, 1999, p. 1581.
23 Eastell R, Dickson ER, Hodgson SF *et al*. Rates of vertebral loss before and after liver transplantation in women with primary biliary cirrhosis. *Hepatology* 1991; **14**: 296.
24 Epstein O, Dick R, Sherlock S. Prospective study of periostitis and finger clubbing in primary biliary cirrhosis and other forms of chronic liver disease. *Gut* 1981; **22**: 203.
25 Faa G, Van Eyken P, Demelia L *et al*. Idiopathic adulthood ductopenia presenting with chronic recurrent cholestasis. *J. Hepatol.* 1991; **12**: 14.
26 FitzPatrick DR. Zellweger syndrome and associated phenotypes. *J. Med. Genet*. 1996; **33**: 863.
27 Fleming CR, Dickson ER, Hollenhorst RW *et al*. Pigmented corneal rings in a patient with primary biliary cirrhosis. *Gastroenterology* 1975; **69**: 220.
28 Fogarty BJ, Parks RW, Rowlands BJ *et al*. Renal dysfunction in obstructive jaundice. *Br. J. Surg*. 1995; **82**: 877.
29 Freedman MR, Holzbach RT, Ferguson DR. Pruritus in cholestasis: no direct causative role for bile acid retention. *Am. J. Med.* 1981; **70**: 1011.
30 Ghent CN, Carruthers SG. Treatment of pruritis in primary biliary cirrhosis with rifampin. Results of a double-blind, crossover, randomized trial. *Gastroenterology* 1988; **94**: 488.
31 Gu M, Cooper JM, Butler P *et al*. Oxidative-phosphorylation defects in liver of patients with Wilson's disease. *Lancet* 2000; **356**: 469.
32 Guanabens N, Pares A, del Rio L *et al*. Sodium fluoride prevents bone loss in primary biliary cirrhosis. *J. Hepatol.* 1992; **15**: 345.
33 Guanabens N, Pares A, Monegal A *et al*. Etidronate vs. fluoride for treatment of osteopenia in primary biliary cirrhosis: preliminary results after 2 years. *Gastroenterology* 1997; **113**: 219.
34 Gubern JM, Sancho JJ, Simo J *et al*. A randomised trial on the effect of mannitol on postoperative renal function in patients with obstructive jaundice. *Surgery* 1988; **103**: 39.
35 Harry D, Anand R, Holt S *et al*. Increased sensitivity to endotoxemia in the bile duct-ligated cirrhotic rat. *Hepatology* 1999; **30**: 1198.
36 Hay JE. Bone disease in cholestatic liver disease. *Gastroenterology* 1995; **108**: 276.
37 Hay JE, Lindor KD, Wiesner RH *et al*. The metabolic bone disease of primary sclerosing cholangitis. *Hepatology* 1991; **14**: 257.
38 Hollands CM, Rivera-Pedrogo FJ, Gonzalez-Vallina R *et al*. Ileal exclusion for Byler's disease: an alternative surgical approach with promising early results for pruritus. *J. Pediatr. Surg.* 1998; **33**: 220.
39 Holt S, Marley R, Fernando B *et al*. Acute cholestasis-induced renal failure: effects of antioxidants and ligands for the thromboxane A(2) receptor. *Kidney Int.* 1999; **55**: 271.
40 Jacquemin E, Cresteil D, Manouvrier S *et al*. Heterozygous nonsense mutation of the MDR3 gene in familial intrahepatic cholestasis of pregnancy. *Lancet* 1999; **353**: 210.
41 Jacquemin E, De Vree JML, Cresteil D *et al*. The wide spectrum of multidrug resistance 3 deficiency: from neonatal cholestasis to cirrhosis of adulthood. *Gastroenterology* 2001; **120**: 1448.
42 Janes CH, Dickson ER, Okazaki R *et al*. Role of hyperbilirubinaemia in the impairment of osteoblast proliferation associated with cholestatic jaundice. *J. Clin. Invest.* 1995; **95**: 2581.
43 Jansen PLM, Moller M. Genetic cholestasis: lessons from the molecular physiology of bile formation. *Can. J. Gastroenterol.* 2000; **14**: 233.
44 Jansen PLM, Moller M. The molecular genetics of familial intrahepatic cholestasis. *Gut* 2000; **47**: 1.
45 Jeffrey GP, Muller DPR, Burroughs AK *et al*. Vitamin E deficiency and its clinical significance in adults with primary

biliary cirrhosis and other forms of chronic liver disease. *J. Hepatol.* 1987; **4**: 307.
46 Jones EA, Bergasa NV. The pruritis of cholestasis. *Hepatology* 1999; **29**: 1003.
47 Jones EA, Dekker LR. Florid opioid withdrawal-like reaction precipitated by naltrexone in a patient with chronic cholestasis. *Gastroenterology* 2000; **118**: 431.
48 Jones EA, Yurdaydin C. Is fatigue associated with cholestasis mediated by altered central neurotransmission? *Hepatology* 1997; **25**: 492.
49 Kanno N, LeSage G, Glaser S *et al*. Functional heterogeneity of the intrahepatic biliary epithelium. *Hepatology* 2000; **31**: 555.
50 Kawaguchi T, Sakisaka S, Mitsuyama K *et al*. Cholestasis with altered structure and function of hepatocyte tight junction and decreased expression of canalicular multispecific organic anion transporter in a rat model of colitis. *Hepatology* 2000; **31**: 1285.
51 Krähenbuhl L, Schäfer M, Krähenbuhl S. Reversibility of hepatic mitochondral damage in rats with long-term cholestasis. *J. Hepatol.* 1998; **28**: 1000.
52 Lai ECS, Mok FPT, Fan ST *et al*. Preoperative endoscopic drainage for malignant obstructive jaundice. *Br. J. Surg.* 1994; **81**: 1195.
53 Lindor KD, Janes CH, Crippin JS *et al*. Bone disease in primary biliary cirrhosis: does ursodeoxycholic acid make a difference? *Hepatology* 1995; **21**: 389.
54 Ljubuncic P, Tanne Z, Bomzon A. Evidence of a systemic phenomenon for oxidative stress in cholestatic liver disease. *Gut* 2000; **47**: 710.
55 Lobo-Yeo A, Senaldi G, Portmann B *et al*. Class I and class II major histocompatibility complex antigen expression on hepatocytes: a study in children with liver disease. *Hepatology* 1990; **12**: 224.
56 Marinelli RA, LaRusso NF. Aquaporin water channels in liver: their significance in bile formation. *Hepatology* 1997; **26**: 1081.
57 Marinelli RA, Pham LD, Tietz PS *et al*. Expression of aquaporin-4 water channels in rat cholangiocytes. *Hepatology* 2000; **31**: 1313.
58 Müller M, Jansen PLM. The secretory function of the liver: new aspects of hepatobiliary transport. *J. Hepatol*. 1998; **28**: 344.
59 Morton, DH, Salen G, Batta AK *et al*. Abnormal hepatic sinusoidal bile acid transport in an Amish kindred is not linked to FIC1 and is improved by ursodiol. *Gastroenterology* 2000; **119**: 188.
60 Muller C, Pongratz S, Pidlich J *et al*. Treatment of pruritus of chronic liver disease with the 5-hydroxy-tryptamine receptor type 3 antagonist ondansetron: a randomized, placebo-controlled, double-blind cross-over trial. *Eur. J. Gastroenterol. Hepatol.* 1998; **10**: 865.
61 O'Donohue JW, Haigh C, Williams R. Ondansetron in the treatment of the pruritis of cholestasis: a randomised controlled trial. *Gastroenterology* 1997; **112**: A1349.
62 Olsson R, Mattsson L-A, Obrant K *et al*. Estrogen-progestogen therapy for low bone mineral density in primary biliary cirrhosis. *Liver* 1999; **19**: 188.
63 Ormarsdottir S, Ljunggren O, Mallmin H *et al*. Low body mass and use of corticosteroids, but not cholestasis, are risk factors in patients with chronic liver disease. *J. Hepatol.* 1999; **31**: 84.
64 Oude Elferink RPJ, Groen AK. The role of mdr2 P-glycoprotein in biliary lipid secretion. Cross-talk between cancer research and biliary physiology. *J. Hepatol.* 1995; **23**: 617.
65 Osman E, Owen JS, Burroughs AK. Review article: *S*-adenosyl-L-methionine—a new therapeutic agent in liver disease? *Aliment. Pharmacol. Ther.* 1993; **7**: 21.
66 Ostrow JD, Mukerjee P, Tiribelli C. Structure and binding of unconjugated bilirubin: relevance for physiological and pathophysiological function. *J. Lipid Res*. 1994; **35**: 1715.
67 Pain JA, Cahill CJ, Gilbert JM *et al*. Prevention of postoperative renal dysfunction in patients with obstructive jaundice: a multicentre study of bile salts and lactulose. *Br. J. Surg.* 1991; **78**: 467.
68 Pares A, Guañabens N, Ros I *et al*. Alendronate is more effective than etidronate for increasing bone mass in osteopenic patients with primary biliary cirrhosis (abstract). *Hepatology* 1999; **30**: 472A.
69 Pastor A, Collado P, Almar M *et al*. Antioxidant enzyme status in biliary obstructed rats: effects of *N*-acetylcysteine. *J. Hepatol.* 1997; **27**: 363.
70 Piotrowicz A, Polkey M, Wilkinson M. Ursodeoxycholic acid for the treatment of flucloxacillin-associated cholestasis. *J. Hepatol.* 1995; **22**: 119.
71 Poupon RE, Poupon R, Balkau B *et al*. Ursodiol for the long-term treatment of primary biliary cirrhosis. *N. Engl. J. Med.* 1994; **330**: 1342.
72 Quigley EMM, Marsh MN, Shaffer JL *et al*. Hepatobiliary complications of total parenteral nutrition. *Gastroenterology* 1993; **104**: 286.
73 Richardet J-P, Mallat A, Zafrani ES *et al*. Prolonged cholestasis with ductopenia after administration of amoxicillin/clavulanic acid. *Dig. Dis. Sci.* 1999; **44**: 1997.
74 Rodrigues CMP, Steer CJ. Mitochondrial membrane perturbations in cholestasis. *J. Hepatol.* 2000; **32**: 135.
75 Schwörer H, Hartmann H, Ramadori G. Relief of cholestatic pruritus by a novel class of drug: 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists; effectiveness of ondansetron. *Pain* 1995; **61**: 33.
76 Setchell KDR, Bragetti P, Zimmer-Nechemias L *et al*. Oral bile acid treatment and the patient with Zellweger syndrome. *Hepatology* 1992; **15**: 198.
77 Sokol RJ, Heubi JE, Iannaccone S *et al*. Mechanism causing vitamin E deficiency during chronic childhood cholestasis. *Gastroenterology* 1983; **83**: 1172.
78 Springer JE, Cole DEC, Rubin LA *et al*. Vitamin D-receptor genotypes as independent genetic predictors of decreased bone mineral density in primary biliary cirrhosis. *Gastroenterology* 2000; **118**: 145.
79 Strazzabosco M. New insights into cholangiocyte physiology. *J. Hepatol.* 1997; **27**: 945.
80 Swain MG, Le T. Chronic cholestasis in rats induces anhedonia and a loss of social interest. *Hepatology* 1998; **28**: 6.
81 Swain MG, Maric M. Defective corticotropin-releasing hormone mediated neuroendocrine and behavioural responses in cholestatic rats: implications for cholestatic liver disease-related sickness behaviours. *Hepatology* 1995; **22**: 1560.
82 Swain MG, Maric M. Improvement in cholestasis-associated fatigue with a serotonin receptor agonist using a novel rat model of fatigue assessment. *Hepatology* 1997; **25**: 291.

83 Trauner M, Meier PJ, Boyer JL. Molecular regulation of hepatocellular transport systems in cholestasis. *J. Hepatol.* 1999; **31**: 165.
84 Tsukada N, Ackerley CA, Phillips MJ. The structure and organization of the bile canalicular cytoskeleton with special reference to actin and actin-binding proteins. *Hepatology* 1995; **21**: 1106.
85 Tygstrup N, Steig BA, Juijn JA *et al*. Recurrent familial intrahepatic cholestasis in the Faeroe Islands. Phenotypic heterogeneity but genetic homogeneity. *Hepatology* 1999; **29**: 506.
86 Walt RP, Kemp CM, Lyness L *et al*. Vitamin A treatment for night blindness in primary biliary cirrhosis. *Br. Med. J.* 1984; **288**: 1030.
87 Weidenbach H, Leiz S, Nussler AK *et al*. Disturbed bile secretion and cytochrome P-450 function during the acute state of experimental colitis in rats. *J. Hepatol.* 2000; **32**: 708.
88 Williams R, Cartter MA, Sherlock S *et al*. Idiopathic recurrent cholestasis: a study of the functional and pathological lesions in four cases. *Q. J. Med.* 1964; **33**: 387.
89 Wolfhagen FJH, Sternieri E, Hop WCJ *et al*. Oral naltrexone treatment for cholestatic pruritus: a double-blind, placebo-controlled study. *Gastroenterology* 1997; **113**: 1264.
90 Wolfhagen FHJ, van Buuren HR, Vleggaar FP *et al*. Management of osteoporosis in primary biliary cirrhosis. *Bailliere's Clin. Gastroenterol.* 2000; **14**: 629.
91 Yerushalmi B, Sokol RJ, Narkewicz MR *et al*. Use of rifampin for severe pruritus in children with chronic cholestasis. *J. Pediatr. Gastroenterol. Nutr.* 1999; **29**: 442.
92 Yoshidome H, Miyazaki M, Shimizu H *et al*. Obstructive jaundice impairs hepatic sinusoidal endothelial cell function and renders liver susceptible to hepatic ischemia/reperfusion. *J. Hepatol.* 2000; **33**: 59.

Chapter 14
Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is a disease of unknown cause in which intra-hepatic bile ducts are progressively destroyed. It was first described in 1851 by Addison and Gull [1] and later by Hanot [37]. The association with high serum cholesterol levels and skin xanthomas led to the term 'xanthomatous biliary cirrhosis'. Ahrens *et al.* [3] termed the condition 'primary biliary cirrhosis'. However, in the early stages nodular regeneration is inconspicuous and cirrhosis is not present.

Aetiology

A profound immunological disturbance has been related to bile duct destruction [31]. Cytotoxic T-cells infiltrate the bile duct epithelium [111] as do class II restricted T4-lymphocytes. The final event is an attack by cytotoxic T-cells on biliary epithelium. Cytokines produced from the activated T-cells contribute to the liver cell damage [61]. Suppressor T-cells are reduced in number and function (fig. 14.1) [7]. Upregulated display of HLA class I antigens and *de novo* expression of HLA class II antigens are compatible with immune-mediated duct destruction [7].

Aberrant expression of HLA class II antigens on bile ducts has been shown, but only in late PBC. This has suggested that the antigen is presented by bile ducts, but this process may take place in the lymph nodes, rather than in the liver. HLA-D8, the autoimmune HLA type, is found in only a minority of patients.

T-helper cells and cytotoxic T-cells are important in pathogenesis. Cytotoxic T-cells may be effective, producing cytokines. However, the Th2 type of CD4 may predominate in the portal zones. This promotes mast cell and eosinophil activation [69]. Analysis of liver-derived T-cell clones shows predominance of Th1 cells, but with considerable heterogeneity [38]. It is possible that in the early stages the Th2 pattern predominates, to be followed by the Th1. The two patterns moreover may convert one to the other.

Epithelioid granulomas suggest a delayed-type hypersensitivity reaction. They are seen in the early, florid stage and may reflect an improved prognosis [55].

Copper is retained in the liver, but in a non-hepato-toxic form.

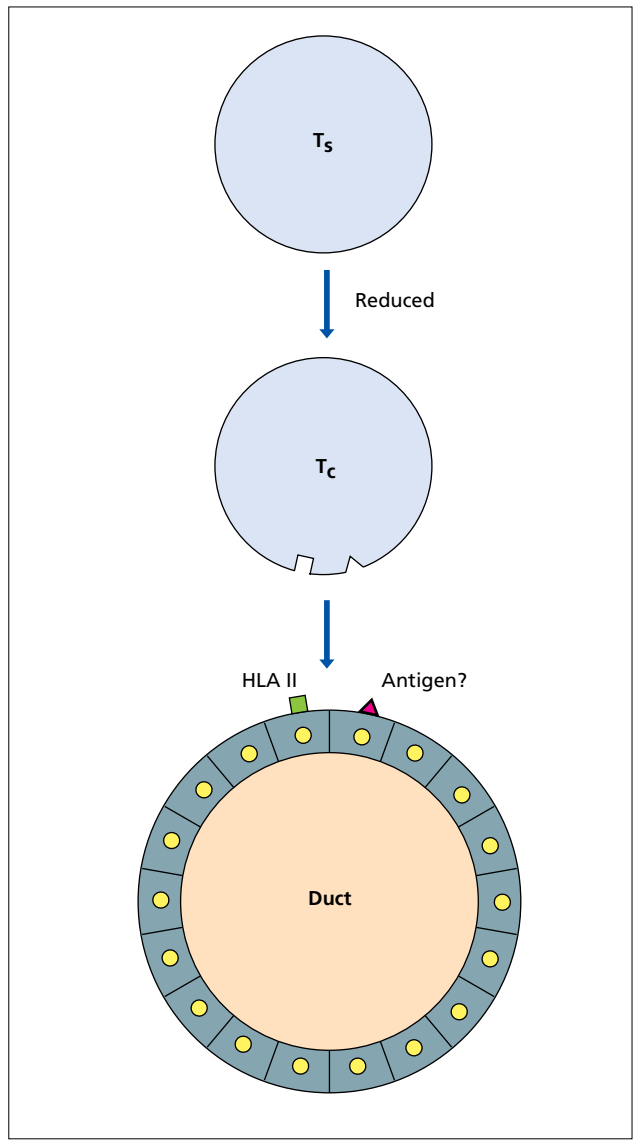


Fig. 14.1. PBC: HLA class II antigens and another unknown antigen are displayed on the bile duct. Suppressor T-cells (T_s) are depressed and there is a breach of tolerance to the biliary antigens. Tc, cytotoxic T-cells.

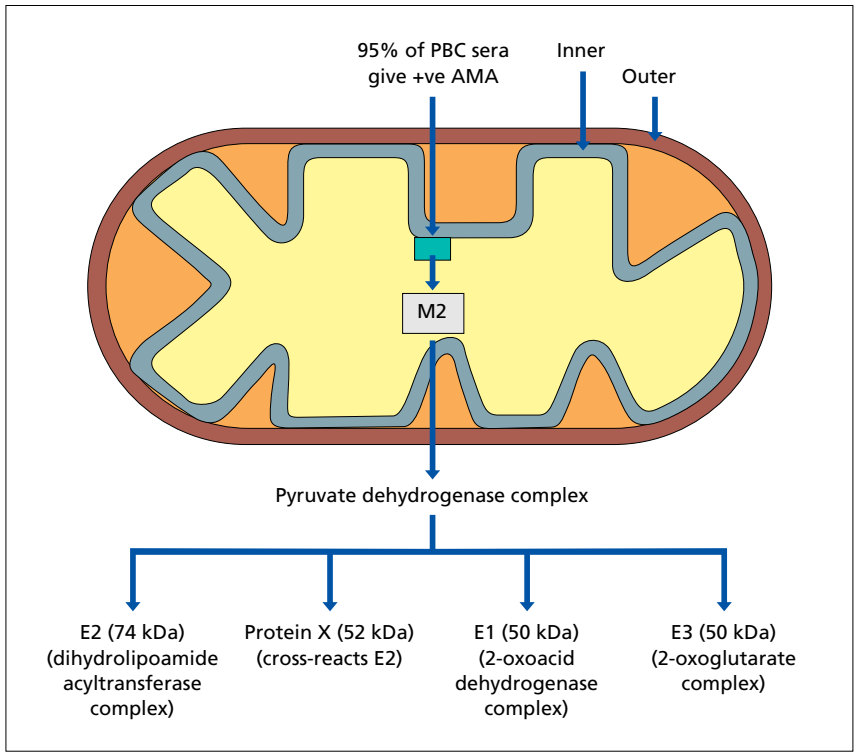


Fig. 14.2. Mitochondrial antibodies and antigens. (AMA, anti-mitochondrial antibody.)

Mitochondrial antigens and antibodies

Circulating antibodies against mitochondria are found in virtually 100% of patients with PBC [107]. They are non-organ and non-species specific. The antigens to which the antibodies are directed are localized on the inner mitochondrial membrane (fig. 14.2) [97]. The antigenic component specific for PBC serum is M2. Four M2 antigen polypeptides have been identified, all components of the pyruvate dehydrogenase complex (PDC) of mitochondrial enzymes (fig. 14.2). E1 is a 50-kDa 2-oxoacid dehydrogenase complex, E2 is the 74-kDa complex of lipoamide acyltransferase, E3 is a 50-kDa 2-oxoglutarate complex. Protein X is a 52-kDa member of the PDC and cross-reacts with E2. An enzyme-linked immunoadsorbent assay (ELISA) test has been developed against E2 and components of the M2 complex. It is 88% sensitive and 96% specific for the diagnosis of PBC [8, 100]. PBC is unlikely in the absence of serum anti-M2. The ELISA-specific test is not generally available and the serum anti-mitochondrial test is usually performed by indirect immunofluorescence on rat kidney substrate. This is a difficult technique and can give false negative results.

The three-dimensional structure of E2 has been determined [44].

The significance of the mitochondrial antibody test remains uncertain and, in particular, its relationship to aetiology [72]. The E2 component of the PDC has been expressed on the bile duct epithelium of patients with early PBC [49].

Other serological autoantibodies are commonly detected, particularly antinuclear antibody (ANA) which is present in a third of cases.

There are other mitochondrial antigens and antibodies. Anti-M9 is associated with early PBC and can be found in healthy relatives of sufferers and technicians handling PBC sera. Between 10 and 15% of normal persons are M9 positive. M4 and M8 are found only in those who are M2 positive. M3 is associated with drug reactions. M6 is related to iproniazid and M5 to collagen diseases.

Possible relation to infection. The antigenic stimulus culminating in the bile duct obstruction may be infectious in nature [39]. There are some similarities between bacterial and mammalian mitochondrial components. Mitochondrial antibodies cross-react with subcellular components of Gram-negative and Gram-positive organisms [29]. Pathogens released from the bacterial walls of *Escherichia coli* might be related aetiologically to the bile duct destruction, but this remains unclear [17, 43, 96]. Patients with PBC have an increased incidence of Gram-negative urinary tract infections.

An association with mycobacterial infection was suggested by the finding of *Mycobacterium gordonae* in liver biopsies of patients with PBC [106]. However, search has failed to reveal mycobacterial DNA from liver

biopsies from patients with PBC [74] and this theory is unproven.

Retroviral infection has also been suggested as 35% of patients with PBC have reactivity to proteins associated with HIV-1 infection [62]. Methodology, however, has been severely criticized [108].

Lymph nodes from PBC patients contain a transmissible factor which can induce biliary epithelial cells from normal subjects to express antigens similar to those seen in PBC [87].

All these observations are inconclusive [99]. They do, however, suggest that the antigens responsible for the autoantibody attack on the biliary epithelium will eventually be identified and are likely to be of infective nature.

Epidemiology and genetics

Asians, Caucasians, Jews, Black and Oriental people are affected. Changing prevalence depends on increasing physician awareness, better diagnosis, especially availability of the serum mitochondrial test, and recognition of more asymptomatic patients.

There is family clustering; mothers and daughters have the highest prevalence [48] with presentation earlier in the second generation [12]. Prevalence of circulating mitochondrial antibodies is increased in relatives of patients [28].

In one study from Sheffield, UK, PBC was associated with a particular water supply [102]. Environmental factors in the water supply could not be identified in Ontario, Canada, where racial predisposition and geographical clustering were not seen [110]. More epidemiological studies are needed.

C4A-QO, an HLA class III allele, is associated with many autoimmune diseases. Genetic typing revealed an increased incidence of C4A-QO allele and a highly significant proportion of PBC patients carried DRw8 and C4A-QO alleles [60]. A mother and two sisters with PBC shared the same histocompatibility haplotype.

Patients with PBC having an autoimmune genetic susceptibility, as evidenced by the presence of HLA-B8, -DR3 or -DR4, may run a more hepatic course [58].

Susceptibility alleles on chromosome 6 include HLA-DPB1*0301 in a German population [64] and DRB1*0803 in Japanese sufferers [75]. Polymorphism, also on chromosome 6, of TNF-α promoter genes have been described [23].

Polymorphism in cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) may increase susceptibility to PBC [2]. It is the first non-histocompatibility complex gene to be associated.

Conflicting results in different studies are difficult to explain but may be related to sample numbers, racial differences and case mix [23]. However, these results do suggest a strong immunogenetic background for PBC that runs in families. Environmental factors presumably act on a genetically predisposed host.

Clinical features

Presentation (table 14.1) [93]

Ninety per cent of patients with PBC are female. The cause for disease prevalence among women is unknown. The patient is usually 40–60 years of age, but can be as old as 80 or as young as 20 [67]. Ten per cent are male, in whom the disease runs a similar course. The disease starts insidiously, most frequently as pruritus without jaundice. Patients may be referred initially to dermatologists. Jaundice may never develop, but in the majority appears within 6 months to 2 years of the onset of pruritus. In about a quarter, jaundice and pruritus start simultaneously. Jaundice preceding pruritus is extremely unusual and jaundice without pruritus at any time is very rare. The pruritus can start during pregnancy and be confused with cholestatic jaundice of pregnancy. Chronic right upper quadrant pain is frequent (17%). This may persist or resolve [54]. ERCP may be necessary for diagnosis. Fatigue is frequent [18].

Examination shows a well-nourished, sometimes pigmented woman. Jaundice is slight or absent. The liver is usually enlarged and firm and the spleen palpable.

The asymptomatic patient

Widespread use of biochemical screening has resulted in an increasing number of patients being diagnosed when asymptomatic, usually by a raised serum alkaline phosphatase level. Liver biopsies performed after finding a

Table 14.1. Diagnosis of primary biliary cirrhosis at presentation [91]

Symptomatic
Middle-aged woman with pruritus followed by slowly progressive jaundice
Liver palpable
Serum bilirubin about twice normal; serum alkaline phosphatase about 4 times normal; serum aspartate transaminase about twice normal; serum albumin normal
Serum mitochondrial antibody 1 : 40
Liver biopsy appearances compatible
ERCP (if diagnosis in doubt): normal intra-hepatic bile ducts
Asymptomatic
Routine laboratory screen
Increased serum alkaline phosphatase
Positive serum mitochondrial antibody
Investigation of other disease, especially collagen or thyroid
Hepatomegaly

positive mitochondrial antibody titre ≥1/40 are nearly always abnormal and usually show features consistent with PBC even if the patient is asymptomatic and the serum alkaline phosphatase is normal.

The diagnosis may be made in patients under investigation for a condition known to be associated with PBC, such as thyroid or collagen disease, or in the course of family surveys.

Abnormal physical signs may be absent. Mitochondrial antibody is always present. Serum alkaline phosphatase and bilirubin may be normal or only minimally increased. Serum cholesterol and transaminases can also be normal.

Course

Asymptomatic patients usually survive at least 10 years (fig. 14.3) [59, 93]. In those with symptomatic disease and jaundice the survival is about 7 years [90].

Diarrhoea may be due to steatorrhoea. Weight loss is slow. The course is afebrile and abdominal pain is unusual but may persist. Fatigue is very common, affecting 60% of sufferers [18]. It is associated with depression, experimentally [98], and poor quality of life and may be assessed by a fatigue severity score [82].

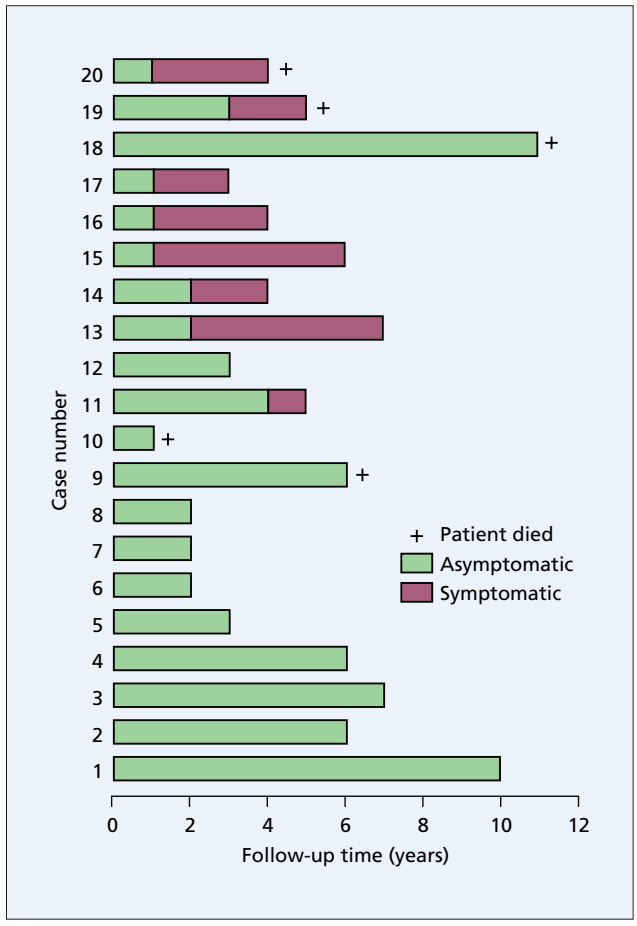


Fig. 14.3. The course of 20 patients with PBC diagnosed when asymptomatic. Note that one patient continued asymptomatic for 10 years [57].

Skin xanthomas develop frequently and sometimes acutely, but many patients remain in the pre-xanthomatous state throughout their course; terminally, xanthomas may disappear.

The skin may be thickened and tough over the fingers, ankles and legs. Pain in the fingers, especially on opening doors, and in the toes may be due to xanthomatous peripheral neuropathy [101]. There may be a butterfly area over the back which is inaccessible and escapes scratching.

The bone changes are particularly profound in the deeply jaundiced. They have been related to the vitamin D receptor genotype which predicts lower bone mineral density in patients with PBC [95]. In the later stages, the patient complains of back ache and pain over the ribs, sometimes with pathological fractures.

Duodenal ulceration and haemorrhage are common.

Bleeding oesophageal varices may be a presenting feature even before nodules have developed [50]. At this stage the portal hypertension is probably pre-sinusoidal. Within 5.6 years, oesophageal varices have developed in 83 of 265 patients (31%), and in 40 (48%) have bled [32].

Hepato-cellular carcinoma is rare, but there is an increased risk for its development, especially in males [46, 73].

Associated diseases

PBC is associated with almost any autoimmune disease. The collagenoses, especially rheumatoid arthritis, dermatomyositis, mixed connective tissue disease and systemic lupus erythematosus [36], are particularly frequent.

PBC may be associated with scleroderma in 4% of patients and with the whole CREST syndrome [83]. The scleroderma is usually limited to sclerodactyly but occasionally involves the face, arms and legs. Keratoconjunctivitis may be present [81]. These patients usually show centromere antibodies [24]. Clonally expanded $CD8^+$ T cells are associated with PBC and CREST [63]. A sicca complex with dry eyes and mouth, with or without arthritis completing the Sjögren's syndrome, is found in about 75% of patients.

Other skin lesions include immune complex capillaritis and lichen planus. Autoimmune thyroiditis affects about 20%. Graves' disease has also been reported.

The prevalence of PBC in coeliac disease is 3% and the prevalence of coeliac disease in patients with PBC is 6% [53]. Patients with PBC should be screened for coeliac

disease by anti-endomysial antibodies and, if necessary, by duodenal biopsy [71].

PBC has been associated with autoimmune thrombocytopenia, autoimmune haemolytic anaemia [19] and insulin receptor autoantibodies. Ulcerative colitis is another rare association [16].

Renal complications include IgM-associated membranous glomerular nephritis.

Renal tubular acidosis is attributed to copper deposits in the distal renal tubule. Hypouricaemia and hyperuricosuria are further expressions of renal tubular damage. Bacteriuria develops in 35% of cases and may be asymptomatic [14].

Association with selective immunoglobulin A deficiency indicates that the pathogenesis does not require IgA-dependent immune mechanisms.

There is a small increase in overall cancer incidence and mortality in patients with PBC [45]. An excess of breast cancer has not been confirmed.

Finger clubbing is common, and occasionally there is hypertrophic osteoarthropathy [26].

Pancreatic insufficiency is secondary to low bile flow and perhaps to immunological damage to the pancreatic duct.

Gallstones, usually of pigment type, have been seen by ERCP in 39% of cases. They are occasionally symptomatic but rarely migrate to bile ducts.

Pulmonary abnormalities include lymphocyte interstitial pneumonitis [109]. Gas transfer studies may be abnormal. Pulmonary interstitial giant cells have been described, usually with Sjögren's syndrome [103]. Radiograms may show nodules, interstitial fibrosis and mediastinal lymphadenopathy.

The CREST syndrome is accompanied by lymphocytic interstitial pneumonitis and pulmonary vascular abnormalities.

CT scanning shows 81% of patients to have enlarged nodes in the gastro-hepatic ligament and porta hepatis. Enlarged paracardiac and mesenteric nodes are also seen.

Biochemical tests

Initially, serum bilirubin values are usually less than 35 µmol/l (2 mg/100 ml) in symptomatic patients. Serum alkaline phosphatase and γ-glutamyl transpeptidase (γ-GT) are raised. The total serum cholesterol is increased but not constantly. The serum albumin level is usually normal at presentation and the total serum globulin only moderately increased. Serum IgM is usually raised. This is not reliable for diagnosis, although an increase may add some diagnostic weight.

Liver biopsy [86]

The only diagnostic lesion is the injured septal or interlobular bile duct. Such ducts are not often seen in needle biopsy specimens, but are usually well represented in surgical biopsies (fig. 14.4).

The disease begins with damage to the epithelium of the small bile ducts. Histometric examinations show that bile ducts less than 70–80 µm in diameter are destroyed, particularly in the early stages [70]. Epithelial cells are swollen, irregular and more eosinophilic. The bile duct lumen is irregular and the basement membrane is disrupted. The bile duct occasionally ruptures. Surrounding the damaged duct is a cellular reaction which includes lymphocytes, plasma cells, eosinophils and histiocytes. Granulomas commonly form, usually in zone 1 (fig. 14.4).

Bile ducts become destroyed. Their sites are marked by aggregates of lymphoid cells, and bile ductules begin to proliferate (fig. 14.5). Hepatic arterial branches can be identified in zone 1, but without accompanying bile ducts. Fibrosis extends from zone 1 and there is a variable degree of piecemeal necrosis. Substantial

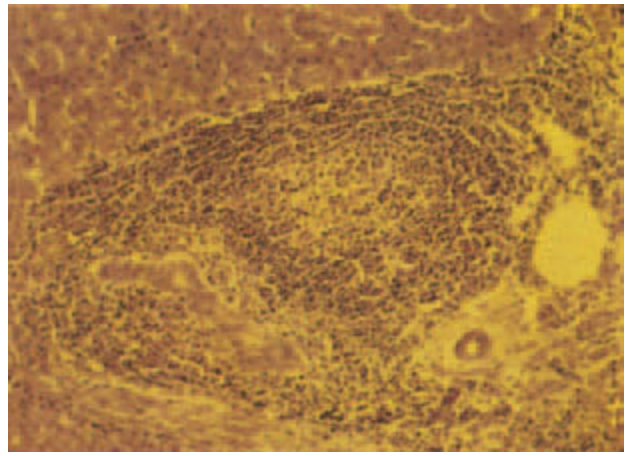


Fig. 14.4. The portal zone contains a well-formed granuloma. An adjacent bile duct shows damage.

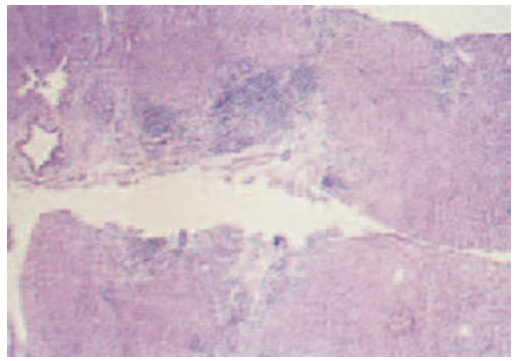


Fig. 14.5. Stage 2 lesion, marked by aggregates of lymphoid cells. Bile ducts begin to proliferate. (H & E, ×10.)

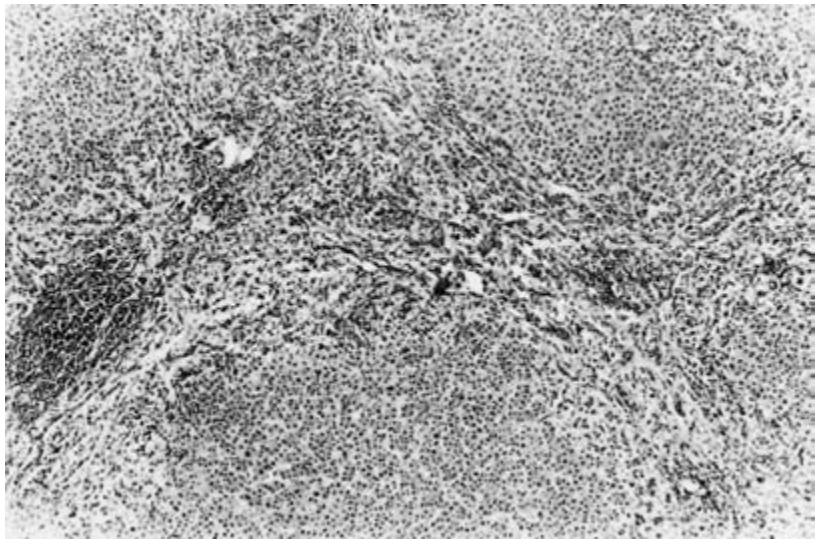


Fig. 14.6. There is scarring and septa contain lymphoid aggregates. Bile ducts are inconspicuous. Hyperplastic 'regeneration' nodules are beginning to develop [93]. (H & E, ×48.)

amounts of copper and copper-associated protein can be demonstrated histochemically. The fibrous septa gradually distort the architecture of the liver and regeneration nodules form (figs 14.6, 14.7). These are often irregular in distribution and cirrhosis may be seen in one part of a biopsy but not in another. In some areas, lobular architecture may be preserved for some time. In the early stages, cholestasis is in zone 1 (portal).

Hepato-cellular hyaline deposits, similar to those of alcoholic disease, are found in hepatocytes in about 25% of cases.

The histological appearances have been divided into four stages [88]: *stage I*, florid bile duct lesions; *stage II*, ductular proliferation; *stage III*, scarring (septal fibrosis and bridging); and *stage IV*, cirrhosis. Such staging is of limited value as the changes in the liver are focal and evolve at different speeds in different parts. Stages overlap.

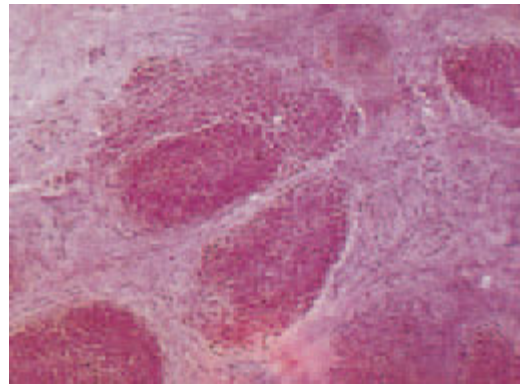


Fig. 14.7. Stage 4: biliary cirrhosis has developed.

Diagnosis (table 14.2)

There are a number of PBC 'look-alikes', the chief difference being that they lack serum mitochondrial antibody.

Visualization of the bile ducts by MR, endoscopic or percutaneous cholangiography may be necessary in atypical patients. These include males and those with a negative serum mitochondrial antibody test, with inconclusive liver biopsy findings or with marked abdominal pain.

Widespread tissue granulomas may suggest cholestatic sarcoidosis (table 14.3) (Chapter 28) [68]. In sarcoidosis, however, the mitochondrial antibody is absent. Liver biopsy shows abundant well-formed granulomas and less bile duct damage than seen in PBC.

T-lymphocytes (predominantly T4-positive cells) and activated alveolar macrophages are found by bronchoalveolar lavage in patients with PBC—similar findings to those of sarcoidosis. There are overlaps and occasionally the distinction is impossible.

In later stages, the differentiation from autoimmune chronic active hepatitis may be difficult. The pattern of biochemical tests of liver function is usually different. Liver biopsy features favouring PBC include intact lobules, slight zone 1 necrosis and peri-septal cholestasis.

Chronic hepatitis C virus infection is occasionally associated with prolonged cholestasis, but biochemical tests suggest hepato-cellular disease and serological tests for hepatitis C virus are positive.

In autoimmune cholangitis, the clinical features of biochemical tests and liver histology resemble those of PBC [9]. Serum mitochondrial antibody is always negative but antinuclear antibodies are present in high titre.

In primary sclerosing cholangitis, the mitochondrial antibody test is always negative or in low titre and cholangiography demonstrates the typical bile duct irregularities.

Table 14.2. Differential diagnosis of primary biliary cirrhosis [91]

Disease	Features	MAb	Liver biopsy
Primary biliary cirrhosis	Female Pruritus High serum alkaline phosphatase	Positive	Bile duct damage Lymphoid aggregates Slight PMN Intact lobules Peri-septal cholestasis
Primary sclerosing cholangitis	Males predominate Associated ulcerative cholitis Cholangiography is diagnostic	Negative or low titre	Ductular proliferation fibrosis Onion-skin duct fibrosis
Cholestatic sarcoidosis	Equal sexes Black patients Pruritus High serum alkaline phosphatase Chest X-ray changes	Negative	Many granulomas Modest bile duct changes
Autoimmune cholangiopathy	Females High serum alkaline phosphatase Serum ANA positive in high titre	Negative	Bile duct damage Lymphoid aggregates Slight PMN
Cholestatic drug reactions	History Usually within 6 weeks of starting drug Acute onset	Negative	Mononuclear portal reaction sometimes with eosinophils, granulomas and fatty change

ANA, antinuclear antibodies; MAb, mitochondrial antibodies; PMN, piecemeal necrosis.

Table 14.3. Cholestatic sarcoidosis compared with primary biliary cirrhosis

	Sarcoidosis	Primary biliary cirrhosis
Sex	Equal	80% female
Age	Young	Middle age
Pruritus	Yes	Yes
Jaundice	Yes	Yes
Respiratory complaints	Yes	No
Hepato-splenomegaly	Yes	Yes
Serum alkaline phosphatase	Raised	Raised
Hilar lymphadenopathy	Usual	Rare
Hepatic granulomas	Discrete Clustered	Poorly formed Surrounded by mixed cells
Serum angiotensin-converting enzyme	Raised	Raised
Mitochondrial antibody	No	Yes (98%)
Kveim–Siltzbach test	Positive	Negative
Broncho-alveolar lavage		
lymphocytosis	Present	Present
activated macrophages	Present	Present

Idiopathic adult ductopenia is marked by absence of interlobular bile ducts. The aetiology is uncertain but some instances may represent small duct primary sclerosing cholangitis [13].

Cholestatic drug reactions are excluded by the history and by the acute onset, with rapidly deepening jaundice developing 4–6 weeks after the drug is started.

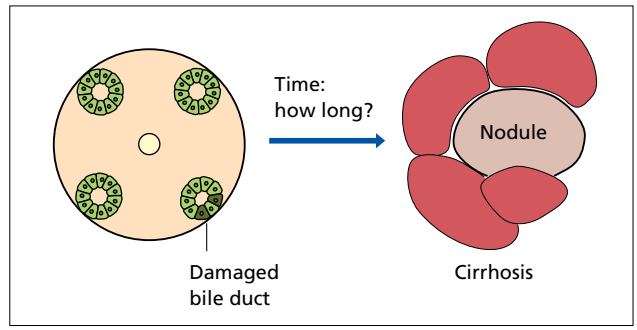


Fig. 14.8. Natural history of PBC: the time taken from acute bile duct damage to end-stage biliary cirrhosis is uncertain [92].

Prognosis

The course of asymptomatic patients is variable and unpredictable, and counselling the patient and her family is very difficult [94]. Some will never become symptomatic and others will run a progressive downhill course (fig. 14.8). Nowadays, the patient with end-stage PBC faces not death, but possible liver transplantation.

Reported results of the time taken to pass from the asymptomatic to the symptomatic stage are very variable and may depend on the patients studied and the mode of referral. Duration of disease depends on the time of first diagnosis. Patients seen at a referral centre such as the Mayo Clinic or Royal Free Hospital are usually more advanced and hence more likely to be symptomatic sooner than those in a regional referral

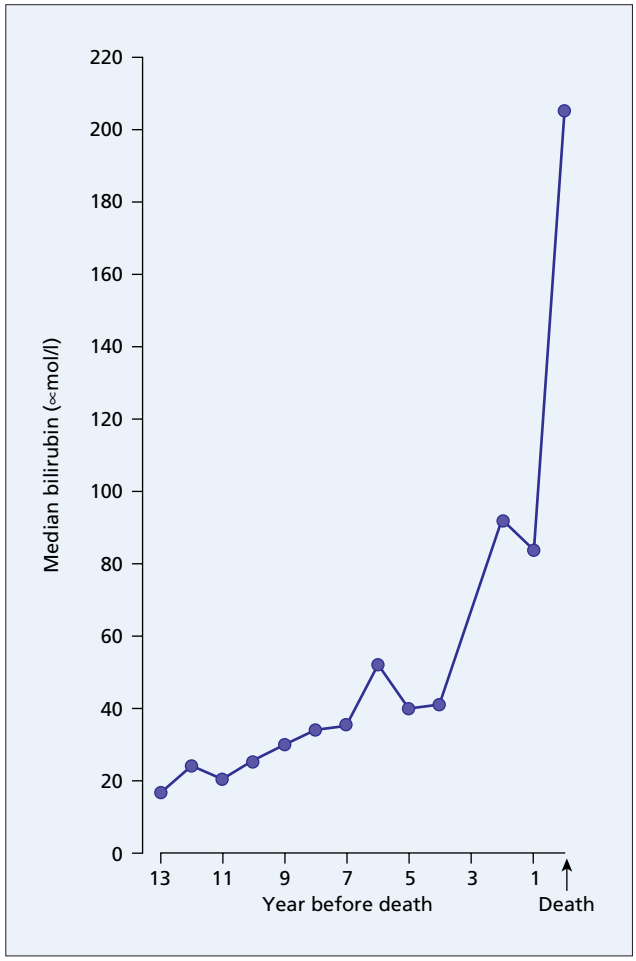


Fig. 14.9. The evolution of liver failure in PBC. This nomogram is derived from the medians of pooled serum bilirubin results in patients followed serially from diagnosis to death. Expected survival for any given bilirubin can be extrapolated from this nomogram [27].

Bilirubin (µmol/l)	Expected survival years
<34	8–13
35–100	2–7
>100	<2
(17 µmol/l = 1 mg)	

centre. By and large, asymptomatic patients become symptomatic when the course mirrors that of the patient who presents symptomatically (table 14.4) [59].

Prognosis is particularly important in determining the best time for hepatic transplantation. When serum bilirubin values are consistently greater than 100 µmol/l (6 mg/dl), the patient is unlikely to survive for more than 2 years (fig. 14.9) [27, 89]. Other features predicting decreased survival include symptoms, advanced age, hepato-splenomegaly, ascites and serum albumin less than 3 g/dl.

Table 14.4. The progression of primary biliary cirrhosis [65]

Stage			
AMA	Biochemistry	Symptoms	Progression time (years)
+	0	0	80% will progress
+	+	0	40% in 6 years
+	+	+	70% in 10 years (50% in 5 years)

Table 14.5. Mayo model for survival [22]

Age
Serum
bilirubin
albumin
Prothrombin time
Oedema

Within a median of 5.6 years, varices have developed in 31% of patients and 48% of these will have bled. Varices are more likely to develop in those with a high serum bilirubin and with an advanced histological stage of the disease. Once varices have developed, 83% survive 1 year and 59% 3 years. Survival after the initial bleed is 65% at 1 year and 46% at 3 years [32].

Autoimmune diseases such as thyroiditis or sicca syndrome correlate with decreased survival.

The Mayo Clinic prognostic model depends on age, serum bilirubin, albumin and prothrombin time, and the presence or absence of oedema (table 14.5) [22]. This predicts survival and has the advantage of being independent of liver biopsy [51]. A study from Glasgow included liver biopsy appearances [33].

No model can yield a precise estimate of survival for the individual patient. These models do not take into account serial time-dependent factors. They cannot predict a life-threatening episode such as bleeding varices.

The terminal stages last about 1 year and are marked by a rapid deepening of jaundice with the disappearance of both xanthomas and pruritus. Serum albumin and total cholesterol levels fall. Oedema and ascites develop. The final events include episodes of hepatic encephalopathy with uncontrollable bleeding, usually from the oesophageal varices. An intercurrent infection, sometimes a Gram-negative septicaemia, may be terminal.

Treatment [40]

General measures apply to all patients with cholestasis. They include maintenance of nutrition and fat-soluble vitamin replacement. Pruritus is usually controlled by cholestyramine, but oral nalmefene and opiate antago-

nists have given promising results in an open label trial [10] (see Chapter 13).

Osteomalacia is rare and corrected by vitamin D and calcium supplements. The major problem is osteoporosis which is of low turnover type. It may be related to the accumulation of toxins that impair osteoblast function. Calcitonin is of no value. Biphosphonates may be useful and cyclical editronate can be tried [35]. Oestrogens stimulate bone formation and post-menopausal women with PBC should receive hormone replacement therapy [85].

The recognition that PBC was probably an autoimmune disease led to trials of immunosuppresive drugs [92]. Drugs tested included azathioprine, D-penicillamine, chlorambucil, cyclosporin A and corticosteroids. Results in terms of survival, biochemical tests and hepatic history tended to be inconclusive. Methotrexate is the last drug to be assessed, but after 6 years, the Mayo score and bilirubin were higher in those receiving the drug than in controls [42]. It may be useful in non-responders to ursodiol [11, 15]. Colchicine is of little, if any, benefit. Combination therapy may be more helpful, in particular ursodeoxycholic acid plus azathioprine or cortisone [56], or methotrexate plus other drugs such as colchicine, but no significant benefit has been reported so far.

Ursodeoxycholic acid

This is a non-hepato-toxic, hydrophilic bile acid. It protects cell membranes against the detergent effect of hydrophobic bile acids. It stimulates the excretion of toxic bile acids. It increases anion exchange in the liver. It reduces HLA class I expression on bile ducts, so decreasing cytolytic attack of T-cells on bile ducts. It stimulates peripheral blood mononuclear cells and suppresses immunoglobulin and IL-2 and IL-4 production [112]. It inhibits the production of nitric oxide synthase.

Original studies from France showed that ursodeoxycholic acid improved liver function and slowed progression and probability of death or transplantation [80]. Results were less satisfactory if, on entry to the trial, the patient had a high serum bilirubin level and cirrhosis was present [78, 79]. Symptoms such as pruritus and fatigue are unaffected. A multi-centre controlled trial confirmed that ursodeoxycholic acid reduces the time to death or transplantation [79]; it does not cure the disease. A 6-year, follow-up study from Spain in early cases showed biochemical and histological improvement, but no difference in time to death or transplant [76]. Meta-analysis of eight trials showed no better results over placebo in death, liver-related death or transplantation [34].

Reported results of the effect on liver histology are variable. Inflammation and necrosis may be less, but ductular proliferation and piecemeal necrosis at 4 years is similar [76]. Fibrosis may progress or be stable [21, 41]. It may not have any significant effect on the progression of the histological stage [4].

Ursodeoxycholic acid should be given to early cases at a dose of 13–15 mg/kg body weight once daily after the evening meal. It is cost-effective [77]. The use of the Mayo model [22] to predict survival remains valid [51]. Ursodeoxycholic acid is certainly not a panacea for the treatment of PBC. Nevertheless, it should be given to all patients unless they have reached the end-stages and are approaching transplantation. The decision to treat the early, asymptomatic patient with ursodeoxycholic acid is a difficult one, and must be based on each individual patient, bearing in mind the cost. At present there is no satisfactory, specific medical treatment for PBC.

Reported trials have usually been too short, too small and poorly controlled. Statistically significant long-term benefits are difficult to establish in a disease with such a long and varied natural history [92]. Any trial must state the number of patients included in each grade. The group in the early, asymptomatic, excellent stage may require no treatment. The ones with the poor outlook will be too near end-stage to respond.

Haemorrhage from oesophageal varices may be early, before a true nodular cirrhosis has developed. It is not surprising therefore that porta-caval shunting gives good results in these patients. Hepatic encephalopathy is unusual. These encouraging results apply particularly to good-risk patients. Transjugular intrahepatic portal-systemic shunt (TIPS) may be useful.

Gallstones should be left *in situ* unless causing severe symptoms or present in the common bile duct. Cholecystectomy is rarely indicated and is badly tolerated.

Hepatic transplantation

Indications are poor quality of life so that the patient is housebound, has intractable pruritus, hepato-cellular failure (deepening jaundice, encephalopathy, ascites) or bleeding varices. Results are better if referral is early and the cost is considerably less. A risk–score model using age, renal failure, Child's class and UNOS (United Network for Organ Sharing) criteria can be used to predict the effects of transplant in terms of intraoperative blood requirements, time in intensive care and severe complications [84]. Results are considerably better if the risk–score is lower [52]. Patients should be considered by a transplant centre when the serum bilirubin level approaches 9 g/dl (150 μmol/l). Using another model, the optimum time for a transplant was when the 6-month survival probability fell below 0.85 [20]. In non-transplant patients, this was usually about 8 months before death.

One-year survival after transplant is about 85–90% and a 5-year survival of 60–70% is reported [104]. About

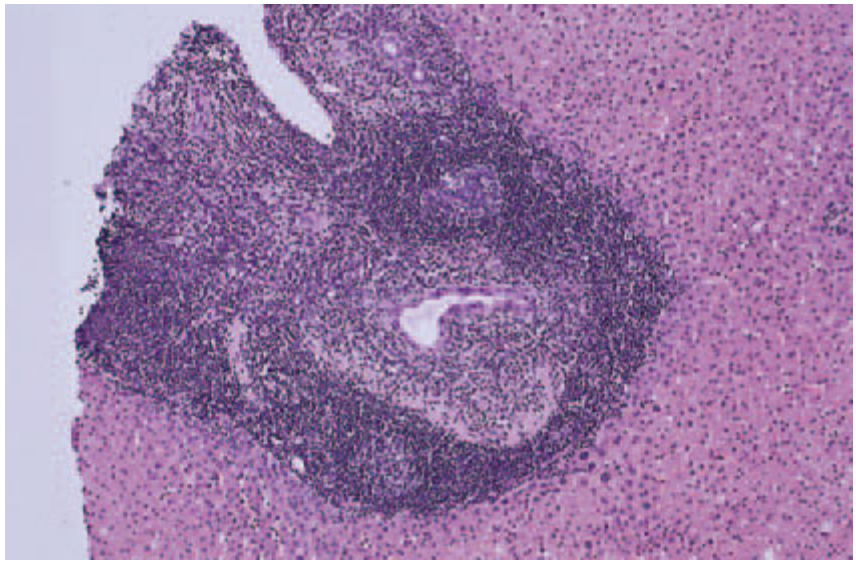


Fig. 14.10. Autoimmune cholangiopathy. Liver biopsy from a young man with mild pruritus, high serum alkaline phosphatase and γ-GT levels. Serum M2 was not detected. Serum ANA was present in high titre. Histology shows damaged zone 1 bile duct with marked inflammation. Appearances resemble PBC. (H & E, ×400.)

10% of patients will need re-transplant, with particularly bad results if this is more than 30 days after the operation [52]. Disease almost certainly recurs in the transplanted liver [5]. Mitochondrial antibody levels increase and the patient may become symptomatic. This is confirmed by finding E2 staining on biliary epithelial cells after the operation [105]. It is, however, difficult to distinguish the features of rejection from recurrent disease which, in any case, is usually non-progressive. Primary malignancies develop later in 10% of patients. In the first 1–3 months, bone density decreases and the results may be catastrophic. The worsening is probably related to bed rest and corticosteroid therapy. After 9–12 months, there is a marked improvement in bone formation and density [25].

Immune cholangiopathy

About 5% of patients presenting with PBC have a negative serum mitochondrial antibody test. Serum antinuclear antibody and anti-actin antibody are usually present in high titre [9, 66]. The patients are usually asymptomatic. Liver histology is identical with that of PBC (fig. 14.10). Prednisolone results in some clinical and biochemical improvement. However, liver histology shows less inflammation, bile duct lesions persist and serum γ-GT levels are very high. These patients provide an overlap between PBC and autoimmune chronic hepatitis.

References

1 Addison T, Gull W. On a certain affection of the skin—vitiligoidea—α plana, β tuberosa. *Guy's Hosp. Rep*. 1851; **7**: 265.

2 Agarwal K, Jones DEJ, Daly AK *et al*. CTL A-4 gene polymorphism confers susceptibility to primary biliary cirrhosis. *J. Hepatol*. 2000: **32**: 538

3 Ahrens EH Jr, Payne MA, Kunkel HG *et al*. Primary biliary cirrhosis. *Medicine (Baltimore)* 1950; **29**: 299.

4 Angulo P, Batts KP, Therneau TM *et al*. Long-term ursodeoxycholic acid delays histological progression in primary biliary cirrhosis. *Hepatology* 1999; **29**: 644.

5 Balan V, Batts KP, Porayko MK *et al*. Histological evidence for recurrence of primary biliary cirrhosis after liver transplantation. *Hepatology* 1993; **18**: 1392.

6 Balasubramaniam K, Grambsch PM, Wiesner RH *et al*. Diminished survival in asymptomatic primary biliary cirrhosis. A prospective study. *Gastroenterology* 1990; **98**: 1567.

7 Ballardini G, Mirakian R, Bianchi FB *et al*. Aberrant expression of HLA-DR antigens on bile duct epithelium in primary biliary cirrhosis: relevance to pathogenesis. *Lancet* 1984; **ii**: 1009.

8 Bassendine MF, Yeaman SJ. Serological markers of primary biliary cirrhosis: diagnosis, prognosis and subsets. *Hepatology* 1992; **15**: 545.

9 Ben-Ari Z, Dhillon AP, Sherlock S. Autoimmune cholangiopathy: part of the spectrum of autoimmune chronic active hepatitis. *Hepatology* 1993; **18**: 10.

10 Bergasa NV, Schmitt JM, Talbot TL *et al*. Open-label trial of oral nalmefene for the pruritus of cholestasis. *Hepatology* 1998; **27**: 679.

11 Bonis PAL, Kaplan M. Methotrexate improves biochemical tests in patients with primary biliary cirrhosis who respond incompletely to ursodiol. *Gastroenterology* 1999; **117**: 397.

12 Brind AM, Bray GP, Portmann BC *et al*. Prevalence and pattern of familial disease in primary biliary cirrhosis. *Gut* 1995; **36**: 615.

13 Bruguera M, Llach J, Rodés J. Nonsyndromic paucity of intrahepatic bile ducts in infancy and idiopathic ductopenia in adulthood: the same syndrome? *Hepatology* 1992; **15**: 830.

14 Burroughs AK, Rosenstein IJ, Epstein O *et al*. Bacteriuria and primary biliary cirrhosis. *Gut* 1984; **25**: 133.

15 Buscher H-P, Zietzschnmann Y, Gerok W. Positive responses to methotrexate and ursodeoxycholic acid in

patients with primary biliary cirrhosis responding insufficiently to ursodeoxycholic acid alone. *J. Hepatol.* 1993; **18**: 9.
16 Bush A, Mitchison H, Walt R *et al.* Primary biliary cirrhosis and ulcerative colitis. *Gastroenterology* 1987; **92**: 2009.
17 Butler P, Valle F, Hamilton-Miller JMT *et al.* M2 mitochondria antibodies and urinary rough mutant bacteria in patients with primary biliary cirrhosis and in patients with recurrent bacteriuria. *J. Hepatol.* 1993; **17**: 408.
18 Cauch-Dudek K, Abbey S, Stewart DE *et al*. Fatigue in primary biliary cirrhosis. *Gut* 1998; **43**: 705.
19 Chen C-Y, Lu C-L, Chiu C-F *et al*. Primary biliary cirrhosis associated with mixed type autoimmune haemolytic anaemia and sicca syndrome: a case report and review of the literature. *Am. J. Gastroenterol*. 1997; **92**: 1547.
20 Christensen E, Grunson B, Neuberger J. Optimal timing of liver transplantation for patients with primary biliary cirrhosis: use of prognostic modelling. *J. Hepatol.* 1999; **30**: 285.
21 Degott C, Zafrani ES, Callard P. Histopathological study of primary biliary cirrhosis and the effects of ursodeoxycholic acid treatment on histology progression. *Hepatology* 1999; **29**: 1007.
22 Dickson ER, Grambsch PM, Fleming TR et al. Prognosis in primary biliary cirrhosis: model for decision making. *Hepatology* 1989; **10**: 1.
23 Donaldson PT. TNF gene polymorphisms in primary biliary cirrhosis: a critical appraisal. *J. Hepatol*. 1999; **31**: 366.
24 Dörner T, Held C, Trebeljahr G *et al*. Serologic characteristics in primary biliary cirrhosis associated with sicca syndrome. *Scand. J. Gastroenterol*. 1994; **29**: 655.
25 Eastell R, Dickson ER, Hodgson SF *et al*. Rates of vertebral bone loss before and after liver transplantation in women with primary biliary cirrhosis. *Hepatology* 1991; **14**: 296.
26 Epstein O, Dick R, Sherlock S. Prospective study of periostitis and finger clubbing in primary biliary cirrhosis and other forms of chronic liver disease. *Gut* 1981; **22**: 203.
27 Epstein O, Fraga E, Sherlock S. Importance of clinical staging for prognosis in primary biliary cirrhosis. *Gut* 1985; **26**: A1126.
28 Feizi T, Naccarato R, Sherlock S *et al.* Mitochondrial and other tissue antibodies in relatives of patients with biliary cirrhosis. *Clin. Exp. Immunol.* 1972; **10**: 609.
29 Flannery GR, Burroughs AK, Butler P. Antimitochondrial antibodies in primary biliary cirrhosis recognize both specific peptides and shared epitopes of the M2 family of antigens. *Hepatology* 1989; **10**: 370.
30 Fox RA, Scheuer PJ, James DG *et al.* Impaired delayed hypersensitivity in primary biliary cirrhosis. *Lancet* 1969; **i**: 959.
31 Gershwin ME, Mackay IR. Primary biliary cirrhosis: paradigm or paradox for autoimmunity. *Gastroenterology* 1991; **100**: 822.
32 Gores GJ, Wiesner RH, Dickson ER *et al*. Prospective evaluation of esophageal varices in primary biliary cirrhosis: development, natural history and influence on survival. *Gastroenterology* 1989; **96**: 1552.
33 Goudie BM, Burt AD, Macfarlane GJ *et al*. Risk factors and prognosis in primary biliary cirrhosis. *Am. J. Gastroenterol*. 1989; **84**: 713.
34 Goulis J, Leandro G, Burroughs AK. Randomized controlled trials of ursodeoxycholic acid therapy for primary biliary cirrhosis: a meta-analysis. *Lancet* 1999; **354**: 1653.
35 Guanaben SN, Pare SA, Monegal A *et al*. Etidronate vs. fluoride for treatment of osteopenia in primary biliary cirrhosis: preliminary results after 2 years. *Gastroenterology* 1997; **113**: 219.
36 Hall S, Axelsen PH, Larson DE *et al*. Systemic lupus erythematosus developing in patients with primary biliary cirrhosis. *Ann. Intern. Med*. 1984; **100**: 388.
37 Hanot V. *Etude sur une Forme de Cirrhose Hypertrophique de Foie (Cirrhose Hypertrophique avec Ictère Chronique)*. Baillière, Paris, 1876.
38 Harada K, Van de Water J, Leung PSC *et al*. *In situ* nucleic acid hybridization of cytokines in primary biliary cirrhosis: predominance of the Th1 subset. *Hepatology* 1997; **25**: 791.
39 Haydon GH, Neuberger J. PBC: an infectious disease? *Gut* 2000; **47**: 586.
40 Heathcote EJ. Management of primary biliary cirrhosis. *Hepatology* 2000; **31**: 1005.
41 Heathcote EJ. Cutch-Dudek K, Walker V *et al*. The Canadian multicenter double-blind randomized controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. *Hepatology* 1994; **19**: 1149.
42 Hendrikse M, Rigney F, Giaffer MH *et al*. Low-dose methotrexate in primary biliary cirrhosis. Long-term results of a placebo-controlled trial. *Hepatology* 1997; **26**: 248 A.
43 Hopf U, Möller B, Stemerowicz R *et al*. Relation between *Escherichia coli* R (rough) forms in gut, lipid A in a liver, and primary biliary cirrhosis. *Lancet* 1989; **ii**: 1419.
44 Howard MJ, Fuller C, Broadhurst RW *et al*. Three-dimensional structure of the major autoantigen in primary biliary cirrhosis. *Gastroenterology* 1998; **115**: 139.
45 Howel D, Metcalf JV, Gray J *et al*. Cancer risk in primary biliary cirrhosis: a study in northern England. *Gut* 1999; **45**: 756.
46 Jones DEJ, Metcalf JV, Collier JD *et al*. Hepatocellular carcinoma in primary biliary cirrhosis and its impact on outcomes. *Hepatology* 1997; **26**: 1138.
47 Jones DEJ, Palmer JM, James OFW et al. T-cell responses to components of pyruvate dehydrogenase complex in primary biliary cirrhosis. *Hepatology* 1995: **21**: 995.
48 Jones DEJ, Watt FE, Metcalf JV *et al*. Familial primary biliary cirrhosis revisited: a geographically based population study. *J. Hepatol.* 1999; **30**: 402.
49 Joplin RE, Johnson GD, Matthews JB *et al*. Distribution of pyruvate dehydrogenase dihydrolipoamide acetyltransferase (PDC-E2) and another mitochondrial marker in salivary gland and biliary epithelium from patients with primary biliary cirrhosis. *Hepatology* 1994; **19**: 1375.
50 Kew MC, Varma RR, Dos Santos HA *et al*. Portal hypertension in primary biliary cirrhosis. *Gut* 1971; **12**: 830.
51 Kilmurry MR, Heathcote EJ, Cauch-Dudek K *et al.* Is the Mayo model for predicting survival useful after the introduction of ursodeoxycholic acid treatment for primary biliary cirrhosis? *Hepatology* 1996; **23**: 1148.
52 Kim WR, Wiesner RH, Therneau TM *et al*. Optimal timing of liver transplantation for primary biliary cirrhosis. *Hepatology* 1998; **28**: 33.
53 Kingham JGC, Parker DR. The association between primary biliary cirrhosis and coeliac disease: a study of relevant prevalence. *Gut* 1998; **42**: 120.

54 Laurin JM, DeSotel CK, Jorgensen RA *et al*. The natural history of abdominal pain associated with primary biliary cirrhosis. *Am. J. Gastroenterol*. 1994; **89**: 1840.

55 Lee RG, Epstein O, Jauregui H *et al*. Granulomas in primary biliary cirrhosis: a prognostic feature. *Gastroenterology* 1981; **81**: 983.

56 Leuschner M, Guildutuna S, Yan T *et al*. Ursodeoxycholic acid and prednisolone vs. ursodeoxycholic acid and placebo in the treatment of early stages of primary biliary cirrhosis. *J. Hepatol*. 1996; **25**: 49.

57 Long RG, Scheuer PJ, Sherlock S. Presentation and course of asymptomatic primary biliary cirrhosis. *Gastroenterology* 1977; **72**: 1204.

58 Lohse AW, Meyer GVM, Buschenfelde K-H *et al*. Characterization of the overlap syndrome of primary biliary cirrhosis (PBC) and autoimmune hepatitis: evidence for it being a hepatic form of PBC in genetically susceptible individuals. *Hepatology* 1999; **29**: 1078.

59 Mahl TC, Shockcor W, Boyer JL. Primary biliary cirrhosis: survival of a large cohort of symptomatic and asymptomatic patients followed for 24 years. *J. Hepatol*. 1994; **20**: 707.

60 Manns MP, Bremm A, Schneider PM *et al*. HLA DRw8 and complement C4 deficiency as risk factors in primary biliary cirrhosis. *Gastroenterology* 1991; **101**: 1367.

61 Martinez OM, Villanueva JC, Gershwin E *et al*. Cytokine patterns and cytotoxic mediators in primary biliary cirrhosis. *Hepatology* 1995; **21**: 113.

62 Mason AL, Lizhe X, Guo L *et al*. Detection of retroviral antibodies in primary biliary cirrhosis and other idiopathic biliary disorders. *Lancet* 1998; **351**: 1620.

63 Mayo MJ, Jenkins RN, Combes B *et al*. Association of clonally expanded T cells with the syndrome of primary biliary cirrhosis and limited scleroderma. *Hepatology* 1999; **29**: 1635.

64 Mella JG, Roschmann E, Maier K-P *et al*. Association of primary biliary cirrhosis with the allele HLA-DPB1*0301 in a German population. *Hepatology* 1995; **21**: 398.

65 Metcalf J, Mitchison H, Palmer J *et al*. Natural history of primary biliary cirrhosis. *Lancet* 1996; **348**: 1399.

66 Michieletti P, Wanless IR, Katz A *et al*. Antimitochondrial antibody negative primary biliary cirrhosis: a distinct syndrome of autoimmune cholangitis. *Gut* 1994; **35**: 260.

67 Mistry P, Seymour CA. Primary biliary cirrhosis—from Thomas Addison to the 1990s. *Q. J. Med*. 1992; **82**: 185.

68 Murphy JR, Sjögren MH, Kikendall JW *et al*. Small bile duct abnormalities in sarcoidosis. *J. Clin. Gastroenterol*. 1990; **12**: 555.

69 Nakamura A, Yamazaki K, Suzuki K *et al*. Increased portal tract infiltration of mast cells and eosinophils in primary biliary cirrhosis. *Am. J. Gastroenterol*. 1997; **82**: 2245.

70 Nakanuma Y, Ohta G. Histometric and serial section observations of the intrahepatic bile ducts in primary biliary cirrhosis. *Gastroenterology* 1979; **76**: 1326.

71 Neuberger J. PBC and the gut: the villi atrophy, the plot thickens. *Gut* 1999; **44**: 594.

72 Neuberger J, Thomson R. PBC and AMA—what is the connection? *Hepatology* 1999; **29**: 271.

73 Nijhawan PK, Therneau TM, Dickson ER *et al*. Incidence of cancer in primary biliary cirrhosis: the Mayo experience. *Hepatology* 1999; **29**: 1396.

74 O'Donohue J, Fidler H, Garcia-Barcelo M *et al*. Mycobacterial DNA not detected in liver sections from patients with primary biliary cirrhosis. *J. Hepatol*. 1998; **28**: 433.

75 Onishi S, Sakamaki T, Maeda T *et al*. DNA typing of HLA class II genes; DRB1*0803 increases the susceptibility of Japanese to primary biliary cirrhosis. *J. Hepatol*. 1994; **21**: 1053.

76 Pares A, Caballeria I, Rodes J *et al*. Long-term effects of ursodeoxycholic acid in primary biliary cirrhosis: results of a double-blind controlled multicentric trial. *J. Hepatol*. 2000; **32**: 561.

77 Pasha R, Heathcote J, Gabriel S *et al*. Cost-effectiveness of ursodeoxycholic acid therapy in primary biliary cirrhosis. *Hepatology* 1999; **29**: 21.

78 Poupon RE, Bonnard A-M, Chretiens Y *et al*. Ten-year survival in ursodeoxycholic acid-treated patients with primary biliary cirrhosis. *Hepatology* 1999; **29**: 1668.

79 Poupon RE, Lindor KD, Cauch-Dudek K *et al*. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. *Gastroenterology* 1997; **113**: 884.

80 Poupon RE, Poupon R, Balkau B *et al*. Ursodiol for the long-term treatment of primary biliary cirrhosis. *N. Engl. J. Med*. 1994; **330**: 1342.

81 Powell FC, Schroeter AL, Dickson ER. Primary biliary cirrhosis and the CREST syndrome. A report of 22 cases. *Q. J. Med*. 1987; **62**: 75.

82 Prince MI, James OFW, Holland NP *et al*. Validation of a fatigue impact score in primary biliary cirrhosis: towards a standard for clinical and trial use. *J. Hepatol*. 2000; **32**: 368.

83 Reynolds TB, Denison EK, Frankl HD *et al*. Primary biliary cirrhosis with scleroderma, Raynaud's phenomenon and telangiectasia: new syndrome. *Am. J. Med*. 1971; **50**: 302.

84 Ricci P, Therneau TM, Malinchoc M *et al*. A prognostic model for the outcome of liver transplantation in patients with cholestatic liver disease. *Hepatology* 1997; **25**: 672.

85 Rosen H. Bones and primary biliary cirrhosis. *Hepatology* 1995; **21**: 253.

86 Rubin E, Schaffner F, Popper H. Primary biliary cirrhosis: chronic nonsuppurative destructive cholangitis. *Am. J. Pathol*. 1965; **46**: 387.

87 Sadamoto T, Joplin R, Keogh A *et al*. Expression of pyruvate-dehydrogenase complex PDC-E-2 on biliary epithelial cells induced by lymph nodes from primary biliary cirrhosis. *Lancet* 1998; **352**: 1595.

88 Scheuer PJ. Primary biliary cirrhosis. *Proc. R. Soc. Med*. 1967; **60**: 1257.

89 Shapiro JM, Smith H, Schaffner F. Serum bilirubin: a prognostic factor in primary biliary cirrhosis. *Gut* 1979; **20**: 137.

90 Sherlock S. Primary biliary cirrhosis (chronic intrahepatic obstructive jaundice). *Gastroenterology* 1959; **31**: 574.

91 Sherlock S. Primary biliary cirrhosis: clarifying the issues. *Am. J. Med*. 1994; **96** (suppl. 1A): 27S.

92 Sherlock S. Therapeutic trials in primary biliary cirrhosis. *Q. J. Med*. 1994; **87**: 701.

93 Sherlock S, Scheuer PJ. The presentation and diagnosis of 100 patients with primary biliary cirrhosis. *N. Engl. J. Med*. 1973; **289**: 674.

94 Springer J, Cauch-Dudet K, O'Rourke K *et al*. Asymptomatic primary biliary cirrhosis: a study of the natural history and prognosis. *Am. J. Gastroenterol*. 1999; **94**: 47.

95 Springer JE, Cole DEC, Rubin LA *et al*. Vitamin D-receptor genotypes as independent genetic predictors of decreased bone mineral density in primary biliary cirrhosis. *Gastroenterology* 2000; **118**: 145.

96 Stemerowicz R, Hopf U, Möller B *et al*. Are antimitochondrial antibodies in primary biliary cirrhosis induced by R (rough) mutants of enterobacteriacea? *Lancet* 1988; **ii**: 1166.
97 Surh CD, Roche TE, Danner DJ *et al*. Antimitochondrial autoantibodies in primary biliary cirrhosis recognize cross-reactive epitope(s) on protein X and dihydrolipoamide acetyltransferase of pyruvate dehydrogenase complex. *Hepatology* 1989; **10**: 127.
98 Swain MG, Le T. Chronic cholestasis in rats induces amhedonia and loss of social interest. *Hepatology* 1998; **28**: 6.
99 Tanaka A, Prindiville TP, Gish R *et al*. Are infectious agents involved in primary biliary cirrhosis? A PCR approach. *J. Hepatol*. 1999; **31**: 664.
100 Teoh K-L, Rowley MJ, Zafirakis H *et al*. Enzyme inhibitory autoantibodies to pyruvate dehydrogenase complex in primary biliary cirrhosis: applications of a semiautomated assay. *Hepatology* 1994; **20**: 1220.
101 Thomas PK, Walker JG. Xanthomatous neuropathy in primary biliary cirrhosis. *Brain* 1965; **88**: 1079.
102 Triger DR. Primary biliary cirrhosis: an epidemiological study. *Br. Med. J*. 1980; **281**: 772.
103 Tsianos EV, Hoofnagle JH, Fox PC *et al*. Sjögren's syndrome in patients with primary biliary cirrhosis. *Hepatology* 1990; **11**: 730.
104 Tzakis AG, Carcassonne C, Todo S *et al*. Liver transplantation for primary biliary cirrhosis. *Semin. Liver Dis*. 1989; **9**: 144.
105 Van de Water J, Gerson L, Ferrell L *et al*. Immunohistochemical evidence of disease recurrence after liver transplantation for primary biliary cirrhosis. *Hepatology* 1996; **24**: 1079.
106 Vilagut I, Villa J, Pares A *et al*. *Mycobacterium gordonae* DNA in liver tissue of patients with primary biliary cirrhosis. *J. Hepatol*. 1994; **21**: S87 (abstract).
107 Walker JG, Doniach D, Roitt IM *et al*. Serological tests in diagnosis of primary biliary cirrhosis. *Lancet* 1965; **i**: 827.
108 Weber P, Berger A, Doerr HW. Detection of retroviral antibodies in primary biliary cirrhosis. *Lancet* 1998; **352**: 149 (letter).
109 Weissman E, Becker NH. Interstitial lung disease in primary biliary cirrhosis. *Am. J. Med. Sci*. 1983; **285**: 21.
110 Witt-Sullivan H, Heathcote J, Cauch K *et al*. The demography of primary biliary cirrhosis in Ontario, Canada. *Hepatology* 1990; **12**: 98.
111 Yamada G, Hodo I, Tobe K *et al*. Ultrastructural immunocytochemical analysis of lymphocytes infiltrating bile duct epithelia in primary biliary cirrhosis. *Hepatology* 1986; **6**: 385.
112 Yoshikawa M, Tsujii T, Matsumura K *et al*. Immunomodulatory effects of ursodeoxycholic acid on immune responses. *Hepatology* 1996; **16**: 158.

Autoimmune cholangitis

Overlaps between PBC and autoimmune chronic hepatitis are being described increasingly [10]. Sometimes these overlaps are termed mitochondrial antibody-negative PBC. Originally some of the speculations on the overlaps were based on liver biopsy interpretation. Tests for serum mitochondrial antibodies were crude and non-specific and made interpretation difficult. The anti-mitochondrial antibody (AMA) negative patients were often presented for inclusion in clinical trials or for liver transplantation [1, 8, 11].

Autoimmune cholangitis is a rare condition. The patient is usually a female, presenting with a slow onset of cholestasis. Biochemical changes are those of cholestasis. No significant biochemical difference is found between AMA-negative and AMA-positive patients classified as PBC. Liver biopsy appearances are virtually indistinguishable from PBC. Liver cell rosettes and multinuclear cells are absent, but a heavy infiltrate of plasma cells in the portal zones is a finding common to autoimmune chronic hepatitis and PBC (see fig. 14.10) [4].

The serum mitochondrial antibody test is negative, although antinuclear antibody is present in high titre, much higher than in PBC. Serum IgM is lower.

The condition has been associated with coeliac disease [3].

The condition probably differs from the PBC–autoimmune hepatitis overlap syndrome. There is only one unexpected feature, such as a low smooth muscle titre in a patient with PBC, or abnormal bile duct epithelium in someone with autoimmune hepatitis [2]. Hepatic histological features may overlap. It remains uncertain whether autoimmune cholangitis is a definite entity or simply a variant of PBC [6] or autoimmune hepatitis. However, the genomic associations of AMA-positive and AMA-negative PBC differ [12].

Prognosis and treatment

The prognosis is probably the same as for PBC. In a limited follow-up, sequential biopsies at up to 20 years showed progression of fibrosis in 10 [9].

Prednisolone therapy results in decreases in serum transaminase levels and evidence of less inflammatory activity in liver biopsy specimens [7]. Serum γ-GT remains high and bile duct damage persists and may increase. Prednisolone has little impact on the bile duct lesions [7]. These are probably irreversible. It should only be administered in small doses of 5–15 mg daily. Ursodeoxycholic acid is the recommended treatment [5]. It may be less effective in the overlap syndromes than in classic PBC. It would be more satisfactory if classification was based on aetiological factors, rather than serum autoantibodies which are simply markers. Unfortunately, the causes of PBC, autoimmune cholangitis and autoimmune hepatitis remain unknown. Autoimmune cholangitis represents an overlap between PBC and autoimmune hepatitis. It closely resembles PBC, but lacks the serum mitochondrial autoantibody.

References

1 Ben-Ari Z, Dhillon AP, Sherlock S. Autoimmune cholan-

giopathy: part of the spectrum of autoimmune chronic active hepatitis. *Hepatology* 1993; **18**: 10.
2 Chazouilleres O, Wendum D, Serfaty L *et al*. Primary biliary cirrhosis—autoimmune hepatitis overlap syndrome: clinical features and response to therapy. *Hepatology* 1998; **28**: 296.
3 Gogos CA, Nikolopoulou V, Zolata V *et al*. Autoimmune cholangitis in a patient with celiac disease: a case report and review of the literature. *J. Hepatol*. 1999; **30**: 321.
4 Goodman ZD, McNally PR, Do DR *et al*. Autoimmune cholangitis: a variant of primary biliary cirrhosis. Clinicopathologic and serologic correlations in 200 cases. *Dig. Dis. Sci*. 1995; **40**: 1232.
5 Lindor KD, Dickson ER, Baldus WP *et al*. Ursodeoxycholic acid in the treatment of primary biliary cirrhosis. *Gastroenterology* 1994; **106**: 1284.
6 Lohse AW, Meyer GVM, Buschenfelde K-H *et al*. Characterization of the overlap syndrome of primary biliary cirrhosis (PBC) and autoimmune hepatitis: evidence for it being a hepatic form of PBC in genetically susceptible individuals. *Hepatology* 1999; **29**: 1078.
7 Masumoto T, Ninomiya T, Michitaka K *et al*. Three patients with autoimmune cholangiopathy treated with prednisolone. *J. Gastroenterol*. 1998; **33**: 909.
8 Michieletti P, Wanless IR, Katz A *et al*. Antimitochondrial antibody negative primary biliary cirrhosis. A distinct syndrome of autoimmune cholangitis. *Gut* 1994; **35**: 260.
9 Okuno T, Seto Y, Okaxloue T *et al*. Chronic active hepatitis with histological features of primary biliary cirrhosis. *Dig. Dis. Sci*. 1987; **32**: 775.
10 Sherlock S. Overview of chronic cholestasis conditions in adults. Terminology and definitions. *Clin. Liver Dis*. 1998; **2**: 217.
11 Sherlock S. Autoimmune cholangitis: a unique entity? *Mayo Clin. Proc*. 1998; **73**: 184.
12 Stone J, Wade JA, Cauch-Dudek K *et al*. Genomic associations in AMA-positive and AMA-negative primary biliary cirrhosis. *Gastroenterology* 1998; 114; A1346 (abstract).

Chapter 15
Sclerosing Cholangitis

This is a syndrome which has many causes (table 15.1). The end result is progressive fibrosis and ultimately disappearance of intra- or extra-hepatic ducts or both. In the early stages the impact is on the biliary system and hepatocyte damage is minor; liver failure occurs late. Consequently the prognosis for sclerosing cholangitis is better than for diseases that affect primarily the hepatocyte. Ultimately, biliary cirrhosis and hepato-cellular failure evolve.

Primary sclerosing cholangitis (PSC)

The condition is of unknown cause [3]. All parts of the biliary tree can be involved in a chronic, fibrosing, inflammatory process which results in obliteration of the biliary tree and ultimately in biliary cirrhosis [13, 39]. The extent of involvement of different parts of the biliary tree varies. The condition may be localized to intra- or extra-hepatic ducts. Eventually interlobular, septal and segmental bile ducts are replaced by fibrous cords. Involvement of very small ducts in the portal (zone 1) areas led to the term *pericholangitis* [70] or *small duct PSC* [7].

Diagnostic criteria are generalized beading and stenosis of the biliary tree on cholangiography. Bile duct cancer must be excluded. There is no specific diagnostic test.

Aetiology

Association with inflammatory bowel disease. There is a 75% association with ulcerative colitis [20, 56]. The prevalence of PSC among ulcerative colitis patients is approximately 5% with an overall 10–15% prevalance of hepatic abnormalities [56]. PSC may complicate large bowel Crohn's disease [40, 59].

The clinical course and progression of ulcerative colitis does not affect the development or progression of PSC [1]. Total colectomy does not prevent the subsequent development of PSC. The cholangitis may precede the colitis by as much as 3 years [64].

Genetics

There is a strong genetic predisposition. An association exists between class I HLA-B8 [14]. The haplotype DR3 is also associated and the B8-DR3 combination is known to be associated with autoimmune conditions. There is a dual association of DR2 and DR3 [19]. The course seems to be accelerated with DR4 [50]. HLA-DRw52A is also said to be of prognostic value [23]. There is no evidence that PSC is inherited as a single gene disorder. Similar HLA patterns can be found in the general population.

Immunology

Circulating antibodies to tissue components are present in low titre or absent. Anti-neutrophil cytoplasmic antibodies (ANCA) are found in the serum of 70% of patients if the alkaline phosphatase level is increased, but also in 30–40% of those with ulcerative colitis or autoimmune chronic hepatitis, but without PSC [62]. The test is sensitive but not specific and there is no evidence of a pathogenic role. The pANCA may be atypical, localized in the neutrophil nucleus [67]. Antibodies persist after liver transplant [25].

Sera also contain autoantibodies against a cross-reactive peptide shared by colon and biliary epithelial cells [48].

Circulating immune complexes may be increased [8] and there is decreased immune complex clearance [51]. Complement metabolism is increased. Immunological abnormalities are frequent but the disease is probably immune-mediated and not autoimmune.

Table 15.1. Types of sclerosing cholangitis

'Primary'
With or without ulcerative colitis
'Infective'
Bacterial
usually with biliary obstruction
'sump' syndrome
Opportunistic
usually with primary or secondary immunodeficiency
Vascular
Hepatic arterial obstruction
Hepatic artery cytotoxics

Relation to infection

Similar cholangiographic and hepatic histological changes are found with known infections such as cryptosporidiosis and with immunodeficiency diseases. PSC might have an infectious basis. The association with ulcerative colitis could be through portal bacteraemia but this cannot be confirmed (fig. 15.1). There are suggestive experimental findings. Rats given toxic bacterial peptides into the colon develop changes in the liver suggestive of cholangitis [27]. Genetically, susceptible rats develop pericholangitis after bacterial overgrowth is induced in blind loops [41]. In rabbits, portal vein injection of killed *Escherichia coli* results in a picture somewhat resembling human pericholangitis [36].

A possible bacterial infection plus genetic susceptibility to infection is possible although few data support this concept [30]. Ulcerative colitis is not constantly present; the disease is unrelated to severity of colitis. Antibiotics are ineffective and proctocolectomy is not beneficial [12]. The aetiology of PSC is still unknown. A specific serological diagnostic test is urgently needed for earlier diagnosis so that controlled therapeutic trials may be instituted.

Clinical features (table 15.2) [13]

Males are twice as commonly affected as females, usually between the ages of 25 and 45 years.

The majority present when asymptomatic, usually when a raised serum alkaline phosphatase level is found, particularly when screening patients with ulcerative colitis. However, PSC can be seen on a cholangiogram even if serum alkaline phosphatase is normal. The disease may even present as a raised serum transaminase value discovered at the time of blood donation [31]. Even if asymptomatic the patient may have underlying advanced liver disease, established cirrhosis and portal hypertension, usually pre-sinusoidal, without signs of cholangitis or cholestasis. The patient may have been treated for 'cryptogenic' cirrhosis for many years.

Presenting symptoms include weight loss, fatigue, right upper quadrant abdominal pain and pruritus, and intermittent jaundice. Symptoms indicate advanced disease. Fever is unusual unless ascending cholangitis has complicated biliary surgery or endoscopy. However, occasionally the patient presents with fever, chills, right

Table 15.2. Symptoms at presentation in 29 patients with PSC [13]

Symptoms	*n*	%
Jaundice	21	72
Pruritus	20	69
Weight loss	23	79
Right upper quadrant pain	21	72
Acute cholangitis	13	45
Bleeding oesophageal varices	4	14
Malaise	1	3
Asymptomatic	2	7
Total	29	

n, number of patients.

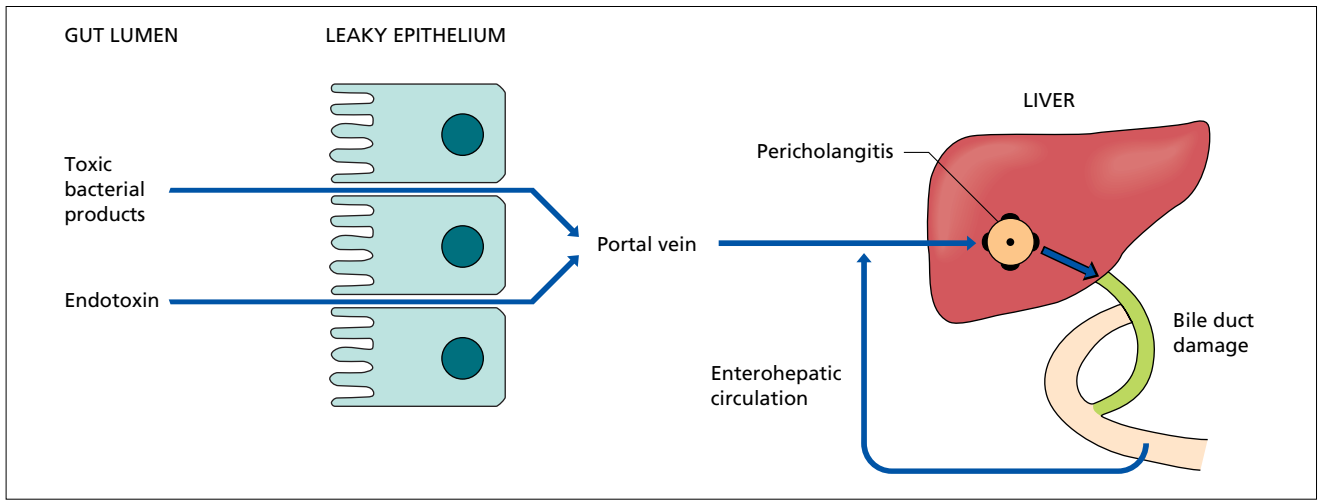


Fig. 15.1. In ulcerative colitis the colonic epithelium is leaky so allowing toxic bacterial products such as endotoxin to enter the lamina propria and ultimately reach the liver via the portal vein. These could cause pericholangitis, biliary excretion and larger bile duct injury. They probably have an enterohepatic circulation.

upper quadrant pain, itching and jaundice resembling acute bacterial cholangitis [39]. Blood cultures are rarely positive and antibiotics may be unhelpful.

Ulcerative colitis (rarely Crohn's disease) should be sought by colonoscopy and rectal biopsy, even if there are no features of colonic disease. The colitis is usually chronic, diffuse and mild to moderate. The activity of the cholangitis is inversely related to that of the colitis. There are prolonged remissions. PSC may be diagnosed before or after the colitis. The course does not differ whether or not ulcerative colitis is associated.

Paediatric disease [73]

The medial age of presentation is 13 years, but can be as young as 2 years. About 50% have inflammatory bowel disease. Alkaline phosphatase can be normal in 50%. The disease may present like autoimmune chronic hepatitis with an HLA-B8-DR2 haplotype. Intra-hepatic disease predominates and significant extra-hepatic strictures are unusual. At a later age, splenomegaly and prolonged prothrombin time predict a poor outcome to progress to death or transplantation.

Laboratory investigations

Serum tests show cholestasis with alkaline phosphatase three times above normal. Serum bilirubin values fluctuate markedly. They can exceed 10 mg/dl (170 µmol/l), but this is unusual. Serum copper, caeruloplasmin and liver copper content are increased, as in all patients with cholestasis. Serum γ-globulin and IgM are increased in 40–50%.

Serum smooth muscle and antinuclear antibodies may be present in low titres but the mitochondrial antibody is absent.

Eosinophilia is a rare finding.

Liver pathology (table 15.3) [13]

Perfusion studies of bile ducts in livers removed at the time of transplantation show intra-hepatic tubular and saccular cholangiectasia with transformation of bile ducts into fibrous cords and eventually complete loss of ducts [46].

The portal zones are infiltrated with small and large lymphocytes, polymorphs and occasional macrophages and eosinophils (fig. 15.2). The interlobular ductules show a peri-ductular inflammation with occasional epithelial desquamation. Intralobular inflammatory cell accumulations may be noted and the Kupffer cells are swollen and prominent. Cholestasis is inconspicuous unless jaundice is deep.

Eventually, fibrosis develops in the portal tracts until the small ducts are surrounded by a tuft of fibrous tissue ('onion-skin' appearance) (fig. 15.3). The remains of bile ducts may be shown only as a fibrous ring (fig. 15.4). The portal zones become stellate (fig. 15.5).

The appearances are not diagnostic, but the association of reduced numbers of bile ducts, ductular proliferation and substantial copper deposition with piecemeal necrosis is very suggestive of PSC and indicates the need for cholangiography [13].

Histology of the common bile duct shows non-diagnostic fibrosis and inflammation.

Table 15.3. Histological findings in 29 patients with PSC [13]

	–	+	++
Portal changes			
Inflammation	0	17	12
Bile duct diminution	12	10	7
Peri-ductal fibrosis	18	9	2
Bile ductular proliferation	4	7	18
Lobular changes			
Piecemeal necrosis	10	8	11
Focal necrosis	11	18	0
Focal inflammation	12	17	0
Kupffer cell hyperplasia	5	11	13

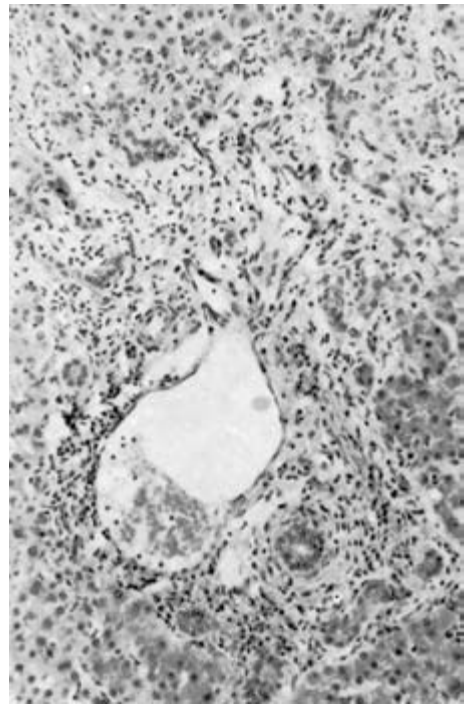


Fig. 15.2. Sclerosing cholangitis and pericholangitis. The portal zone is oedematous and expanded with proliferated bile ducts and an inflammatory cell infiltrate. (H & E, ×160.)

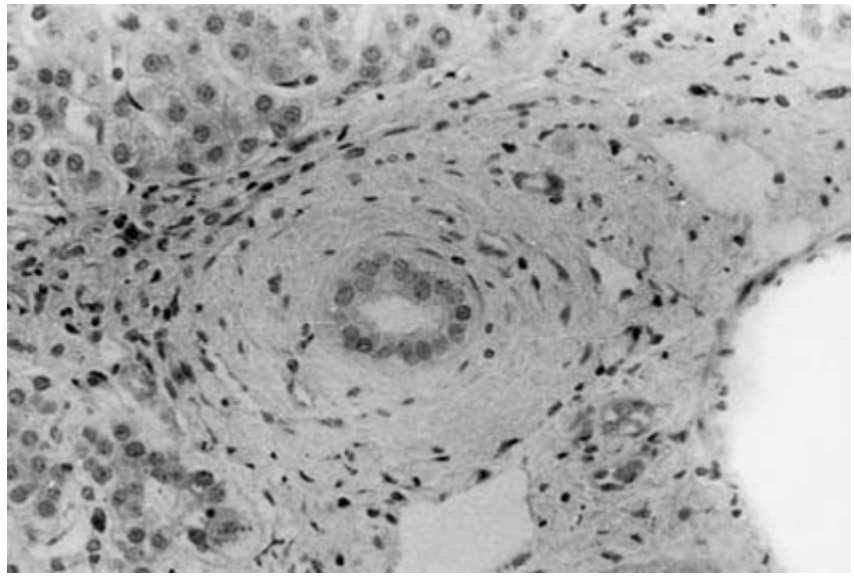


Fig. 15.3. Intra-hepatic bile duct shows abnormal epithelium and concentric peri-ductal whorls of collagen ('onion-skin' appearance).

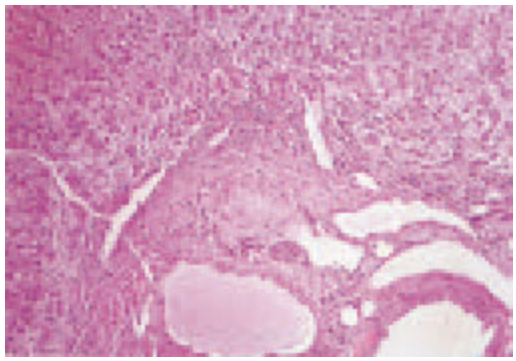


Fig. 15.4. A heavily fibrosed portal zone containing a ring representing an obliterated bile duct.

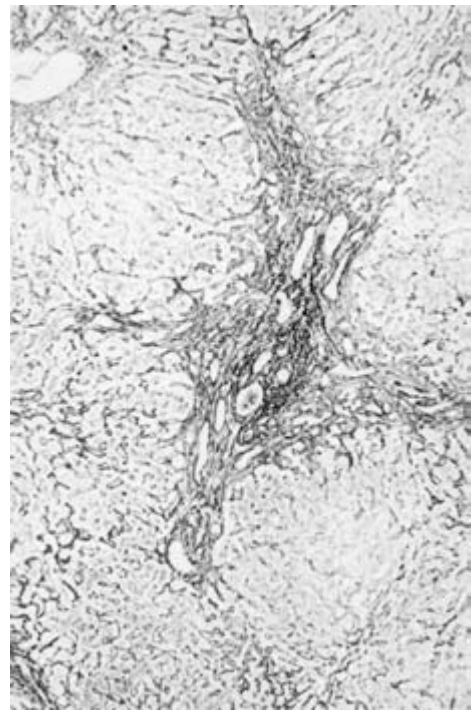


Fig. 15.5. Reticulin preparation of liver biopsy showing stellate expansion of portal zones.

Imaging

ERCP appearances are diagnostic with areas of irregular stricturing and dilatation (beading) of the intra- and extra-hepatic biliary tree (fig. 15.6). The strictures are short (0.5–2 cm long) and angular with intervening segments of apparently normal or slightly dilated ducts. Diverticulum-like outpouching may be seen along the common bile duct [47].

Cholangiograms may show involvement of intra-hepatic ducts alone, the extra-hepatic ducts alone or even one hepatic duct. Appearances are normal with small duct disease [7].

Ultrasound shows thickening of bile ducts.

CT shows focal discontinuous minimal biliary dilatation, mimicked only by rare, diffuse cholangiocarcinoma [58].

MRI cholangiography shows slightly dilated peripheral ducts not connected with central ducts in several hepatic segments [21]. Liver parenchyma may be enhanced [29].

Cholangiocarcinoma

Cholangiocarcinoma complicates approximately 10% of patients with PSC. It is found in 30% of autopsies and in 10–20% of those presenting at liver transplant. It may complicate large or small duct disease and usually accompanies ulcerative colitis (fig. 15.7). Mean survival is only 6 months after diagnosis.

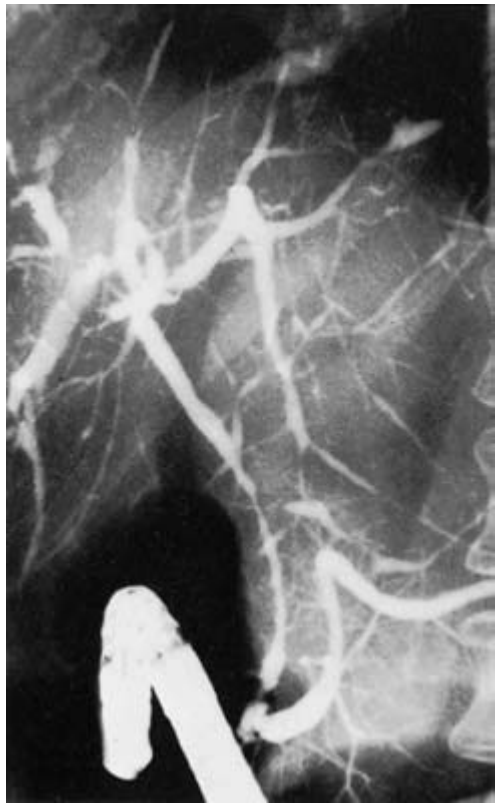


Fig. 15.6. ERCP in PSC showing an irregular common bile duct and beading irregularities in the intra-hepatic bile ducts.

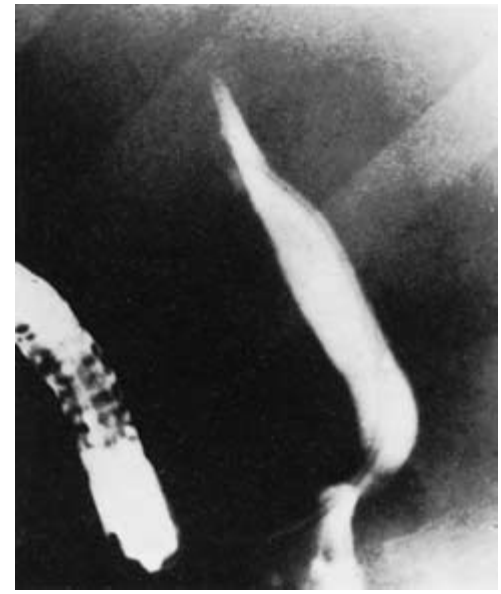


Fig. 15.7. ERCP in bile duct carcinoma showing the common bile duct terminating in a nipple-like deformity.

Cholangiocarcinoma is extremely difficult to diagnose. Progressive jaundice is suggestive, but probably too late for effective treatment. Serum tumour markers such as CA 19-9 may be useful, but increases are probably detected too late [55].

Suggestive ERCP features are localized biliary dilatation, progressive strictures and intra-duct polyps [47]. Bile and brush cytology and biopsy should be routine [37]. However, the cholangiocarcinoma may be sclerotic and false negative results obtained. Bile duct dysplasia remote from the tumour is suggestive [6]. Endobiliary fine-needle aspiration cytology should be considered, also image-guided brush cytology [28]. Sophisticated imaging techniques, particularly if repeated, probably offer the best chance of positive diagnosis. If all modalities are available, including CT, cholangiography and MRI, bile duct carcinomas can be demonstrated as definite or probable in 83% [11]. Image-guided brush biopsies can be included. Contrast-enhanced CT with delayed imaging is particularly important.

PET using radio-labelled tracers may detect small cholangiocarcinomas [32]. Clearance differs between malignant and non-malignant tissues.

Relation to colo-rectal cancer

Patients with PSC and ulcerative colitis are said to be at greater risk of colo-rectal neoplasm than patients with ulcerative colitis alone [9]. The risk, however, seems to be low [44]. Nonetheless, a patient with PSC and ulcerative colitis should be regularly checked for colonic cancer both before and after liver transplantation [43].

Diagnosis

Cholangiographic appearances and the negative mitochondrial antibody test distinguish PSC from primary biliary cirrhosis (PBC) (table 15.4). PSC can present as chronic hepatitis, especially in children [73], or as cryptogenic cirrhosis. The increased serum phosphatase level is the diagnostic clue and indicates confirmatory cholangiography.

The differentiation from secondary sclerosing cholangitis due to such conditions as post-operative biliary stricture or choledocholithiasis depends on the history of previous surgery or on the demonstration of gallstones.

Differentiation must be made from ischaemic bile duct damage due to intra-hepatic arterial floxuridine, from congenital biliary abnormalities, from infectious cholangiopathy in immunosuppressed patients with AIDS or following liver transplantation, from bile duct neoplasms, and from histiocytosis X.

Prognosis

The mean survival from diagnosis is about 10–12 years

[14, 23, 71]. Six-year follow-up of asymptomatic patients showed 70% with disease progression and liver failure developing in one-third [39, 57]. Nevertheless, many patients remain asymptomatic for many years. Ultimately, deepening jaundice, liver failure and cholangiocarcinoma supervene [39, 57].

Involvement of extra-hepatic ducts has a worse prognosis than intra-hepatic alone (fig. 15.8). Females have a poorer survival than males [61].

Peristomal varices may bleed after proctocolectomy [49, 72].

Survival models are used to evaluate therapy to stratify patients in clinical trials and to define the time for liver transplantation. The Mayo Clinic model is based on 406 patients and uses serum bilirubin, histological stage and the presence of splenomegaly. It may be particularly useful in early cases [18, 34]. The Swedish prognostic model is based on 305 patients and uses age, serum bilirubin and histological stage as bad prognostic features [10]. Cholangiocarcinoma was found at surgery in 8%, and 44% were asymptomatic at the time of diagnosis.

A simple Child–Pugh classification was found to be a satisfactory alternative to disease-specific models in both research studies and clinical decision-making [63]. Models are of less use in individual cases because of the great variability of the disease. Moreover, they do not identify the patient with cholangiocarcinoma [10].

Table 15.4. Primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC)

	PSC	PBC
Sex	66% male	90% female
Presentation	Fatigue, jaundice, pruritus, cholangitis, weight loss, RUQ pain	Pruritus, jaundice
Serum mitochondrial antibody	Negative	Positive
Cholangiography (bile ducts)	Beaded, irregular	Pruned
Liver biopsy		
bile duct lesions	+	+
granulomas	–	+
copper	+	+
Associated diseases	Ulcerative colitis Retro-orbital and retroperitoneal fibrosis Immunodeficiency Cholangiocarcinoma	Arthritis Sicca syndrome Autoimmune diseases Thyroiditis

RUQ, right upper quadrant.

Treatment

There is no satisfactory treatment short of liver transplantation. The measures for chronic cholestasis and pruritus must be adopted. Replacement of fat-soluble vitamins is particularly important.

Immunosuppressants including corticosteroids, methotrexate, D-penicillamine and azathioprine are of no proven value [30]. Combinations are under investigation. Although ursodeoxycholic acid improves biochemical parameters it is of no clinical benefit and has no effect on disease progression, complications, death or need for transplantation [42]. A randomized controlled trial of ursodeoxycholic acid in a single dose showed some biochemical improvement but no change in symptoms or radiographic appearances [69].

Endoscopic treatment. Prominent biliary strictures, gallstones or debris may be treated by endoscopic biliary dilatation or stent insertion, but there are no controlled trials to evaluate this therapy [38, 73]. Biliary surgery should be avoided because of the risk of complicating cholangitis [22].

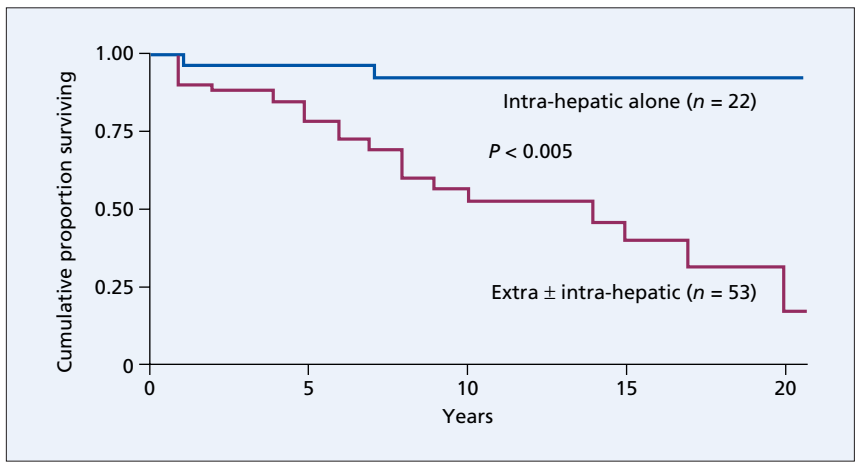


Fig. 15.8. Cumulative survival of patients with PSC according to distribution of cholangiographic changes.

Antibiotics are used to cover ERCP and to control episodes of cholangitis. In some patients the antibiotics have to be prolonged, but must be stopped 1 month before a transplant to avoid overwhelming fungal infection in the post-transplant period.

Transplantation

The 3-year survival is 85% at most centres [2]. The timing of the operation is controversial. The problem is cholangiocarcinoma which is found in 10–36% of patients at the time of transplant. This finding gives a 30% survival at 1 year [52]. Early transplant may be recommended to reduce the operative risk and prevent the development of cholangiocarcinoma [22]. If cholangiocarcinoma is found at surgery, the abdomen is immediately closed and another recipient for the donor liver is sought (fig. 15.9).

It has been recommended that transplant should be done when the Mayo Index exceeds 4. Serum bilirubin increase is not a good indicator of cholangiocarcinoma. A Cox regression showed the following significant pre-transplant variables: inflammatory bowel disease, ascites, previous upper abdominal surgery, serum creatinine and biliary tree malignancy [54].

Recurrence of PSC has been recorded in the transplanted liver [26], but the hepatic histological appearances are very difficult to distinguish from rejection and from hepatic arterial lesions.

Previous biliary surgery makes the transplant more difficult, it takes longer and greater quantities of blood transfusion are required. If there is a diseased recipient bile duct, a choledochojejunostomy is needed.

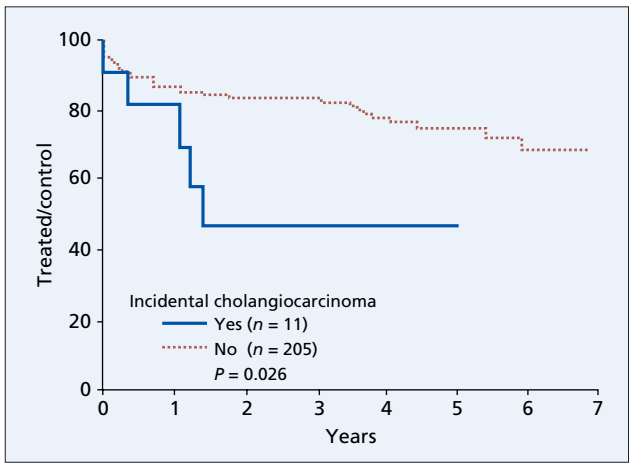


Fig. 15.9. Kaplan–Meier survival plot after transplantation in patients with PSC with and without detection of cholangiocarcinoma in the excised liver. The difference was statistically significant with a 5-year survival rate of 0.47±0.17 and 0.75±0.04, respectively. (From [2].)

Post-transplant biliary complications are therefore frequent.

Post-transplant the colitis usually improves. However, colon cancer can develop [43].

Infective sclerosing cholangitis

Patients having a well-recognized infective cause for their sclerosing cholangitis may show identical biochemical, hepatic histological and cholangiographic features to those of patients with PSC.

Bacterial cholangitis

Bacterial cholangitis is rare in the absence of mechanical, usually partial, biliary obstruction. The infection presumably ascends from the gut. The presence of a biliary stricture results in overgrowth of enteric organisms in the upper small intestine.

The damaged ducts show infiltration of their walls with polymorphs and destruction of the epithelium. Ultimately, the bile duct is replaced by a fibrous cord. The causes include choledocholithiasis, biliary strictures and stenosis of biliary–enteric anastomoses. The bile duct loss is irreversible and a point comes when, even if the cause of the biliary obstruction can be removed, for instance gallstones, the bile duct destruction with biliary cirrhosis persists.

If the common bile or hepatic duct is surgically anastomosed to a stagnant loop of duodenum, continued access of the biliary system to gut organisms can result in bacterial cholangitis without biliary obstruction (fig. 15.10). A similar sequence may follow sphincteroplasty.

The sclerosing cholangitis associated with infection by the Chinese liver fluke (*Clonorchis sinensis*) is related to secondary infection, usually with *E. coli*, following biliary obstruction by the fluke.

Multiple pyogenic abscesses may lead to the picture of sclerosing cholangitis (Figs 15.11, 15.12) [65].

Immunodeficiency-related opportunistic cholangitis

Opportunistic organisms can invade the bile ducts causing the picture of sclerosing cholangitis. There is usually a background of immunodeficiency which may be congenital or acquired.

In the neonate, cytomegalovirus and reovirus type III have a tropism for bile epithelium and obliterative cholangitis results.

Associated immunodeficiency syndromes include familial combined immunodeficiency, hyperimmunoglobulin M immunodeficiency [17], angioimmunoblastic lymphadenopathy [4], X-linked immunodeficiency [53] and immunodeficiency with transient T-cell abnor-

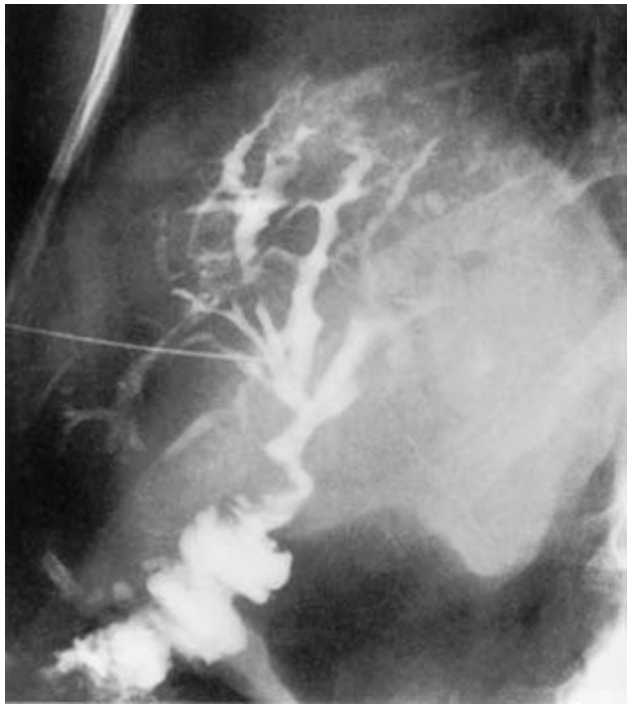


Fig. 15.10. Percutaneous cholangiography following choledocho-jejunostomy. There is no obstruction to flow of contrast into the jejunum but an intra-hepatic sclerosing cholangitis, marked by strictures and beading, has developed.

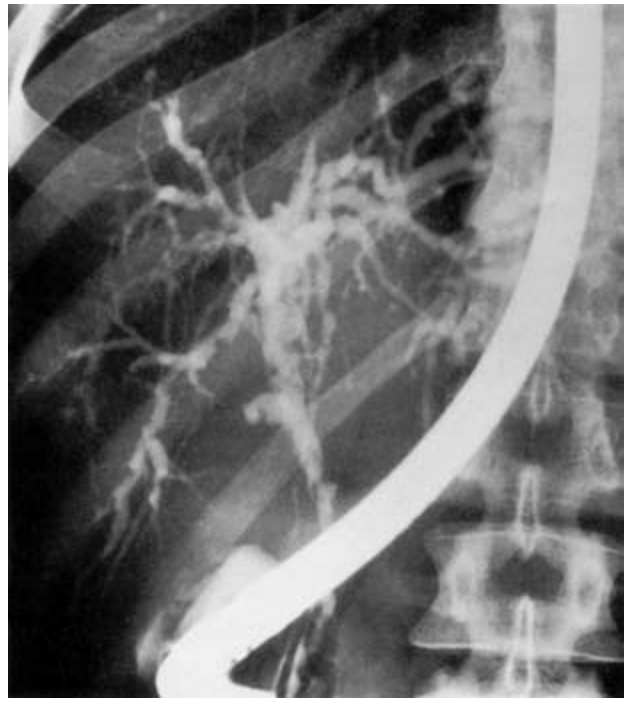


Fig. 15.11. ERCP showing distortion of the intra-hepatic biliary tree with irregularities in a patient with severe skin sepsis following burning. The picture resembles PSC.

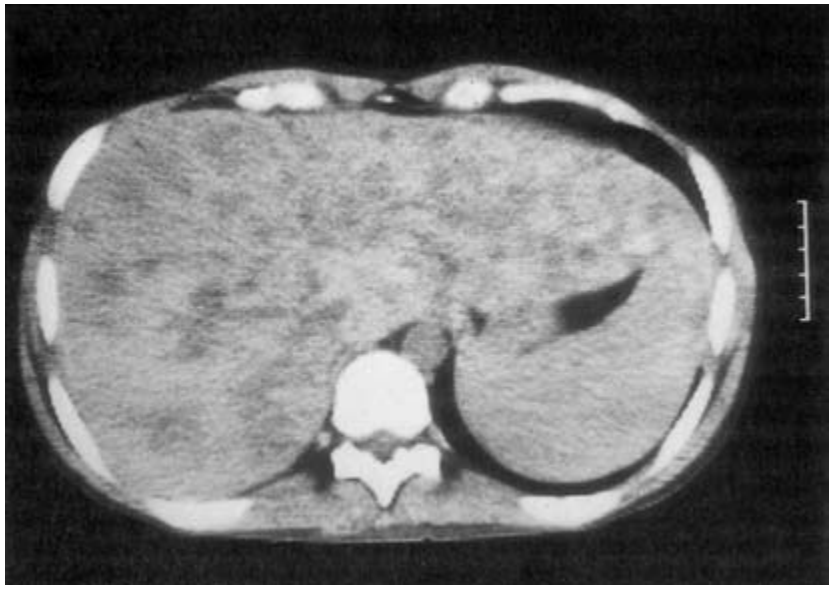


Fig. 15.12. CT from the same patient as in fig. 15.11 showing multiple space-occupying lesions due to metastatic bacterial abscesses.

malities [16, 24]. The usual causative organism is cytomegalovirus or cryptosporidia alone or in combination. *Cryptococcus*, *Candida albicans* and *Klebsiella pneumoniae* may be associated [15].

Abnormalities of the biliary system are associated with AIDS. In one series, 20 of 26 patients with AIDS and biliary problems had markedly abnormal cholangiograms. In 14 of these, the pattern was of sclerosing cholangitis with or without papillary stenosis.

PSC and AIDS cholangiopathy differ in the inflammatory infiltration surrounding the diseased bile ducts. In PSC, it is rich in T_4-lymphocytes, the subpopulation specifically depleted in patients with AIDS [60].

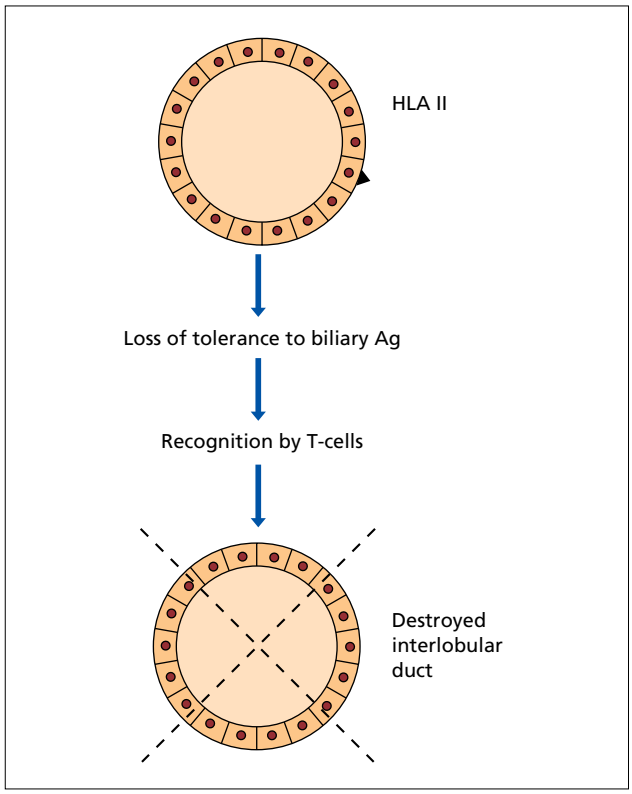


Fig. 15.13. Hepatic rejection (graft-versus-host disease). HLA class antigens are displayed on the bile duct. There is loss of tolerance to biliary antigens (Ag) which are recognized by cytotoxic T-cells and the interlobular ducts are destroyed.

Graft-versus-host disease

Aberrant expression of HLA class II antigen on bile ducts is seen in the transplanted human liver undergoing rejection and in patients with graft-versus-host disease following allogenic bone marrow transplantation (fig. 15.13). Rejection is marked by progressive non-suppurative cholangitis culminating in disappearance of interlobular bile ducts. The bile duct epithelium is penetrated by mononuclear cells with focal necrosis and rupture of the epithelium. Similar lesions are found in graft-versus-host disease following allogenic bone marrow transplantation. In one such patient, marked cholestatic jaundice lasted 10 years, and serial liver biopsies confirmed progressive biliary-type fibrosis and cirrhosis [35]. She ultimately died in liver failure.

Vascular cholangitis

The bile ducts are richly supplied by the hepatic artery which forms a peri-biliary vascular plexus. Interference leads to ischaemic necrosis of the bile ducts, both extra- and intra-hepatic, and to their ultimate disappearance. Injury to hepatic arterial branches, for instance during cholecystectomy, leads to ischaemia of the duct wall, damage to the ductal mucosa and entry of bile into the duct wall so causing fibrosis and stricture [66]. A similar sequence can complicate hepatic transplantation [74], especially if the segment of the recipient duct is too short and thus deprived of its arterial supply.

Biliary ischaemia secondary to intimal thickening of hepatic arterioles is a rare feature of chronic allograft rejection in man.

Diffuse small vessel arteritis, part of a systemic vasculitis, can be followed by bile duct loss.

Floxuridine (5-FUDR) can be infused by pump into the hepatic artery for the treatment of colo-rectal hepatic metastases. Biliary strictures can follow [33, 45]. The picture resembles PSC. The loss of bile ducts may be so severe that hepatic transplantation becomes necessary.

Drug-related cholangitis

Caustic cholangitis can be related to the injection of a scolicidal solution into a hydatid cyst. Only a part of the biliary tree is usually affected [5]. Within months the strictures result in jaundice, biliary cirrhosis and portal hypertension.

Histiocytosis X

A cholangiographic picture identical with that of PSC may complicate histiocytosis X [68]. The biliary lesions progress from a hyperplastic to a granulomatous, xanthomatous and, finally, a fibrotic stage. Clinically, the picture resembles PSC.

References

1 Aadlund E, Schrumpf E, Fausa O *et al*. Primary sclerosing cholangitis: a long-term follow up study. *Scand. J. Gastroenterol*. 1987; **22**: 655.
2 Abu-Elmagd KM, Malinchoc M, Dickson ER *et al*. Efficacy of hepatic transplantation in patients with primary sclerosing cholangitis. *Surg. Gynecol. Obstet*. 1993; **177**: 335.
3 Angulo P, Lindor KD. Primary sclerosing cholangitis. *Hepatology* 1999; **30**: 325.
4 Bass NM, Chapman RW, O'Reilly A *et al*. Primary sclerosing cholangitis associated with angioimmunoblastic lymphadenopathy. *Gastroenterology* 1983; **85**: 420.
5 Belghiti J, Benhamou J-P, Heuly S *et al*. Caustic sclerosing cholangitis. A complication of the surgical treatment of hydatid disease of the liver. *Arch. Surg*. 1986; **121**: 1162.
6 Berquist A, Glaumann H, Persson B *et al*. Risk factors and clinical presentation of hepatobiliary carcinoma in patients with primary sclerosing cholangitis: a case–control study. *Hepatology* 1998; **27**: 311.
7 Boberg KM, Schrumpf E, Fausa O *et al*. Hepatobiliary disease in ulcerative colitis. An analysis of 18 patients with hepatobiliary lesions classified as small-duct primary sclerosing cholangitis. *Scand. J. Gastroenterol*. 1994; **29**: 744.
8 Bodenheimer HC, LaRusso NF, Thayer WR *et al*. Elevated

circulating immune complexes in primary sclerosing cholangitis. *Hepatology* 1983; **3**: 150.
9 Broome U, Lofberg R, Veress B *et al*. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. *Hepatology* 1995; **22**: 1404.
10 Broome U, Olsson R, Loof L *et al*. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. *Gut* 1996; **38**: 610.
11 Campbell WL, Ferris JV, Holbart BL *et al*. Biliary tract carcinoma complicating primary sclerosing cholangitis: evaluation with CT, cholangiography, US and MR imaging. *Radiology* 1998; **207**: 41.
12 Cangemi JR, Wiesner RH, Beaver SJ *et al*. Effect of proctocolectomy for chronic ulcerative colitis on the natural history of primary sclerosing cholangitis. *Gastroenterology* 1989; **96**: 790.
13 Chapman RWG, Arborgh BAM, Rhodes JM *et al*. Primary sclerosing cholangitis—a review of its clinical features, cholangiography and hepatic histology. *Gut* 1980; **21**: 870.
14 Chapman RWG, Varghese Z, Gaul R *et al*. Association of primary sclerosing cholangitis with HLA-B8. *Gut* 1983; **24**: 38.
15 Cockerill FR, Hurley DV, Malagelada JR *et al*. Polymicrobial cholangitis and Kaposi's sarcoma in blood product transfusion-related acquired immune deficiency syndrome. *Am. J. Med*. 1986; **80**: 1237.
16 Davis JJ, Heyman MB, Ferrell L *et al*. Sclerosing cholangitis associated with chronic cryptosporidiosis in a child with a congenital immunodeficiency disorder. *Am. J. Gastroenterol*. 1987; **82**: 1196.
17 Di Palma JA, Strobel CT, Farrow JG. Primary sclerosing cholangitis associated with hyperimmunoglobulin M immuno-deficiency (dysgammaglobulinemia). *Gastroenterology* 1986; **91**: 464.
18 Dickson ER, Murtaugh PA, Wiesner RH *et al*. Primary sclerosing cholangitis: refinement and validation of survival models. *Gastroenterology* 1992; **103**: 1893.
19 Donaldson PT, Farrant JM, Wilkinson ML *et al*. Dual association of HLA DR2 and DR3 with primary sclerosing cholangitis. *Hepatology* 1991; **13**: 129.
20 El-Shabrawi M, Wilkinson ML, Portmann B *et al*. Primary sclerosing cholangitis in childhood. *Gastroenterology* 1987; **92**: 1226.
21 Ernst O, Asselah T, Sergent G *et al*. MR cholangiography in primary sclerosing cholangitis. *Am. J. Roentgenol.* 1998; **171**: 1027.
22 Farges O, Malassagne B, Sebagh M *et al*. Primary sclerosing cholangitis: liver transplantation or biliary surgery. *Surgery* 1995; **117**: 146.
23 Farrant JM, Hayllar KM, Wilkinson ML *et al*. Natural history and prognostic variables in primary sclerosing cholangitis. *Gastroenterology* 1991; **100**: 1710.
24 Gremse DA, Bucuvalas JC, Bongiovanni GL. Papillary stenosis and sclerosing cholangitis in an immunodeficient child. *Gastroenterology* 1989; **96**: 1600.
25 Haagsma EB, Mulder AHL, Bouw ASH *et al*. Neutrophil cytoplasmic autoantibodies after liver transplantation in patients with primary sclerosing cholangitis. *J. Hepatol*. 1993; **19**: 8.
26 Harrison RF, Davies MH, Neuberger JM *et al*. Fibrous and obliterative cholangitis in liver allografts: evidence of recurrent primary sclerosing cholangitis. *Hepatology* 1994; **20**: 356.
27 Hobson CH, Butt TJ, Ferry DM *et al*. Enterohepatic circulation of bacterial chemotactic peptide in rats with experimental colitis. *Gastroenterology* 1988; **94**: 1006.
28 Howell DA, Beveridge RP, Bosco J *et al*. Endoscopic needle aspiration biopsy at ERCP in the diagnosis of biliary strictures. *Gastrointest. Endosc*. 1992; **38**: 531.
29 Ito K, Mitchell DG, Outwater EK *et al*. Primary sclerosing cholangitis. MR imaging features. *Am. J. Roentgenol.* 1999; **172**: 1527.
30 Kaplan MM. Toward better treatment of primary sclerosing cholangitis. *N. Engl. J. Med*. 1997; **336**: 719.
31 Keeffe EB. Diagnosis of primary sclerosing cholangitis in a blood donor with elevated serum alanine aminotransferase. *Gastroenterology* 1989; **96**: 1358.
32 Keiding S, Hansen SB, Rasmussen HH *et al*. Detection of cholangiocarcinoma in primary sclerosing cholangitis by positron emission tomography. *Hepatology* 1998; **28**: 700.
33 Kemeny MM, Battifora H, Blayney DW *et al*. Sclerosing cholangitis after continuous hepatic artery infusion of FUDR. *Ann. Surg*. 1985; **202**: 176.
34 Kim WR, Poterucha JJ, Wiesner RH *et al*. The relative role of the Child–Pugh classification and the Mayo natural history in the assessment of survival in patients with primary sclerosing cholangitis. *Hepatology* 1999; **29**: 1643.
35 Knapp AB, Crawford JM, Rappeport JM *et al*. Cirrhosis as a consequence of graft-versus-host disease. *Gastroenterology* 1987; **92**: 513.
36 Kono K, Ohnishi K, Omata M *et al*. Experimental portal fibrosis produced by intraportal injection of killed nonpathogenic *Escherichia coli* in rabbits. *Gastroenterology* 1998; **94**: 787.
37 Kurzawinski TR, Deery A, Dooley JS *et al*. A prospective study of biliary cytology in 100 patients with bile duct strictures. *Hepatology* 1993; **18**: 1399.
38 Lee JG, Schutz SM, England RE *et al*. Endoscopic therapy of sclerosing cholangitis. *Hepatology* 1995; **21**: 661.
39 Lee Y-M, Kaplan MM. Primary sclerosing cholangitis. *N. Engl. J. Med*. 1995; **332**: 924.
40 Lefkowitch JH. Primary sclerosing cholangitis. *Arch. Intern. Med*. 1982; **142**: 1157.
41 Lichtman SN, Sartor RB, Keku J *et al*. Hepatic inflammation in rats with experimental small intestinal bacterial overgrowth. *Gastroenterology* 1990; **98**: 414.
42 Lindor KD for the Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. Ursodiol for primary sclerosing cholangitis. *N. Engl. J. Med.* 1997; **336**: 691.
43 Loftus EV Jr, Aguilar HI, Sandborn WJ *et al*. Risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulceraive colitis following orthotropic liver transplantation. *Hepatology* 1998; **27**: 685.
44 Loftus EV Jr, Sandborn WJ, Tremaine WJ *et al*. Risk of colorectal neoplasia in patients with primary sclerosing cholangitis. *Gastroenterology* 1996; **110**: 432.
45 Ludwig J, Kim CH, Wiesner RH *et al*. Floxuridine-induced sclerosing cholangitis: an ischemic cholangiopathy? *Hepatology* 1989; **9**: 215.
46 Ludwig J, MacCarty RL, LaRusso NF. Intrahepatic cholangiectases and large duct obliteration in primary sclerosing cholangitis. *Hepatology* 1986; **6**: 560.
47 MacCarty RL, LaRusso NF, Wiesner RH *et al*. Primary sclerosing cholangitis: findings on cholangiography and pancreatography. *Radiology* 1983; **149**: 39.
48 Mandal A, Dasgupta A, Jeffers L *et al*. Autoantibodies in

sclerosing cholangitis against a shared peptide in biliary and colon epithelium. *Gastroenterology* 1994; **106**: 185.
49 Martin FM, Rossi RL, Nugent FW *et al*. Surgical aspects of sclerosing cholangitis: results in 178 patients. *Ann. Surg*. 1990; **212**: 551.
50 Mehal WZ, Dennis Lo Y-M, Wordsworth BP *et al*. HLA DR4 is a marker for rapid disease progression in primary sclerosing cholangitis. *Gastroenterology* 1994; **106**: 160.
51 Minuk GY, Hershfield NB, Lee WY *et al*. Reticuloendothelial system Fc receptor-mediated clearance of IgG-tagged erythrocytes from the circulation of patients with idiopathic ulcerative colitis and chronic liver disease. *Hepatology* 1986; **6**: 1.
52 Nashan B, Schlitt HJ, Tusch G *et al*. Biliary malignancies in primary sclerosing cholangitis: timing for liver transplantation. *Hepatology* 1996; **23**: 1105.
53 Naveh Y, Mendelsohn H, Spira G *et al*. Primary sclerosing cholangitis associated with immunodeficiency. *Am. J. Dis. Child*. 1983; **137**: 114.
54 Neuberger J, Gunson B, Komolmit P *et al*. Pretransplant prediction of prognosis after liver transplantation in primary sclerosing cholangitis using a Cox regression model. *Hepatology* 1999; **29**: 1375.
55 Nichols JC, Gores GJ, LaRusso NF *et al*. Diagnostic role of serum CA 19-9 for cholangiocarcinoma in patients with primary sclerosing cholangitis. *Mayo Clin. Proc*. 1993; **68**: 874.
56 Olsson R, Danielsson Å, Järnerot G *et al*. Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. *Gastroenterology* 1991; **100**: 1319.
57 Porayko MK, Wiesner RH, LaRusso NF *et al*. Patients with asymptomatic primary sclerosing cholangitis frequently have progressive disease. *Gastroenterology* 1990; **98**: 1594.
58 Rahn RH III, Koehler RE, Weyman PJ *et al*. CT appearance of sclerosing cholangitis. *Am. J. Roentgenol*. 1983; **141**: 549.
59 Rasmussen HH, Fallingborg JF, Mortensen PB *et al*. Hepatobiliary dysfunction and primary sclerosing cholangitis in patients with Crohn's disease. *Scand. J. Gastroenterol.* 1997; **32**: 604.
60 Roulot D, Valla D, Brun-Vezinet F *et al*. Cholangitis in the acquired immuno-deficiency syndrome: report of two cases and review of the literature. *Gut* 1987; **28**: 1653.
61 Schrumpf E, Abdelnoor M, Fausa O *et al*. Risk factors in primary sclerosing cholangitis. *J. Hepatol*. 1994; **21**: 1061.
62 Seibold F, Weber P, Klein P *et al*. Clinical significance of antibodies against neutrophils in patients with inflammatory bowel disease and primary sclerosing cholangitis. *Gut* 1992; **33**: 657.
63 Shetty K, Rybicki L, Carey WD. The Child–Pugh classification as a prognostic indicator for survival in primary sclerosing cholangitis. *Hepatology* 1997; **25**: 1049.
64 Steckman M, Drossman DA, Lesesne HR. Hepatobiliary disease that precedes ulcerative colitis. *J. Clin. Gastroenterol*. 1990; **6**: 425.
65 Steinhart AH, Simons M, Stone R *et al*. Multiple hepatic abscesses: cholangiographic changes simulating sclerosing cholangitis and resolution after percutaneous drainage. *Am. J. Gastroenterol*. 1990; **85**: 306.
66 Terblanche J, Allison HE, Northover JMA. An ischemic basis for biliary strictures. *Surgery* 1983; **94**: 52.
67 Terjung B, Herzog V, Worman HJ *et al*. Atypical anti-neutrophil cytoplasmic antibodies with perinuclear fluorescence in chronic inflammatory bowel diseases and hepatobiliary disorders colocalize with nuclear lamina proteins. *Hepatology* 1998; **28**: 332.
68 Thompson HH, Pitt HA, Lewin KJ *et al*. Sclerosing cholangitis and histocytosis X. *Gut* 1984; **25**: 526.
69 Van Hoogstraten HJF, Wolfhagen FJH, van de Meebert PC *et al*. Ursodeoxycholic acid therapy for primary sclerosing cholangitis: results of a 2-year randomized controlled trial to evaluate single versus multiple daily doses. *J. Hepatol*. 1998; **29**: 417.
70 Wee A, Ludwig J. Pericholangitis in chronic ulcerative colitis: primary sclerosing cholangitis of the small bile ducts? *Ann. Intern. Med*. 1985; **102**: 581.
71 Wiesner RH, Grambsch PM, Dickson ER *et al*. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. *Hepatology* 1989; **10**: 430.
72 Wiesner RH, LaRusso NF, Dozois RR *et al*. Peristomal varices after proctocolectomy in patients with primary sclerosing cholangitis. *Gastroenterology* 1986; **90**: 316.
73 Wilschanski M, Chait P, Wade JA *et al*. Primary sclerosing cholangitis in 32 children: clinical, laboratory, and radiographic features. *Hepatology* 1995; **22**: 1415.
74 Zajko AB, Campbell WL, Logsdon GA *et al*. Cholangiographic findings in hepatic artery occlusion after liver transplantation. *Am. J. Roentgenol*. 1987; **149**: 485.

Chapter 16
Viral Hepatitis: General Features, Hepatitis A, Hepatitis E and Other Viruses

The first reference to epidemic jaundice has been ascribed to Hippocrates. The earliest record in Western Europe is in a letter written in 751 AD by Pope Zacharias to St Boniface, Archbishop of Mainz. Since then there have been numerous accounts of epidemics, particularly during wars. Hepatitis was a problem in the Franco-Prussian War, the American Civil War and World War I. In World War II huge epidemics occurred, particularly in the Middle East and Italy [11].

There are many varieties of hepatitis (table 16.1). Hepatitis A is a self-limited, faecally spread disease. Hepatitis B is a parenterally transmitted disease that often becomes chronic. Hepatitis D is parenterally spread and affects only those with a hepatitis B infection. Hepatitis C is a parenterally spread disease with a high chronicity rate. Hepatitis E is enterically spread, usually via water, and causes a self-limited hepatitis in developing countries. There is increasing evidence for other viral causes of hepatitis.

Pathology

All forms of viral hepatitis have a basic pathology. The essential lesion is an acute inflammation of the entire liver [2]. Hepatic cell necrosis is associated with leucocytic and histiocytic reaction and infiltration. Zone 3 shows the necrosis most markedly and the portal tracts the greatest cellularity (figs 16.1, 16.2, 16.3). The sinusoids show mononuclear cellular infiltration, polymorphs and eosinophils. Surviving liver cells retain their glycogen. Fatty change is rare. Zone 3 liver cells may show eosinophilic change (*acidophil bodies*), ballooning pleomorphism and giant multi-nucleated cells may be present. Mitoses are sometimes prominent. Zone 3 cholestasis may be found. Focal 'spotty' necrosis may be seen. Bile duct proliferation is usual and damage is an occasional feature [7].

The reticulin framework is usually well preserved even in the midst of extreme disorganization. It provides a scaffolding when the liver cells regenerate. Inflammatory cells disappear gradually, and some new zone 1

Table 16.1. Viral hepatitis A, B, C, D and E contrasted

	HAV	HBV	HCV	HDV	HEV
Genome	RNA	DNA	RNA	RNA	RNA
Family	Picorna	Hepadna	Flavi : Pesti	Viroid	Calici
Incubation (days)	15–45	30–180	15–150	30–180	15–60
Transmission	Faecal	Blood	Blood	Blood	Faecal
	Oral	Saliva	Saliva	—	Oral
Acute attack	Depends on age	Mild or severe	Usually mild	Mild or severe	Usually mild
Rash	Yes	Yes	Yes	Yes	Yes
Serum diagnosis	IgM anti-HAV	IgM anti-HBc	Anti-HCV	IgM anti-HDV	IgM anti-HEV
		HBsAg	HCV RNA		
		HBV DNA			
Peak ALT	800–1000	1000–1500	300–800	1000–1500	800–1000
Up and down	No	No	Yes	No	No
Prevention	Vaccine	Vaccine	—	—	—
Chronicity	No	Yes	Yes	Yes	No
Treatment	Symptomatic	Symptomatic	Symptomatic	Symptomatic	Symptomatic
		?Antivirals	?Antivirals	?Antivirals	

ALT, alanine aminotransferase

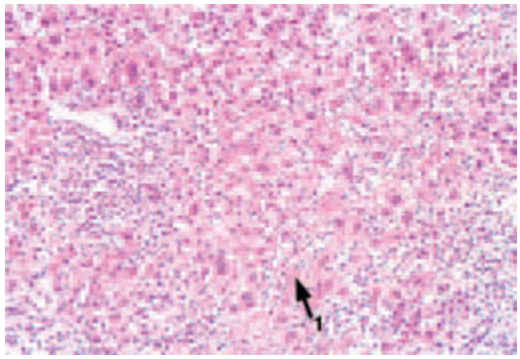


Fig. 16.1. Viral hepatitis: zone 3 (central) (arrow) shows marked loss of liver cells. Zone 1 (portal) shows expansion with cellular infiltration and bile duct proliferation. (H & E,×40.)

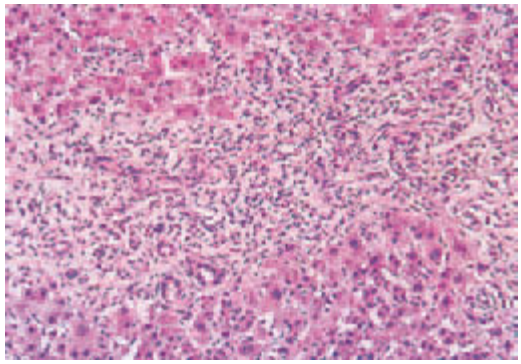


Fig. 16.3. Viral hepatitis: zone 1 (portal tract) shows an acute inflammatory reaction with ductular proliferation. (H & E,×50.)

portal connective tissue can often be found for many months (fig. 16.4). During recovery reticulo-endothelial activity increases throughout. A slight increase in stainable fat is seen. The Kupffer cells contain lipofuscin pigment and iron.

Occasionally the necrosis may be *confluent* (submassive), affecting substantial groups of adjacent liver cells, usually in zone 3.

In *massive fulminant necrosis* the whole acinus is involved. The liver is reduced in size, being smallest in those who die the soonest. It is flaccid and shrunken and the left lobe may be disproportionately atrophied. Nodular regeneration is seen in those surviving for more than 2 weeks (fig. 16.5). The cut surface shows a 'nutmeg' appearance, red areas of haemorrhage alternating with yellow patches of necrosis. Necrosis in life is always less than that seen in autopsy material as autolysis proceeds particularly rapidly in the presence of acute hepatitis.

If the necrosis extends from zone 3 to zone 1 the reticulum collapses leaving connective tissue septa. This is termed *bridging* (fig. 16.6). This may be followed by the

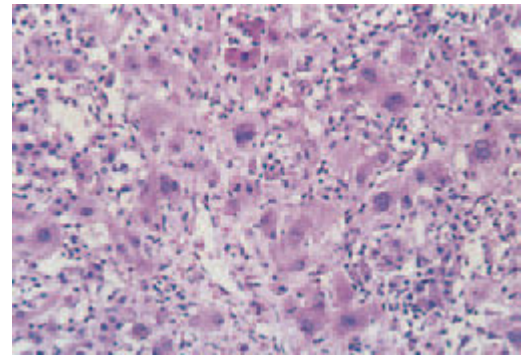


Fig. 16.2. Viral hepatitis: zone 3 shows swollen cells, mitoses and acidophilic bodies. (H & E,×80.)

development of active fibrous septa, nodules and cirrhosis. More usually it is followed by scar formation (*post-necrotic scarring*) (fig. 16.7).

Acute viral hepatitis may be followed by chronic hepatitis, cirrhosis and hepato-cellular cancer.

Changes in other organs

Regional lymph nodes enlarge. Splenomegaly is related to cellular proliferation and venous congestion. The bone marrow is moderately hypoplastic, but maturation is usually normal. In about 15% of fatal cases there is ulceration of the gastrointestinal tract—particularly caecal ulceration.

The brain shows an acute non-specific degeneration of ganglion cells. Occasionally acute pancreatitis and myocarditis have been noted. Haemorrhages are found in most organs.

Viral hepatitis is a multi-system infection involving many organs.

Clinical types

Acute hepatitis

Note is taken of ethnic origin, contacts, recent travel, injections, tattooing, dental treatment, transfusions, homosexuality or ingestion of shellfish. All drugs taken in the previous 2 months are listed.

In general, type A, B and C hepatitis run the same clinical course. Hepatitis B and C may be associated with a serum sickness-like syndrome.

The mildest attack is without symptoms and marked only by a rise in serum transaminase levels. Alternatively, the patient may be anicteric but suffer gastrointestinal and influenza-like symptoms. Such patients are likely to remain undiagnosed unless there is a clear history of exposure. Increasing grades of severity are then encountered, ranging from the icteric, from which recovery is usual, through to fulminant, fatal viral hepatitis.

The usual icteric attack in the adult is marked by a prodromal period, usually about 3 or 4 days, even up to several weeks, during which the patient feels generally unwell, suffers digestive symptoms, particularly anorexia and nausea, and may, in the later stages, have a mild pyrexia. Rigors are unusual. An ache develops in the right upper abdomen. This is increased by jolting movements. There is loss of desire to smoke or to drink alcohol. Malaise is profound and increases towards evening; the patient feels wretched.

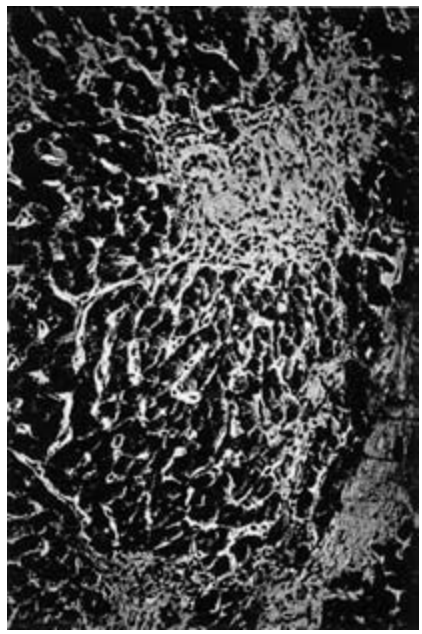


Fig. 16.4. Residual portal zone scarring seen 33 days after the onset of jaundice. (Best's carmine,×100) [9].

Occasionally headache may be severe and, in children, its association with neck rigidity may suggest meningitis. Protein and lymphocytes in the CSF may be raised.

The prodromal period is followed by darkening of the urine and lightening of the faeces. This heralds the development of jaundice and symptoms decrease in severity. The temperature returns to normal and there may be bradycardia. Appetite returns and abdominal discomfort and vomiting cease. Pruritus may appear transiently for a few days. Persistent vomiting and/or drowsiness or confusion indicate urgent hospital referral because they may reflect worsening liver function and incipient liver failure.

The liver is palpable with a smooth, tender edge in 70% of patients. The spleen is palpable in about 20% of patients. A few vascular spiders may appear transiently.

After an icteric period of about 1–4 weeks the adult patient usually makes an uninterrupted recovery. In children, improvement is particularly rapid and jaundice mild or absent. The stools regain their colour. The appetite returns. After apparent recovery, lassitude and fatigue persist for some weeks. Clinical and biochemical recovery is usual within 6 months of onset. However, chronic hepatitis may follow types B and C.

Neurological complications, including the Guillain–Barré syndrome, can complicate all forms of viral hepatitis [10].

Prolonged cholestasis

Onset is acute; jaundice appears and deepens but, within 3 weeks, the patient starts to itch. After the first few weeks the patient feels well, gains weight and there are no physical signs apart from icterus and slight

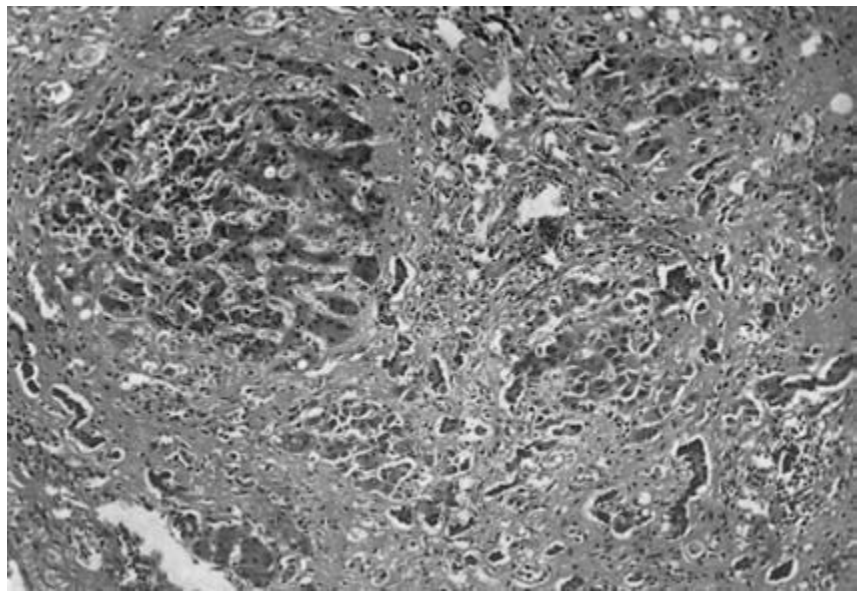


Fig. 16.5. Acute viral hepatitis. Subacute massive necrosis with nodular regeneration. (H & E,×120.)

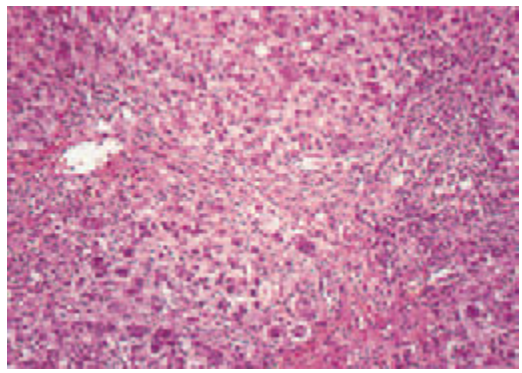


Fig. 16.6. Acute viral hepatitis. A passive septum (bridge) has formed between zones 1 and 2. (H & E, ×40.)

Table 16.2. Fulminant viral hepatitis in the UK: aetiology, duration from onset to fulminant, and survival [3]

	A	B	Non-A, non-B, non-C
Proportion (%)	31.5	24.7	43.8
Duration from onset (days)	10	7	21
Survival (%)	43.4	16.6	9.3

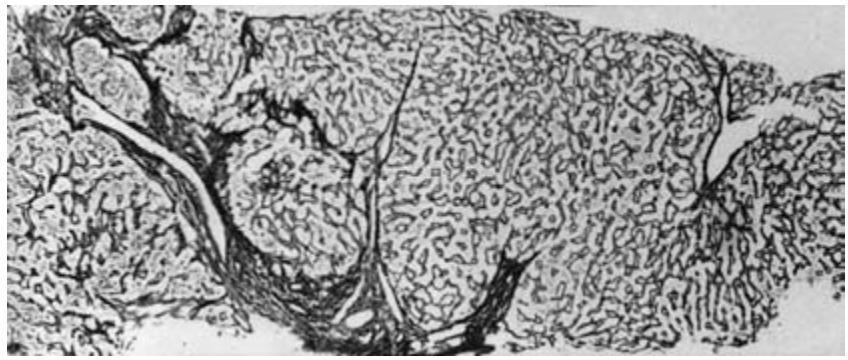


Fig. 16.7. Post-necrotic scarring. The liver biopsy specimen shows scarring, involving and extending from portal tracts. (Reticulin, ×34.)

hepatomegaly. Jaundice persists for 8–29 weeks and recovery is then complete. It is particularly associated with hepatitis A [4].

Liver biopsy shows conspicuous cholestasis which tends to mask the definite, usually mild, hepatitis.

This type must be differentiated from surgical obstructive jaundice [4]. The acute onset and only moderately enlarged liver are the most helpful points. Cholestatic drug jaundice is excluded by the history.

If doubt remains, ultrasound and liver biopsy are helpful.

The prognosis is usually excellent with complete clinical recovery and restitution of a normal liver [8].

Relapses

These occur in 1.8–15% of cases, particularly with hepatitis A infection. In some the original attack is duplicated, usually in a milder form. More often, the relapse is simply shown by an increase in serum transaminases and sometimes bilirubin. The relapse may be precipitated by premature activity. Multiple episodes may occur. Recovery is usually complete. In some patients relapses may indicate progression to chronic hepatitis.

Acute liver failure (fulminant hepatitis) (Chapter 8)

This rare form of the disease usually overwhelms the patient within 10 days. It may develop so rapidly that jaundice is inconspicuous and the disease is confused with an acute psychosis or meningo-encephalitis. Alternatively, the patient, after a typical acute onset, becomes deeply jaundiced. Ominous signs are repeated vomiting, fetor hepaticus, confusion and drowsiness. The 'flapping' tremor may be only transient, but rigidity is usual. Coma supervenes rapidly and the picture becomes that of acute liver failure. Temperature rises, jaundice deepens and the liver shrinks. Widespread haemorrhages may develop.

Leucocytosis may be found in contrast to the usual leucopenia of viral hepatitis. The biochemical changes are those of acute liver failure (Chapter 8). The height of the serum bilirubin and transaminase are poor indicators of prognosis. Transaminase levels may actually fall as the patient's clinical condition worsens. Blood coagulation is grossly deranged and prothrombin is the best indicator of prognosis.

The time and course depend on whether the cause is A, B or non-A, non-B, non-C hepatitis (table 16.2) [3].

Fulminant hepatitis is associated with viruses A, B and E. In the USA and Europe, HCV does not often seem to be related to fulminant hepatitis which may be due to another cause, presumably viral [5].

The frequency of the fulminant course in the various types of viral hepatitis depends on the type of patient and the prevalence of hepatitis B carriage. In the UK and California the non-A, non-B, non-C type is more frequent, whereas in Denmark and Greece, hepatitis B predominates.

There are clinical differences in the fulminant course of the three main types [3]. Pyrexia is most frequent with hepatitis A. The duration of illness before encephalopathy is longer with hepatitis non-A, non-B, non-C. The prothrombin time is greatest with hepatitis B. The bad prognosis in those with a longer duration from onset of illness to encephalopathy is probably related to the greater number of non-A, non-B, non-C hepatitis patients in that group (table 16.2).

Post-hepatitis syndrome

Adult patients feel below par for variable periods after acute hepatitis. Usually this is a matter of weeks but it may extend to months. This is termed the post-hepatitis syndrome [9]. Features are anxiety, fatigue, failure to regain weight, anorexia and alcohol intolerance, and right upper abdominal discomfort. The liver edge may be palpable and tender.

Serum transaminases may be raised up to three times normal. Continuing fluctuating transaminases may indicate the development of chronic hepatitis, usually due to HCV or HBV.

Hepatic histology does not differ from that found in patients recovering normally who are now symptom-free.

Treatment consists of reassurance after full investigation. If the acute attack has been type A, chronicity is excluded; if type B or C it must be considered.

Investigations

Urine and faeces

Bilirubin appears in the urine before jaundice. Later it disappears although serum levels remain elevated.

Urobilinogenuria is found in the late pre-icteric phase. At the height of the jaundice, very little bilirubin reaches the intestine, so urobilinogen disappears. Its reappearance indicates commencing recovery.

The onset of jaundice is marked by lightening of the faeces. There is moderate steatorrhoea. Reappearance of stool colour denotes impending recovery.

Blood changes

Total serum bilirubin levels range widely. Deep jaundice generally implies a prolonged clinical course. An increase in conjugated bilirubin is early, even when the total bilirubin level is still normal.

Serum alkaline phosphatase level is usually less than three times the upper limit of normal. Serum albumin and globulin are quantitatively unchanged. The serum iron and ferritin levels are raised.

Serum immunoglobulins G and M are raised in about one-third of patients during the acute phase.

Serum transaminase estimations are useful in early diagnosis, in detecting the anicteric case, and for detection of inapparent cases in epidemics. The peak level is found 1 or 2 days before or after onset of jaundice. Later in the course the level falls, even if the clinical condition is worsening. The estimation cannot be used prognostically. Values may remain elevated for 6 months in those recovering completely.

Haematological changes

The pre-icteric stage is marked by leucopenia, lymphopenia and neutropenia. These revert towards normal as jaundice appears. Some 5–28% of patients show atypical lymphocytes, resembling those seen in infectious mononucleosis. Acute Coombs' test positive haemolytic anaemia is a rare complication. Haemolysis may develop [6], especially in those with glucose-6-phosphate dehydrogenase deficiency [1].

Aplastic anaemia is very rare. It appears weeks or months after the acute episode and is particularly severe and irreversible. It is not usually associated with A, B or C infection and may be due to a hitherto unidentified non-A, non-B, non-C type. It has been treated by bone marrow transplantation.

The *prothrombin time* is lengthened in the more severe cases and does not return completely to normal with vitamin K therapy.

The *erythrocyte sedimentation rate* (ESR) is high in the pre-icteric phase, falls to normal with jaundice, and rises again when the jaundice subsides. It returns to normal with complete recovery.

Needle liver biopsy

This is rarely indicated in the acute stage. It may occasionally be needed in older patients to differentiate from extra-hepatic or other forms of intra-hepatic cholestasis and from drug jaundice. It may be used to diagnose the presence and type of chronic complications but should not be performed too soon after the acute episode as the distinction between the picture of normal recovery and chronic hepatitis may be impossible.

Differential diagnosis

In the *pre-icteric stage*, hepatitis can be confused with

other acute infectious diseases, with acute surgical abdomen, especially acute appendicitis, and with acute gastroenteritis. Bile in the urine, tender enlargement of the liver and a rise in serum transaminase values are the most helpful points. The distinction from infectious mononucleosis is given in table 16.4 (p. 280). Viral markers are essential.

In the *icteric stage*, the diagnosis must be made from surgical cholestasis. This is outlined in Chapter 12.

The diagnosis of acute viral hepatitis from drug reactions depends largely on the history.

Needle liver biopsy is valuable in the problem case. Attempts at a surgical diagnosis are disastrous.

The distinction from Weil's disease is discussed in Chapter 29.

In the *post-icteric stage*, the diagnosis of organic from non-organic complications necessitates routine investigations for the diagnosis of chronic hepatitis, and these may include needle biopsy.

Prognosis (table 16.2)

Type B infection is said to have the highest mortality. In a survey of 1675 cases in a group of Boston hospitals, one in eight sufferers from transfusion hepatitis (B and C) succumbed whereas only one in 200 died with the type A disease. Since many non-icteric cases are not included in the statistics, the overall mortality rate is undoubtedly very much lower.

In the UK, non-A, non-B hepatitis, not due to hepatitis C but to another virus, has the poorest survival [3].

Those who are elderly or in poor general health have a poor prognosis. Fulminant hepatitis is rare in those less than 15 years old. The survival rate is the same for males as for females.

Treatment

Prevention

Compulsory notification leads to earlier detection and identification of methods of infection, for instance food or water contamination, sexual spread or carriage by blood donors. Vaccination is discussed below.

Treatment of the acute attack

Treatment has little effect in altering the course. At the outset this is unpredictable and it is wise to treat all attacks as potentially fatal and to insist upon bed rest with bathroom privileges. Traditionally this is enforced until the patient is free of jaundice. A less strict regime may be possible if the patients are young and previously healthy. They can be allowed up when they feel well, regardless of the degree of jaundice. They should rest after each meal. If symptoms return, the patient is immediately returned to bed rest. Selected patients treated along these liberal lines do not show an increased incidence of later complications.

Convalescence is not allowed until the patient is symptom-free, the liver no longer tender, and the serum bilirubin less than 1.5 mg/dl(25 µmol/l). The period of convalescence should be twice the period spent in hospital or in bed at home.

The traditional low-fat, high-carbohydrate diet is popular because it has proved the most palatable to the anorexic patient. Apart from this, no benefit accrues from a rigid insistence upon a low-fat diet.

When the appetite returns, high protein intake may hasten recovery. The usual diet in hepatitis is composed of the food most appetizing to the patient. Supplementary vitamins, amino acids and lipotropic agents are not necessary.

Corticosteroids do not accelerate the rate of healing or assist in immunity in viral hepatitis. Hepatitis tends towards spontaneous recovery and any benefit is not sufficient to justify their use, except occasionally in cholestatic hepatitis A. The drug must be continued into convalescence because premature withdrawal leads to relapse. The steroid whitewash improves the morale of both patient and physician but probably has little effect on the healing process.

Patients showing signs of acute hepato-cellular failure with pre-coma require more active measures and the regime described in Chapter 8 must be instituted.

Follow-up

The patient should be seen 3–4 weeks after discharge, and if necessary at monthly intervals for the next 3 months. Special attention should be paid to recurrence of jaundice and to the size of the liver and spleen. Tests should include serum bilirubin, transaminase levels and hepatitis B and C markers if originally positive.

Exercise must be undertaken within the limits of fatigue. Alcohol must be denied for 6 months, and preferably for 1 year. The patient often has little inclination for it and excessive consumption leads to relapses. Diet can be unrestricted.

References

1 Chan TK, Todd D. Haemolysis complicating viral hepatitis in patients with glucose-6-phosphate dehydrogenase deficiency. *Br. Med. J.* 1975; **i**: 131.

2 Dible JH, McMichael J, Sherlock SPV. Pathology of acute hepatitis. Aspiration biopsy studies of epidemic, arsenotherapy and serum jaundice. *Lancet* 1943; **ii**: 402.

3 Gimson AES, White YS, Eddleston ALWF *et al*. Clinical and prognostic differences in fulminant hepatitis type A, B, and non-A, non-B. *Gut* 1983; **24**: 1194.

4 Gordon SG, Reddy KR, Schiff L *et al*. Prolonged intrahepatic cholestasis secondary to acute hepatitis A. *Ann. Intern. Med.* 1984; **101**: 635.
5 Kuwada SK, Patel VM, Hollinger FB *et al*. Non-A, non-B fulminant hepatitis is also non-E, and non-C. *Am. J. Gastroenterol*. 1994; **89**: 57.
6 Lyons DJ, Gilvarry JM, Fielding JF. Severe haemolysis associated with hepatitis A and normal glucose-6-phosphate dehydrogenase status. *Gut* 1990; **31**: 838.
7 Poulsen H, Christoffersen P. Abnormal bile duct epithelium in liver biopsies with histological signs of viral hepatitis. *Acta Path. Microbiol. Scand*. 1969; **76**: 383.
8 Shaldon S, Sherlock S. Virus hepatitis with features of prolonged bile retention. *Br. Med. J*. 1957; **2**: 734.
9 Sherlock S, Walshe VM. The post-hepatitis syndrome. *Lancet* 1946; **ii**: 482.
10 Tabor E. Guillain–Barré syndrome and other neurologic syndromes in hepatitis A, B, non-A, non-B. *J. Med. Virol.* 1987; **21**: 207.
11 Zuckerman AJ. The chronicle of viral hepatitis. *Bull. Hyg. Trop. Dis*. 1977; **54**: 113.

Hepatitis A virus

Hepatitis A accounts for 20–25% of clinical hepatitis in the developed world. It is due to a small, 27-nm cubically symmetrical RNA picorna virus (fig. 16.8) [5]. The capsid consists of 60 capsomeres, each made of the same four viral proteins, VP1, VP2, VP3 and VP4. Only a single serotype has been identified.

The virus is absorbed from the gastrointestinal tract and reaches the liver where it is engulfed (fig. 16.9). Viral proteins are synthesized and packed into vesicles to be released into the bile.

The virus is not directly cytopathic and damage is caused by T-cell mediated immune responses.

The virus has been transmitted to marmosets and chimpanzees, and cultivated *in vitro* (fig. 16.10). DNA complementary to genomic HAV RNA has been cloned in *Escherichia coli*.

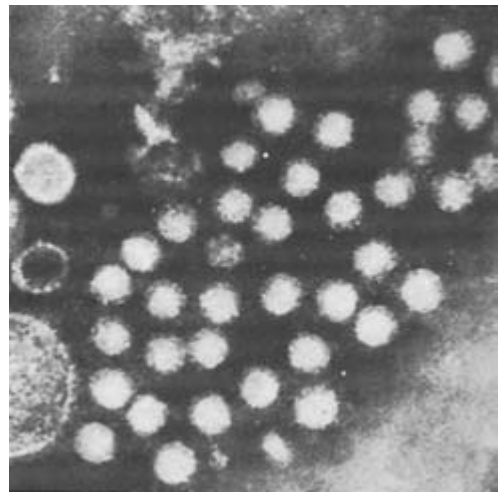


Fig. 16.8. Electron microscopy of hepatitis A antigen particles in faeces. These are shown as 27-nm spheres. (×250 000.)

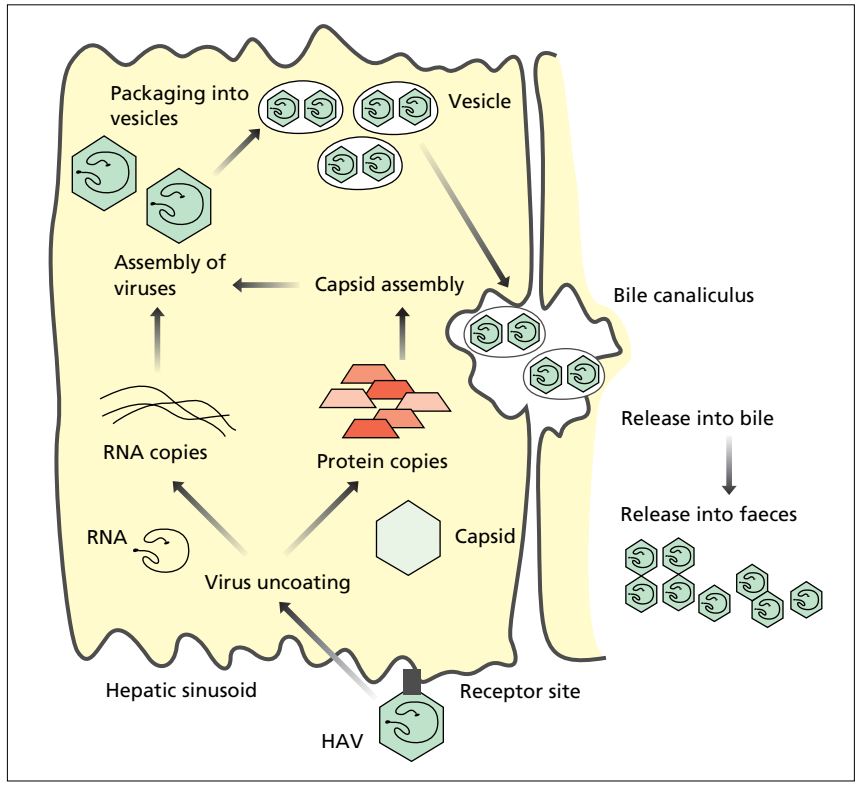


Fig. 16.9. The replication cycle of HAV.

A serum antibody (anti-HAV), appears as the stool becomes negative for virus, reaches a maximum in several months and is detectable for many years (fig. 16.11). IgG anti-HAV gives immunity from further infection with hepatitis A. The appearance of serum IgM anti-HAV is more helpful diagnostically and implies a recent infection. This antibody persists for only 2–6 months (fig. 16.11) and rarely, in low titre, for up to 1 year.

PCR shows that faecal excretion of virus can persist for months [23]. A chronic carrier state has not been identified.

Epidemiology

The disease occurs sporadically or in epidemic form and has an incubation time of 15–50 days. It is usually spread by the faecal–oral route. Parenteral transmission is extremely rare, but can follow transfusion of blood from a donor who is in the incubation stage of the disease [8].

The group most affected is aged 5–14 years, and adults are often infected by spread from children.

Spread is related to overcrowding, and to poor hygiene and sanitation. With improvements, the prevalence is decreasing worldwide (fig. 16.12). The annual incident rate varies from 5 per 100000 in Northern Europe and Japan to 9.1 in 1993 in the USA and 60 per 100000 in Africa and parts of South America [1, 2]. In developing countries, 90% of children have the antibody by the age of 10. Adults, not previously exposed, visiting endemic areas are at risk. Hospital staff in developed countries are affected.

Outbreaks have been reported among haemophiliacs receiving solvent–detergent-treated factor VIII concentrates [14]. Most sporadic cases follow person-to-person contact. Children in day-care centres and promiscuous homosexual men are at risk.

Explosive water-borne and food-borne epidemics are described. Fruit-related epidemics are related to poor hygiene in the handlers and to use of human sewage for soil fertilization [9].

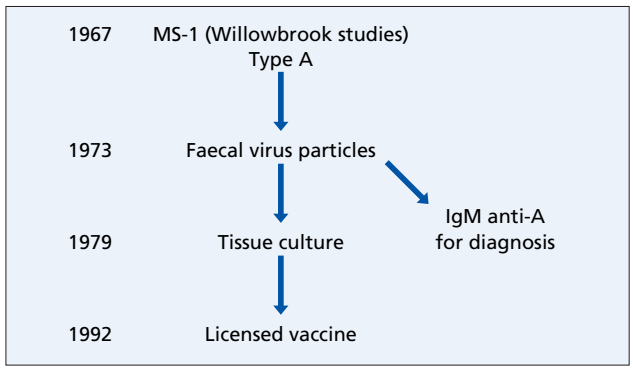


Fig. 16.10. Landmarks in the history of hepatitis A.

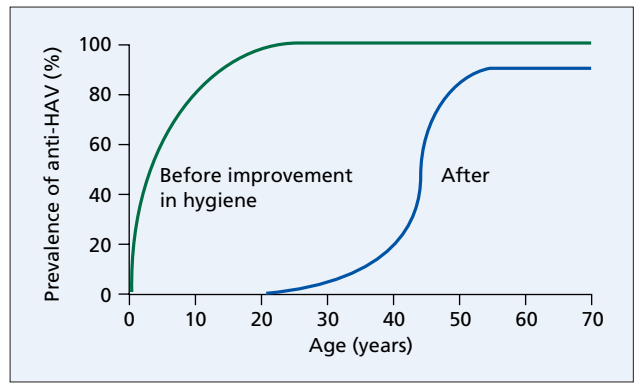


Fig. 16.12. Prevalence changes with improved hygiene. Older people lack immunity (IgG anti-HAV) to hepatitis A.

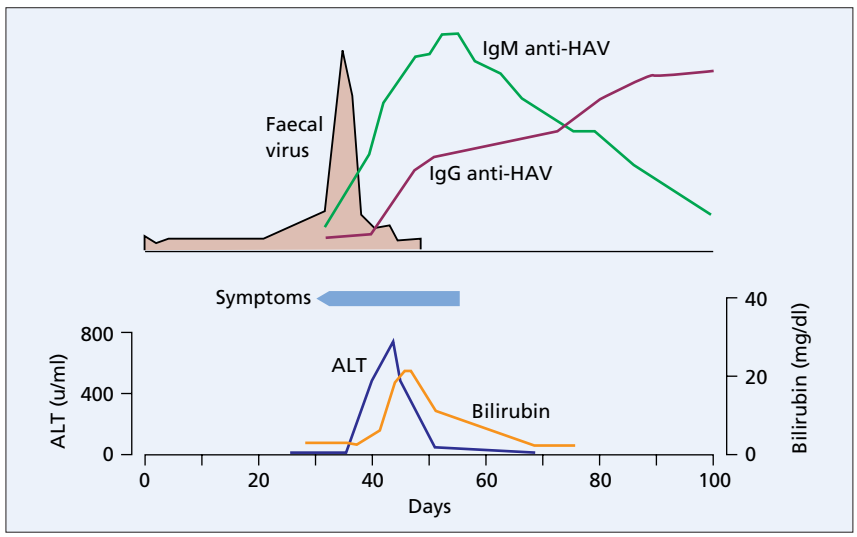


Fig. 16.11. The course of acute hepatitis A. ALT, alanine aminotransferase (GPT).

Ingestion of raw clams and oysters from polluted waters has caused epidemics. Steaming the clams may not kill the virus, for the temperature achieved inside the clams is not sufficiently high.

Contamination during preparation has resulted in transmission via other foods, including sandwiches, orange juice, potato salad and meat.

Clinical course

The hepatitis is usually mild, particularly in children where it is frequently sub-clinical or passed off as gastroenteritis. The disease is more serious and prolonged in adults.

Needle liver biopsy in patients with acute type A hepatitis shows a particularly florid portal zone lesion with expansion, marked cellular infiltration and erosion of the limiting plate. Cholestasis is marked. It is therefore surprising that hepatitis A infection never leads to ongoing chronic hepatitis or cirrhosis. Fibrin ring granulomas are described [16].

Cholestatic hepatitis A affects adults [7]. The jaundice lasts 42–110 days and itching is severe. Serum IgM anti-HAV is positive. The prognosis is excellent. A case can be made for cutting short the jaundice and relieving the itching by a short course of prednisolone 30 mg reducing to zero over about 3 weeks.

The *nephrotic syndrome* has been reported with immune complex, mesangial, proliferative glomerulonephritis [25].

Hepatitis A may trigger *chronic autoimmune hepatitis type 1* in genetically predisposed individuals [19]. This may be related to defects in T-cell suppressor-inducer cells.

Relapsing hepatitis A. Occasionally after 30–90 days the patient relapses. The serum transaminase levels have never returned to normal. The relapse resembles the original attack clinically and biochemically and virus A is found in the stools [18]. The relapse may last several months but recovery eventually ensues [6].

Rarely, the relapse can be associated with arthritis, vasculitis and cryoglobulinaemia [4].

Prognosis

This is excellent and recovery is usually full. Mortality in large epidemics is less than one per 1000 and HAV accounts for less than 1% of cases of fulminant viral hepatitis. In older people, however, the disease has considerable morbidity, mortality and treatment costs [1]. In non-hospitalized adults, the symptoms lasts about 34 days with 33 days' work loss. In a hospitalized patient, symptom duration is longer (68 days) with 33 days' work loss.

Chronicity does not develop. Follow-up of large epidemics in World War I [3] showed no long-term sequelae.

Prevention

The virus is excreted in the faeces for as long as 2 weeks before the appearance of jaundice. The anicteric patient may excrete the virus for a similar period. The virus is therefore disseminated before the diagnosis is made. For this reason, isolation of patients and contacts cannot be expected to influence significantly the spread of hepatitis.

HAV is relatively resistant to inactivation by heat, ether or acid, but it is inactivated by formalin 1 in 4000 at 37°C for 72 h, chlorine 1 p.p.m. for 30 min and by microwaving.

Immune serum globulin (ISG) prophylaxis

Efficacy depends on the antibody content and hence the source of the plasma. ISG is being largely replaced by vaccine; however, vaccine takes 1–2 weeks to achieve adequate antibody levels. Immunoglobulin is still used in those acutely exposed, such as household contacts. It is ineffective in the control of hepatitis A in hyperendemic areas or for interrupting community-wide or common-source outbreaks.

Anti-ISG must be given within 2 weeks of exposure and the protection lasts 4–6 months. ISG may be given with the first dose of vaccine but the resultant HAV antibody titres will be reduced [24].

Hepatitis A vaccines (table 16.3)

Viral particles are inactivated with formaldehyde. The vaccine is safe and immunogenic [21, 22]. The only side-effect is mild soreness of the arm. A single 1-ml dose of vaccine is followed by a booster 6–12 months later. The single dose gives rapid protection within 15 days which lasts for 1 year. If followed by the booster, 95% seroconversion ensues with long-lasting protection [17]. Prevaccination serum testing for HAV antibody is necessary only in those born after 1945, living in countries with low prevalence and who, presumably, have had a small chance of contracting the disease (fig. 16.12).

Table 16.3. Hepatitis A vaccine

Formol inactivated
2 doses, initial and 6–12 months booster
Indications
travellers
occupational exposure
epidemics
?mass immunization in children
?chronic liver disease (HCV)

In one dose the formol-inactivated vaccine was shown to be highly protective in children in a Jewish community in New York [22]. In a large study of children in Thailand, two doses protected against HAV for at least 1 year [10].

Live attenuated HAV vaccine

This has been prepared from HAV in cell culture. It is inexpensive and has been widely used in developing countries such as China. Given subcutaneously, it seems safe and effective [15].

Indications for HAV vaccine (table 16.3)

HAV vaccine is indicated for travellers to areas where hygiene is at risk. Unvaccinated, three to six visitors per 1000 per month will develop HAV. Children and staff in day-care units and their parents, and nurses, particularly working in intensive care units, should be vaccinated. Global control will require early mass immunization in childhood (routine aged 2, catch-up aged about 10) [12, 13]. Eventually, vaccination will be combined with other paediatric vaccines. Such worldwide vaccination is a long way off being achieved.

Food handlers and sewage workers are candidates for vaccination. The military should be vaccinated, particularly if they are going to areas where hygiene is poor.

Promiscuous, homosexual males should be vaccinated.

HAV infection has a harmful effect on patients with chronic liver disease, especially HCV [20]. The HAV vaccine is effective in such patients [11]. It should probably be given to those with non-end-stage disease although there may be economic constraints. HAV antibody testing should be done as the patient is likely to have been previously exposed to HAV.

References

1 Berge JJ, Drennan DP, Jacobs RJ *et al*. The cost of hepatitis A infections in American adolescents and adults in 1997. *Hepatology* 2000; **31**: 469.
2 Center for Disease Control. Prevention of hepatitis through active or passive immunization, recommendations of the Advisory Committee of Immunization Practices (ACIP). *MMWR* 1999; **48**: 1.
3 Cullinan ER, King RC, Rivers JS. The prognosis of infective hepatitis. A preliminary account of a long-term follow-up. *Br. Med. J.* 1958; **i**: 1315.
4 Dan M, Yaniv R. Cholestatic hepatitis, cutaneous vasculitis and vascular deposits of immunoglobulin M and complement associated with hepatitis A virus infection. *Am. J. Med.* 1990; **89**: 103.
5 Feinstone SM, Kapikian AZ, Purcell RH. Hepatitis A: detection by immune electron microscopy of a virus-like antigen associated with acute illness. *Science* 1973; **182**: 1026.
6 Glikson M, Galun E, Oren R *et al*. Relapsing hepatitis A. Review of 14 cases and literature survey. *Medicine (Baltimore)* 1992; **71**: 14.
7 Gordon SG, Reddy KR, Schiff L *et al*. Prolonged intrahepatic cholestasis secondary to acute hepatitis A. *Ann. Intern. Med.* 1984; **101**: 635.
8 Hollinger FB, Khan NC, Oefinger PE. Post-transfusion hepatitis type A. *JAMA* 1983; **250**: 2313.
9 Hutin YJF, Pool V, Cramer EH *et al*. A multistate, food-borne outbreak of hepatitis. *N. Engl. J. Med.* 1999; **340**: 595.
10 Innis BL, Snitbhan R, Kunasol P *et al*. Protection against hepatitis A by an inactivated vaccine. *JAMA* 1994; **271**: 1328.
11 Keeffe EB, Iwarson S, McMahon BJ *et al*. Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease. *Hepatology* 1998; **27**: 881.
12 Koff RS. Hepatitis A. *Lancet* 1998; **341**: 1643.
13 Koff RS. The case for routine childhood vaccination against hepatitis A. *N. Engl. J. Med.* 1999; **340**: 644.
14 Mannuccio PM, Godvin S, Gringeri A *et al*. Transmission of hepatitis A to patients with haemophilia by factor VIII concentrates treated with organic solvent and detergent to inactivate viruses. *Ann. Intern. Med.* 1994; **120**: 1.
15 Mao JS, Chai SA, Xic RY *et al*. Further evaluation of the safety and protective efficacy of live attenuated hepatitis A vaccine (H-2 strain). *Vaccine* 1997; **15**: 944.
16 Ponz E, Garcia-Pagán JC, Bruguera M *et al*. Hepatic fibrin-ring granulomas in a patient with hepatitis A. *Gastroenterology* 1991; **100**: 268.
17 Sjögren MH, Hoke CH, Binn LN *et al*. Immunogenicity of an inactivated hepatitis A vaccine. *Ann. Intern. Med.* 1991; **114**: 470.
18 Sjögren MH, Tanno H, Fay O *et al*. Hepatitis A virus in stool during clinical relapse. *Ann. Intern. Med.* 1987; **106**: 221.
19 Vento S, Garofano T, Di Perri G *et al*. Identification of hepatitis A virus as a trigger for autoimmune chronic hepatitis type I in susceptible individuals. *Lancet* 1991; **337**: 1183.
20 Vento S, Garafano T, Renzini C *et al*. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N. Engl. J. Med.* 1998; **338**: 286.
21 Werzberger A, Kuter R, Nalin D. Six years follow-up after hepatitis A vaccination. *N. Engl. J. Med.* 1998; **338**: 1160.
22 Werzberger A, Mensch B, Kuter B *et al*. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. *N. Engl. J. Med.* 1992; **327**: 453.
23 Yotsuyanagi H, Koike K, Yasuda K *et al*. Prolonged fecal excretion of hepatitis A virus in adult patients with hepatitis A virus as determined by polymerase chain reaction. *Hepatology* 1996; **24**: 10.
24 Zaaijer HL, Leentvaar-Kuijpers A, Rotman H *et al*. Hepatitis A antibody titres after infection and immunization: implications for passive and active immunization. *J. Med. Virol.* 1993; **40**: 22.
25 Zikos D, Grewal KS, Craig K *et al*. Nephrotic syndrome and acute renal failure associated with hepatitis A viral infection. *Am. J. Gastroenterol.* 1995; **90**: 295.

Hepatitis E virus

This accounts for sporadic and major epidemics of viral hepatitis in developing countries [2]. Many large epidemics of hepatitis believed to be due to HAV have now been identified as caused by HEV. The disease is enterically transmitted, usually by sewage-contaminated water.

Hepatitis E is a 32–34-nm RNA virus, unenveloped and with three open reading frames (ORFs). It resembles calciviruses but has not been classified and has been placed in a new group called *herpesviridae*. It is a cytopathic virus causing minimal immunological injury.

HEV is excreted in the bile which is a rich source of virus. Low faecal excretion accounts for the rare examples of secondary spread.

Nucleotide viral sequences have been obtained from isolates from Burma [13], Mexico [16], Pakistan and China [9]. There are marked variations in the nucleotide sequence of HEV strains isolated from all over the world. Isolation of virus is difficult from stools, and low faecal excretion probably accounts for low secondary spread [11]. Immunity probably wains and longevity of protective antibody is uncertain.

Clinical features

In general, hepatitis E resembles hepatitis A. It affects young adults and is rare in children [3]. It has a self-limited course. Human volunteer studies have given an incubation period of 22–46 days for blood and 34–46 days for faeces [5]. The onset is abrupt. The majority of clinical cases are jaundiced and there are no extra-hepatic features. Chronicity does not develop.

Epidemic. Infection comes from drinking water contaminated by leakage of sewage. Monsoon seasons are at high risk for epidemics. The mortality rate is high: 1–2%, and up to 10–20% in pregnant women. Death is due to fulminant liver failure.

Sporadic HEV. This is a common cause of acute viral hepatitis in endemic areas. It presents with moderate or severe symptoms, including acute liver failure, sub-acute liver failure and prolonged cholestatic hepatitis [1]. Mortality is 45% for fulminant or sub-acute liver failure. Unlike epidemic HEV, the mortality is not high in pregnant women [8].

Diagnostic tests

Serum IgG and IgM antibodies are measured by ELISA assay using recombinant antigens and synthetic peptides prepared from cloned HEV [6]. HEV RNA can be detected by RT-PCR [12].

IgM HEV can be detected within 10–12 days of acute illness and has disappeared in the majority by 6 months. Anti-HEV IgG appears at about 10–12 days of illness and remains positive for long periods. Viraemia is transient and the HEV PCR is usually negative by 3 weeks.

Positive antibody tests have been reported from almost all parts of the developing world. They include Egyptian children [7], Kashmiris [8], Taiwanese [17] and migrant workers in Qatar [14]. Sufferers diagnosed in Western countries have usually been visitors to developing areas [4, 15]. Nucleotide analysis can be used to confirm the source. Infection is very unusual in the West, although antibody has been found in Italian intravenous drug users and in American blood donors [10].

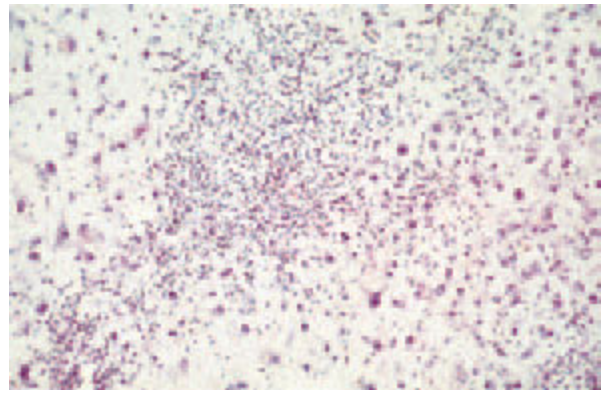


Fig. 16.13. Liver biopsy from a pregnant Arab girl suffering from acute hepatitis E showing cholestasis, pseudo-glandular formations, ballooning degeneration of hepatocytes and very prominent portal zone cellular infiltrates. She recovered. (H & E, ×100.)

Liver biopsy

This shows cholestasis, pseudo-glandular formations, ballooning of hepatocytes and very prominent zone 1 infiltrates containing polymorphs (fig. 16.13). Massive and sub-massive necrosis is seen in fulminant cases and bridging necrosis is the prominent feature of sub-acute hepatitis. Even after 5–10 years of follow-up cirrhosis is not seen.

Prevention

This is by clean water, better sanitation and hygiene education. A vaccine may prove possible, as there is a common genotype.

References

1 Acharya SK, Dasarathy S, Kumer TL *et al*. Fulminant hepatitis in a tropical population, clinical course, aetiology and early predictors of outcome. *Hepatology* 1996; **23**: 1443.
2 Aggarwal R, Naik SR. Epidemiology of hepatitis E past, present and future. *Top. Gastroenterol.* 1997; **18**: 19.
3 Arankalle VA, Tsarev SA, Chadha MS *et al*. Age-specific prevalences of antibodies to hepatitis A and E viruses in Pune, India, 1982 and 1992. *J. Infect. Dis.* 1995; **171**: 447.
4 Buisson Y, Coursaget P, Bercion R *et al*. Hepatitis E virus infection in soldiers sent to endemic regions. *Lancet* 1994; **344**: 1165.
5 Chauhan A, Jameel S, Dilawari JB *et al*. Hepatitis E virus transmission to a volunteer. *Lancet* 1993; **341**: 149.

6 DeGuzman LJ, Pitrak DL, Dawson GJ *et al*. Diagnosis of acute hepatitis E infection using enzyme immunoassay. *Dig. Dis. Sci*. 1994; **39**: 1691.
7 Goldsmith R, Yarbough PO, Reyes GR *et al*. Enzyme-linked immunosorbent assay for diagnosis of acute sporadic hepatitis E in Egyptian children. *Lancet* 1992; **339**: 328.
8 Khuroo MS, Rustgi VK, Dawson GJ *et al*. Spectrum of hepatitis E virus infection in India. *J. Med. Virol*. 1994; **43**: 281.
9 Krawczynski K. Hepatitis E. *Hepatology* 1993; **17**: 932.
10 Lok ASF, Soldevila-Pico C. Epidemiology and serologic diagnosis of hepatitis E. *J. Hepatol*. 1994; **20**: 567.
11 Nanda SK, Ansari IH, Acharya SK *et al*. Protracted viremia during acute sporadic hepatitis E virus infection. *Gastroenterology* 1995; **108**: 225.
12 Ray R, Aggarwal R, Salunke PN *et al*. Hepatitis E virus genome in stools of hepatitis patients during large epidemic in North India. *Lancet* 1991; **338**: 783.
13 Reyes GR, Purdy MA, Jungsuh PK *et al*. Isolation of a cDNA from the virus responsible for enterically transmitted non-A, non-B hepatitis. *Science* 1990; **247**: 1335.
14 Shidrawi RG, Skidmore SJ, Coleman JC *et al*. Hepatitis E—an important cause of important non-A, non-B hepatitis among migrant workers in Qatar. *J. Med. Virol*. 1994; **43**: 412.
15 Skidmore SJ, Yarbrough PO, Gabor KA *et al*. Imported hepatitis E in UK. *Lancet* 1991; **337**: 1541.
16 Velázquez O, Stetler HC, Avila C *et al*. Epidemic transmission of enterically transmitted non-A, non-B hepatitis in Mexico, 1986–87. *JAMA* 1990; **263**: 3281.
17 Wu J-C, Sheen JJ, Chiang T-Y *et al*. The impact of travelling to endemic areas on the spread of hepatitis E virus infection: epidemiological and molecular analysis. *Hepatology* 1998; **27**: 1415.

Hepatitis G virus

The aetiology of some liver disease in man remains unknown. Twenty-five per cent of cases of fulminant hepatitis have an unknown origin; 17.5% of cirrhosis remains cryptogenic. In 60% of post-transfusion hepatitis, the cause is never found. Two 'new' viruses have been found, but their relation to human liver disease remains uncertain.

HGV was cloned from a patient with chronic hepatitis whose plasma had transmitted hepatitis to tamarin monkeys [6]. It is a member of the *flaviviridae* family and has 25% homology with HCV [5]. It is found in 1–2% of blood donors in the USA. Risk factors are similar to those for hepatitis C. Its presence in liver tissue is probably due to serum contamination [7]. It is doubtful whether it is a hepatotrophic virus. Persistent infection is common, but does not lead to chronic liver disease [2]. It does not play a major role in idiopathic fulminant hepatic failure [8] or in chronic liver disease in man [3]. It is prevalent in liver transplant recipients, but does not have a long-term harmful effect on the graft [4]. It does not worsen the course of concurrent HCV infection [1].

HGV does not seem to be a serious human pathogen.

References

1 Alter HJ, Nakatsuji Y, Melpolder J *et al*. The incidence of transfusion associated hepatitis G virus infection and its relation to liver disease. *N. Engl. J. Med*. 1997; **336**: 747.
2 Alter MJ, Gallagher M, Morris TT *et al*. Acute non A-E hepatitis in the United States and the role of hepatitis G virus infection. *N. Engl. J. Med*. 1997; **336**: 741.
3 Guilera M, Satz JC, Lopez-Labrador FX *et al*. Hepatitis G virus infection in chronic liver disease. *Gut* 1998; **42**: 107.
4 Haagsma EB, Cuypers HTM, Gouw AS *et al*. High prevalence of hepatitis G virus after liver transplantation without apparent influence on long-term graft function. *J. Hepatol*. 1997; **26**: 921.
5 Leary TP, Muerhoff AS, Simon SJN *et al*. Sequence and genomic organization of GBV-C: a novel member of the flaviviridae associated with human non-A-E hepatitis. *J. Med. Virol*. 1996; **48**: 60.
6 Linnen J, Wages J Jr, Zhang-Keek ZY *et al*. Molecular cloning and disease association of hepatitis G virus: a transfusion-transmissable agent. *Science* 1996; **271**: 505.
7 Pessoa MG, Terbault NA, Detmer J *et al*. Quantification of hepatitis G and C viruses in the liver: evidence that hepatitis G virus is not hepatotropic. *Hepatology* 1998; **27**: 877.
8 Satz JC, Sans M, Mas A *et al*. Hepatitis G virus infection in fulminant hepatic failure. *Gut* 1997; **41**: 696.

Hepatitis TT virus

In 1997, this virus was described in a Japanese patient (initials, TT) with non-A-G post-transfusion hepatitis [3]. It is an unenveloped single-stranded DNA virus of the circoviridiae family. It is found in the blood of about 1% of US blood donors [1]. The prevalence depends on methodology, particularly the sets of primers used for PCR [2]. It is not a causative agent for hepatitis. It is common in patients with acute and chronic liver disease, but is of no identifiable clinical significance [1, 4]. With such a high carriage rate in healthy individuals [4], it is unlikely to be a significant cause of liver disease.

References

1 Charlton M, Adjel P, Poterucha J *et al*. TT-virus in North American blood donors, patients with fulminant hepatic failure and cryptogenic cirrhosis. *Hepatology* 1998; **28**: 839.
2 Mizokami M, Albrecht JK, Kato T *et al*. TT virus infection in patients with chronic hepatitis C virus infection—effect of primers, prevalence and clinical significance. *J. Hepatol*. 2000; **32**: 339.
3 Nishikawa T, Okamoto H, Konishi K *et al*. A novel DNA virus (TTV) associated with elevated transaminase levels in post-transfusion hepatitis of unknown aetiology. *Biochem. Bio. Phys. Res. Comm*. 1997; **241**: 92.
4 Parquet M, Del C, Yatsuhashi H, Koga M *et al*. Prevalence and clinical characteristics of TT virus (TTV) in patients with sporadic acute hepatitis of unknown aetiology. *J. Hepatol*. 1999; **31**: 985.

Yellow fever

This acute infection is due to a group B arbovirus transmitted to man by the bite of infected mosquitoes [3]. The virus cycle is a direct human one in urban yellow fever, or may involve wild monkeys in the jungle variety.

The two endemic regions are South America and equatorial Africa.

Pathology

In humans, the liver histology shows predominantly mid-zonal acidophilic hepato-cellular necroses (Councilman bodies). Ceroid is abundant and inflammation scanty. Under electron microscopy viral particles are absent. The acidophilic bodies are composed of round cytoplasmic masses densely packed with organelles, fat vacuoles, ceroid pigment and residual bodies [2]. Appearance differs from acidophilic bodies found in other liver diseases. Inflammation is absent. Intranuclear inclusions (*Torres bodies*) are diagnostic. With recovery, regeneration is complete without chronicity.

Clinical features

Following an incubation period of 3–6 days, onset is sudden with fever, chills, headache, backache, prostration and vomiting, often of altered blood. The blood pressure falls, haemorrhages become widespread, jaundice and albuminuria are conspicuous and there is a relative bradycardia. Delirium proceeds to coma and death may occur within 9 days. With recovery, the temperature becomes normal and convalescence progresses rapidly. There are no sequelae and life-long immunity follows. The majority of infections are probably milder, with no detectable jaundice and only a few constitutional symptoms.

Diagnosis

Laboratory confirmation is by demonstrating specific IgM antibodies to yellow fever virus. Yellow fever antigen may be detected in formalin-fixed, paraffin-embedded tissue cut from blocks made as long as 8 years before [1].

Prothrombin deficiency parallels the severity of the liver lesion. The serum cholesterol and glucose levels fall in the fatal case. Serum transaminases are increased relative to severity.

Treatment

There is no specific treatment. Death results principally from renal damage. The hepatic lesion is self-limited and short-lived and does not demand special treatment.

Prevention consists of vaccination at least 10 days before arrival in an endemic area and by control of mosquitoes.

References

1 Hall WC, Crowell TP, Watts DM *et al*. Demonstration of yellow fever and dengue antigens in formalin-fixed, paraffin-embedded human liver by immunohistochemical analysis. *Am. J. Trop. Med. Hyg*. 1991; **45**: 408.

2 Vieira WT, Gayotto LC, Dé Lima CP *et al*. Histopathology of the human liver in yellow fever with special emphasis on the diagnostic role of the Councilman body. *Histopathology* 1983; **7**: 195.

3 World Health Organization. Present status of yellow fever: memorandum from a PAHO meeting. *Bull. WHO* 1986; **64**: 511.

Infectious mononucleosis (Epstein–Barr virus)

This is due to human herpes virus IV (EBV), which excites a generalized reticulo-endothelial reaction [2].

Primary infection in children is usually asymptomatic. In adolescents and young people, it causes a hepatitis which may mimic HAV, HBV or HCV hepatitis. Presentation, particularly in adults, may be as fever with right, upper quadrant, abdominal discomfort. Pharyngitis and lymphadenopathy may be absent. It can cause fulminant hepatitis in elderly people [3]. It may be a trigger for autoimmune hepatitis in susceptible people [5]. In the immunosuppressed, whether congenital or recipients of solid organ or bone marrow transplants, or sufferers from AIDS, EBV infection may be associated with lymphoproliferative disorders. This is especially so in children having liver transplants (Chapter 38) [4].

Hepatic histology

The changes are seen within 5 days and reach their peak between the 10th and 30th days.

The sinusoids and portal tracts are infiltrated with large, mononuclear cells (fig. 16.14). Polymorphonuclear leucocytes and lymphocytes increase, and the Kupffer cells proliferate. The appearances may resemble leukaemia. The lesions resemble those of early A, B or C viral hepatitis. The architecture of the liver is preserved.

Zone 3 focal necroses may be randomly distributed. There is no surrounding cellular reaction.

Later binucleate liver cells and mitoses are conspicuous. The regeneration is out of proportion to cell necrosis. After clinical recovery, abnormal cells disappear, although this may take as long as 8 months. Chronic hepatitis and cirrhosis are not sequelae.

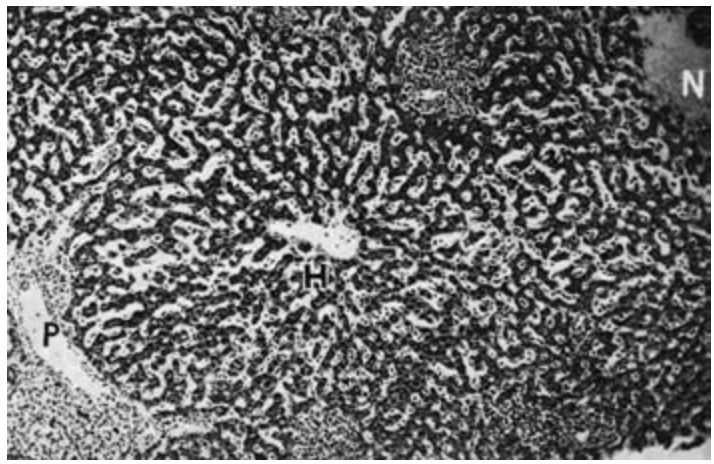


Fig. 16.14. Infectious mononucleosis. The sinusoids and portal tracts (P) are filled with mononuclear cells. One small local necrosis (N) is seen in the upper right-hand corner. H, central hepatic vein. (Best's carmine, ×70.)

Clinical features

Occasionally jaundice can be deep [1]. It is not due to large glands in the porta hepatis.

Persistent infection is a cause of chronic ill health.

Immune responses determine the clinical and pathological expression. Using monoclonal antibodies, direct hepatic viral infection has been shown.

Diagnosis

The serum albumin level may be slightly decreased and the serum globulin value slightly elevated.

Hyperbilirubinaemia is present in about one-half of patients. Serum transaminase values are raised to about 20 times the normal in 80% of patients. Values are usually less than those found in the early stages of an acute virus A, B or C hepatitis. In about one-third the serum alkaline phosphatase value is increased, often more so than that of bilirubin.

The monospot reaction is positive. The disease is diagnosed conclusively by an increase in serum IgM antibodies against EBV capsid antigens.

In the immunosuppressed, particularly with post-transplant lymphoproliferative disease, EBV proteins may be shown by immunofluorescence on liver biopsy material. PCR is used for DNA *in situ* hybridization in blood and tissues [2].

Distinction from viral hepatitis (table 16.4)

Although the diagnosis of viral hepatitis from infectious mononucleosis is usually easy, in an occasional patient with mild anicteric hepatitis or severe mononucleosis this may be impossible.

Table 16.4. Comparison of infectious mononucleosis and viral hepatitis

	Infectious mononucleosis	Viral hepatitis
Epidemic history	Suggestive	Suggestive
Onset		
Fever	+	+
Anorexia	–	+
Sore throat	+	–
Rash	+	Rare
Pruritus	–	+
Physical signs		
Lymphadenopathy	++	±
Jaundice	Mild, transient	Well developed, persisting
Liver	Enlarged; not usually tender	Enlarged and tender
Spleen	Enlarged and tender	Enlarged but not tender
Pale stools	–	+
Dark urine	±	++
Peripheral blood		
Leucocytes	Usually increased; characteristic cells	Decreased, with relative lymphocytosis
Monospot	Positive	Negative
IgM EBV	Present	Absent
HBsAg	Negative	Positive, type B
IgM anti-HAV	Negative	Positive, type A
Liver biopsy	Diffuse mononuclear infiltration; focal necroses	Zone 3 'spotty' necrosis; mononuclear infiltration

References

1 Fuhrman SA, Gill R, Horwitz CA *et al*. Marked hyperbilirubinemia in infectious mononucleosis. *Arch. Intern. Med*. 1987; **147**: 850.
2 Markin RS. Manifestations of Epstein–Barr virus-associated disorders in liver. *Liver* 1994; **14**: 1.
3 Papatheodoridis GV, Delladetsima JK, Kavallierou L *et al*. Fulminant hepatitis due to Epstein–Barr virus infection. *J. Hepatol*. 1995; **23**: 348.
4 Smets F, Bodeus M, Goubau P *et al*. Characteristics of Epstein–Barr virus primary infection in paediatric liver transplant recipients. *J. Hepatol*. 2000; **32**: 100.
5 Vento S, Guella L, Mirandola F *et al*. Epstein–Barr virus as a trigger for autoimmune hepatitis in susceptible individuals. *Lancet* 1995; **346**: 608.

Other viruses

All viruses may affect the liver in common with other organs. The histological changes are usually non-specific, consisting of fatty change, or focal necrosis and lymphocytic infiltration of the portal zones. Biochemical tests are usually unchanged or show mild rises in transaminases. Occasionally, the patient may be frankly icteric when the picture of type A, B or C hepatitis is closely simulated.

The upsurge of AIDS has increased the prevalence of hepatitis due to various unusual viruses. These frequently prove fatal (Chapter 29). They are also important in those receiving large doses of immunosuppressive drugs, such as liver and bone marrow recipients, or patients with reticulosis. They are seen in neonates (Chapter 26) and may follow a blood transfusion.

Cytomegalovirus

In neonates, cytomegalovirus is usually inapparent. Confirmed disease in early infancy is rare. Sometimes, however, in association with the respiratory distress syndrome, cytomegalovirus may cause a devastating fatal pneumonitis. In adults, the clinical picture can be very diverse.

Cytomegalovirus can cause a disease strongly resembling EBV-related mononucleosis. Patients usually lack pharyngitis and posterior cervical lymphadenopathy. Serum transaminase and alkaline phosphatase levels are increased and atypical lymphocytes are found in the peripheral blood. The monospot test is usually negative.

The picture may simulate type A, B or C hepatitis, having a similar onset but with failure of the pyrexia to subside with the onset of jaundice. Icterus lasts 2–3 weeks and even up to 3 months.

Occasionally, massive hepatic necrosis may be fatal.

Granulomatous hepatitis can develop in a previously normal adult with prolonged unexplained fever and without lymphadenopathy [1]. In these patients, liver biopsy shows non-caseating granulomas. The immunosuppressed show characteristic inclusions.

Cholangitis, papillary stenosis and sclerosing cholangitis can accompany cytomegalovirus infections in patients with AIDS (Chapter 29).

Cytomegalovirus infection is a rare cause of post-transfusion hepatitis.

Cytomegalovirus may cause disseminated disease, of which hepatitis is only a part, in the immunosuppressed, such as those with leukaemia.

Cytomegalovirus hepatitis is a real problem in adult and paediatric recipients of kidneys and, particularly, liver transplants [4]. The infection is usually a primary one, rather than reactivation, and the donor is cytomegalovirus antibody positive (Chapter 29).

Diagnosis is by isolation of virus from urine or saliva. Complement-fixing antibodies rise and cytomegalovirus IgM antibodies can be found. The virus cannot usually be shown in liver biopsy but direct hepatic involvement has been confirmed by demonstrating nuclear and cytoplasmic inclusions in hepatocytes [9].

Herpes simplex

Human herpes virus types I and II affect all humans at some time during their lives.

In *infants*, herpes hepatitis may be part of generalized herpetic disease.

In *adults*, disseminated herpes simplex is very rare. It can affect those with underlying diseases, e.g. ulcerative colitis [10], with AIDS, those receiving immunosuppressive treatment or having organ transplants. Fulminant hepatic failure can also affect the previously normal and immunocompetent [3]. It may complicate genital herpes [8] and be seen in pregnancy [5].

Herpetic mucocutaneous lesions are usually absent. The onset is with fever, prostration, marked elevation of transaminases and leucopenia. Jaundice is absent. Fulminant liver failure with fatal coagulopathy can develop.

Liver biopsy shows patchy areas of coagulative necrosis with surrounding hepatocytes containing viral inclusions (fig. 16.15) [3]. The virus can be shown by electron microscopy. It can be cultured from the liver and, using immunoperoxidase staining, may be shown in affected hepatocytes.

Acyclovir or gancyclovir is curative.

Miscellaneous

Coxsackie virus B may cause hepatitis in the adult. Coxsackie virus, group A, type IV, has been isolated from the plasma of a child with hepatitis, and complement-fixing antibodies appeared in the serum during convalescence.

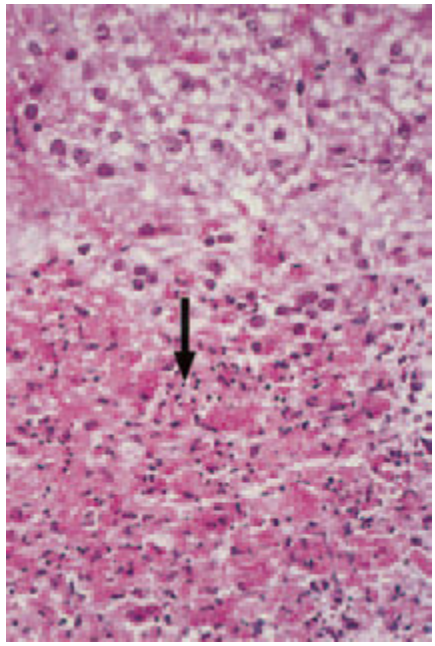


Fig. 16.15. Herpes virus II hepatitis. An area of coagulative necrosis can be seen (arrow). Adjacent liver cells were shown to have nuclear viral inclusions. (H & E,×100.)

Varicella and *varicella-zoster* may be complicated by hepatitis in both normal and immunologically compromised individuals [6]. In children, the picture must be distinguished from Reye's syndrome [6].

Measles is affecting an older age group. Eighty per cent of adult sufferers have liver involvement; 5% becoming jaundiced [2]. It is most frequent in the seriously ill. Resolution is complete.

Rubella can be associated with serum transaminase elevations and may be mistakenly diagnosed as hepatitis C [11].

Paramyxoma viruses. Severe sporadic hepatitis with histologically large syncytial giant hepatocytes may be related to the paramyxoma viruses [7]. Virological confirmation and classification is awaited.

References

1 Clarke J, Craig RM, Saffro R *et al*. Cytomegalovirus granulomatous hepatitis. *Am. J. Med*. 1979; **66**: 264.

2 Gavish D, Kleinman Y, Morag A *et al*. Hepatitis and jaundice associated with measles in young adults. *Arch. Intern. Med*. 1983; **13**: 674.

3 Goodman ZD, Ishak KG, Sesterhenn IA *et al*. Herpes simplex hepatitis in apparently immunocompetent adults. *Am. J. Clin. Pathol*. 1986; **85**: 694.

4 King SM, Petric M, Superina R *et al*. Cytomegalovirus infections in paediatric liver transplantation. *Am. J. Dis. Child*. 1990; **144**: 1307.

5 Klein NA, Mabie WC, Shaver DC *et al*. Herpes simplex virus hepatitis in pregnancy. Two patients successfully treated with acyclovir. *Gastroenterology* 1991; **100**: 239.

6 Myers MG. Hepatic cellular injury during varicella. *Arch. Dis. Child*. 1982; **57**: 317.

7 Phillips MJ, Blendis LM, Poucell S *et al*. Syncytial giant-cell hepatitis. Sporadic hepatitis with distinctive pathological features, a severe clinical course, and paramyxoviral features. *N. Engl. J. Med*. 1991; **324**: 455.

8 Rubin MH, Ward DM, Painter J. Fulminant hepatic failure caused by genital herpes in a healthy person. *JAMA* 1985; **253**: 1299.

9 Sacks SL, Freeman HJ. Cytomegalovirus hepatitis: evidence for direct hepatic viral infection using monoclonal antibodies. *Gastroenterology* 1984; **86**: 346.

10 Shlien RD, Meyers S, Lee JA *et al*. Fulminant herpes simplex hepatitis in a patient with ulcerative colitis. *Gut* 1988; **29**: 257.

11 Zeldis JB, Miller JG, Dienstag JL. Hepatitis in an adult with rubella. *Am. J. Med*. 1985; **79**: 515.

Hepatitis due to exotic viruses

These very dangerous viruses have the liver as the primary target [2]. They include Marburg, Lassa and Ebola viruses. They are becoming increasingly important as man encroaches into underdeveloped areas, as ecology changes and as a source of infection to medical or laboratory staff dealing with patients or their blood.

Lassa fever is due to an arenavirus transmitted from rodents to man or from man to man. It is largely found in West Africa. The case fatality rate is 36–67%. Diagnosis is made by demonstrating virus in the blood during the first few days and by IgM antibodies from the fifth day. It has been successfully treated with ribavirin [3].

The liver shows eosinophilic necrosis of individual hepatocytes with little inflammation. Bridging necrosis is usual.

Marburg virus disease is due to an RNA virus transmitted by Vervet monkeys. In 1967, an outbreak of this disease occurred in persons in contact with monkeys in experimental institutes in Germany [4]. Further patients have been reported from South Africa and Kenya [5].

After an incubation period of 4–7 days the patients present with headache, pyrexia, vomiting, a characteristic rash, a haemorrhagic diathesis and central nervous system involvement. Serum transaminase levels are very high.

Liver pathology shows single-cell acidophilic necrosis and Kupffer cell hyperactivity. This is followed by eccentric and radial extension of the necrosis, cytoplasmic inclusions and portal zone cellularity. Steatosis is noted in the severely affected. The virus can persist in the body for 2–3 months after initial infection.

Ebola virus infection resembles Marburg in clinical course, hepatic histology and electron microscopy [1]. It has been reported from Zaïre and the Sudan and has been transmitted to biologists working with it.

Treatment

There is no specific treatment for these exotic virus infections. Symptomatic measures are used and very strict precautions are necessary to avoid spread to contacts.

References

1 Ellis DS, Simpson DIH, Francis DP *et al*. Ultra-structure of Ebola virus particles in human liver. *J. Clin. Pathol*. 1978; **31**: 201.
2 Howard CR, Ellis DS, Simpson DIH. Exotic viruses and the liver. *Semin. Liver Dis*. 1984; **4**: 361.
3 McCormick JB, King IJ, Webb PA *et al*. Lassa fever. Effective therapy with ribavirin. *N. Engl. J. Med*. 1986; **314**: 20.
4 Martini GA, Knauff HG, Schmidt HA *et al*. Uber eine bisher unbekannte von Affen eingeschleppte Infektions-krankheit: Marburg-Virus-Krankheit. *Dtsch. Med. Wschr*. 1968; **57**: 559.
5 Smith DH, Johnson BK, Isaacson M. Marburg-virus disease in Kenya. *Lancet* 1982; **i**: 816.

Chapter 17
Hepatitis B Virus and Hepatitis Delta Virus

Hepatitis B virus (HBV)

In 1965, Blumberg *et al*. in Philadelphia found an antibody in two multiply transfused haemophiliac patients which reacted with an antigen in a single serum in their panel which came from an Australian Aborigine [8]. Later the antigen was found in patients with viral hepatitis. Because of its discovery in an aboriginal serum, the antigen was called Australia Antigen. In 1977, Blumberg was awarded the Nobel prize for his discovery. Australia Antigen is now known to be the surface of the hepatitis B virion and is termed hepatitis B surface antigen (HBsAg).

Over 2 billion people alive today have been infected with HBV and over 350 million of them are chronically infected carriers who have no significant liver disease. However, the majority will progress to chronic hepatitis, cirrhosis and hepato-cellular cancer. The worldwide prevalence of HBV infection is falling (fig. 17.1). This is related not only to vaccine, but to better hygiene and to the AIDS campaign which addresses the dangers of promiscuity and of shared syringes and needles (fig. 17.1) [27]. The World Health Organization (WHO) believe that by 2001 there will be an 80% fall in carrier rate, but the reservoir of those patients already infected will still have to be treated.

The virus for hepatitis B is a small encapsulated DNA virus (fig. 17.2). The core is formed in the nucleus and the surface particles in the cytoplasm. The core contains a DNA polymerase. DNA structure is double-stranded and circular with a single-stranded gap of 600–2100 nucleotides. The DNA polymerase reaction appears to repair the gap. The core contains a core antigen, and another antigen called 'e' (HBe) is a protein subunit of the core. HBV sequences are frequently integrated with hepato-cellular DNA (fig. 17.3). The double-stranded DNA genome has four open reading frames (ORFs) (fig. 17.4). The S gene codes for HBsAg. The pre-S1 domain is involved in viral recognition by

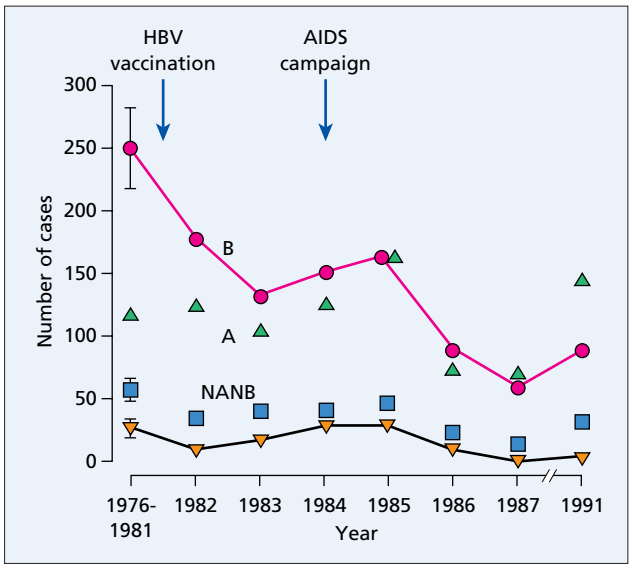


Fig. 17.1. Occurrence of acute hepatitis B in Zurich (1.1 million inhabitants) from 1976 to 1991. ●, hepatitis B; ▲, hepatitis A; ■, non-A, non-B hepatitis; ▼, unclassified. (Modified from [27].)

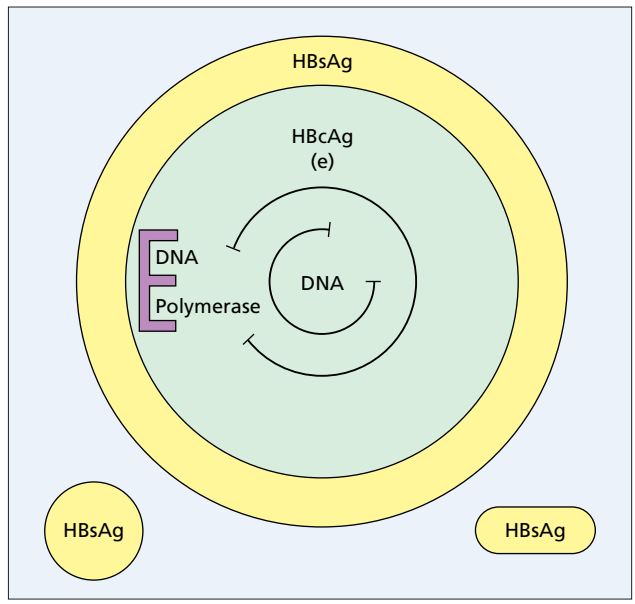


Fig. 17.2. Diagram of the virion of hepatitis B (HBV: Dane particle). The core contains DNA polymerase, double-stranded DNA, core antigen and 'e' antigen. The surface consists of HBsAg. Spheres and tubules of HBsAg are free in the serum.

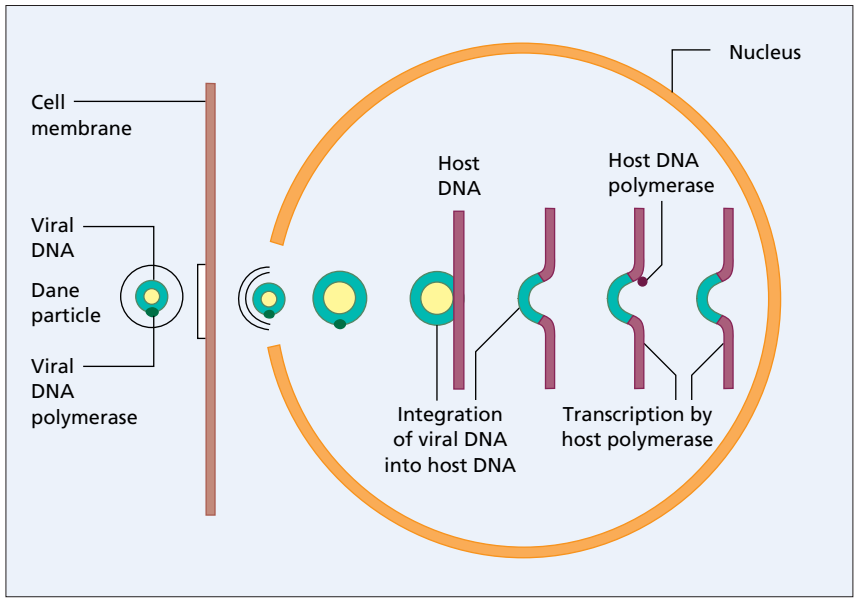


Fig. 17.3. The hepatitis B virion enters the hepatocyte and the core reaches the nucleus. At first the virus replicates using its own viral DNA. Then the viral DNA integrates with host DNA and the host DNA polymerase transcribes for the virus.

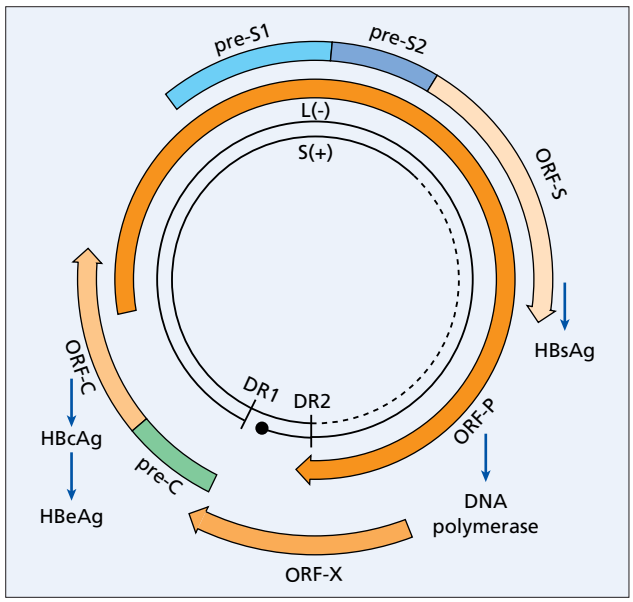


Fig. 17.4. Organization of the genome of HBV showing the four open reading frames (ORF), polymerase (P), surface antigen (S), core antigen and X, and the pre-S1 and pre-S2 regions.

hepatocyte receptors. This effect may be important in the development of chronic hepatitis B (pre-S2 is similar). The C gene codes for a hepatitis B core antigen (HBcAg). The P gene codes for putative DNA polymerase. The X gene codes for a protein with a transcriptional transactivating function, perhaps related to viral replication [29].

A similar disease affects woodchucks, ground squirrels and Peking ducks. The whole group has been termed *hepadnaviruses*.

Sub-types of HBsAg

HBsAg particles have surfaces that are antigenically complex and this has led to the recognition of antigenic determinants. A common determinant is 'a'. The other sub-determinants are designated 'd', 'y', 'w' and 'r'. The four major determinants are therefore adw, adr, ayw and ayr. They breed true and are very helpful epidemiologically.

HBV mutants

HBV, a DNA virus, uses RNA and a reverse transcriptase for its replication and hence is associated with mutations in the various reading frames (fig. 17.5). Nucleotide substitutions, deletions, duplications, insertions and rearrangements may have no consequence, may impair viral replication, may change host susceptibility or may lead to viral escape from host immune attack. The effect is very variable, possibly related to the immune status of the patient or to the effects of vaccination or therapy.

Guanosine to adenine mutation in the *pre-core region* prevents HBe antigen (HBeAg) secretion. The patient is HBV DNA positive, but 'e' antigen negative and usually suffers from severe active disease [1, 11, 12]. There are great geographical differences in the prevalence of this pre-core mutation and in its association with fulminant disease.

Mutation in the *surface region* has been associated with infants born to carrier mothers becoming HBsAg positive, despite apparently successful vaccination. There is substitution of arginine for glycine at amino acid 145, the 'a' determinant to which the vaccine promotes anti-

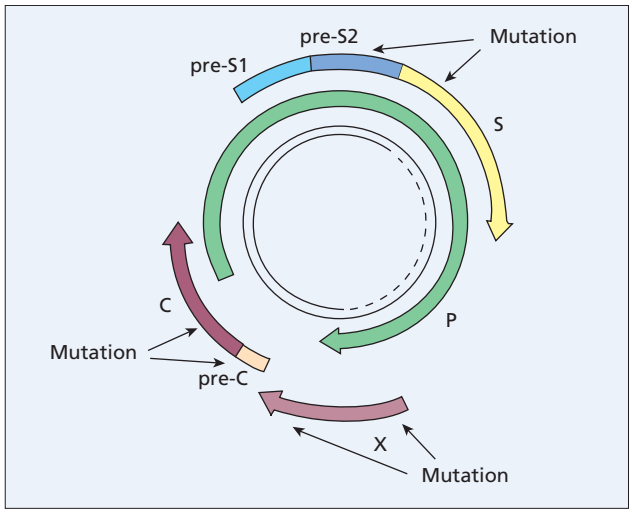


Fig. 17.5. The site of HBV mutations.

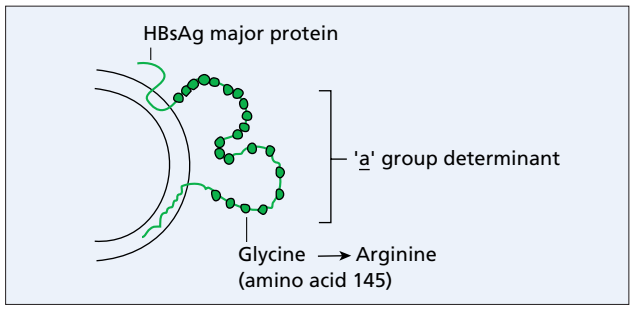


Fig. 17.6. HBV: vaccine-induced escape mutant.

bodies (fig. 17.6). *X gene mutants* are described, but their significance is not clearly defined [7].

YMDD mutants of the *polymerase gene* account for some cases of lamivudine resistance.

Mutants may determine the clinical course and by conferring an advantage favour fulminant disease. Serum HBeAg becomes less useful as an indicator of infection. HBV vaccines may have to change so that mutants are represented in them.

Mechanism of hepato-toxicity

The virus is not directly cytopathic and lysis of infected hepatocytes, probably by apoptosis, depends on the immune response of the host [23]. Viral persistence is probably related to specific failure of cytotoxic T-lymphocytes (CTL) to recognize HBV antigen (fig. 17.7) [38]. Hepato-cellular injury begins with antigen recognition by HBV-specific CTLs. Recruitment of host-derived antigen non-specific inflammatory cells—including macrophages, neutrophils and cells—by the CTLs leads to the inflammation and a rise in serum aminotransferase.

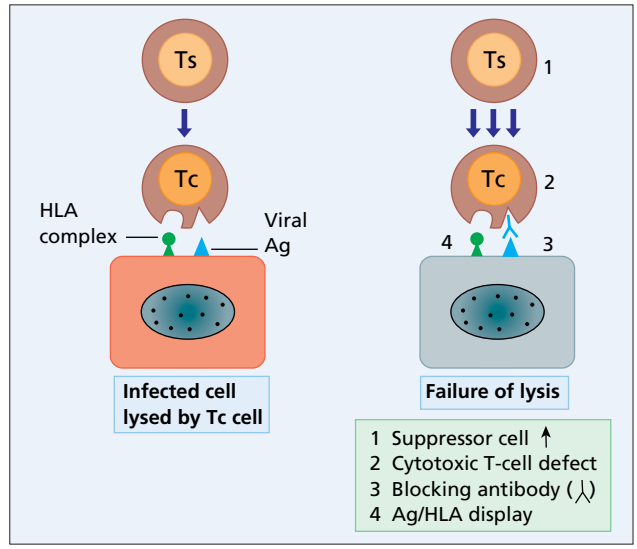


Fig. 17.7. T-lymphocyte lysis of infected hepatocytes and mechanisms of failure of lysis in chronic hepatitis. Tc, cytotoxic cell; Ts, suppressor cell.

During acute self-limited infection, pathology is mild to moderate with eventual termination of viral infection and resolution of hepatitis. In selected cases, the non-specific inflammation is so augmented that massive hepato-cellular injury and fulminant hepatitis results.

If the immunological response is particularly poor, little or no hepatic damage ensues but the virus continues to proliferate and chronic hepatitis results. If the immunological response is markedly reduced, little liver damage ensues; the liver contains enormous amounts of virus in the presence of normal liver function. Such a patient would be an asymptomatic 'healthy' carrier. Reduced humoral and cell-based immunity is particularly important in patients with leukaemia, liver failure or organ transplant, in those receiving immunosuppressive treatment, in homosexual men, in patients with AIDS and in neonates.

Some patients with adult-acquired hepatitis B show defective expression of HLA class I antigens on the hepatocyte membrane [63].

Antigen-specific activation of CTLs results in release of a variety of lymphokines/cytokines, which can recruit and activate antigen non-specific effector cells leading to hepato-cellular injury. These cytokines may be directly cytopathic, but the predominant mechanism is non-cytopathic.

Acute hepatitis B

Stages of HBV infection (fig. 17.8, table 17.1)

Exposure to HBV can have varying results (see fig. 17.11). The acute attack varies from anicteric to fulminant.

Table 17.1. Stages of hepatitis B viral infection

Age	Stage	HBV DNA	AST	Biopsy
Neonate	Immune tolerance	+++	Normal	CH (mild)
10–20 years	Immune clearance	++	+++	CH (severe)
Over 35 years	Quiescent	Low	Normal	Cirrhosis HCC

AST, aspartate transaminase; CH, chronic hepatitis; HCC, hepato-cellular carcinoma.

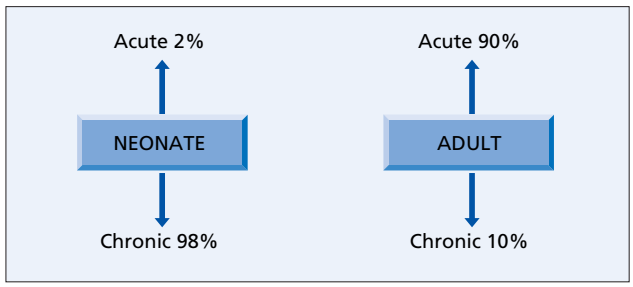


Fig. 17.8. The course of acute hepatitis B in the neonate and adult.

Previously normal people usually clear the antigen from the serum within about 4–6 months. Development of neutralizing antibodies is crucial for viral clearance. The more florid and acute the original attack, the less likely are chronic sequelae.

In the neonate, *immune tolerance* allows large amounts of circulating HBV DNA and a positive HBeAg but transaminases are normal and liver biopsy shows a mild chronic hepatitis. Chronicity develops in 98% compared with about 10% in the adult (fig. 17.8).

In the *child* and *young adult*, the stage is *immune clearance*. Circulating HBV DNA falls, but HBeAg remains positive. HBcAg and possibly other viral antigens are displayed on the hepatocyte membrane. The patient is highly infectious and there is rapid progression of hepatic inflammation. Finally, in the *older patient*, the disease becomes *quiescent*, circulating HBV DNA is low, serum HBeAg is negative and serum HBe antibody (HBeAb) is positive.

In the *later stages* hepatocytes secrete HBsAg but not core markers. Serum transaminases are normal or modestly increased and liver biopsy histology shows an inactive chronic hepatitis, cirrhosis or carcinoma. However, in some patients, viral replication is undoubtedly continuing as HBV DNA can be detected in the hepatocyte nuclei in an integrated form. There are considerable differences in the time intervals between these various stages. This varies worldwide. Asians are particularly likely to have a prolonged stage of viraemia with immunological tolerance, a positive HBeAg and high HBV DNA levels. Europeans typically have a long asymptomatic period, where HBeAg is negative, biochemical tests are normal and the risk of hepato-cellular cancer may be reduced.

Table 17.2. Hepatitis B and delta: significance of serological markers

Marker	Significance
HBsAg	Acute or chronic hepatitis B carriage
IgM anti-HBc	Acute hepatitis B (high titre) Chronic hepatitis B (low titre)
IgG anti-HBc	Past exposure to hepatitis B (with negative HBsAg) Chronic hepatitis B (with positive HBsAg)
Anti-HBs	Immune to hepatitis B
HBeAg	Acute hepatitis B. Persistence means continued infectious state
Anti-HBe	Convalescence or continued infectious state
HBV DNA	Continued infectious state
Delta	
IgM anti-delta	Acute or chronic infection with delta agent
IgG anti-delta	Chronic delta infection (high titre with positive IgM anti-delta) Past delta infection (low titre with negative IgM anti-delta)

Serological diagnosis (table 17.2)

HBsAg appears in the blood about 6 weeks after infection and has usually disappeared by 3 months after the clinical illness (fig. 17.9). Persistence for more than 6 months implies the development of a carrier state.

Anti-HBs appears late, some 3 months after the onset of symptoms, and persists. Anti-HBs levels are rarely high and 10–15% of patients with acute type B hepatitis never develop the antibody. Anti-HBs accounts for recovery and immunity. In the past, HBsAg and HBsAb were believed to be mutually exclusive. However, as many as one-third of carriers of HBsAg also have HBsAb. The mechanism is uncertain, but it has been attributed to simultaneous infection with different subtypes.

HBeAg correlates with ongoing viral synthesis and with infectivity. It is transiently present during the acute attack. It is present for a shorter time than HBsAg. Persistence for more than 10 weeks strongly suggests the development of chronicity.

Anti-HBe is a marker of relatively low infectivity. The appearance of anti-HBe is strong evidence that the patient will recover completely.

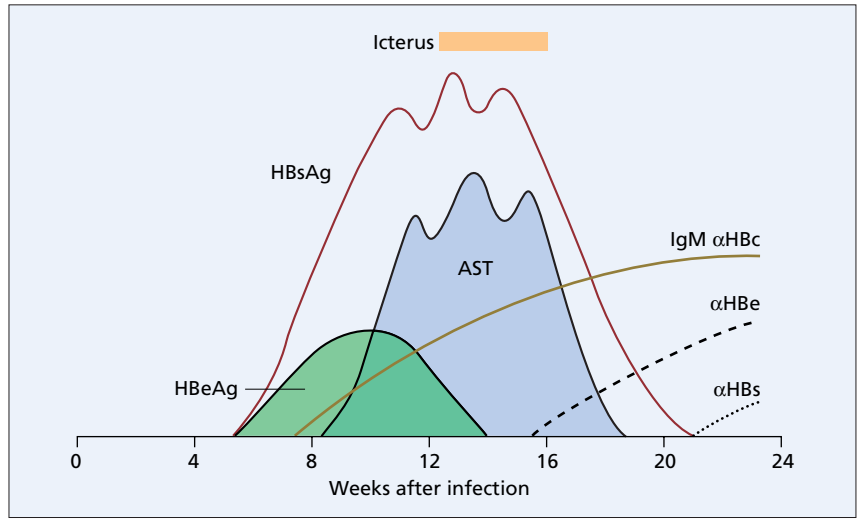


Fig. 17.9. The course of acute type B hepatitis. HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B 'e' antigen; IgM αHBc, IgM antibody against hepatitis B core antigen; AST, aspartate transaminase; αHBe, antibody against hepatitis 'e' antigen; αHBs, antibody against hepatitis B surface antigen.

HBcAg cannot be detected in circulating blood, but anti-HBc can. High titres of IgM anti-HBc mark present acute viral hepatitis. This antibody is detected after HBsAg has been cleared from the serum. This is true of 5–6% of cases with acute hepatitis B and is encountered particularly in fulminant hepatitis. It is also used in determining whether an acute attack of hepatitis is due to HBV or to superinfection with another virus. Persistence of IgM anti-HBc implies ongoing HBV-related chronic disease, usually chronic hepatitis. Lower titres of IgG anti-HBc with anti-HBs mark HBV infection in the remote past. High titres of IgG anti-HBc without anti-HBs indicate persistence of viral infection [34]. The significance of high titres of IgG anti-HBc without anti-HBs is uncertain. It may indicate the last phase of an acute attack. It may be due to an inability to produce HBsAb. Some have immune complex-associated HBsAg and HBV DNA may be positive [57]. Some still have ongoing HBV infection.

HBV DNA is the most sensitive index of viral replication. It is detected by PCR. Using PCR, HBV DNA can be found in serum and liver after the loss of HBsAg, particularly in those receiving antiviral treatment [48]. HBV DNA in serum detected by PCR is a good marker of the level of viraemia, can be correlated with serum transaminase levels and parallels the presence of HBsAg in serum [3]. Patients with an HBV pre-core mutant are HBeAg negative and HBV DNA positive.

HBV in hepatocytes

HBsAg may be stained orange with orcein (fig. 17.10) in the hepatocytes of carriers and chronic hepatitis patients, but not in those in the acute stage. HBcAg is variably present in the liver. It may be diffuse in asymptomatic carriers, the inactive and immunosuppressed, and focal

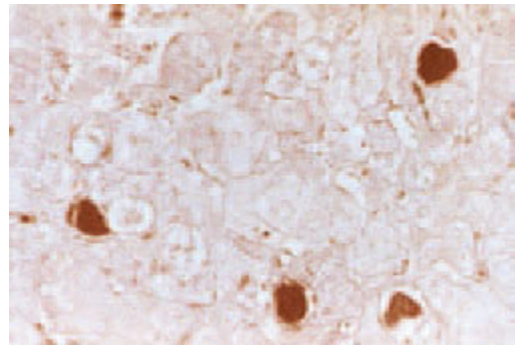


Fig. 17.10. Orcein staining shows liver cells containing HBsAg (brown).

in those with much hepatic inflammation or with later disease.

HBV DNA can be demonstrated in formol-fixed paraffin-embedded liver tissue by PCR [61].

HBeAg may be demonstrated by immune electron microscopy in endoplasmic reticulum and cytosol [73].

Infectivity of body fluids

HBV-containing blood or any body fluid contaminated with blood is infectious. Mere positivity of a fluid for HBsAg is not synonymous with infectivity. However, saliva, urine and seminal fluid from HBeAg-positive males have shown the presence of HBV DNA.

Peripheral blood mononuclear cells can contain HBV DNA [4]. At autopsy, replicative viral intermediates have been found in lymph nodes, spleen, kidney, pancreas, brain and some endocrine tissues [74]. This extra-hepatic proliferation is particularly important in hepatitis B pos-

Table 17.3. Groups in which acute and chronic type B hepatitis should be suspected

Immigrants from Mediterranean countries, Africa or the Far East
Drug abusers
Homosexual men
Neonates of HBsAg-positive mothers
Hospital staff
Patients with
renal failure
reticuloses
cancer
organ transplants
Staff and patients of hospitals for the mentally retarded
Post-transfusion

itive patients receiving hepatic transplants and accounts for re-infection of the graft.

Epidemiology (table 17.3)

The disease is transmitted parenterally or by intimate, often sexual, contact. The carrier rate of HBsAg varies worldwide from 0.1 to 0.2% in Britain, the USA and Scandinavia, to more than 3% in Greece and southern Italy and even up to 10–15% in Africa and the Far East. If anti-HBs is measured, the rate of exposure to hepatitis B in any community is much higher. Carriage of HBsAg is even higher in some isolated communities: 45% in Alaskan Eskimos [47] and 85% in Australian Aborigines.

In high carriage rate areas, infection is acquired by passage from the mother to the neonate. The infection is usually not via the umbilical vein, but from the mother at the time of birth and during close contact afterwards. The chance of transmission increases as term approaches and is greater from HBeAg-positive than HBeAg-negative mothers. Antigenaemia develops in the baby within 2 months of birth and tends to persist [9].

In high endemic areas, such as Africa, Greece and the Far East, the transmission is in childhood and probably horizontal through kissing, shared utensils such as toothbrushes and razors, and injections [49]. Contact in pre-school day-care centres is possible. Sexual contacts in the family are at risk.

Infection among homosexual men is related to duration of homosexual activity, number of sexual contacts and anal contact.

Blood-sucking arthropods such as mosquitoes or bed bugs may be important vectors, particularly in the tropics, although insecticide spraying of dwellings has had no effect on HBV infection [50].

The MHC class II allele DRB1*1302 is associated with protection against persistent HBV in children and adults in the Gambia [63].

Blood transfusion continues to cause hepatitis B in countries where donor blood is not screened. Transmission is more likely with blood from paid donors than from volunteers.

Opportunities for parenteral infection exist in the use of instruments for dental treatment, ear piercing and manicures, neurological examination, prophylactic inoculations, subcutaneous injections, acupuncture, tattooing and autohaemotherapy [69].

Parenteral drug abusers develop hepatitis from using shared, unsterile equipment. The mortality may be very high in this group. Multiple attacks are seen and chronicity is frequent. Liver biopsy may show, in addition to acute or chronic hepatitis, foreign material, such as chalk, injected with illicit drugs.

Hospital staff in contact with patients, and especially patients' blood, usually have a higher carrier rate than the general community. This applies particularly to staff on renal dialysis or oncology units. Patients are immunosuppressed and, on contracting the disease, become chronic carriers. The patient's attendant is infected from contact with blood parenterally, such as from pricking or through skin abrasions. Surgeons and dentists are particularly at risk in operating on HBsAg-positive patients with a positive HBeAg. Holes in gloves and cuts on hands are common. Wire sutures may be a particular hazard in penetrating the skin.

Spread from a health-care worker is usually through a surgeon performing complex invasive procedures [70]. In the UK, proof of immunity (through vaccination or past infection) is required of all surgeons and other medical staff performing invasive procedures. Students have to show certificates of immunization and immunity on registration for a medical or dental course.

Use of standard cleansing procedures means that HBV infection is not spread by endoscopes.

Institutionalized mentally retarded children (especially with Down's syndrome) and their attendants have a high carrier rate [35].

Clinical course (fig. 17.11)

The course may be anicteric. Sub-clinical episodes are extremely frequent. The non-icteric case is more liable to become chronic than the icteric one.

The usual acute clinical attack, diagnosed in the adult, tends to be more severe than for HAV or HCV infections. The overall picture is, however, similar. The self-limited, benign, icteric disease usually lasts less than 4 months. Jaundice rarely exceeds 4 weeks. Occasionally, a prolonged benign course is marked by increased serum transaminase values for more than 100 days. Relapses are rare. Cholestatic hepatitis with prolonged deep jaundice is unusual.

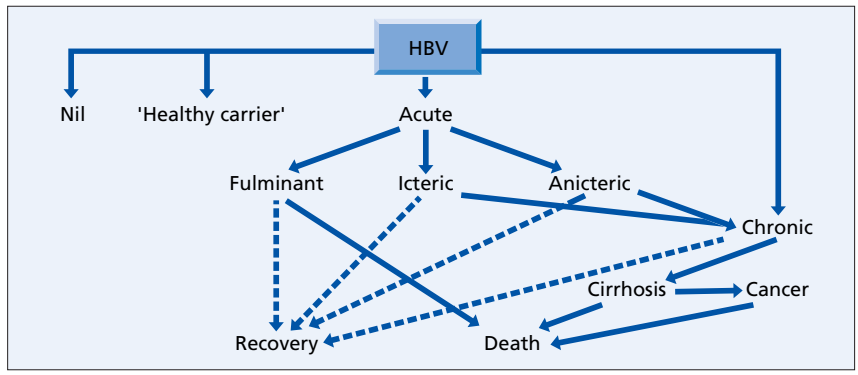


Fig. 17.11. The effect of exposure to HBV.

There may be features suggesting immune complex disease. This is shown in the prodromal period by a serum sickness-like syndrome. This develops about a week before jaundice. It can be associated with an icteric or an anicteric attack. The syndrome has also been described with chronic hepatitis B. Fever is usual. The skin lesion is urticarial, and rarely, in children, a papular acrodermatitis develops. The arthralgia is symmetrical, non-migratory and affects small joints. Serum rheumatoid factor is negative. It is usually transitory but can persist.

A fulminant course of hepatitis B in the first 4 weeks is related to an enhanced immune response with more rapid clearing of the virus. Antibodies to surface and 'e' antigen increase, and multiplication of the virus ceases. In fulminant hepatitis B, the surface antigen may be in low titre or undetectable. The diagnosis may be made only by finding serum IgM anti-HBc.

Another viral hepatitis, superimposed on the symptomless HBV carrier, may precipitate a fulminant course. The new agent may be HAV, HDV or HCV.

Sub-acute hepatic necrosis is marked by increasingly severe disease evolving over 1–3 months.

Extra-hepatic associations

These are often associated with circulating immune complexes containing HBsAg. The accompanying liver disease is usually mild. Acute and chronic type B hepatitis can develop in patients with agammaglobulinaemia.

Polyarteritis. This involves largely medium and small arteries and appears early in the course of the disease. Immune complexes containing HBsAg are found in the vascular lesions and their blood levels correlate with disease activity. Polyarteritis is a rare complication of hepatitis B [46]. Plasmapheresis and adenine arabinoside have been used for treatment [65].

Glomerulonephritis. This has been associated with HBV infection, largely in children [43]. Liver disease is minimal. The patients are usually HBsAg positive. Immune complexes of HBsAg and HBsAb, HBcAg and anti-HBc or HBeAg and anti-HBe are found in glomerular basement membranes [66]. In children, interferon treatment may lead to a remission. Remission may precede HBeAg seroconversion to anti-HBe. In children, the glomerulonephritis usually resolves spontaneously in 6 months to 2 years. In adults the disease is slowly but relentlessly progressive in one-third and the response to interferon is disappointing [37].

Essential mixed cryoglobulinaemia is a rare association of HBV infection although very frequent in HCV (Chapter 18).

The *Guillain–Barré syndrome* has been reported with HBsAg-containing immune complexes in serum and cerebrospinal fluid [55].

HBV carriers

Approximately 10% of patients contracting hepatitis B as adults and 98% of those infected as neonates will not clear HBsAg from the serum within 6 months (see fig. 17.8). Such patients become carriers and this is likely to persist. Reversion to a negative HBsAg is rare, but may develop in old age. Males are six times more likely to become carriers than females.

The dilemma of a person, such as a hospital worker, carrying the antigen and coming from an area where it is prevalent is a very difficult one. Hospital staff who develop HBsAg-positive hepatitis and clear the antigen from the blood are immune to type B hepatitis. If they become carriers, the position is difficult.

'Healthy' carriers may show changes on liver biopsy ranging from non-specific minimal abnormalities through to chronic hepatitis and cirrhosis. The extent of the changes is not reflected by serum biochemical tests and may only be revealed by liver biopsy. The carrier presenting by chance is likely to have minor hepatic changes compared to the patient presenting to a gastroenterology department where more serious liver disease is probable. In a survey of patients found to be HBsAg positive at blood donation, 95% had near normal

Table 17.4. Immunoprophylaxis of viral hepatitis B

Type	Immunoglobulin	Indication	Regime
B (adults)	HBIG	Exposure to HBsAg-positive blood Sexual consorts	0.06 ml/kg, as soon as possible, combined with first dose of vaccine*
B (neonates)	HBIG	HBsAg-positive mother	0.5 ml, as soon as possible, combined with first dose of vaccine†

* Full course of vaccine given if subject is anti-HBc negative.
† Full course of vaccine given.

liver biopsies and only 1.6% proceeded to chronic hepatitis or cirrhosis [22].

Chronic organic sequelae

Exposure to HBV can have difficult results (fig. 17.11). Some patients are immune and have no clinical attack; they presumably have anti-HBs. In others, an acute attack develops, varying from anicteric to fulminant. Previously normal people usually clear the antigen from the serum within about 4–6 weeks from the onset of symptoms. Chronic liver disease is associated with persistent antigenaemia. In general, the more florid and acute the original attack, the less likely the chronic sequelae.

If the patient survives a fulminant attack of viral hepatitis, ultimate recovery is complete without the development of chronic disease. Chronicity is more likely in those with immunological incompetence such as neonates, homosexual men, patients with AIDS, leukaemia and cancer, renal failure or those receiving immunosuppressive treatment.

Prevention

Hepatitis B immunoglobulin (HBIG)

HBIG is a hyperimmune serum globulin with a high antibody titre. It is effective for passive immunization if given prophylactically or within hours of infection (table 17.4) [60]. Hepatitis vaccine should always be given with HBIG, particularly if the subject is at risk of re-infection. It is indicated for sexual contacts of acute sufferers, babies born to HBsAg-positive mothers and victims of parenteral exposure (needle stick) to HBsAg-positive blood (tables 17.5, 17.6).

Repeated HBIG injections are being used to prevent re-infection of a donor liver inserted into an HBV DNA positive patient (Chapter 38).

HBV vaccines

Available vaccines are prepared from the non-infectious outer surface of the virus HBsAg. The plasma derived and the recombinant are equally effective and safe.

Table 17.5. Indication for hepatitis vaccination

Surgical and dental staff including medical students
Hospital and laboratory staff in contact with blood
Patients and staff in departments of oncology and haematology, kidney, mental subnormality and liver disease
Mental subnormality
Accidental exposure to HBsAg-positive blood
Close family and sexual contacts of HBsAg-positive carriers
Babies born to HBsAg-positive mothers
Children as part of 'Expanded Program on Immunization' (EPI)
Drug abusers
Homosexually active men
Travellers to high-risk areas

Table 17.6. Prophylaxis of persons accidentally exposed to possibly infectious blood

- **Check** donor blood for HBsAg; victim's blood for HBsAg and HBcAb
- **Give at once** 0.06 ml/kg HBIG plus first dose of hepatitis B vaccine

	HBsAg	HBcAb	Further action to victim
Victim	–ve	+ve	None: immune
Donor	+ve		Continue vaccine course
	–ve		None or continue vaccine course if victim is at risk of further hepatitis B exposure

Hepatitis B vaccines are effective in preventing hepatitis B in promiscuous homosexual men (fig. 17.12) [62], haemodialysis patients, Down's syndrome and other mentally retarded patients, health-care workers, babies born to HBsAg-positive mothers' and those not already immune in Alaska [47]. In Gambia, vaccination of infants was 84% effective against HBV infection and 94% effective against chronic carriage [71]. A 12-year follow-up of infants vaccinated in Senegal showed that 81% who received a booster at school age had anti-HBs. The protective efficacy of the vaccine was 88% [18].

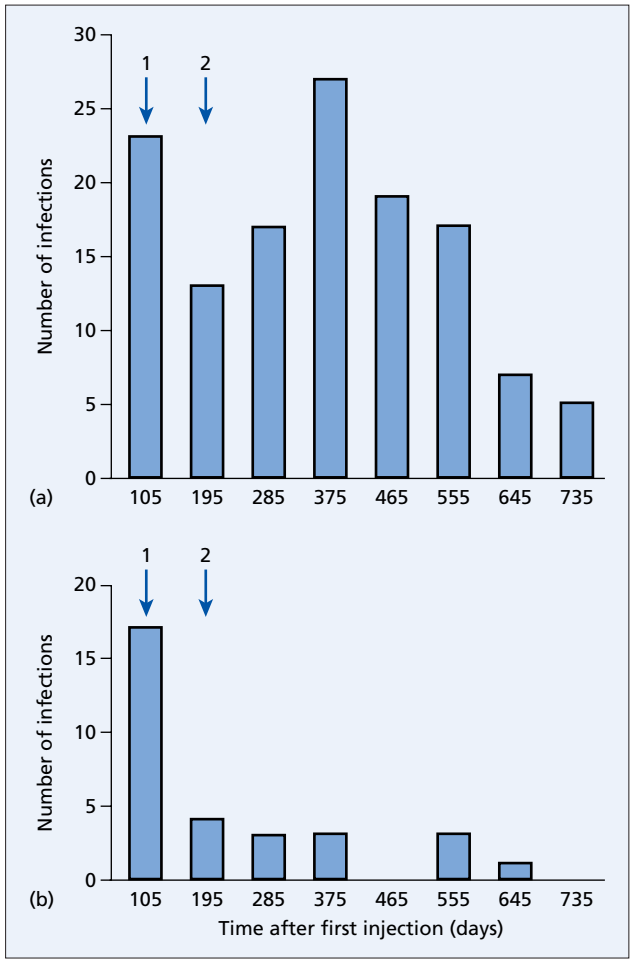


Fig. 17.12. Efficacy of hepatitis B vaccine. Results of a double-blind trial of the efficacy of hepatitis B vaccine in 1083 homosexual men. Distribution of infections in recipients of (a) placebo and (b) vaccine over 735 days. Arrows show time of first and second injections. (Modified from [62].)

In healthy individuals the recombinant vaccine is given in a dose of 10 µg (1 ml) intramuscularly, repeated at 1 month with a booster at 6 months. This induces sufficient antibody response in at least 94% of individuals. It is given intramuscularly into the arm.

Pre-testing. Vaccination is unnecessary if the person has a positive HBsAb or HBcAb.

The cost-effectiveness of pre-testing to save vaccine depends on the prevalence of serum B markers in a community.

The finding of an isolated serum anti-HBs does not necessarily mean immunity to hepatitis B. A positive serum anti-HBc is preferable as this detects infected as well as immune persons.

Duration of protection. Protection probably persists after the anti-HBs response has declined to undetectable levels. Immunological memory provides continued protection [64]. However, a booster should be considered at 5–7 years after the initial course if the subject is still being exposed to hepatitis B [24]. Antibody levels at the time of the booster dose may give a good indication of a duration of adequate antibody titres.

Table 17.7. Failure of antibody response to hepatitis B vaccine

Age > 50 years
Underlying disease
HIV positive
Genetics (HLA-B8)
Buttock injection
Frozen vaccine
Unknown

Antibody response

The long-term protection depends on the antibody response, which is 85–100% in healthy young subjects. Anti-HBs should be measured 1–3 months after completion of the basic course of vaccine.

Non-responders have peak anti-HBs levels of <10 iu/l and lack protection.

Low responders have peak anti-HBs levels of 10–100 iu/l and generally lack detectable anti-HBs levels within about 5–7 years. They may respond to a further booster of double the dose of vaccine.

Good responders have peak anti-HBs >100 iu/l and usually have long-term immunity.

Failure to develop adequate antibodies may be related to freezing the vaccine or giving it into the buttock, rather than the deltoid region. A poor antibody response is seen in the aged and in the immunocompromised, including HIV-positive persons (table 17.7). They should be given doses of 20 µg.

Approximately 5–10% of normal persons have an absent or poor antibody responses. Some may respond to a booster.

Indications for vaccination (see table 17.5)

The need for vaccination depends on the chance of being exposed to hepatitis B [52]. Vaccination is mandatory for health-care staff in close contact with hepatitis B patients, particularly those working on renal dialysis units, liver units, haemophilia and oncology units, genitourinary departments treating homosexual men or those working in homes for the mentally retarded. Surgeons and dentists and their assistants, medical students and laboratory workers regularly exposed to blood are candidates. The vaccine should be given to medical personnel going overseas to areas where the prevalence of hepatitis B is high.

Acute sufferers from hepatitis B are highly infectious and their sexual contacts should be vaccinated and

given HBIG. Sexual and family contacts of HBV carriers should be vaccinated after their antibody status has been determined.

Promiscuous homosexual men, if they are not immune, should be vaccinated. The same rule applies to drug abusers.

Babies born to HBsAg-positive and, particularly, HBeAg-positive mothers should be vaccinated and given immune globulin at birth. Even in countries with a lower carrier rate, it is essential to screen all pregnant women for HBsAg and not only those with a high risk of being carriers. If possible, the pregnant woman should be tested at 14 weeks of gestation and supplemented at delivery by rapid screening of those who escaped routine prenatal care [28].

The introduction of HBV vaccine has had a disappointing effect on the overall prevalence of HBV in the USA. Transmission amongst homosexual men has fallen, but intravenous drug abuse has increased with spread to non-abuser social and sexual contacts. Healthcare workers show a reduction of HBV.

The addition to infant vaccination of targeting adolescents will give preventative protection before the subject is exposed to risk factors such as sexual lifestyle, abuse of drugs or joining the healthcare profession.

Unfortunately, integration of HBV vaccination into all extended immunization programmes is not being implemented, whether because of cost or apathy. Some of the richest countries in the world are the most to blame, although the programme is cost-effective, even in low-risk countries.

Other vaccines

The most simple vaccine is derived from heat-inactivated plasma containing HBsAg, and is based on the original observation of Krugman [35] who boiled infectious HBV-positive serum and showed that it protected against hepatitis B. This vaccine is relatively crude, highly immunogenic and inexpensive.

The pre-S region. A mutation in the surface (S) has been associated with infants born to carrier mothers becoming HBV positive, despite successful vaccination. The mutation is in the 'a' determinant of S to which the vaccine promotes antibodies (see figs 17.5, 17.6). New vaccines will contain pre-S1 and pre-S2 domains and may be effective in those failing to respond to conventional vaccination. They may also be useful in those who fail to show an adequate antibody response to standard vaccination [75].

Chronic hepatitis B

Chronic hepatitis B is found predominantly in males. Features associated with an increased risk of HBV include ethnic origin, sexual contacts of sufferers, work in contact with human blood, patients having transplants or immunosuppressive treatment, drug abusers and homosexual activity. Neonates born to an HBeAg carrier have an 80–90% chance of chronic infection. In healthy adults, the risk of chronicity after an acute attack is very low (about 5.5%) [32]. There may be none of these associations. The condition may follow unresolved acute hepatitis B. The acute attack is usually mild and of a 'grumbling' type.

Following the attack, serum transaminase levels fluctuate with intermittent jaundice. The patient may be virtually symptom-free with only biochemical evidence of continued activity, and may simply complain of fatigue and being generally unwell—the diagnosis being made after a routine medical check.

The diagnosis may be made at the time of a blood donation or routine blood screen when the HBsAg is found to be positive and serum transaminases modestly raised.

Chronic hepatitis is often a silent disease. Symptoms do not correlate with the severity of liver damage.

In about one-half, presentation is as established chronic liver disease with jaundice, ascites or portal hypertension. Encephalopathy is unusual at presentation. The patient usually gives no history of a previous acute attack of hepatitis. Some present as hepato-cellular carcinoma.

Clinical relapse and reactivation

An apparently stable patient may have a clinical relapse. This is marked by increasing fatigue and, usually, rises in serum transaminase values. Relapse may be related to seroconversion from an HBeAg-positive state to an HBeAg-negative one (fig. 17.13). Liver biopsy shows an acute interface hepatitis which ultimately subsides and the serum transaminase values fall.

Seroconversion may be spontaneous in 10–15% of patients per annum or it may follow antiviral therapy. HBV DNA can remain positive even when anti-HBe has

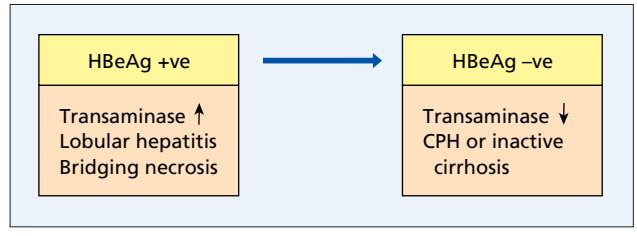


Fig. 17.13. Changes in a patient with chronic hepatitis B on conversion from HBeAg positive to HBeAg negative. CPH, chronic persistent hepatitis.

developed. In some HBeAg-positive patients, flare-ups of viral replication and transaminase elevation are found without eventual clearing of HBeAg.

Spontaneous reactivation from HBeAg negative to HBeAg and HBV DNA positive has also been described. The clinical picture ranges from absence of manifestations to fulminant liver failure. Reactivation is particularly severe in HIV-positive patients.

Reactivation may be marked serologically simply by finding a positive IgM anti-HBc.

Reactivation can follow cancer chemotherapy, low-dose methotrexate to treat rheumatoid arthritis [25], organ transplantation or administration of corticosteroids to HBeAg-positive patients.

Severe exacerbations have been associated with precore mutants [54] where HBV DNA is present, but 'e' antigen is absent.

The patient may be superinfected with HDV. This leads to a marked acceleration in the progress of chronic hepatitis.

Superinfection with HAV or HCV must also be considered.

Finally, any deterioration in a HBV carrier should raise the possibility of hepato-cellular carcinoma.

Laboratory tests

Serum bilirubin, aspartate transaminase and gamma-globulin are only moderately increased. Serum albumin is usually normal. At time of presentation, features of hepato-cellular disease are usually mild. Smooth muscle antibody, if present, is in low titre. Serum mitochondrial antibody is negative.

Serum HBsAg is present. In the later stages, HBsAg may be detected with difficulty in the blood yet IgM anti-HBc is usually present. HBe antigen or antibody and HBV DNA are variably detected.

HBV DNA can be detected by the PCR technique even in the plasma of people negative for HBsAg [69].

Needle liver biopsy

Hepatic histology varies widely and includes chronic hepatitis, active cirrhosis and hepato-cellular carcinoma. There are no constant diagnostic features, unless HBsAg is demonstrated as 'ground glass' cells by the orcein method or HBcAg by immunoperoxidase. The amount of replicating virus in the serum does not correlate with the degree of histological activity [51].

Course and prognosis

The clinical course varies considerably (fig. 17.14). Many patients remain in a stable, compensated state. This is particularly so in the asymptomatic and where hepatic histology shows only a mild, chronic hepatitis.

Clinical deterioration in a previously stable HBV carrier can have varying explanations. The patient may be converting from a replicative to an integrated state. This is usually followed by a remission which may be permanent, serum enzyme levels falling into the normal

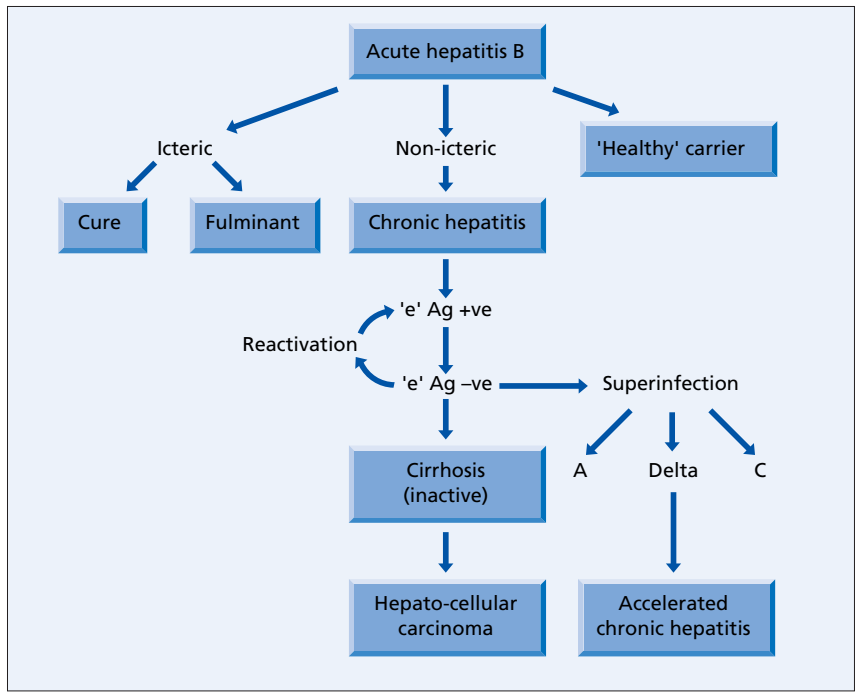


Fig. 17.14. The natural history of HBV infection.

range and liver histology improving; 10–20% per year may follow this course.

Prognosis is proportional to the severity of the underlying liver disease. Women have less severe liver disease. Age over 40 years and ascites are bad signs. There seem to be geographical and age-related differences in the natural history. HBV DNA positive Italian children have a 70% chance, before they are adults, of becoming HBeAb positive and HBV DNA negative with normalization of the transaminases irrespective of previous antiviral therapy; 25% will clear HBsAg [9, 10]. In contrast, only 2% of healthy Chinese carriers or chronic hepatitis patients cleared HBsAg in a mean of 4.0 ± 2.3 years [41].

Patients aged over 40 years, HBeAg negative and with established cirrhosis are more likely to clear HBsAg.

In general, the prognosis for the healthy HBV carrier is good. A 16-year follow-up of asymptomatic HBV carriers from Montreal, showed that they remained asymptomatic and the risk of death from HBV-related cirrhosis and/or hepato-cellular carcinoma was low. The annual clearance rate for HBsAg was 0.7% [68]. Similarly, HBsAg carriers with normal transaminase levels in Italy have an excellent prognosis. A mortality follow-up of sufferers in the 1942 epidemic of HBV in the American army, showed a slight excess for hepato-cellular cancer. However, the mortality from non-alcoholic chronic liver disease was less [19]. Very few immunocompetent adult males became carriers.

Recurrence of HBV in the graft is usual after liver transplantation in patients with HBV infection, especially if HBV DNA and HBeAg positive (Chapter 38).

Treatment

The patient must be counselled concerning personal infectivity. This is particularly important if he or she is HBeAg positive. Close family and sexual contacts should be checked for HBsAg and HBcAb and, if negative, hepatitis B vaccination should be offered.

Bed rest is not helpful. Physical fitness is encouraged by graduated exercises. Diet is normal. Alcohol should be avoided as this enhances the effects of HBsAg carriage. However, one or two glasses of wine or beer a day are allowed if this is part of the patient's lifestyle.

The majority of patients with chronic hepatitis B lead normal lives. Strong reassurance will prevent introspection by the patient.

Antiviral therapy

The aim is to control infectivity, eradicate the virus and prevent the development of cirrhosis. However, permanent loss of HBeAg and HBV DNA are unusual and HBsAg usually persists. Treatment does result in a reduction of infectivity and of necrotic inflammation in the liver. Thus cirrhosis may be prevented and with it the risk of hepatocellular carcinoma.

Table 17.8. Factors determining the response of patients with chronic hepatitis B to antiviral therapy

Good
Female
Heterosexual
Compliant
Recent infection
High serum transaminases
'Active' liver biopsy
High HBV DNA
Bad
Homosexual
HIV positive
Disease acquired early
Oriental

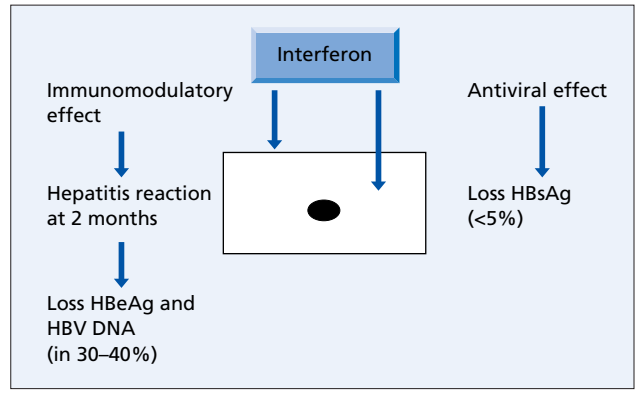


Fig. 17.15. Interferon, used to treat chronic hepatitis B, acts as an immunomodulatory agent resulting in loss of circulating HBeAg and HBV DNA in 30–40% of cases, and to a lesser extent as an antiviral agent resulting in loss of HBsAg in less than 5% of cases.

Those most likely to respond have a history of acute hepatitis, high serum ALT and low serum HBV levels (table 17.8).

Interferon-α (IFN-α). This is licensed to treat chronic HBV infection. It acts immunologically by enhancing the display of HLA class I antigens and increasing mechanisms to destroy diseased hepatocytes (fig. 17.15). It also has antiviral effects.

The usual regime in the USA is 5 million units daily or 10 million units three times a week by injection for 16 weeks. Extending the duration or using higher doses does not seem to increase the response rate.

Early symptomatic side-effects, usually temporary, occur 4–8 h after the injection during the first week and are relieved by analgesics (table 17.9). Later, psychiatric complications, especially in those with pre-existing

Table 17.9. Interferon side-effects

Early
Flu-like
Myalgia, usually temporary
Headaches
Nausea
Late
Fatigue
Muscle aches
Irritability
Anxiety and depression
Weight loss
Diarrhoea
Alopecia
Bone-marrow suppression
Bacterial infections
Autoimmune autoantibodies
Optic tract neuropathy
Lichen planus worsens

Table 17.10. The effect of interferon for HBeAg-positive patients: meta-analysis (15 studies) [72]

	Loss (%)	
	HBsAg	HBeAg
Interferon	7.8	33
Spontaneous	1.8	12

nervous diseases, indicate cessation of therapy. Autoimmune changes develop 4–6 months after starting and include positive serum ANA, AMA and anti-thyroid antibodies. Pre-existing antibodies against thyroid microsomes are a contraindication to starting interferon. Bacterial infections develop, especially in cirrhotics.

A positive response is shown by loss of HBeAg and HBV DNA with a transient rise in transaminases at about 8 weeks as infected cells are lysed (fig. 17.15). Interferon results in a sustained loss of HBeAg and HBV DNA in only 30–40% of Caucasian patients, but progression of the disease seems to be prevented (table 17.10) [53, 72]. These results apply to white adults, in good health and with compensated liver disease. Only 17% of Chinese patients lose HBeAg and become HBV DNA negative [44].

Patients with decompensated cirrhosis suffer severe side-effects, particularly infections. Some patients may respond to low doses (e.g. 1 million units, three times a week).

Interferon-α has resulted in long-term remission of patients with chronic HBV with glomerulonephritis [15].

About 25% of patients with the pre-core HBV mutant (HBeAg negative, HBV DNA positive) respond to treatment.

After relapse, re-treatment with interferon is sometimes successful [13].

Lamivudine. This nucleoside analogue inhibits reverse transcriptase and HBV DNA polymerase enzymes necessary for HBV replication.

Nucleoside analogues interfere with mitochondrial function and can cause severe side-effects. These led to the withdrawal of one, fialuridine, which caused fatalities [45]. Fortunately, lamivudine is only a weak inhibitor of the cellular enzymes required for mitochondrial DNA replication and serious side-effects have not been reported.

Lamivudine is given orally in a dose of 100–300 mg daily. It is cleared by the kidney and adjustments may be necessary in those with impaired kidney function.

Controlled trials have shown that after 1 year of treatment (100–300 mg daily), 70–100% of patients will become HBV DNA negative as shown by PCR. Seventeen per cent of Caucasian or Chinese patients show HBeAg seroconversion and this increases to 24% after 2 years of treatment [36]. Histology improves and, in the majority, serum ALT falls.

Results are better in those with higher ALT levels [14]. Those with initially normal ALT levels should probably not be treated.

After 1 year, 45% of initially positive patients have lost HBV DNA with normal ALT, but only 15% remain HBV DNA negative 16 weeks after stopping therapy [59]. Exacerbations after stopping therapy are due to viral resistance (mutants) and to recrudescence of viraemia [31]. This can lead to hepatic decompensation [6, 40]. It is difficult to decide when to stop therapy. This could probably be done following HBeAg seroconversion and 18 months of therapy [20, 21].

Cirrhotic patients, especially if decompensated, must be treated cautiously, although in some patients biochemical tests and Child's grade may so improve that liver transplant becomes possible [67].

Lamivudine (300 mg daily) inhibits HBV replication in HIV-infected patients. However, lamivudine-resistant HBV may occur in 20% of patients per year [5].

Combination therapy. The combination of lamivudine with interferon increases the HBeAg seroconversion rate [58]. Ribavirin may be added [16]. In Chinese patients, the combination of lamivudine with famciclovir was superior to monotherapy [39].

In preliminary studies, priming with prednisolone enhanced the efficacy of subsequent lamivudine therapy [42].

Lamivudine resistance. Unfortunately, lamivudine therapy is followed by viral resistance in a high proportion of cases. This develops, with return of viral replication in 27% of patients at 1 year, and 58% after 2 years of treatment.

The resistance is marked by amino acid mutations in the highly conserved YMDD motifs of the active site of the polymerase [2, 40]. These mutants impair HBV replication, but the virus is still pathogenic.

Use in liver transplantation. Pre-transplant prophylaxis and treatment of post-transplant recurrence may improve the outlook for liver transplanation [26, 56]. Lamivudine should be continued in liver transplant patients who develop resistance.

Other therapies

Adenofivir (dipivoxil) inhibits HBV polymerase and is under trial but renal toxicity is a problem.

Lobucavir gave initially encouraging results, but animal carcinogenicity is urging caution.

Experimental agents including *EMS 200475*, a novel guanosine analogue, have not reached clinical trials [33].

Immunotherapy

Patients with chronic HBV lack a long-term polyclonal non-specific T-cell response. This can be stimulated by repeated doses of standard recombinant HBV vaccines [17].

DNA-based vaccines are being tested to provide a specific T-cell response and induce cell-mediated immunity [30].

Molecular therapy

These therapies attempt to interfere directly with viral replication. Antisense oligonucleotides and antisense RNA bind to specific RNA targets causing arrest of translation and degradation.

Ribosomes are RNA enzymes that catalyse RNA cleavage and splicing reactions.

Permanent negative mutants and intracellular antibodies interfere with nucleocapsid assembly. All these molecular therapies are in the pre-clinical phase of development.

Outstanding problems

There are many uncertainties in the management of chronic HBV. How should patients be selected to receive interferon as opposed to lamivudine? Lamivudine should be given for at least 2 years, but for how long? When should the drug be withdrawn because of success or failure? Lamivudine resistance inhibits its use, but the clinical significance of the mutants that develop remains uncertain.

Screening for hepato-cellular carcinoma

Patients who are HBsAg positive with chronic hepatitis or cirrhosis, especially if male and more than 45 years old, should be screened regularly so that hepato-cellular carcinoma may be diagnosed early when surgical resection may prove possible (see Chapter 31). Serum α-fetoprotein should be measured and ultrasound examination performed at 6-monthly intervals.

References

1 Akahane Y, Yamanaka T, Suzuki H *et al*. Chronic active hepatitis with hepatitis B virus DNA and antibody against e antigen in the serum. Disturbed synthesis and secretion of e antigen from hepatocytes due to a point mutation in the precore region. *Gastroenterology* 1990; **99**: 1113.

2 Atkins M, Gray DF. Lamivudine resistance in chronic hepatitis. *J. Hepatol*. 1998; **28**: 169.

3 Baker BL, Di Bisceglie AM, Kaneko S *et al*. Determination of hepatitis B virus DNA in serum using the polymerase chain reaction: clinical significance and correlation with serological and biochemical markers. *Hepatology* 1991; **13**: 632.

4 Bartolome J, Moraleda G, Molina J *et al*. Hepatitis B virus DNA in liver and peripheral blood mononuclear cells during reduction in virus replication. *Gastroenterology* 1990; **99**: 1745.

5 Benhamou Y, Mochet M, Thibault V *et al*. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. *Hepatology* 1999; **30**: 1302.

6 Bessesen M, Ives D, Condrea YL *et al*. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to withdrawal of lamivudine. *Clin. Infect. Dis*. 1999; **28**: 1302.

7 Bloom HE. Variants of hepatitis B, C and D viruses: molecular biology and clinical significance. *Digestion* 1995; **56**: 85.

8 Blumberg BS, Alter HJ, Visnich S. A 'new' antigen in leukaemia sera. *JAMA* 1965; **191**: 541.

9 Bortolotti F, Cardrobbi P, Crivellaro C *et al*. Long-term outcome of chronic type B hepatitis in patients who acquire hepatitis B virus infection in childhood. *Gastroenterology* 1990; **99**: 805.

10 Bortolotti F, Jara P, Barbera C *et al*. Long-term effect of alpha interferon in children with chronic hepatitis B. *Gut* 2000; **46**: 715.

11 Brunetto MR, Stemler M, Schodel F *et al*. Identification of HBV variants which cannot produce precore derived HBeAg and may be responsible for severe hepatitis. *Ital. J. Gastroenterol*. 1989; **21**: 151.

12 Carman WF, Hadziyannis S, McGarvey MJ *et al*. Mutation preventing formation of hepatitis B e antigen in patients with chronic hepatitis B infection. *Lancet* 1989; **ii**: 588.

13 Carreno V, Marcellin P, Hadziyannis S *et al*. Retreatment of chronic hepatitis B e antigen-positive patients with recombinant interferon alfa-2a. *Hepatology* 1999; **29**: 277.

14 Chien RN, Liaw Y-F, Atkins M. Pre-therapy alanine transferase level as a determinant for hepatitis B e antigen seroconversion during lamivudine therapy in patients with chronic hepatitis B. *Hepatology* 1999; **30**: 770.

15 Conjeevaram HS, Hoofnagle JH, Austin HA *et al*. Long-term outcome of hepatitis B virus-related glomerulonephritis after therapy with interferon alfa. *Gastroenterology* 1995; **109**: 540.

16 Cotonat T, Quiroga JA, Lopez-Alcorocho JM *et al*. Pilot study of combination therapy with ribavirin and interferon alfa for the retreatment of chronic hepatitis B e antibody-positive patients. *Hepatology* 2000; **31**: 502.

17 Couillin I, Pol S, Mancini M *et al*. Specific vaccine therapy in chronic hepatitis B: induction of specific T-cell proliferative responses for envelope antigens. *J. Infect. Dis.* 1999; **180**: 15.

18 Coursaget P, Leboulleux D, Soumare M *et al*. Twelve-year follow-up study of hepatitis B immunization of Senegalese infants. *J. Hepatol.* 1994; **21**: 250.

19 Di Bisceglie AM, Goodman ZD, Ishak KG *et al*. Long-term clinical and histopathological follow-up of clinical post-transfusion hepatitis. *Hepatology* 1991; **14**: 969.

20 Dienstag JL, Schiff ER, Mitchell M *et al*. Extended lamivudine retreatment for chronic hepatitis B: maintenance of viral suppression after discontinuation of therapy. *Hepatology* 1999; **30**: 1082.

21 Dienstag JL, Schiff ER, Wright TL *et al*. Lamivudine as initial treatment for chronic hepatitis B in the United States. *N. Engl. J. Med.* 1999; **341**: 1256.

22 Dragosics B, Ferenci P, Hitchman E *et al*. Long-term follow-up study of asymptomatic HBsAg-positive voluntary blood donors in Austria: a clinical and histological evaluation of 242 cases. *Hepatology* 1987; **7**: 302.

23 Dudley FJ, Fox RA, Sherlock S. Cellular immunity and hepatitis associated (Australia) antigen liver disease. *Lancet* 1972; **i**: 743.

24 European Consensus Group of Hepatitis B Immunity. Are booster immunizations needed for lifelong hepatitis B immunity? *Lancet* 2000; **255**: 561.

25 Flowers MA, Heathcote J, Wanless IR *et al*. Fulminant hepatitis as a consequence of reactivation of hepatitis B virus infection after discontinuation of low-dose methotrexate therapy. *Ann. Intern. Med.* 1990; **112**: 381.

26 Grellier L, Mutimer D, Ahmed M *et al*. Lamivudine prophylaxis against reinfection in liver transplantation for hepatitis B cirrhosis. *Lancet* 1996; **348**: 1212.

27 Grob P. Introduction to epidemiology and risk of hepatitis B. *Vaccine* 1995; **13**: 514.

28 Grosheide PM, Wladimiroff JW, Heijtink RA *et al*. Proposal for routine antenatal screening at 14 weeks for hepatitis B surface antigen. *Br. Med. J.* 1995; **311**: 1197.

29 Haruna Y, Hayashi N, Katayama K *et al*. Expression of X protein and hepatitis B virus replication in chronic hepatitis. *Hepatology* 1991; **13**: 418.

30 Heathcote J, McHutchinson J, Lee S *et al*. A pilot study of the CY-1899 T-cell vaccine in subjects chronically infected with the hepatitis B virus. *Hepatology* 1999; **30**: 531.

31 Honkoop P, de Man RA, Niesters HGM *et al*. Acute exacerbation of chronic hepatitis B virus infection after withdrawal of lamivudine therapy. *Hepatology* 2000; **32**: 635.

32 Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. *Clin. Infect. Dis.* 1995; **20**: 992.

33 Innaimo SF, Seifer M, Bissacchi GS *et al*. Identification of EMS-200475 as a potent and selective inhibitor of hepatitis B virus. *Antimicrob. Agents Chemother*. 1997; **41**: 1444.

34 Joller-Jemelka HI, Wicki AN, Grob PJ. Detection of HBs antigen in 'anti-HBe alone' positive sera. *J. Hepatol.* 1994; **21**: 269.

35 Krugman S, Overby LR, Mushahwar IK *et al*. Viral hepatitis type B: studies on natural history and prevention re-examined. *N. Engl. J. Med.* 1979; **300**: 101.

36 Lai CL, Chien RN, Leung NW *et al*. A one-year trial of lamivudine for chronic hepatitis B. *N. Engl. J. Med.* 1998; **339**: 61.

37 Lai KN, Li PKT, Lui SF *et al*. Membranous nephropathy related to hepatitis B virus in adults. *N. Engl. J. Med*. 1991; **324**: 1457.

38 Lau JYN, Wright TL. Molecular virology and pathogensis of hepatitis B. *Lancet* 1992; **342**: 1335.

39 Law GKK, Tsang M, Hou J *et al*. Combination therapy with lamivudine and famciclovir for chronic hepatitis B-infected Chinese patients: a viral dynamics study. *Hepatology* 2000; **32**: 394.

40 Liaw Y-F, Chien RN, Leung N *et al*. Acute exacerbations and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy. *Hepatology* 1998; **30**: 567.

41 Liaw Y-F, Sheen I-S, Chen T-J *et al*. Incidence, determinants and significance of delayed clearance of serum HbsAg in chronic hepatitis B virus infection: a prospective study. *Hepatology* 1991; **13**: 627.

42 Liaw Y-F, Tsai S-L, Chien R-N *et al*. Prednisolone priming enhances Th1 response and efficacy of subsequent lamivudine therapy in patients with chronic hepatitis B. *Hepatology* 2000; **32**: 604.

43 Lin C-Y. Hepatitis B virus-associated membranous nephropathy: clinical featuers, immunological profiles and outcome. *Nephron* 1990; **55**: 37.

44 Lok ASF, Ma OCK, Lau JYN. Interferon alpha therapy in patients with chronic hepatitis B patients treated with interferon alfa. *Gastroenterology* 1993; **105**: 1883.

45 McKenzie R, Fruied MW, Sallie R *et al*. Hepatic failure and lactic acidosis due to fialuridine (FIAU), an investigational nucleoside analogue for chronic hepatitis B. *N. Engl. J. Med.* 1995; **333**: 1099.

46 McMahon BJ, Heyward WL, Templin DW *et al*. Hepatitis B-associated polyarteritis nodosa in Alaskan Eskimos: clinical and epidemiologic features and long-term follow-up. *Hepatology* 1989; **9**: 97.

47 McMahon BJ, Rhoades ER, Hayward WL *et al*. A comprehensive programme to reduce the incidence of hepatitis B virus infection and its sequelae in Alaskan natives. *Lancet* 1987; **ii**: 1134.

48 Marcellin P, Martinot-Peignoux M, Loriot M-A *et al*. Persistence of hepatitis B virus DNA demonstrated by polymerase chain reaction in serum and liver after loss of HBsAg induced by antiviral therapy. *Ann. Intern. Med.* 1990; **112**: 227.

49 Mayans MV, Hall AJ, Inskip HM *et al*. Risk factors for transmission of hepatitis B virus to Gambian children. *Lancet* 1990; **336**: 1107.

50 Mayans MV, Hall AJ, Inskip HM *et al*. Do bedbugs transmit hepatitis B? *Lancet* 1994; **343**: 761.

51 Mills CT, Lee E, Perillo R. Relationship between histology, aminotransferase levels, and viral replication in chronic hepatitis B. *Gastroenterology* 1990; **99**: 519.

52 MMWR. Protection against viral hepatitis. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1990; **39**: 1.

53 Niederau C, Heintges T, Lange S *et al*. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N. Engl. J. Med.* 1996; **334**: 1422.

54 Omata M, Ehata T, Yokosuka O *et al*. Mutations in the precore region of hepatitis B virus DNA in patients with fulminant and severe hepatitis. *N. Engl. J. Med.* 1991; **324**: 1699.

55 Penner E, Maida E, Mamoli B *et al*. Serum and cerebrospinal fluid immune complexes containing hepatitis B surface antigen in Guillain–Barré syndrome. *Gastroenterology* 1982; **82**: 576.
56 Perrilllo R, Rakela J, Dienstag J *et al*. Multicentre study of lamivudine therapy for hepatitis B after liver transplantation. *Hepatology* 1999; **29**: 1581.
57 Sanchez-Quijano A, Jauregui JI, Leal M *et al*. Hepatitis B virus occult infection in subjects with persistent isolated anti-HBc reactivity. *J. Hepatol*. 1993; **17**: 288.
58 Schalm SW, Heathcote J, Cianciar AJ *et al*. Lamivudine and interferon combination treatment of patients with chronic hepatitis B infection: a randomized trial. *Gut* 2000; **46**: 562.
59 Schiff E, Karavalcin S, Grimm I *et al*. A placebo-controlled study of lamivudine and interferon alpha-2b in patients with chronic hepatitis B who previously failed interferon therapy. *Hepatology* 1998; **28**: 388A.
60 Seeff LB, Koff RS. Passive and active immunoprophylaxis of hepatitis B. *Gastroenterology* 1984; **86**: 958.
61 Shindo M, Okuno T, Arai K *et al*. Detection of hepatitis B virus DNA in paraffin-embedded liver tissues in chronic hepatitis B or non-A, non-B hepatitis using the polymerase chain reaction. *Hepatology* 1991; **13**: 167.
62 Szmunes SW, Stevens CE, Harley EJ *et al*. Hepatitis B vaccine: demonstration of efficacy in a controlled trial in a high-risk population in the United States. *N. Engl. J. Med*. 1980; **303**: 833.
63 Thursz MR, Kwiatkowski D, Allsopp CEM *et al*. Association between an MHC class II allele and clearance of hepatitis B virus in The Gambia. *N. Engl. J. Med*. 1995; **332**: 1065.
64 Tilzey AJ. Hepatitis B vaccine boosting: the debate continues. *Lancet* 1995; **345**: 1000.
65 Trepo CG, Ouzan D. Successful therapy of polyarteritis due to hepatitis B virus by combination of plasma exchanges and adenine arabinoside therapy. *Hepatology* 1985; **5**: 1022 (abstract).
66 Venkatasehan VS, Lieberman K, Kim DU *et al*. Hepatitis B-associated glomerulonephritis: pathology, pathogenesis and clinical course. *Medicine (Baltimore)* 1990; **69**: 200.
67 Villeneuve J-P, Condreay LD, Bernard W *et al*. Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B. *Hepatology* 2000; **31**: 207.
68 Villeneuve J-P, Desrochers M, Infante-Rivard C *et al*. Long-term, follow-up study of asymptomatic hepatitis B surface antigen-positive carriers in Montreal. *Gastroenterology* 1994; **106**: 1000.
69 Webster GJM, Hallett R, Whalley SA *et al*. Molecular epidemiology of a large outbreak of hepatitis B linked to autohaemotherapy. *Lancet* 2000; **356**: 379.
70 Welch J, Webster M, Tilzey AJ *et al*. Hepatitis B infections after gynaecological surgery. *Lancet* 1989; **i**: 205.
71 Whittle HC, Maine N, Pilkington J *et al*. Long-term efficacy of continuing hepatitis B vaccination in two Gambian villages. *Lancet* 1995; **345**: 1089.
72 Wong DKH, Chung AM, O'Rourke K *et al*. Effects of alpha-interferon in patients with hepatitis B antigen-positive chronic hepatitis B. A meta analysis. *Ann. Intern. Med*. 1993; **119**: 312.
73 Yamada G, Takaguchi K, Matsueda K *et al*. Immunoelectron microscopic observation of intrahepatic HBeAg in patients with chronic hepatitis B. *Hepatology* 1990; **12**: 133.
74 Yoffe B, Burns DK, Bhatt HS *et al*. Extra-hepatic hepatitis B virus DNA sequences in patients with acute hepatitis B infection. *Hepatology* 1990; **12**: 187.
75 Zuckerman JN, Sabin C, Craig FM *et al*. Immune response to a new hepatitis B vaccine in healthcare workers who had not responded to standard vaccine: randomised double blind dose–response study. *Br. Med. J*. 1997; **314**: 329.

Hepatitis delta virus (HDV)

The delta agent is a very small (36 nm) RNA particle coated with HBsAg (fig. 17.16) [19]. It is not able to replicate on its own, but is capable of infection when activated by the presence of HBV. It resembles satellite viruses of plants which cannot replicate without another specific virus. The interaction between the two viruses is very complex. Synthesis of HDV may depress the appearance of hepatitis B viral markers in infected cells and even lead to the elimination of active hepatitis B viral replication.

The delta virus is a single-stranded, circular, antisense RNA. It is highly infectious and can induce hepatitis in an HBsAg-positive host.

There are at least three genotypes having variable geographical distribution and clinical associations [6, 28].

HBV and HDV infection may be simultaneous (*co-infection*) or HDV may infect a chronic HBsAg carrier (*superinfection*) (figs 17.17, 17.18).

Epidemiology

HDV infection is not a new disease. Analysis of stored blood shows it to have been present in the American army in 1947, in Los Angeles since 1967 [7] and in liver specimens from Brazil in the 1930s.

HDV infection is strongly associated with intravenous

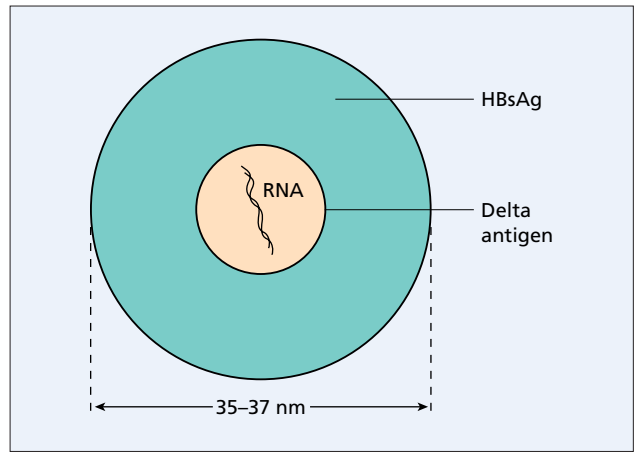


Fig. 17.16. Delta antigen is a small RNA particle coated by HBsAg.

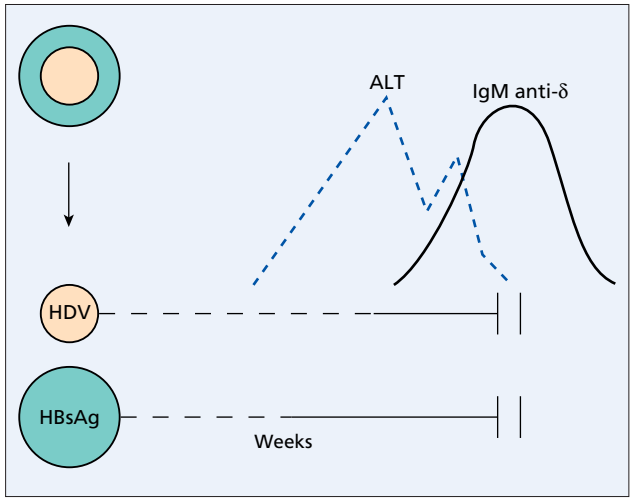


Fig. 17.17. Simultaneous infection with HBV and HDV results in acute hepatitis B with a rise in alanine transaminase (ALT). HDV infection follows with a second peak of ALT and the appearance of IgM anti-delta in the blood. Clearing of HBsAg is associated with clearing of delta [19].

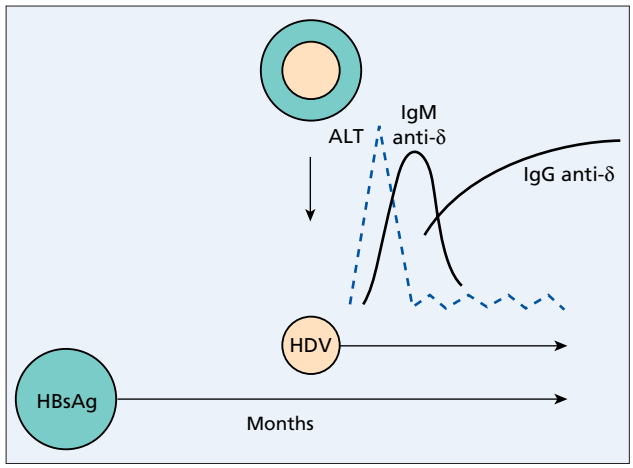


Fig. 17.18. HDV infection in an HBsAg carrier results in an attack of acute hepatitis with the appearance of IgM anti-delta followed by IgG anti-delta in the blood [19].

drug abuse [15], but can affect all risk groups for HBV infection. It is infrequent in homosexual men [26] but can affect health-care workers, transfusion recipients, haemophiliacs, immigrants and the developmentally disabled [12]. HDV can spread heterosexually [15]. Intrafamily spread has been noted in southern Italy [3]. Children can be affected. HDV infection may be reactivated by HIV infection.

HDV infection is worldwide, but is particularly found in southern Europe, the Balkans, the Middle East, South India, Taiwan and parts of Africa. An endemic area has been identified in Okinawa, Japan [22].

Epidemics of HDV infection have been reported from the Amazon Basin, Brazil (Labrea fever) [2], Colombia

Table 17.11. The diagnosis of delta virus infection

	Acute co-infection		
	Early	Convalescence	Chronic
Serum			
IgG anti-delta	+	+ (low titre)	+ (high titre)
IgM anti-delta	+ (late)	–	+
HDAg	+	–	+
HDV RNA	+	–	+
Liver			
HDAg	+	–	–
HDV RNA	+	–	+

(Santa Marta hepatitis) [4], Venezuela [11] and Equatorial Africa. In these areas children of the indigent population are affected and mortality is high.

Along with HBV, HDV infection is declining rapidly. This is particularly true in Italy [20, 25]. Universal HBV vaccination is particularly important in reducing the prevalence.

Diagnosis (table 17.11)

Acute delta hepatitis is diagnosed by rising titres of serum IgG anti-HDV (anti-delta).

Co-infection is diagnosed by finding serum IgM anti-HDV in the presence of high-titre IgM anti-HBc. These markers appear at 1 week, and IgM anti-HDV is gone by 5–6 weeks but may last for up to 12 weeks [1]. When serum IgM anti-HDV disappears, serum IgG anti-HDV is found. There may be a window period between the disappearance of one and the detection of the other. Loss of IgM anti-HDV confirms the resolution of HDV infection, whereas persistence predicts chronicity [9].

HBsAg is positive, but often in low titre and may be undetectable. Serum IgM anti-HBc is also suppressed. Unless delta markers are sought, the patient may be misdiagnosed as having acute hepatitis C.

Superinfection with HDV is marked by the early presence of serum IgM anti-HDV, usually at the same time as early IgG anti-HDV and both antibodies persist [5]. These patients are usually IgM anti-HBc negative, but may have low titres of this antibody. Sufferers of chronic delta infection with chronic hepatitis and active cirrhosis usually have a positive serum IgM anti-HDV.

Serum and liver HDV RNA, by staining or PCR, are found in delta antibody-positive patients with acute and chronic HDV infection [16, 27].

Clinical features (figs 17.17, 17.18)

With *co-infection*, the acute delta hepatitis is usually self-limited as HDV cannot outlive the transient HBs antigenaemia. The long-term outlook is therefore good. The

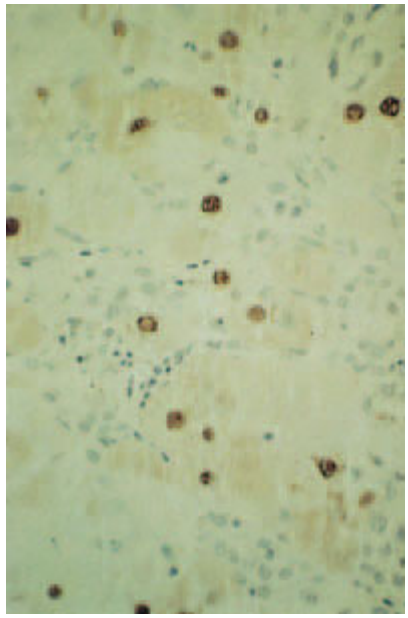


Fig. 17.19. Fulminant acute delta virus hepatitis (Labrea hepatitis) in a 3-year-old girl from northern Brazil who died with fulminant hepatitis after 3 days' symptoms. An autopsy liver sample shows microvesicular fatty change in large hepatocytes with central nucleus (Morular, vegetable-type cells). (Immunoperoxidase, × 500.)

clinical picture is usually indistinguishable from hepatitis B alone. However, a biphasic rise in aspartate transaminase may be noted, the second rise being due to the acute effects of delta [8].

With *superinfection*, the acute attack may be severe and even fulminant, or may be marked only by a rise in serum transaminase levels. HDV infection should always be considered in any HBV carrier, usually clinically stable, who has a relapse.

HDV infection reduces active hepatitis B viral synthesis and patients are usually HBeAg and HBV DNA negative. Between 2 and 10% lose HBsAg. However, chronic delta hepatitis is usual and this results in acceleration towards cirrhosis.

Episodes of reactivation with delta viraemia can develop [10]. If hepatitis B viraemia persists, the outcome is worse [24]. Hepato-cellular cancer seems less common in HBsAg carriers with HDV. This may be due to inhibition of hepatitis B or rapid progression so that the patient dies before the cancer develops. However, when delta is found with late-stage chronic liver disease it does not seem to influence survival and hepatocellular cancer may be a complication in these patients.

Hepatic histology

Inflammation and focal confluent and bridging necrosis are marked. Acidophil bodies are seen.

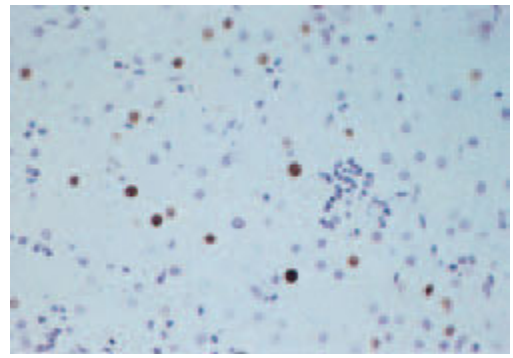


Fig. 17.20. Delta virus hepatitis: immunoperoxidase staining showing delta in the hepatocyte nuclei (× 100).

The South American and Equatorial African epidemics are marked by microvesicular fat in hepatocytes, intense eosinophilic necrosis and large amounts of delta antigen within the liver (fig. 17.19) [4]. These changes have also been noted in a New York drug abuser with HDV infection [14]. Morular (plant-like) cells may be seen.

Using immunoperoxidase, delta antigen is shown in hepatocyte nuclei, more in chronic than in acute infection (fig. 17.20). It falls with cirrhosis. It correlates with viraemia [27].

Prevention

Vaccination against hepatitis B makes the recipient immune to HBV infection and protects against HDV infection. Patients likely to contract HDV infection should be encouraged to have a hepatitis B vaccine.

HBV carriers must be educated concerning the risks of acquiring HDV by continued drug abuse.

Treatment

Treatment is unsatisfactory. High doses of interferon given for long periods result in reductions of AST but recurrence is usual [18, 21].

Lamivudine does not improve disease activity or lower HDV RNA levels in patients with chronic delta hepatitis [13].

Patients receiving a liver transplant for HDV and HBV end-stage liver disease show reduced HBV recurrence [17]. The hepatocytes contain large amounts of HDV but hepatitis develops only if there is persistent infection with HBV (Chapter 38). The HDV virion in the post-transplantation setting is typical HDV and requires the helper function of HBV infection [23].

References

1 Aragona M, Macagno S, Caredda F *et al*. Serological

response to the hepatitis delta virus in hepatitis D. *Lancet* 1987; **i**: 478.
2 Bensabath G, Hadler SC, Soares MCP *et al*. Hepatitis delta virus infection and Labrea hepatitis. Prevalence and role in fulminant hepatitis in the Amazon Basin. *JAMA* 1987; **258**: 479.
3 Bonino F, Caporaso N, Dentico P *et al*. Familiar clustering and spreading of hepatitis delta virus infection. *J. Hepatol*. 1985; **1**: 221.
4 Buitrago B, Popper H, Hadler SC *et al*. Specific histological features of Santa Marta hepatitis: a severe form of hepatitis delta-virus infection in northern South America. *Hepatology* 1986; **6**: 1285.
5 Buti M, Amengual J, Esteban R *et al*. Serological profile of tissue autoantibodies during acute and chronic delta hepatitis. *J. Hepatol*. 1989; **9**: 345.
6 Cortrina M, Buti M, Jardi R *et al*. Hepatitis delta genotypes in chronic delta infection in the north-east of Spain (Catalonia). *J. Hepatol*. 1998; **28**: 971.
7 De Cock KM, Govindarajan S, Chin KP *et al*. Delta hepatitis in the Los Angeles area: a report of 126 cases. *Am. Intern. Med*. 1986; **105**: 108.
8 Govindarajan S, De Cock KM, Redeker AG. Natural course of delta superinfection in chronic hepatitis B virus-infected patients: histopathologic study with multiple liver biopsies. *Hepatology* 1986; **6**: 640.
9 Govindarajan S, Gupta S, Valinluck B *et al*. Correlation of IgM antihepatitis D virus (HDV) to HDV RNA in sera of chronic HDV. *Hepatology* 1989; **10**: 34.
10 Govindarajan S, Smedile, A, De Cock KM *et al*. Study of reactivation of chronic hepatitis delta infection. *J. Hepatol*. 1989; **9**: 204.
11 Hadler SC, De Monzon M, Ponzetto A *et al*. Delta virus infection and severe hepatitis: an epidemic in the Yupca Indians of Venezuela. *Ann. Intern. Med*. 1984; **100**: 339.
12 Hershow RC, Chomel BB, Graham DR *et al*. Hepatitis D virus infection in Illinois state facilities for the developmentally disabled. *Ann. Intern. Med*. 1989; **110**: 779.
13 Lau DT-Y, Doo E, Park Y *et al*. Lamivudine for chronic delta hepatitis. *Hepatology* 1999; **30**: 546.
14 Lefkowitch JH, Goldstein H, Yatto R *et al*. Cytopathic liver injury in acute delta virus hepatitis. *Gastroenterology* 1987; **92**: 1262.
15 Lettau LA, McCarthy JG, Smith MH *et al*. Outbreak of severe hepatitis due to delta and hepatitis B viruses in parenteral drug abusers and their contacts. *N. Engl. J. Med*. 1987; **317**: 1256.
16 Madejón A, Castillo I, Bartolomé J *et al*. Detection of HDV-RNA by PCR in serum of patients with chronic HDV infection. *J. Hepatol*. 1990; **11**: 381.
17 Ottobrelli A, Marzano A, Smedile A *et al*. Patterns of hepatitis delta virus reinfection and disease in liver transplantation. *Gastroenterology* 1991; **101**: 1649.
18 Porres JC, Carreño V, Bartolomé J *et al*. Treatment of chronic delta infection with recombinant human interferon alpha 2c at high doses. *J. Hepatol*. 1989; **9**: 338.
19 Rizzetto M. The delta agent. *Hepatology* 1983; **3**: 729.
20 Rosina F, Conoscitore P, Cuppone R *et al*. Changing pattern of chronic hepatitis D in Southern Europe. *Gastroenterology* 1999; **117**: 163.
21 Rosina F, Pintus C, Meschievitz C *et al*. A randomized controlled trial of a 12-month course of recombinant human interferon-alpha in chronic delta (type D) hepatitis: a multicentre Italian study. *Hepatology* 1991; **13**: 1052.
22 Sakugawa H, Nakasone H, Shokita H *et al*. Seroepidemiological study of hepatitis delta virus infection in Okinawa, Japan. *J. Med. Virol*. 1995; **45**: 312.
23 Smedile A, Casey JL, Cote PJ *et al*. Heptatitis D viremia following orthotopic liver transplantation involves a typical HDV virion with a hepatitis B surface antigen envelope. *Hepatology* 1998; **27**: 1723.
24 Smedile A, Rosina F, Saracco G *et al*. Hepatitis B virus replication modulates pathogenesis of hepatitis D virus in chronic hepatitis D. *Hepatology* 1991; **13**: 413.
25 Stroffolini T, Ferrigno L, Cialdea L *et al*. Incidence and risk factors of acute delta hepatitis in Italy: results from a national surveillance system. *J. Hepatol*. 1994; **21**: 1123.
26 Weisfuse IB, Hadler SC, Fields HA *et al*. Delta hepatitis in homosexual men in the United States. *Hepatology* 1989; **9**: 872.
27 Wu J-C, Chen T-A, Huang Y-S *et al*. Natural history of hepatitis D viral superinfection: significance of viremia detected by polymerase chain reaction. *Gastroenterology* 1995; **108**: 796.
28 Wu J-C, Choo K-B, Chen C-M *et al*. Genotyping of hepatitis D virus by restriction-fragment length polymerase and relation to outcome of hepatitis D. *Lancet* 1995; **346**: 939.

Chapter 18
Hepatitis C Virus

The ability to diagnose hepatitis virus A and B infection did not resolve the problem of acute and chronic hepatitis. A third major category had always been suspected but, in the absence of a diagnostic test, had been designated non-A, non-B virus hepatitis. A third type has now been identified and called hepatitis C virus (HCV) [119]. This followed identification of a viral clone of the HCV virus from chimpanzee liver which had been infected with non-A, non-B virus [119]. An antibody test followed. Hepatitis C is a major health problem [20]. Global prevalence of chronic hepatitis C is estimated to average 3% (ranging from 0.1 to 5% in different countries). There are some 175 million chronic HCV carriers throughout the world, of which an estimated 2 million are in the USA and 5 million in Western Europe. HCV accounts for 20% of cases of acute hepatitis, 70% of cases of chronic hepatitis, 40% of cases of end-stage cirrhosis, 60% of cases of hepato-cellular carcinoma and 30% of liver transplants. It is the most frequent indication for hepatic transplantation. The incidence of new symptomatic infections has been estimated to be 1–3 per 100 000 persons annually. The actual incidence is obviously much higher as the majority of cases are asymptomatic. The incidence is declining as transmission by blood products has now been reduced to near zero.

Universal precautions have markedly reduced transmission in medical settings. Intravenous drug use remains the main mode of transmission; but this route of transmission is diminishing due to a heightened awareness of the risk of needle sharing and, in some countries, the availability of needle-exchange programmes. However, a huge backlog of infected patients continue to progress towards cirrhosis and hepato-cellular carcinoma. The cost of investigating and treating these patients remains and continues to be enormous.

Molecular virology

The structure and replicating cycle are still incompletely understood due to the lack of an efficient cell culture system.

HCV has been classified as a member of the *flaviviridae* family. The other members include classical flaviviruses such as yellow fever, dengue and bovine diarrhoea virus. All members of this family are small-sized enveloped viruses containing antisense single-stranded RNA encoding viral polyprotein (fig. 18.1) [26]. The viral genome is composed of a 5′ non-coding region, a long open reading frame encoding a polyprotein precursor of about 3000 amino acids, and a 3′ non-coding region. The 5′ non-coding region is highly conserved. Because of this and the crucial role played in the translation of the viral polyprotein, the 5′ non-coding region has become a target for the development of nucleic acid-based antiviral agents such as antisense oligonucleotides and ribosomes. The structural proteins include the core protein and two envelope glycoproteins, E1 and E2.

HCV quasi-species

HCV exists within an individual as a mixture of closely related, yet heterogeneous viral sequences known as *quasi-species*. Although mutations occur throughout the entire genome, studies have focused on the hypervariable region, HV01, located at the end terminus of the E2NS1 region. The degree of diversity is related to the progression of liver disease [50]. Mutations follow therapy allowing HCV to escape antiviral effects [45]. Lower heterogeneity increases the response to antiviral therapy for there are fewer variants to evade immune surveillance and so resist treatment [60].

Genotypes

HCV shows considerable heterogeneity, particularly in the viral envelope. Using sequence comparisons, known variants of HCV collected from different parts of the world can be divided into six main genotypes. There are at least 50 more closely related variants [106]. There is considerable geographical variation in the prevalence of the various genotypes (table 18.1).

The major clinical difference between genotypes is the response to antiviral therapy. Sustained response to interferon-α alone or in combination with ribavirin is markedly less for genotype 1 than for genotypes 2 and 3 [15]. Suggestions that genotype 1b results in more serious hepatic disease have not been confirmed [93].

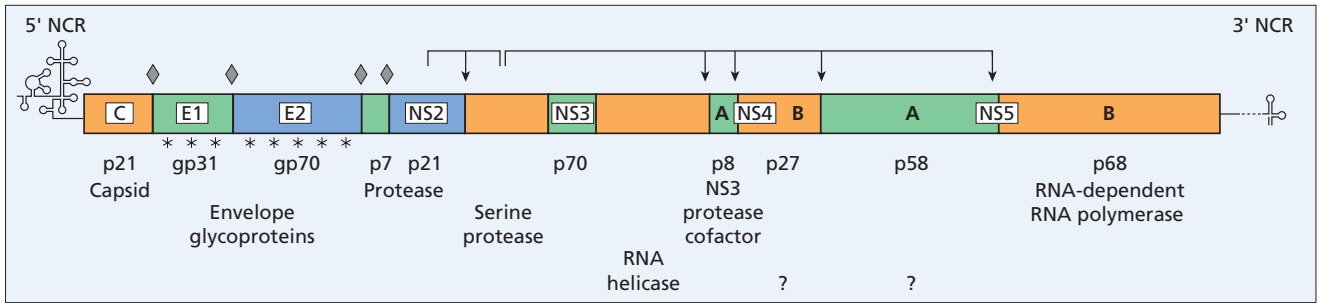


Fig. 18.1. The hepatitis C viral genome. Asterisks in the E1 and E2 region indicate glycosylation of the envelope proteins. Diamonds denote cleavages of the HCV polyprotein precursor by the endoplasmic reticulum signal peptidase. Arrows indicate cleavages by HCV NS2–3 and NS3 proteases. NCR, non-coding region. (From [83].)

Table 18.1. Geographical distribution of HCV genotypes

Area	Type
Europe	1, 2, 3
Australia	1, 2, 3
USA	1, 2, 3
Far East	1, 2
Middle East	4
North Africa	4
South Africa	5
Southeast Asia	6

Type 4, largely found in the Middle East, is also associated with a poor response to interferon.

Other types are not routinely investigated. The method depends on sequence analysis of different regions of the genome [106]. It identifies infection with the genotypes likely to be encountered in Europe, other Western countries and Japan. The investigation is costly. It is used as a preliminary to starting antiviral therapy. Genotype 1 implies worse results and indicates therapy for 1 year, rather than 6 months (see tables 18.5 and 6) [20].

Serological tests

Serological tests for HCV detect antibodies to viral antigens. ELISA is satisfactory for routine screening, particularly of blood donors; it is less sensitive in haemodialysis and immunocompromised patients.

cDNA PCR has been used to detect hepatitis C viral sequences (HCV RNA) in liver and serum [34]. PCR is a supersensitive technique which is complicated, time-consuming and costly. It is also subject to interlaboratory error [125]. It will not achieve routine general use.

The quantitative method is branched DNA (bDNA) signal amplification [63]. It is costly, generally available and easy to perform although less sensitive than PCR. The bDNA signal amplification method is based on hybridization with specific probes in the 5′ non-coding region which are used to capture the HCV bDNA on the surface of the tube. The lower limit of detection is 2×10^5 HCV genome equivalents/ml. The bDNA method is less sensitive than the Amplicor method and may not be sensitive enough to detect virus in all pre-treatment samples.

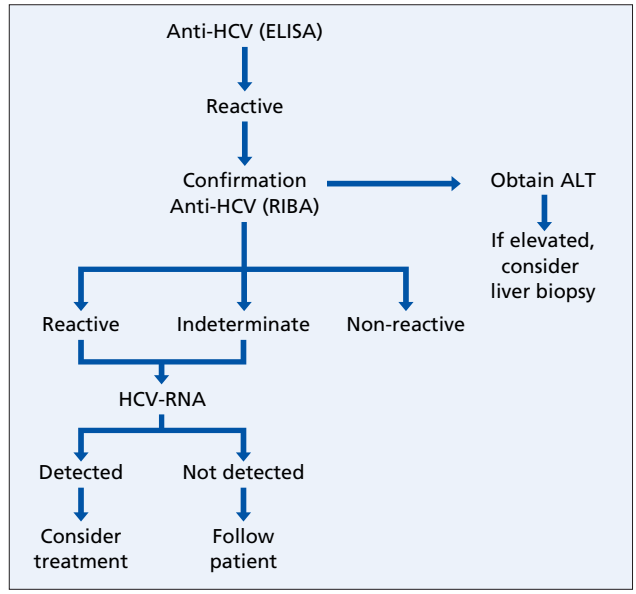


Fig. 18.2. Algorithm for further evaluation of anti-HCV ELISA-positive specimens [27].

The Amplicor HCV kit amplifies HCV RNA in a single reaction using the fairly stable enzyme rTth DNA polymerase [67]. The detection limit is 1000 genome equivalents/ml. Either this or the bDNA technique can be used to follow therapy [77, 78].

In low-risk settings such as blood banks and other general screening situations, approximately 25% of ELISA-positive tests may be false. A supplemental specificity test such as a strip immunoblot assay (RIBA) is recommended (fig. 18.2). Then, quantitative HCV RNA should be performed if anti-HCV positivity is confirmed.

In high-risk populations, and in clinical settings where HCV is suspected, a positive ELISA should be confirmed by a quantitative HCV RNA.

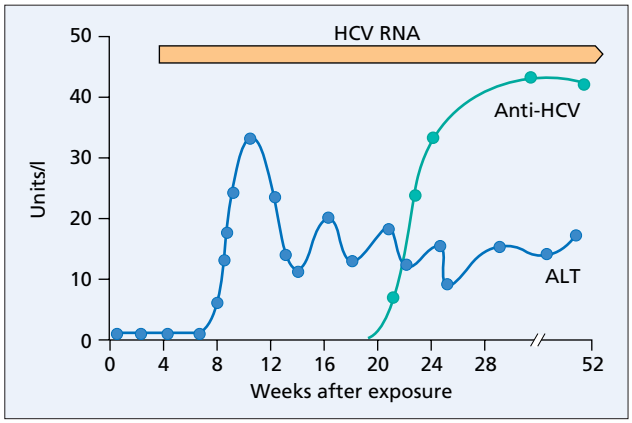


Fig. 18.3. The serology of hepatitis C infection with a chronic course. Note that HCV RNA appears early, before the rise in alanine transferase (ALT) and persists. Anti-HCV positivity is delayed, appearing between 11 and 20 weeks of the onset. ALT shows characteristic fluctuations as chronicity develops.

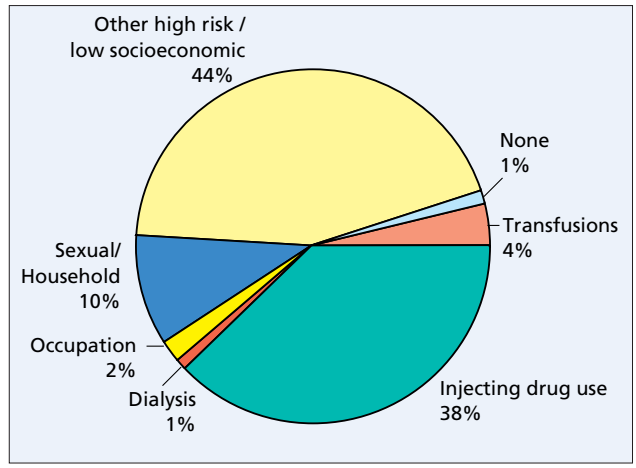


Fig. 18.4. Risk factors associated with acute hepatitis C in the USA (1990–1993). These include sexual or household contacts, health-care employment, multiple exposures to blood and injecting drug abuse. Other high-risk patients include low socioeconomic status and multiple sexual partners. (From the Sentinel Counties, Centers for Disease Control and Prevention [4].)

The ELISA is positive as early as 11 weeks after infection and always within 20 weeks of the onset (fig. 18.3). In patients with acute hepatitis of unknown cause, an ELISA should be performed first. If hepatitis A and B tests are negative, quantitative HCV RNA must be performed. In ELISA-negative patients with chronic hepatitis of unknown cause, particularly in haemodialysis and immunocompromised patients, a quantitative HCV RNA test is essential.

Immune response

The virus-specific CD4+ and Th1+ T-cell response, that eliminates the virus during the acute stage, has to be maintained permanently to achieve long-term control of the virus [39, 86].

There is no association between the course of the disease and the HLA class I alleles (HLA A, B, C) which present viral antigens to CD8+ cytotoxic T-cells. However, there is a significant association between HLA class II alleles (DR, DQ and DP) and protection from HCV chronicity. HLA class II alleles DRB1*1101 and DQB1*0301 are associated with viral clearance [110].

Serological tests for autoantibodies (antinuclear, smooth muscle and rheumatoid factor) may be weakly positive, but have not been shown to have a causative role [66].

Epidemiology

Blood transfusion

Hepatitis C is carried by about 0.01–2% of blood donors worldwide [4, 103, 105]. The risk factors associated with acute hepatitis C in the USA are present or past injecting of drugs, previous transfusions, health-care employment, sexual/household contact and a low socioeconomic status (fig. 18.4) [4]. Egypt seems to have the highest prevalence in blood donors [1]. Anti-HCV was found in 12% of rural primary children, 22.1% of army recruits and 16.4% in children with hepato-splenomegaly [1].

The introduction of second-generation screening for anti-HCV has greatly reduced the incidence of post-transfusion hepatitis [31, 41, 54].

Other blood products

Thalassaemics, because of repeated blood transfusions, have an anti-HCV prevalence of between 10 and 50%.

Until about 1964, therapeutic coagulation factors contained HCV. This has resulted in a prevalence of nearly 100% HCV in haemophiliac patients receiving unsterilized large-pool coagulation factors [70, 117]. Introduction of vapour-heated and recombinant clotting factors has controlled this method of spread.

Patients with primary hypogammaglobulinaemia have developed hepatitis C after treatment with contaminated immunoglobulin [13, 122].

Contaminated anti-rhesus D immunoglobulin has caused large outbreaks of HCV in Ireland [92] and Germany [30].

Parenteral exposure

The chances of HCV after a needle-stick exposure to a patient with a positive HCV, RNA is 3–10% [82, 107].

Dentists are at risk of acquiring HCV, presumably from the blood and saliva of their patients. Oral surgeons are at particular risk [59]. An infected surgeon can transmit HCV to patients [32].

Dialysis patients develop HCV, not only from blood transfusions, but also by negligent dialysis techniques [89]. The chances of infection increase with the years on dialysis.

Injecting drug users using shared needles and syringes account for most HCV in the USA [85]. The injection may have occurred many years ago, forgotten by the patient [21].

Sexual and intra-familial spread

This is believed to be very low. In most population studies, anti-HCV does not appear until the age of 16 years. This would suggest that sexual transmission is important [108]. There are geographical differences in reported prevalence of sexual transmission. However, consorts of anti-HCV positive haemophiliac patients have tested positive and HCV has been linked with multiple sexual partners [5]. But in a Spanish study, only 6% of heterosexual contacts of injecting drug users were positive [31].

Serum samples of 94 husbands of women with HCV following infection with contaminated immunoglobulin showed no HCV RNA [79]. Only three of their 231 children showed serological evidence of HCV.

Where one member is HCV positive, those with a steady partner should not change their sexual practices. Those with multiple partners should use safe sex methods. Prevalence in homosexuals is 3%, in prostitutes 6% and in heterosexuals attending a sexually transmitted disease clinic 4%.

Intra-familial spread is rare but has been reported with the same strain of HCV [50, 58].

Vertical transmission is infrequent. It is greater if the mother is serum HCV RNA positive [88]. Transmission may be increased by concomitant maternal HIV infection [126]. Infection is more likely if the mother suffers an acute attack in the last trimester. Breast milk does not transmit HCV [72]. Babies born to anti-HCV positive mothers usually have circulating antibody for 6 months, presumably due to passive transfer, but HCV RNA is absent.

In those with no obvious risk factors

Where did the disease come from in the millions of carriers without risk factors? Family spread is possible but rare. Infection may be through sharing razors, toothbrushes or unsterile syringes and needles with infected people. Other possibilities include past abuse of intravenous drugs and folk remedies such as acupuncture and cutting skin using non-sterilized knives [58].

Direct questioning may reveal a risk factor such as a past blood transfusion or intravenous drug abuse.

Hepatitis C is much less infectious than hepatitis B. The passage of large quantities of infective material is necessary for transmission.

Natural history (fig. 18.5)

Hepatitis C is a disease with varying rates of progression, but is generally only slowly progressive. About 15% of infected individuals recover spontaneously. An additional 25% have an asymptomatic disease with persistently normal ALT and generally benign hepatic histology [20]. Hence, 40% of patients recover or have a benign outcome. The majority of those with raised ALT and evidence of chronic hepatitis, have only mild histological changes and the long-term outcome is unknown, but probably most of them will not succumb to the liver disease [3]. About 20% of patients develop cirrhosis in 10–20 years. The incidence of hepato-cellular carcinoma is 1–4% per year in patients with cirrhosis.

Other co-factors such as hepatitis B and D are associated with more serious disease [64]. Alcohol is also an important risk factor and intake should be recorded [91].

Clinical course [73]

Acute hepatitis C

Descriptions are largely based on findings in transfused patients where the time of infection is certain. Clinical presentation of disease after other modes of transmission, such as intravenous drug addiction, is not well documented.

The incubation period is about 7–8 weeks (range 2–26 weeks). Prodromal symptoms are rare. Only 20% of patients become icteric. The symptoms resemble those of

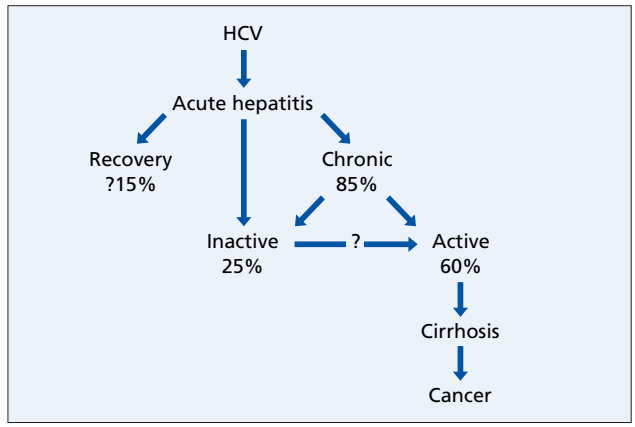


Fig. 18.5. The natural history of HCV infection.

other forms of viral hepatitis. Serum HCV RNA becomes positive 1–2 weeks after infection. At 7–8 weeks, serum ALT is moderately increased to about 15 times the upper limit of normal. Clinical diagnosis is rarely made and this depends on viral markers. Icteric hepatitis is rare and fulminant hepatic failure is controversial [51]. The anti-HIV positive patient may have a rapidly progressive course [76].

Those with self-limited disease develop a normal serum ALT and HCV RNA becomes negative. Anti-HCV persists for many years. Aplastic anaemic [9], agranulocytosis and peripheral neuropathy may be complications.

Chronic hepatitis C

About 85% of those infected with HCV will not clear the virus and will develop chronic hepatitis of varying severity (fig. 18.5) [73]. Viral load fluctuates and in many patients declines with time [33]. The disease is an indolent one extending over many years.

Chronic hepatitis with normal ALT

This is seen in approximately one-third of patients despite detectable HCV RNA in serum. The patients are often diagnosed by chance at the time of blood donation, routine medical check or during investigation for another condition. In most instances, hepatic histology shows only mild disease. HCV RNA is lower than in those with a raised ALT; hepatic fibrosis progression and activity are also lower [53].

Chronic hepatitis with elevated ALT

The severity of the liver disease varies considerably.

Mild chronic hepatitis affects 50% [73]. The main symptom is fatigue associated with musculo-skeletal pain [10]. When HCV is diagnosed the quality of life falls [96]. Part of this may be the result of labelling. There is no correlation between symptoms, ALT levels and the hepatic histological score.

The course is a slow one, marked by fluctuating transaminases over many years. Each elevation probably represents an episode of HCV viraemia, perhaps due to quasi-species.

Moderate or severe chronic hepatitis is seen in about 50% of newly diagnosed patients with a raised ALT. There are no abnormal physical signs and the ALT is usually 2–10 times the upper limit of normal, but this is a poor marker of disease activity [46]. Serum bilirubin, albumin and prothrombin time are usually normal. Serum HCV RNA values exceeding 10^5 genome equivalents per ml correlate with active disease.

If possible, viral genotype should be checked. Type 1b may be related to increased severity, worse response to antivirals, recurrence after liver transplantation and the possible development of cancer. Type 4 is related to antiviral failure.

Serum autoantibodies should be sought for diagnosis from autoimmune chronic hepatitis and especially if interferon therapy is being considered.

Liver biopsy remains the most accurate way of distinguishing mild from moderate or severe chronic hepatitis.

Cirrhosis

Within two or three decades, cirrhosis develops in 20–30% of HCV-infected patients. It is usually clinically silent and features of end-stage liver disease are late. It may be discovered by liver biopsy in the asymptomatic patient or present as variceal haemorrhage or jaundice. Evidence of portal hypertension is rare; splenomegaly is present in only one-half the patients at presentation. Bleeding from oesophageal varices is unusual until late on. Thrombocytopenia develops as the spleen size increases and this is a good indication that cirrhosis has developed.

Hepato-cellular carcinoma (Chapter 31)

This is generally associated with cirrhosis. It can be found in the compensated case and can be clinically silent for long periods. Screening for hepato-cellular carcinoma is done by 6-monthly serum α-fetoprotein levels and ultrasound of the liver. These should be performed in all cirrhotic patients, particularly if male and more than 40 years old.

Hepatic histology

This is not diagnostic but often makes a characteristic pattern [99]. The most striking feature is the presence of lymphoid aggregates or follicles in the portal tracts, either alone or as part of a general inflammatory infiltration of the tracts (figs 18.6, 18.7) [99]. The aggregates comprise a core of B-cells mixed with many T-helper/inducer lymphocytes. The outer ring is predominantly T-suppressor/cytotoxic lymphocytes [37]. Their presence does not correlate with features of autoimmunity. The prevalence of bile duct damage varies amongst different series [8]. Interface hepatitis is mild but lobular cellular activity is usual. Fatty change is found in 75% of cases, though the mechanism is unclear. The characteristic picture is of mild chronic hepatitis. Chronic hepatitis can exist with cirrhosis or the picture may simply be that of inactive cirrhosis. Appearances bear no relationship to duration or to the transaminase levels at presentation.

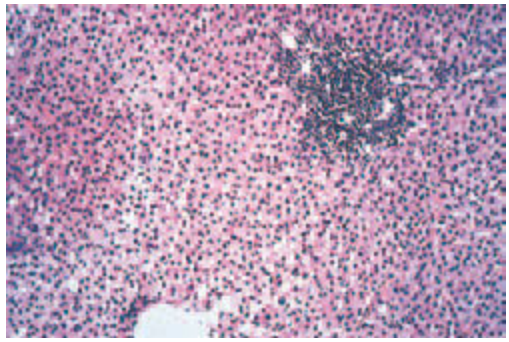


Fig. 18.6. Chronic hepatitis C. Liver biopsy shows a mild chronic active hepatitis with normal zonal architecture and expansion of the portal zone which contains a lymphoid aggregate. Sinusoids show cellular infiltration. (H & E, ×70.)

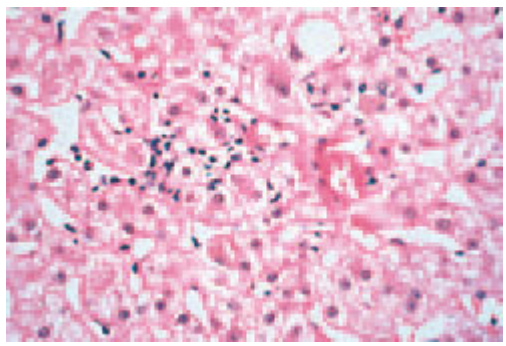


Fig. 18.7. Higher power view of liver biopsy shown in fig. 18.6 shows sinusoidal infiltration with lymphocytes, and acidophil bodies. (H & E, ×100.)

HCV RNA may be detected in liver tissue by PCR assay [52].

Liver biopsy has become increasingly important in the management of HCV infections. Activity and fibrosis score must always be recorded (Chapter 19). Errors in interpretation may be due to difficulties in diagnosing macronodular cirrhosis and to the small size of the sample. Liver biopsies are essential for diagnosis and prognosis, particularly in relation to therapeutic decisions.

Hepatitis C and serum autoantibodies

About 5% of patients with autoimmune hepatitis give false positive tests for anti-HCV and about 10% of patients with HCV have circulating autoantibodies [19]. The two conditions, however, are completely different (table 18.2) [80]. Clinical features of HCV are not modified by the presence of autoantibodies.

An association has been found between HCV and a positive antibody test for LKM-I. This might be related to shared antigenic sites between chronic HCV infection and LKM-I autoimmune chronic hepatitis although detailed analysis has shown the sites to differ [121]. There are clinical differences between the two types. The HCV-related patients are elderly, usually male and have a lower titre of LKM-I.

Table 18.2. Comparison of autoimmune and hepatitis C chronic hepatitis

	Autoimmune	Hepatitis C
Age	Young and middle age	All ages
Sex	Predominantly female	Sexes equal
Transaminases		
AST (10 times)	Usual	Rare
'yo-yo'	Very rare	Usual
HCV RNA	Absent	Present
Contact blood	Absent	Frequent
Corticosteroid response	Rapid fall of transaminases	None or modest

Autoimmune hepatitis can be precipitated by interferon in patients with chronic HCV [38]. This cannot be predicted by pre-treatment autoantibody levels. It is marked by sudden increases in serum ALT values and autoantibody titres. There is a good response to immunosuppressive therapy.

Associated diseases [16, 90]

Cryoglobulins. About 80% of essential mixed cryoglobulinaemia is hepatitis C virus-related [2]. The clinical triad is of asthenia, segmental, non-migratory arthralgias and palpable purpura (fig. 18.8). These classical clinical features are rare, although cryoglobulinaemia can be detected in 36% of HCV-positive patients. These affect more patients in south than in north Europe [120]. It can present after liver transplant, probably related to an increase in HCV RNA levels [43]. It may be associated with more severe liver disease [100].

HCV is not only hepato-trophic, but also lymphotropic. Chronic HCV antigenic stimulation results in polyclonal B-cell activation. The immune complexes consist of HCV and anti-HCV, monoclonal IgM rheumatoid factor, polyclonal IgG and complement (table 18.3). HCV is several times more concentrated in the complexes, than in the corresponding serum [120].

Small vessel vasculitis is associated and this may also affect the kidney as membranous glomerulonephritis [129].

The cryoglobulinaemia may evolve into occult, low-grade, B-cell, non-Hodgkin's lymphoma [95].

Therapy with interferon-α is effective in 50%. Vasculitis and renal function improve and HCV and cryoglobu-

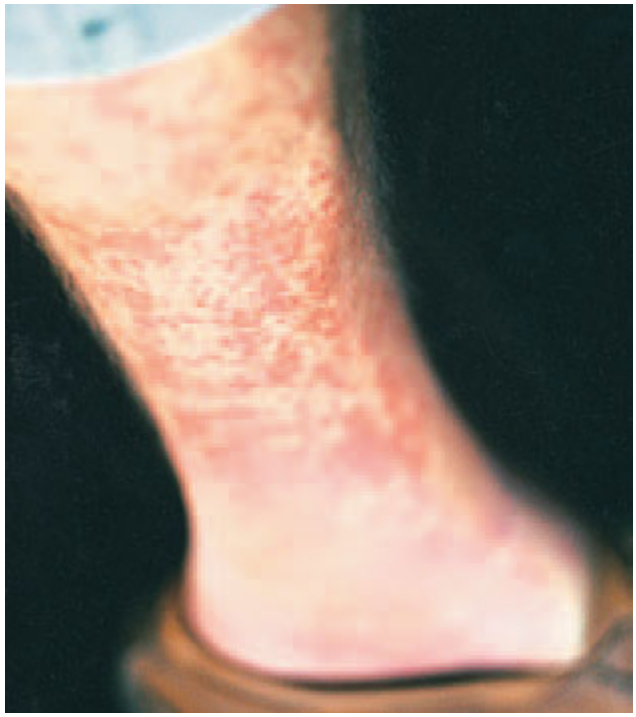


Fig. 18.8. Palpable purpura in a 60-year-old man with chronic HCV infection and cryoglobulinaemia.

Table 18.3. Immune complexes in HCV-related cryoglobulinaemia

Composition	HCV and anti-HCV Monoclonal IgM rheumatoid factor Polyclonal IgG Complement
Clinical associations	Vasculitis Palpable purpura Polyarthritis Non-Hodgkin's lymphoma Glomerulonephritis
Treatment	Interferon-α (?with ribavirin) 80% relapse

lin levels fall [22]. Unfortunately, 80% relapse. The associated underlying chronic liver disease is usually mild.

A lymphocytic sialo-adenitis, resembling Sjögren's syndrome, has been described but without features of sicca syndrome [90].

There is an association with thyroiditis even in patients not treated with interferon [113].

There is a strong association with porphyria cutanea tarda [35] and HCV may be the trigger in predisposed people [49].

Lichen planus is associated with chronic liver disease and HCV has been implicated [44, 90].

Coexistence with alcoholic liver disease increases viraemia and accelerates liver damage.

The strong association of HCV with hepato-cellular carcinoma is discussed in Chapter 31.

Diagnosis

All possible *hepato-toxic drugs* must be sought.

Markers of present *hepatitis B* must be absent. However, some patients with chronic hepatitis due to HBV do get misdiagnosed as HCV when titres of HBsAg and HBV DNA are too low to be detected.

Autoimmune chronic hepatitis is suggested by very high serum transaminase and γ-globulin levels combined with high titres of autoantibodies.

Wilson's disease is excluded.

Prognosis

This is very variable [28]. The risk of a previously healthy person, positive for HCV, developing progressive liver disease is quite low. Of 8568 young United States recruits, 17 were found to be positive for HCV. In a 45-year follow-up, only two developed liver disease [101]. A 17-year follow-up of young women infected with HCV-contaminated globulin revealed little significant chronic liver disease [55].

The prognosis is much worse if the patient has already developed significant fibrosis or cirrhosis [102]. The difficulty is in identifying patients who, over the years, will have progressive fibrosis [93]. Within 5 years, 18% of patients diagnosed with compensated cirrhosis will decompensate and there is a 70% chance of developing hepatocellular carcinoma [36]. The mortality is 2–5% per year.

In an Italian study, 77% of 135 patients with post-transfusion hepatitis developed chronic hepatitis. By the end of 15 years, 65 patients in whom a liver biopsy was performed had developed cirrhosis. Half of the cirrhotic patients progressed to life-threatening complications [114]. In a Japanese study, 20–25 years elapsed after transfusion-hepatitis before the diagnosis of cirrhosis, and about 30 years to hepato-cellular carcinoma [57]. In a group of patients with chronic post-transfusion HCV referred to a tertiary care centre in the USA, the disease was progressive, leading to death from liver failure and hepato-cellular cancer [112].

Progress is usually slower in drug-related than in sporadic disease [36, 42, 56]. Of patients with blood transfusion-related disease, 18% succumb to or develop hepato-cellular cancer within 18 years [29, 112].

Age affects prognosis, but only because it indicates a disease of longer duration.

Males have a worse prognosis than females, perhaps due to the increased likelihood of the development of hepato-cellular cancer.

Genotypes 1b and 4 have been associated with more liver complications [81]. However, this might not be an independent factor, but rather an indicator of longer duration and hence worse hepatic function and more fibrosis.

Viral load does not seem to influence the prognosis. Markers of hepatitis B infection and of HIV worsen the prognosis [12].

Increased alcohol intake is associated with decreased survival. However, this is difficult to assess as patients may reduce their consumption when told of the diagnosis of HCV infection.

Serum albumin is an important indicator of complications such as liver failure and hepato-cellular cancer, and the need for liver transplantation. Patients with a serum albumin level of less than 3 g/dl have a 75% chance of liver transplant or liver-related death after 5 years [56]. Serum bilirubin is also associated with liver-related death and transplant, but to a lesser extent than albumin. Correlation with ALT is poor, but very high values are serious. Liver failure and hepato-cellular cancer are rarely seen less than 20 years after infection. Many patients avoid these complications. Identification of those with severe progressive disease is essential so that cirrhosis and hepato-cellular cancer can be prevented.

Prevention: vaccines

The problem is the lack of an animal model for testing, other than the chimpanzee. A reproducible culture system to propagate the virus is lacking.

Efforts have been made to generate recombinant vaccines by expressing part of the individual structural proteins in soluble form. Unfortunately, the antibody response to these recombinant envelope proteins is late and weak and they do not confer immunity to heterologous or homologous HCV infection [17].

DNA-based immunization is promising in the animal model, but further work is needed against HCV structural proteins in man [61].

HCV-like particles have been synthesized in insects and are capable of inducing a humoral response targeted against various regions of HCV structural proteins [11]. They may be vaccine candidates. Exogenous stimulation of T-cell responses may be a strategy. T-cell epitopes within the core and NS3 and NS4 domains are immunodominant and conserved. They may be ideal components of preventative or therapeutic T-cell vaccines [62].

Treatment (fig. 18.9)

Selection of patients [20] (table 18.4)

Liver biopsy should be performed. Patients with moderate or severe necro-inflammation and/or fibrosis should

Table 18.4. Possible factors predicting a favourable response to antiviral therapy in chronic HCV infection

Host
Age less than 45 years
Female
Non-obese
Duration of infection less than 5 years
No co-infection with HBV
Not immunosuppressed
No alcoholism
ALT modestly increased
Normal γ-glutamyl transpeptidase
Liver biopsy: low activity score
No cirrhosis
Liver iron low
Virus
Low serum HCV RNA
Genotype 2 or 3

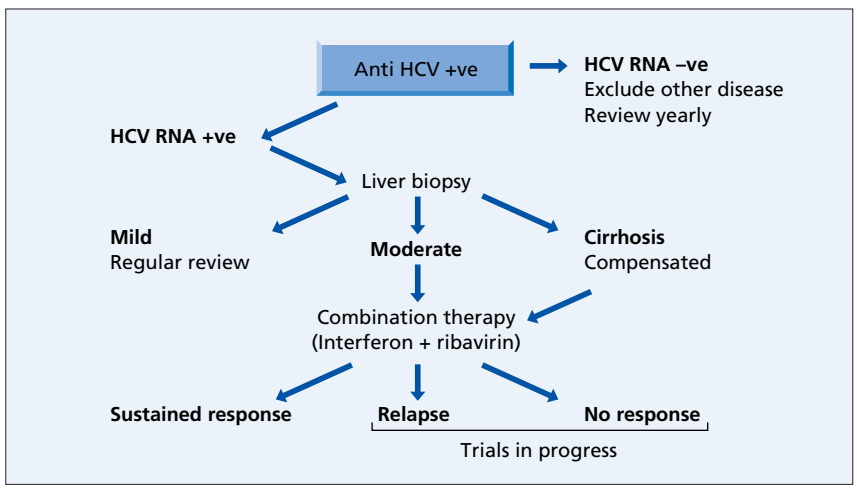


Fig. 18.9. Algorithm for management of the HCV-positive patient.

be considered [87]. It is difficult to decide on treatment in patients with mild hepatic histological changes. These patients should be monitored regularly and, if possible, regression assessed by a further liver biopsy performed about 3 years later [73].

Age. The physiological age is more important than the chronological. General health and cardiovascular status must be considered.

Clinical status. There is a poor correlation between liver histology and clinical status. Symptoms do lessen in patients who achieve a sustained loss of HCV RNA after treatment.

Viraemia. Those with levels exceeding 2 million genome equivalents/ml are less likely to respond, but should not be denied treatment.

Genotype. If possible, this should be recorded. Those with genotype 1 respond less well than genotype 2 or 3 but should not be denied therapy. The lower response in genotype 1 has been attributed to amino acid variations in the NS5A protein of the HCV [84].

HIV co-infection. Therapy can be given in stabilized patients (CD4+ count exceeding 200). Drug interactions should be considered.

Cirrhosis. Compensated patients can be treated. In general, those who are decompensated are excluded.

Persistently normal ALT. Underlying liver disease is usually mild and treatment is withheld. Follow-up of ALT is necessary every 4–6 months.

Acute HCV infection. The decision to treat is not yet certain, but with only a small chance of spontaneous recovery (about 15%), the patient and physician may decide on therapy.

Children [97]. They respond to interferon in a similar fashion to adults and should be accepted using the same guidelines. The effects on growth are not clear. Data for combination are awaited.

Contraindications. These include active, heavy alcohol intake. Active intravenous drug abusers are excluded because of re-infection risk and poor compliance. Those with histologically mild disease may be excluded, particularly if older and with co-morbid conditions.

Monitoring therapy

If possible, liver biopsy is performed. Genotype is recorded. Quantitative tests for HCV RNA are done before treatment and, if possible, after 3 months treatment, at the end of treatment and 6 months later [20].

All patients should be tested for thyroid function before treatment and at regular intervals.

Because of the risk of teratogenicity with ribavirin, women of reproductive potential should have a negative pregnancy test. Men and women should practice safe sex during therapy and for 6 months afterwards.

A full blood count is performed before treatment and at weekly intervals for 4 weeks, then every 3 months during therapy and 6 months later. Baseline ultrasound of the liver should be performed to assess liver size and shape, splenomegaly, portal vein diameter and any space-occupying lesions.

Evaluation of response

In the assessment of efficacy an end of treatment response (ETR) must be distinguished from a sustained response (SR) when HCV-RNA is negative and ALT normal 6 months after stopping treatment. Thus after an ETR, a proportion of patients relapse. Once SR is achieved, relapse is unusual and the long-term outcome is good [74].

Selection of therapy

Previously untreated patients

The combination of interferon-α with ribavirin is the current standard of care for chronic hepatitis C where there is no contraindication [20, 23]. A higher SR using pegylated interferon-α with ribavirin has recently been reported for genotype 1 [71]. Pegylated interferon is more convenient for patients. This combination is becoming accepted as the current choice for untreated patients.

Interferon-ribavirin combination. Ribavirin is an oral guanosine analogue with a broad spectrum of activity against RNA and DNA viruses, including the flavivirus family. It also has immunomodulatory effects. Used alone in patients with chronic HCV, it decreases transaminase levels and hepatic histology may improve, but HCV RNA levels do not fall. Relapse occurrs after withdrawal of therapy. When combined with interferon-α, the antiviral effect is enhanced.

Two large randomized trials in previously untreated (naïve) patients compared combination therapy (interferon-α_{2b} and ribavirin) against monotherapy with interferon-α_{2b} for 48 weeks [69, 94]. Both studies showed more than a two-fold great SR with combination therapy than with monotherapy (38 v 13%, and 43 v 19%). One of the trials compared 24 weeks of treatment [69]. The SR with combined therapy was 31%, and with interferon monotherapy, 6%. Histological improvement was greater in those receiving combination therapy.

An analysis of six other randomized controlled trials in previously untreated patients showed that combined interferon-ribavirin resulted in an approximately three-fold increase in SR over interferon alone (table 18.5) [98]. Although patients with genotype 1 still had a lower SR than genotype 2 and 3, results were a considerable improvement compared with interferon therapy alone.

The recommended dose of ribavirin is 1000–1200 mg (depending on body weight <75 kg or >75 kg) daily by mouth in two doses. Interferon-α is given in a dose of 3 million units three times a week by injection (table 18.6). After 24 weeks of treatment, if HCV RNA by PCR is still positive, treatment is stopped since there is little likelihood of response after this time. If HCV RNA is negative, patients with genotype 1 receive a further 24 weeks of treatment, since SR is higher after 48 than 24 weeks (e.g. 28% versus 16%) [69]. In HCV-RNA negative patients with genotype 2 or 3, treatment is stopped since for these genotypes SR after 24 weeks is similar to that after 48 weeks of therapy (64 v 66%) [69].

Data have shown that SR differs according to the viral load, defined in studies as less than or greater than 2×10^6 genome equivalents/ml. This measure is not, however, currently used to direct the duration of therapy, because of naturally occurring fluctuations in viral load over time, and the variability of quantitative HCV RNA assays.

Combination therapy adds considerably to the cost. It is cost effective, however, if genotype is assessed and therapy continued to 1 year only in those who are genotype 1 and have achieved negative HCV RNA at 24 weeks [124].

Absolute contraindications to combination therapy. Interferon-α should not be used if there is psychiatric disease (psychosis, severe depression, risk of suicide), neutropenia or thrombocytopenia, coronary artery disease or cardiac arrhythmias, decompensated cirrhosis, or renal transplantation. These also rule out interferon monotherapy. Ribavirin should not be used in the absence of a reliable form of contraception or during pregnancy, if there is anaemia or renal insufficiency, or if there is severe heart disease. A minimum baseline of haemoglobin >12 g/dl, neutrophils $>1.5 \times 10^9$/l and platelets $>75 \times 10^9$/l is required.

Adverse effects to combination therapy. These are frequent and often lead to dose reduction. In one study, of those randomized to combination therapy for 48 weeks, 21% discontinued treatment because of side effects [69]. Ribavirin causes dose-dependent haemolysis due to membrane oxidative damage [25], and haemoglobin and serum bilirubin must be monitored during therapy. Haemoglobin can drop by 3–4 g/dl and precipitate symptoms of ischaemic heart disease in those susceptible. Ribavirin is also hyperuricaemic.

The side effects of interferon are described in Chapter 17 (see table 17.8). HCV patients with anti-LKM antibodies may have an increased risk of an adverse hepatic reaction with interferon. Patients must be monitored closely for possible liver dysfunction [111]. Positive pretherapy serum thyroid autoantibodies are a risk factor for subsequent thyroid dysfunction [75, 116].

Pegylated interferon-ribavirin combination. Pegylated interferon is interferon-α covalently bound to a large 40-kDa or 12-kDa branched polyethylene glycol moiety. After one dose, interferon is still present in serum 1 week later [40]. This eliminates the large fluctuations in serum concentration seen with non-pegylated interferons, which have a short half-life, disappearing from blood between daily administration. Treatment based on low doses of standard interferon-α, administered three times a week, is associated with troughs between the doses allowing viral replication to rebound post-injection (day 2) [109]. Thus the estimated half-life of free HCV virions is 2.7 hours. 12×10^6 virions are produced each day. Troughs of interferon concentration facilitate the emergence of resistant forms. Various strategies have been

Table 18.5. Percentage sustained response in six trials of interferon (IFN)–ribavirin (RV) therapy in cirrhotic and non-cirrhotic patients with chronic HCV infection [98]

		Genotype	
Patients	Treatment	1	2 and 3
No cirrhosis	IFN	8	24
	IFN + RV	23	65
Cirrhosis	IFN	1	5
	IFN + RV	7	24

Table 18.6. Chronic hepatitis C: interferon and ribavirin therapy

Pre-treatment		
Serum HCV RNA by PCR		
Liver biopsy		
Genotype		
Routine biochemistry		
Routine haematology		
Prothrombin time		
Abdominal ultrasound		
Thyroid antibodies/function		
Regimen for 6 months		
Interferon-α 3 million units, three times a week*		
Ribavirin 1000–1200 mg daily		
End of 6 months' treatment		
HCV RNA positive	Stop therapy	
HCV RNA negative	Genotype 1	Genotype 2, 3
	Continue 6 more months	Stop therapy
6 months' post-treatment		
Serum HCV RNA		
Serum ALT		

* Pegylated interferon-α if available (see text)

tried to avoid these troughs, including daily large doses [118]. However, compliance and cost were disadvantages.

Pegylated interferon-α has a more sustained antiviral effect. Weekly dosage has the advantage of improved patient convenience and compliance.

The combination of pegylated interferon-α_{2b} (1.5 μg/kg/week) with ribavirin (800 mg/day) for 48 weeks had a significantly higher SR compared with standard interferon-α_{2b} and ribavirin (54% versus 47%) [71]. This benefit was seen particularly in patients with genotype 1 (42% versus 33%), and those without bridging fibrosis/cirrhosis (57% versus 49%). Dose reduction because of adverse effects was necessary in 42% and 34% of patients respectively. Optimization of the dose of the two drugs will require further study [65, 71]. The recommendations for duration of treatment are being assessed in current series.

Patients with contraindications to or side effects from ribavirin

Interferon-α monotherapy is appropriate for these patients. Studies using pegylated interferon-α show it to be more effective than standard interferon. A course of 180 μg weekly pegylated interferon-α_{2a} for 48 weeks gave a 39% SR compared with 19% for standard interferon [127]. In another study pegylated interferon-α_{2b} (1.0 μg/kg/week) for 48 weeks gave an SR of 25% compared with 12% for standard interferon [65]. There was a slightly higher rate of dose reduction and drug discontinuation in those given pegylated interferon in some but not all studies [48, 65, 127].

If standard interferon-α is used the dose is 3 million units by injection three times a week for 12 months. Treatment should be stopped in those not recording a negative HCV RNA after 3 months. Re-treatment of relapsers may be considered if the HCV RNA was undetectable at the end of the first course. Prolonged therapy to 60 weeks may increase the percentage with SR. Long-term therapy may be especially useful in those with high pre-treatment viral load.

Table 18.7. Compensated HCV cirrhosis: once weekly (180 μg) pegylated interferon-α_{2a} compared with thrice weekly non-pegylated interferon [48]

	% ETR	% SR
Pegylated	44	30
Non-pegylated	14	8

ETR, end of treatment response; SR, sustained response.

Patients with compensated HCV cirrhosis

Combination therapy with ribavirin and interferon-α is more effective than interferon-α alone (table 18.5) [69, 94, 98]. The overall results with pegylated interferon/ribavirin are similar to non-pegylated interferon/ribavirin [71]. If ribavirin cannot be used, monotherapy with pegylated interferon-α_{2a} (180 μg/kg/week) has a higher SR than standard interferon after 48 weeks treatment (30% versus 8%) (table 18.7) [48].

Treatment of patients who have relapsed after interferon monotherapy

These patients benefit from combination therapy. In a randomized trial, the SR after combination therapy with ribavirin (49%) was superior to retreatment with interferon-α_{2b} (5%) [24]. In patients with a contraindication to ribavirin, longer courses of higher dose interferon or pegylated interferon-α alone are options [20].

There are currently no guide-lines for the treatment of patients who relapse after combination therapy, or who do not respond to combination or interferon monotherapy [23].

Consensus interferon is genetically engineered to contain the commonest amino acids in natural interferons and may be useful in relapsers or non-responders to previous interferon-α therapy [47]. Further trials are needed to find optimal approach for these patients.

Other treatments

Ursodeoxycholic acid does not affect HCV RNA clearance or liver histology [7]. *Amantadine* has been used in combination with interferon-α. There is conflicting evidence of efficacy and at present there is no clear role for this combination [128].

New antiviral agents. Knowledge of the molecular biology of HCV has led to the identification of specific functions associated with particular regions of the virus. Treatments may be targeted to inhibit specifically encoded functions. These include antisense oligonucleotides targeted against the ribosomal binding site of the 5′ non-translated region of the HCV genome [68]. Protease and helicase inhibitors are under development. Unfortunately, they have not reached the stage of clinical trials. Inosine monophosphate dehydrogenase (IMPDH) inhibitors are being tested.

Conclusion

Combination therapy with interferon-α and ribavirin is the current standard of care for chronic hepatitis C. This offers a 30–65% chance of sustained virological

response, depending on various factors in particular the HCV genotype. For those unable to take ribavirin, interferon-α monotherapy may be used. Pegylated interferon is more convenient than non-pegylated interferon, and gives superior results both as monotherapy, and, on the basis of recently completed large trials, in combination with ribavirin.

The cost and availability makes all these treatments out of reach of the millions of sufferers worldwide. Monitoring therapy, particularly with genotyping and HCV RNA testing, adds to the cost.

The place of suppressive antiviral regimens which reduce the rate of hepatic fibrosis and presumably hepato-cellular carcinoma, despite persistent viraemia, is under discussion. The role of antiviral therapy in reducing the risk of hepato-cellular carcinoma, particularly in responders [123], needs further long-term follow-up.

Hepatic transplantation

Clearly, transplantation should not be considered at the stage of chronic hepatitis but only when the stage of advanced cirrhosis is reached. Age, psychosocial status, economics, infections and previous upper abdominal surgery are among the pre-operative considerations (Chapter 38). Transplant of the cirrhotic liver is difficult because of portal hypertension and poor blood clotting. Removal of a small cirrhotic liver may be difficult.

Hepatitis C usually returns after transplantation and most patients will have histological changes of hepatitis and sometimes cirrhosis [104]. Sixty per cent have biochemical abnormalities but are asymptomatic [14]. However, survival of HCV patients is similar to that seen after transplantation for other aetiologies. HCV-positive donors may be used for HCV-positive recipients [115].

References

1 Abdel-Wahab MF, Zakaria S, Kamel M *et al*. High seroprevalence of hepatitis C infection among risk groups in Egypt. *Am. J. Trop. Med. Hyg*. 1994; **51**: 563.

2 Agnello V, Chung RT, Kaplan IM. A role for hepatitis C virus infection in type II cryoglobulinaemia. *N. Engl. J. Med*. 1992; **327**: 1490.

3 Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. *Semin. Liver Dis*. 2000; **20**: 17.

4 Alter MJ. Epidemiology of hepatitis C in the West. *Semin. Liver Dis*. 1995; **15**: 5.

5 Alter MJ, Coleman PJ, Alexander WJ *et al*. Importance of heterosexual activity in the transmission of hepatitis B and non-A, non-B hepatitis. *JAMA* 1989, **262**: 1201.

6 Alter MJ, Margolis HS, Krawcqnski K *et al*. The natural history of community-acquired hepatitis C in the United States. *N. Engl. J. Med*. 1992; **327**: 1899.

7 Attili AF, Rusticali A, Varriale M *et al*. The effect of ursodeoxycholic acid on serum enzymes and liver histology in patients with chronic active hepatitis. A 12-month double-blind, placebo-controlled trial. *J. Hepatol*. 1994; **20**: 315.

8 Bach N, Thung SN, Schaffner F. The histological features of chronic hepatitis C and autoimmune chronic active hepatitis: a comparative analysis. *Hepatology* 1992; **15**: 572.

9 Bannister P, Miloszewski K, Barnard D *et al*. Fatal marrow aplasia associated with non-A, non-B hepatitis. *Br. Med. J*. 1983; **286**: 1314.

10 Barkhuizen A, Rosen HR, Wolf S *et al*. Musculosketal pain and fatigue are associated with chronic hepatitis C. *Am. J. Gastroenterol*. 1999; **94**: 1355.

11 Baumert TF, Vergalla J, Satol J *et al*. Hepatitis C virus-like particles synthesized in insect cells as a potential vaccine candidate. *Gastroenterology* 1999; **117**: 1379.

12 Benhamou Y, Bochet M, Di Martino V *et al*. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. *Hepatology* 1999; **30**: 1034.

13 Bjoro K, Froland SS, Yun Z *et al*. Hepatitis C infection in patients with primary hypogammaglobulinemia after treatment with contaminated immune globulin. *N. Engl. J. Med*. 1994; **331**: 1607.

14 Böker KHW, Dalley G, Bahr MJ *et al*. Long-term outcome of hepatitis C virus infection after liver transplantation. *Hepatology* 1997; **25**: 203.

15 Brechot C. Hepatitis C virus genetic variability: clinical implications. *Am. J. Gastroenterol*. 1994; **89**: S41.

16 Cacoub P, Renou C, Rosenthal E *et al*. Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicentre study of 321 patients. *Medicine (Baltimore)* 2000; **79**: 47.

17 Choo Q-L, Kuo G, Ralston R *et al*. Vaccination of chimpanzees against infection by the hepatitis C virus. *Proc. Natl. Acad. Sci. USA* 1994; **91**: 1294.

18 Choo Q-L, Kuo G, Weiner AJ *et al*. Isolation of a cDNA clone derived from blood-borne non-A, non-B, viral hepatitis genome. *Science* 1989; **244**: 359.

19 Clifford BD, Donahue D, Smith L *et al*. High prevalence of serological markers of autoimmunity in patients with chronic hepatitis C. *Hepatology* 1995; **21**: 613.

20 Consensus Panel. EASL consensus conference on hepatitis C. *J. Hepatol*. 1999; **30**: 956.

21 Contry-Cantilena C, Van Raden M, Gibble J *et al*. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C infection. *N. Engl. J. Med*. 1996; **334**: 1691.

22 Cresta P, Musset L, Cacoub P *et al*. Response to interferon alpha treatment and disappearing of cryoglobulinaemia in patients infected by hepatitis C virus. *Gut* 1999; **45**: 122.

23 Davis GL. Current therapy for chronic hepatitis C. *Gastroenterology* 2000; **118**: S104.

24 Davis GL, Esteban-Mur R, Rustgi V *et al*. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. *N. Engl. J. Med*. 1998; **339**: 1439.

25 De Franceschi L, Fattovich G, Turrini F *et al*. Hemolytic anaemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: role of membrane oxidative damage. *Hepatology* 2000; **31**: 997.

26 De Francisco R. Molecular virology of the hepatitis C virus. *J. Hepatol.* 1999; **31** (suppl. 1): 47.
27 De Medina M, Schiff ER. Hepatitis C: diagnostic assays. *Semin. Liver Dis.* 1995; **15**: 33.
28 Di Bisceglie AM. Natural history of hepatitis C. Its impact on clinical management. *Hepatology* 2000; **31**: 1014.
29 Di Bisceglie AM, Goodman ZD, Ishak KG *et al*. Long-term clinical and histopathological follow-up of clinical post-transfusion hepatitis. *Hepatology* 1991; **14**: 968.
30 Dittmann S, Roggendorf M, Dukrop J *et al*. Long-term persistence of hepatitis C virus antibodies in a single source outbreak. *J. Hepatol.* 1991; **13**: 323.
31 Esteban JI, Esteban R, Viladomiu L *et al*. Hepatitis C virus antibodies among risk groups in Spain. *Lancet* 1989; **2**: 294.
32 Esteban JI, Gomez J, Martell M *et al*. Transmission of hepatitis C virus by a cardiac surgeon. *N. Engl. J. Med.* 1996; **334**: 555.
33 Fanning L, Kenny-Walsh E, Levis J *et al*. Natural fluctuations of hepatitis C viral load in a homogeneous patient population: a prospective study. *Hepatology* 2000; **31**: 225.
34 Farci P, Alter HJ, Wong D *et al*. A long-term study of hepatitis C virus replication in non-A, non-B hepatitis. *N. Engl. J. Med.* 1991; **325**: 98.
35 Fargion S, Piperno A, Cappellini MD *et al*. Hepatitis C virus and prophyria cutanea tarda: evidence of a strong association. *Hepatology* 1992; **16**: 1322.
36 Fattovich G, Giustini G, Degos C *et al*. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997; **112**: 463.
37 Freni MA, Artuso D, Gerken G *et al*. Focal lymphocytic aggregates in chronic hepatitis C: occurrence, immunohistochemical characterization and relation to markers of autoimmunity. *Hepatology* 1995; **22**: 389.
38 Garcia-Buey L, Garcia-Monzon C, Rodriguez S *et al*. Latent autoimmune hepatitis triggered during interferon therapy in patients with chronic hepatitis C. *Gastroenterology* 1995; **108**: 1770.
39 Gerlach JT, Diepoider HM, Jung M-C *et al*. Recurrence of hepatitis C virus after loss of virus-specific CD4+ T-cell response in acute hepatitis C. *Gastroenterology* 1999; **117**: 933.
40 Glue P, Rouier-Panis R, Sabo R *et al*. A dose-ranging study of pegylated interferon alfa-2b and ribavirin in chronic hepatitis C. *Hepatology* 2000; **32**: 647.
41 Gonzalez A, Esteban JI, Madoz P *et al*. Efficacy of screening donors for antibodies to the hepatitis C virus to prevent transfusion-associated hepatitis: final report of a prospective trial. *Hepatology* 1995; **22**: 439.
42 Gordon SC, Bayati N, Silverman A. Clinical outcome of hepatitis C as a function of mode of transmission. *Hepatology* 1998; **28**: 562.
43 Gourlay J, Ferrell LD, Roberts JP *et al*. Cryoglobulinaemia presenting after liver transplantation. *Gastroenterology* 1996; **110**: 265.
44 Gumber SC, Chopra S. Hepatitis C: a multifaceted disease. Review of extrahepatic manifestations. *Ann. Intern. Med.* 1995; **123**: 615.
45 Hassoba HM, Bzowej N, Berenguer M *et al*. Evolution of viral quasi species in interferon-treated patients with chronic C virus infection. *J. Hepatol.* 1999; **31**: 618.
46 Healy CJ, Chapman RWG, Fleming KA. Liver histology in hepatitis C infection: a comparison between patients with persistently normal or abnormal transaminases. *Gut* 1995; **37**: 274.
47 Heathcote EJL, James S, Mullen KD *et al*. Chronic hepatitis C patients with break-through during interferon therapy can successfully be retreated with consensus interferon. *Hepatology* 1999; **30**: 562.
48 Heathcote EJ, Shiffman ML, Cooksley JE *et al*. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N. Engl. J. Med*. 2000; **343**: 1673.
49 Herrero C, Vicente A, Bruguera M *et al*. Is hepatitis C virus infection a trigger of prophyria cutanea tarda? *Lancet* 1993; **341**: 788.
50 Honda M, Kaneko S, Sakai A *et al*. Degree of diversity of hepatitis C virus quasispeces and progression of liver disease. *Hepatology* 1994; **20**: 1144.
51 Hoofnagle JH, Carrithers RL, Shapiro C *et al*. Fulminant hepatic failure: summary of a workshop. *Hepatology* 1995; **21**: 240.
52 Hosoda K, Omata M, Yukosuka O *et al*. Non-A, non-B chronic hepatitis is chronic hepatitis C: a sensitive assay for detection of hepatitis C virus RNA in the liver. *Hepatology* 1992; **15**: 777.
53 Jamal MM, Soni A, Quinn PG *et al*. Clinical features of hepatitis-C infected patients with persistently normal alanine transferase levels in the south-western United States. *Hepatology* 1999; **30**: 1307.
54 Japanese Red Cross Non-A, Non-B Hepatitis Research Group. Effect of screening for hepatitis C virus antibody and hepatitis B virus core antibody on incidence of post-transfusion hepatitis. *Lancet* 1991; **338**: 1040.
55 Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. *N. Engl. J. Med.* 1999; **140**: 1228.
56 Khan MH, Farrell GC, Byth K *et al*. Which patients with hepatitis C develop liver complications? *Hepatology* 2000; **31**: 513.
57 Kiyosawa K, Sodeyama T, Tanaka E *et al*. Inter-relationship of blood tranfusion, non-A, non-B hepatitis and hepatocellular carcinoma: analysis by detection of antibody to hepatitis C virus. *Hepatology* 1990; **12**: 671.
58 Kiyosawa K, Tanaka E, Sodeyama T *et al*. Transmission of hepatitis C in an isolated area in Japan: community-acquired infection. *Gastroenterology* 1994; **106**: 1596.
59 Klein RS, Freeman K, Taylor PE *et al*. Occupational risk for hepatitis C virus infection among New York City dentists. *Lancet* 1991; **338**: 1539.
60 Koizumi K, Enomoto N, Kurosaki M *et al*. Diversity of quasispecies in various disease stages of chronic hepatitis C virus infection and its significance in interferon treatment. *Hepatology* 1995; **22**: 30.
61 Koziel M, Liang T. DNA vaccines and viral hepatitis. Are we going around in circles? *Gastroenterology* 1997; **112**: 1410.
62 Lamonaca V, Missale G, Urbani S *et al*. Conserved hepatitis C virus sequences are highly immunogenic for CD4+ T-cells: implications for vaccine development. *Hepatology* 1999; **30**: 1088.
63 Lau JYN, Davis GL, Kniffen J *et al*. Significance of serum hepatitis C virus RNA levels in chronic hepatitis C. *Lancet* 1993; **341**: 1501.

64 Liaw YF. Role of hepatitis C virus in dual and triple hepatitis virus infection. *Hepatology* 1995; **22**: 1101.

65 Lindsay KL, Trepo C, Heintges T *et al*. A randomised, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. *Hepatology* 2001; **34**: 395.

66 Lunel F. Hepatitis C virus and autoimmunity: fortuitous association or reality? *Gastroenterology* 1994; **107**: 1550.

67 Lunel F, Cresta P, Vitour D *et al*. Comparative evaluation of hepatitis C virus RNA quantification by branched DNA, NASBA and monitor assays. *Hepatology* 1999; **29**: 528.

68 Macejak DG, Jensen SF, Domenico K *et al*. Inhibition of hepatitis C virus (HCV)-RNA-dependent transaction and replication of a chimeric HCV poliovirus using synthetic stabilized ribozymes. *Hepatology* 2000; **31**: 769.

69 McHutchinson JG, Gordon SC, Schiff ER *et al*. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for hepatitis C. *N. Engl. J. Med.* 1998; **339**: 1485.

70 Makris M, Preston FE, Triger DR *et al*. Hepatitis C antibody and chronic liver disease in haemophilia. *Lancet* 1990; **335**: 1117.

71 Manns MP, McHutchinson JG, Gordon SC *et al*. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958.

72 Manzini P, Saracco G, Cerchier A *et al*. Human immunodeficiency virus infection as risk factor for mother-to-child hepatitic C virus transmission: persistence of anti-hepatitis C virus in children is associated with the mother's antihepatitis C immunoblotting patterns. *Hepatology* 1995; **21**: 328.

73 Marcellin P. Hepatitis C: the clinical spectrum of the disease. *J. Hepatol.* 1999; **31** (suppl. 1): 9.

74 Marcellin P, Boyer N, Gervais A *et al*. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alfa therapy. *Ann. Intern. Med.* 1997; **127**: 875.

75 Marcellin P, Pouteau M, Benhamou J-P. Hepatitis C virus infection, alpha interferon therapy and thyroid dysfunction. *J. Hepatol.* 1995; **22**: 364.

76 Martin P, Di Bisceglie AM, Kassianides C et al. Rapidly progressive non-A, non-B hepatitis in patients with human immunodeficiency virus infection. *Gastroenterology* 1989; **97**: 1559.

77 Martinot-Peignous M, Boyer N *et al*. A new step toward standardization of serum hepatitis C virus-RNA quantification in patients with chronic hepatitis C. *Hepatology* 2000; **31**: 726.

78 Martinot-Peignous M, Marcellin P, Gournay J *et al*. Detection and quantification of serum HCV-RNA by branched DNA amplification in anti-HCV positive blood donors. *J. Hepatol.* 1994; **20**: 676.

79 Meisel H, Reip A, Faltus B *et al*. Transmission of hepatitis C virus to children and husbands by women infected with contaminated anti-D immunoglobulin. *Lancet* 1995; **345**: 1209.

80 Meyer zum Buschenfelde K-H, Lohse AW. Immune hepatitis. *N. Engl. J. Med.* 1995; **333**: 1004.

81 Mita E, Hayashi N, Kanazawa Y *et al*. Hepatitis C virus genotype and RNA titre in progression of type C chronic liver disease. *J. Hepatol.* 1994; **21**: 486.

82 Mitsui T, Iwano K, Masuko K *et al*. Hepatitis C infection in medical personnel after needlestick accident. *Hepatology* 1992; **16**: 1109.

83 Moradpour D, Blum HE. Hepatitis C—virology and diagnosis. *Falk. Liver week Basle* 1998.

84 Murakami T, Enomoto N, Kubosaki M *et al*. Mutations in nonstructural protein 5A gene and response to interferon in hepatitis C virus genotype 1 infection. *Hepatology* 1999; **30**: 1045.

85 Murphy EL, Bryzman SM, Glynn SA *et al*. Risk factors for hepatitis C virus infection in United States blood donors. *Hepatology* 2000; **31**: 756.

86 Naoumov NV. Hepatitis C virus-specific CD4+ T-cells: do they help or damage? *Gastroenterology* 1999; **117**: 1012.

87 National Institutes of Health. Consensus development conference. Panel statement: management of hepatitis C. *Hepatology* 1997; Suppl. 1: 25.

88 Ohto H, Terazawa S, Sasaki N *et al*. Transmission of hepatitis C virus from mothers and infants. *N. Engl. J. Med*. 1994; **330**: 744.

89 Okuda K, Hayashi H, Kobayashi S *et al*. Mode of hepatitis C infection not associated with blood transfusion among chronic haemodialysis patients. *J. Hepatol.* 1995; **23**: 28.

90 Pawlotsky J-M, Yahia MB, Andre C *et al*. Immunological disorders in C virus chronic active hepatitis: a prospective case-controlled study. *Hepatology* 1994; **19**: 841.

91 Pessione F, Degos F, Marcellin P *et al*. Effect of alcohol consumption on serum hepatitis C virus RNA and histological lesions in chronic hepatitis C. *Hepatology* 1998; **27**: 1717.

92 Power JP, Lawlor E, Davidson F *et al*. Molecular epidemiology of an outbreak of infection with hepatitis C virus in recipients of anti-D immunoglobulin. *Lancet* 1995; **345**: 1211.

93 Poynard T, Bedossa P, Opolon P *et al*. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *Lancet* 1997; **349**: 825.

94 Poynard T, Marcellin P, Lee SS *et al*. Randomised trial of interferon α 2b plus ribavirin for 48 weeks or for 24 weeks versus interferon α 2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet* 1998; **352**: 1426.

95 Rasul I, Shepherd FA, Kamel-Reid S *et al*. Detection of occult low-grade B-cell non-Hodgkin's lymphoma in patients with chronic hepatitis C infection and mixed cryoglobulinemia. *Hepatology* 1999; **29**: 543.

96 Rodger AJ, Jolley D, Thompson SC *et al*. The impact of a diagnosis of hepatitis C virus on quality of life. *Hepatology* 1999; **30**: 1299.

97 Sawada A, Tajiri H, Kozawara K *et al*. Favourable response to lymphoblastoid interferon-alpha in children with chronic hepatitis C. *J. Hepatol.* 1998; **28**: 184.

98 Schalm SW, Weiland O, Hawsen BE *et al*. Interferon-ribavirin for chronic hepatitis C with and without cirrhosis: analysis of individual patient data of six controlled trials. *Gastroenterology* 1999; **117**: 408.

99 Scheuer PJ, Ashrafzadeh P, Sherlock S *et al*. The pathology of hepatitis C. *Hepatology* 1992; **15**: 567.

100 Schmidt WN, Stapleton JT, La Brecque DB *et al*. Hepatitis C virus (HCV) infection and cryoglobulinemia: analysis of whole blood and plasma HCV-RNA concentrations and correlation with liver histology. *Hepatology* 2000; **33**: 737.

101 Seeff LB, Miller RN, Rabkin CS *et al*. 45-year follow-up of

hepatitis C virus infection in healthy young adults. *Ann. Intern. Med.* 2000; **132**: 105.
102 Serfaty L, Annatire H, Chazowillieres O *et al*. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. *Hepatology* 1998; **27**: 1435.
103 Shakil AO, Conrry-Cantilena C, Alter HJ *et al*. Volunteer blood donors with antibody to hepatitis C virus: clinical, biochemical and virologic and histological features. *Ann. Intern. Med.* 1995; **123**: 330.
104 Sheiner PA. Hepatitis C after liver transplantation. *Semin. Liver Dis*. 2000; **20**: 201.
105 Sherlock S. Chronic hepatitis C. *Disease-a-Month* 1994; **40**: 122.
106 Simmonds P. Viral heterogeneity of the hepatitis C virus. *J. Hepatol.* 1999; **31** (Suppl. 1): 54.
107 Sodeyama T, Kiyosawa K, Urushihara A *et al*. Detection of hepatitis C virus markers and hepatitis C virus genomic RNA after needlestick accident. *Arch. Intern. Med.* 1993; **153**: 1565.
108 Tedder RS, Gibson RJC, Briggs M *et al*. Hepatitis C virus: evidence for sexual transmission. *Br. Med. J.* 1991; **302**: 1299.
109 Thomas HC, Torok ME, Forton DM *et al*. Possible mechanisms of action and reasons for failure of antiviral therapy in chronic hepatitis C. *J. Hepatol.* 1999; **31** (suppl. 1): 152.
110 Thursz M, Yallon R, Goldin R *et al*. Influence of MHC class II genotype on outcome of infection with hepatitis C virus. *Lancet* 1999; **354**: 2119.
111 Todros L, Saracco G, Durazzo M *et al*. Efficacy and safety of interferon alfa therapy in chronic hepatitis C with autoantibodies to liver–kidney microsomes. *Hepatology* 1995; **22**: 1374.
112 Tong MJ, el-Farra NS, Reikes AR *et al*. Clinical outcomes after tranfusion-associated hepatitis C. *N. Engl. J. Med.* 1995; **332**: 1463.
113 Tran A, Quaranta J-F, Benzaken S *et al*. High prevalence of thyroid autoantibodies in a prospective series of patients with chronic hepatitis C before interferon therapy. *Hepatology* 1993; **18**: 253.
114 Tremolada F, Casarin C, Alberti A *et al*. Long-term follow-up of non-A, non-B (type C) post-tranfusion hepatitis. *J. Hepatol.* 1992; **16**: 273.
115 Vargas HE, Laskus T, Wang L-F *et al*. Outcome of liver transplantation in hepatitis C virus-infected patients who received hepatitis C virus-infected grafts. *Gastroenterology* 1999; **117**: 149.
116 Watanabe U, Hashimoto E, Hisamitsu T *et al*. The risk factor for development of thyroid disease during interferon-alpha therapy for chronic hepatitis C. *Am. J. Gastroenterol.* 1994; **89**: 399.
117 Watson HG, Ludlam CA, Rebus S *et al*. Use of several second-generation serological assays to determine the true prevalence of hepatitis C virus infection in haemophiliacs treated with non-virus inactivated factor VII and IX concentrates. *Br. J. Haematol.* 1992; **80**: 514.
118 Weiland O. New pieces in the hepatitis C treatment puzzle. *J. Hepatol*. 2000; **33**: 452.
119 Weiner AJ, Kuo G, Bradley DW *et al*. Detection of hepatitis C viral sequences in non-A, non-B hepatitis. *Lancet* 1990; **335**: 1.
120 Weiner SF, Berg T, Berthold H *et al*. A clinical and virologic study of hepatitis C virus-related cryoglobulinemia in Germany. *J. Hepatol.* 1998; **29**: 375.
121 Yamamoto AM, Cresteil D, Homberg JC *et al*. Characterization of antiliver–kidney microsome antibody (anti-LKM1) from hepatitis C virus-positive and virus-negative sera. *Gastroenterology* 1993; **104**: 1762.
122 Yap PL, McOmish F, Webster ADB *et al*. Hepatitis C virus transmission by intravenous immunoglobulin. *J. Hepatol.* 1994; **21**: 455.
123 Yoshida H, Shiratori Y, Moriyama M *et al*. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. *Ann. Intern. Med.* 1999; **131**: 174.
124 Younossi ZM, Singer ME, McHutchinson JC *et al*. Cost effectiveness of interferon alfa 2b combined with ribavirin for the treatment of chronic hepatitis C. *Hepatology* 1999; **30**: 1318.
125 Zaaijer HL, Cuypers HTM, Reesink HW. Reliability of polymerase chain reaction for detection of hepatitis C virus. *Lancet* 1993; **341**: 722.
126 Zanetti AR, Tanzi E, Paccagnini S *et al*. Mother-to-infant transmission of hepatitis C virus. *Lancet* 1995; **345**: 289.
127 Zeuzem S, Feinman SV, Rasenack J *et al*. Peginterferon alfa-2a in patients with chronic hepatitis C. *N. Engl. J. Med*. 2000; **343**: 1666.
128 Zeuzem S, Teuber G, Naumann U *et al*. Randomized, double-blind, placebo, controlled trial of interferon-alfa 2a with and without amantadine as initial treatment for chronic hepatitis C. *Hepatology* 2000; **32**: 835.
129 Zignego AL, Brechot C. Extra-hepatic manifestations of HCV infection: facts and controversies. *J. Hepatol.* 1999; **31**: 369.

Chapter 19
Chronic Hepatitis: General Features, and Autoimmune Chronic Disease

The spectrum of chronic inflammatory diseases of the liver extends from acute hepatitis to chronic hepatitis and finally to cirrhosis. Whatever the aetiology, the same basic underlying liver histology is seen. The physician must be aware of the mode of presentation and of the associated laboratory findings which suggest the diagnosis (table 19.1).

Chronic hepatitis is defined as a chronic inflammatory reaction in the liver.

Clinical presentation

The most important symptom is fatigue. Viral causes (hepatitis B and C) may be identified at the time of a blood donation. Abnormal biochemical tests or viral markers may be found at the time of a routine check-up. Rarely, the disease may be recognized when recovery fails following an attack of acute viral hepatitis.

Chronic hepatitis B is suggested by the ethnic origin of the patient, homosexuality, drug abuse or a likely contact with the blood of persons carrying HBV.

The history of receiving a blood transfusion or blood products, or of drug abuse, however distant, suggests hepatitis C. The patient may bring a chart recording fluctuating serum transaminase levels over many months or years.

An autoimmune aetiology may be suggested (p. 328), but in some patients the cause is unknown.

Symptoms include nausea, upper abdominal pain, and muscle and joint aches. A patient questionnaire may be useful but difficult to interpret.

Clinical signs include jaundice, rarely vascular spiders, a large or small liver and splenomegaly.

Clinically diagnosable and symptomatic portal hypertension (ascites, bleeding oesophageal varices) are late.

Serum transaminase values are usually increased and γ-globulin concentration is also elevated. Serum bilirubin, albumin and phosphatase are normal except in severe disease.

Serum transaminase levels do not always reflect the severity of the underlying liver disease as shown by liver biopsy, but can be used for an approximate grading:

Table 19.1. The investigation of suspected chronic hepatitis

Presentation
Fatigue: generally unwell
Following blood donation—positive hepatitis B or C test
Following acute hepatitis—failure of recovery, whether clinical or biochemical or both
Abnormal liver function tests or positive hepatitis B or C markers at routine check-up
Abnormal physical findings—hepatomegaly, splenomegaly, jaundice
Blood transfusions in the past
Drug abuse in the past
Careful history and physical examination
Routine laboratory tests
Liver function tests
Bilirubin
Aspartate transaminase (SGOT)
Alanine transaminase (SGPT)
Gamma-globulin
Albumin
Alkaline phosphatase
Haematology
Haemoglobin
White cell count
Platelet count
Prothrombin time
Special tests
Serum antibodies
nuclear
smooth muscle
mitochondrial
liver/kidney microsomal
HBsAg
HBeAg
HBeAb
HBV DNA
Anti-HCV and HCV RNA
Serum iron, transferrin
Serum ferritin
Serum caeruloplasmin and copper
Slit lamp cornea
Alpha-fetoprotein
Needle liver biopsy
Haematoxylin and eosin and connective tissue stains
Ultrasound
Liver, spleen, portal vein

- *Mild:* less than 100 iu/l (up to three times the upper limit of normal).
- *Moderate:* 100–400 iu/l (up to 10 times the upper limit of normal).
- *Severe:* more than 400 iu/l (over 10 times the upper limit of normal).

Hepatic histology [22]

The portal zones are expanded by an inflammatory infiltrate primarily of lymphocytes and plasma cells (figs 19.1, 19.2). There is some fibrosis with increasing severity. The inflammation extends into the liver lobule causing erosion of the limiting plate (fig. 19.3). Individual hepatocytes show swelling (ballooning degeneration), shrinkage (acidophilic change) and the formation of acidophil bodies. Cholestasis is rare. There may be bile duct damage especially in hepatitis C virus-related cases. The histological picture may resemble acute viral hepatitis but the duration is longer and the picture is predominantly that of intra-lobular inflammation and necrosis. The necrosis may be focal (spotty) involving single cells or groups of cells.

The most severe form is marked by large areas of confluent necrosis with isolation of groups of liver cells in the form of rosettes (figs 19.4, 19.5, 19.6).

Confluent necrosis linking vascular structures is called *bridging necrosis* (fig. 19.1). This may be between portal tracts or between portal zones and terminal venules which is more serious.

Cirrhosis is defined as widespread fibrosis with nodule formation (Chapter 21). The normal zonal architecture of the liver cannot be recognized (fig. 19.7). This is a sequel of chronic hepatitis.

The role of liver biopsy (table 19.2)

This is essential for diagnosis and to indicate the possible aetiology. Activity may be graded and the stage of the disease evaluated. The presence of cirrhosis may be established. Treatment can be evaluated.

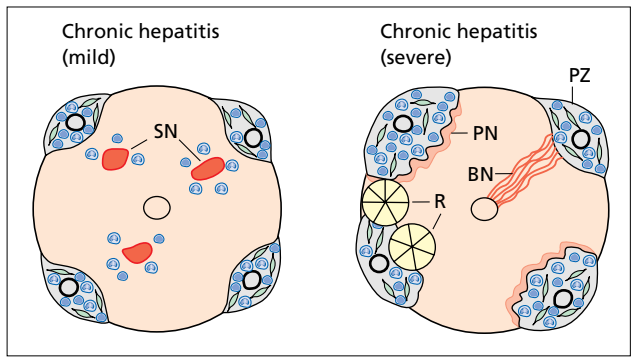


Fig. 19.1. Pattern of histological charges in chronic hepatitis. BN, bridging necrosis; PN, piecemeal necrosis; PZ, portal zone; R, rosettes; SN, spotty necrosis.

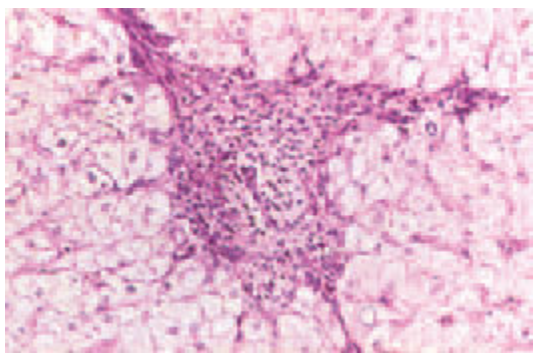


Fig. 19.2. Mild chronic hepatitis. Part of the liver biopsy shows an inflamed expanded portal zone but a well-defined limiting plate and no interface hepatitis. (H & E, ×100.)

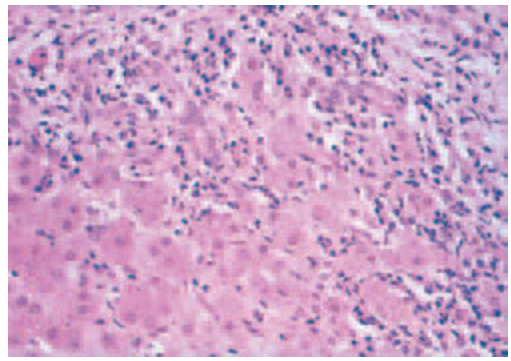


Fig. 19.3. Mild chronic hepatitis. Part of a liver biopsy specimen, showing necrosis of the limiting plate in the portal zone. (H & E, ×100.)

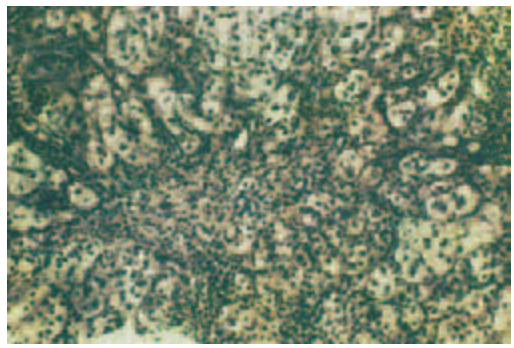


Fig. 19.4. Severe chronic hepatitis. The zonal architecture is completely disturbed. Isolated groups of liver cells, which often assume a rosette-like appearance, are separated by the septa of connective tissue. Remaining cells are large with clear cytoplasm. Lymphocytic and plasma cell infiltration is conspicuous. (H & E, ×40.)

The liver lesion may vary in severity from place to place and this accounts for sampling errors which are particularly likely if the liver biopsy is small.

It can be difficult to distinguish peri-portal necrosis from simple spillover of inflammatory cells, as in acute hepatitis.

In cholestatic diseases, peri-portal hepatocytes may swell and become necrotic. However, lymphocytes are usually sparse, neutrophils prominent and hepatocellular copper is often increased.

Difficulties in diagnosing cirrhosis on small samples are discussed in Chapter 21. An experienced histopathologist, armed with reticulin stains, is needed.

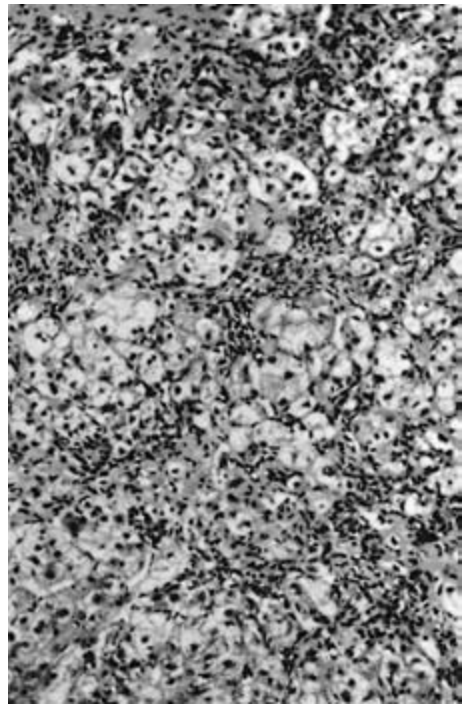


Fig. 19.6. Severe chronic hepatitis, showing the isolation of cell groups, fibrosis and many plasma cells. (H & E,×40.)

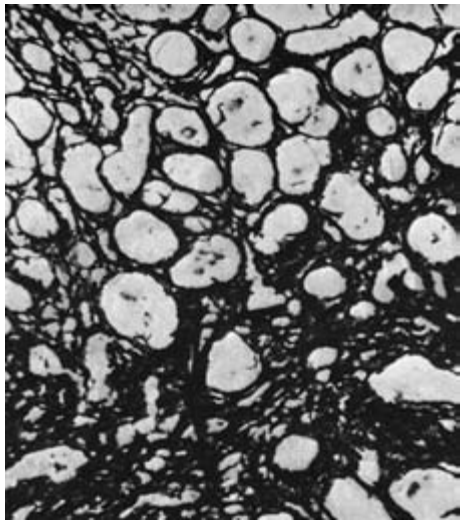


Fig. 19.5. Same case as fig. 19.4. Reticulin stains confirm the isolation of liver cells by bands of fibrous tissue. (×120.)

Table 19.2. Liver biopsy in chronic hepatitis

Confirms diagnosis
Suggests possible aetiology
Grades activity (inflammation)
Stages progress (fibrosis)
Confirms cirrhosis
Evaluates treatment

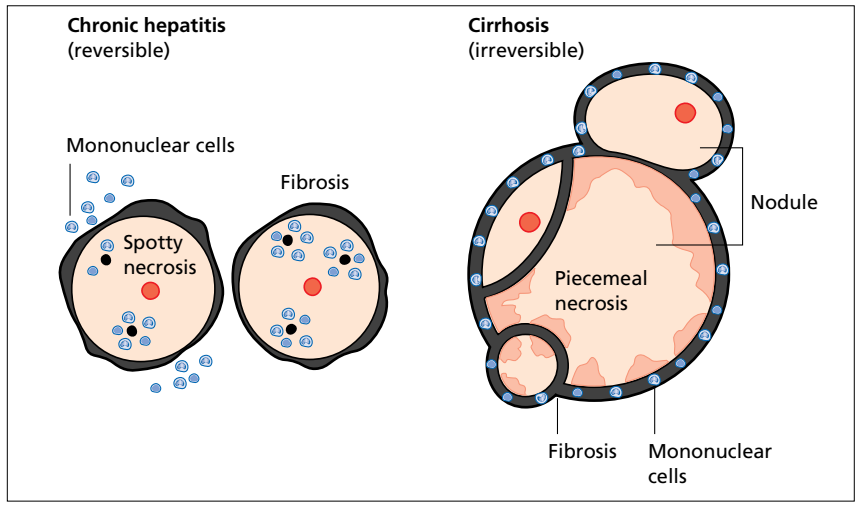


Fig. 19.7. In chronic hepatitis the zonal architecture of the liver is preserved. In cirrhosis, nodular regeneration leads to loss of the essential hepatic architecture. Chronic hepatitis is essentially reversible, cirrhosis is not.

Classification

This is based on aetiology, clinical grade, histological grade (necro-inflammatory activity) and the stage (extent of fibrosis) (table 19.3) [8, 12].

Aetiology

A common clinical, biochemical and hepatic histological picture can be associated with more than one aetiological agent (fig. 19.8). Three main types are seen. One is associated with continuing hepatitis B infection, another is related to chronic hepatitis C infection and the third is termed 'autoimmune' because of the association with positive serum autoantibodies (table 19.4).

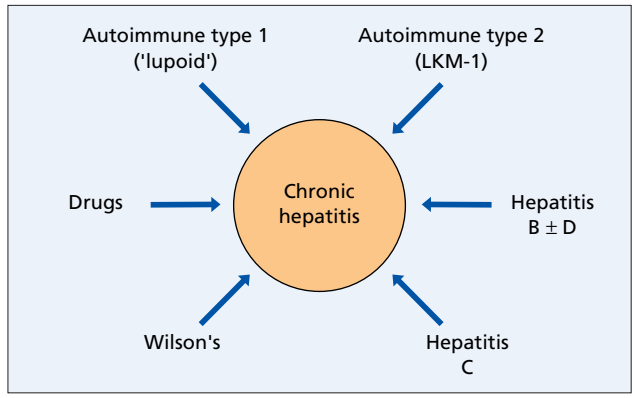


Fig. 19.8. The spectrum of chronic hepatitis.

Table 19.3. Classification of chronic hepatitis [35]

Aetiology	Sex predominance	Age predominance	Associations	Diagnostic tests	Histological features
Hepatitis B and delta	Male	All	Immigrants from Orient, Africa and Mediterranean, health-care workers, homosexuals, drug abusers, immunosuppressed	HBsAg HBeAg Anti-HBe HBV DNA Anti-HDV	Usually mild. Ground glass cells, orcein positive. Delta antigen in hepatocyte nuclei
Hepatitis C	Equal	All ages	Blood transfusion, blood products, drug abuse	Anti-HCV HCV RNA	Fat, lobular component Lymphoid aggregates
Autoimmune	Female	14–25 years and post-menopausal	Multi-system (diabetes, arthralgia, haemolytic anaemia, nephritis)	Antinuclear antibody +ve 70% Smooth muscle antibody +ve 70% Serum γ-globulin high	Rosettes, plasma cell infiltrates, bridging Florid picture
Drug	Female	Middle-aged and elderly	Isoniazid, methyl dopa, nitrofurantoin, dantrolene propylthiouracil, etc.	History, liver histology	Eosinophils, fat, granulomas
Wilson's	Equal	10–30 years	Family history, haemolysis, neurological signs	Kayser–Fleischer rings Serum copper, caeruloplasmin, urinary copper, liver copper	Ballooned hepatocytes, glycogenic nuclei, fat

Table 19.4. Chronic active hepatitis: comparison of types

	Autoimmune type 1	Hepatitis B	Hepatitis C
Sex predominance	Female	Male	Equal
Age preference	15–25 years Menopause	Older Neonates	All ages
Serum HBsAg	Absent	Present	Absent
Serum anti-HCV	Absent	Absent	Present
Autoimmune disease	Frequent	Rare	Occasional
Serum γ-globulin increase	Marked	Moderate	Moderate
Smooth muscle antibody and ANF	High titre (70%)	Low or absent titre	Low or absent titre
Risk of primary liver cancer	Low	High	High
Response to corticosteroids	Good	Poor	Poor

ANF, antinuclear factor.

In the neonate, and occasionally in the immunosuppressed patient, other viral infections such as cytomegalovirus may lead to chronic hepatitis. Identical clinical, functional and morphological features may be found associated with some drug reactions (Chapter 20). α_1-Antitrypsin deficiency may lead to a chronic hepatitis but more often presents as cholestasis in the neonate (Chapter 25). A liver biopsy in the alcoholic occasionally shows the picture of chronic hepatitis (Chapter 22).

Clinical severity

Transaminases are commonly used to approximate clinical severity. Once cirrhosis has developed, the Child's grade is used which is related to bilirubin, albumin, prothrombin values and whether or not hepatic encephalopathy and ascites are present (Chapters 10, 21).

Histological grade and stage

In 1981, Knodell *et al.* introduced the *histological activity index* (HAI), a scoring system based on three categories for necro-inflammation and one for fibrosis (table 19.5) [26]. This has since been modified to cover grade and stage. *Grade* is based on necro-inflammation and is a measure of ongoing disease (table 19.6). *Stage* is based on fibrosis and remodelling and indicates long-term disease progression (table 19.7).

Intra- and inter-observer error is greater for grade than stage. Many scoring systems exist for grade and stage [3]. These are particularly important in viral hepatitis where grade and stage are used to measure the effects of treatment.

Table 19.5. Histological activity index (HAI) (excluding fibrosis): grades [26]

Component	Scores
Peri-portal necrosis with or without bridging necrosis	0–10
Intra-lobular degeneration and focal necrosis	0–4
Portal inflammation	0–4

Table 19.6. Correlation of HAI score (excluding fibrosis) and diagnosis in chronic hepatitis

HAI	Diagnosis
1–3	Minimal
4–8	Mild
9–12	Moderate
13–18	Severe

Examples of classification

Suggestive profiles for two types of chronic hepatitis are shown in table 19.8. Activity score and staging are particularly important in predicting the development of cirrhosis.

Immunological mechanisms of hepato-toxicity

Chronic hepatitis is the liver disease *par excellence* where immunological factors are invoked in the perpetuation of the liver cell injury.

Liver histology shows heavy infiltration by lymphocytes and plasma cells with peri-portal interface hepatitis. Hyperglobulinaemia and circulating tissue antibodies are often present. In chronic hepatitis, it is postulated that an immunological reaction is mounted against membrane constituents of the hepatocyte which serve as antigens. Cell-mediated immunity to liver cell antigens has been demonstrated in chronic hepatitis and this process is mediated by sensitized lymphocytes and mononuclear cells.

Chronic hepatitis is more a mode of progression than a disease entity.

Autoimmune chronic hepatitis

This is defined as chronic liver disease of unknown aetiology with aberrant autoreactivity and a genetic predisposition. Autoimmune hepatitis must be distinguished from secondary autoreactivity against viruses, particularly HCV, and drugs such as halothane.

Table 19.7. Scoring system for staging of chronic hepatitis on the basis of fibrosis and architectural alterations [12]

Score	Grade	Description
0	None	—
1	Mild	Portal expansion
2	Moderate	Portal–portal septa
3	Severe	Bridging with distortion
4	Cirrhosis	Cirrhosis

Table 19.8. Examples of the classification of chronic hepatitis

		Severity		
Aetiology	Clinical	Child's grade	Histology (score*)	Stage (score†)
Hepatitis C	Mild	A	Mild (5)	Mild (1)
Autoimmune	Moderate	B	Moderate (12)	Severe (3)

*See table 19.6.
†See table 19.7.

It is characterized by female predominance, hyperglobulinaemia, positive circulating autoantibodies, and association with HLA-DR3 and HLA-DR4 [30]. Those with known aetiological factors, such as virus, drugs and alcohol, are excluded. The condition usually responds to immunosuppressive treatment. Classification into various types is made on the basis of circulating autoantibody patterns (table 19.9) [21].

In general, those with no known aetiology are more florid clinically and have higher serum transaminase and γ-globulin levels with more active liver histology than those with a known aetiology; the response to corticosteroid therapy is better.

Type 1 (formerly called lupoid)

This type covers the vast majority of patients with autoimmune chronic hepatitis. It is associated with high circulating titres of anti-DNA and anti-actin (smooth muscle). This type will be described in detail later as a prototype.

Type 2

This is associated with autoantibodies against liver–kidney microsomes (LKM) type 1. It is subdivided into types 2a and 2b.

Type 2a [20]. Cytochrome mono-oxygenase P450 2D6 is the target antigen. Antibodies react specifically with an amino acid sequence. This is absent in patients with non-specific reactivity such as HCV. It is associated with a severe chronic hepatitis. Other autoantibodies are usually absent. The disease largely affects girls, mainly in Europe and not the USA. There is a good response to corticosteroid treatment. Extra-hepatic immunological diseases such as diabetes can be found. The disease may be fulminant in children.

Table 19.9. Chronic liver disease with circulating autoantibodies

	Antibody				
Type	ANA	SMA	LKM	AMA	SLA
1 ('lupoid')	+++	+++	–	–	++
2a	–	–	+++	–	
2b (HCV)	–	–	+	–	
3	+	+	–	–	++
Autoimmune cholangiopathy	+++	+	–	–	
Primary biliary cirrhosis	–	±	–	+++	

ANA, antinuclear antibody; SMA, smooth muscle (actin) antibody; LKM, liver-kidney microsomal antibody; AMA, anti-mitochondrial antibody; SLA, soluble liver antigen.

Type 2b. Antibodies to LKM-1 are found in up to 7% of patients with chronic hepatitis C infection in Europe, but not in the USA or the UK. The antibody reacts with cytochrome P450 2D6 related to shared antigenic sites (molecular mimicry). However, more detailed analysis of the microsomes shows that anti-LKM-1 antibody from patients with HCV is directed against different antigenic sites on the P450 2D6 proteins than those with autoimmune LKM positivity [40]. Patients with type 2b tend to be male and older. There is no clear association with other autoimmune diseases and they respond better to antiviral than immunosuppressive therapy.

Type 3. This is characterized by antibodies to soluble liver antigen (SLA) and to liver and pancreas antigen (LPA) [28]. Patients lack anti-LKM but may have ANA. Anti-SLA could be a marker for type 1 autoimmune chronic hepatitis [9]. The target antigen for SLA/LPA autoantibodies has been cloned [39].

Chronic hepatitis D

Some patients with chronic delta virus infection have a circulating autoantibody against LKM-3. The microsomal target is uridine diphosphate glucuronyl transferase [31]. The relationship of this autoantibody to disease progression is uncertain.

Primary biliary cirrhosis and immune cholangitis

These cholestatic syndromes are marked by serum mitochondrial antibodies in the case of primary biliary cirrhosis (Chapter 14) and to DNA and actin in the case of immune cholangitis (Chapter 14) [2].

Chronic autoimmune hepatitis (type 1)

In 1950, Waldenström [38] described a chronic hepatitis occurring predominantly in young people, especially women. The syndrome has since been given various titles [1]. It is now termed 'chronic autoimmune hepatitis'. The condition seems to be decreasing, but this may simply be due to more accurate diagnosis of other causes of chronic hepatitis, for instance drug-related or hepatitis B or C.

Aetiology

The aetiology is unknown. Immunological changes are conspicuous. Serum γ-globulin levels are grossly elevated. The finding of a positive LE cell test in about 15% led to the term 'lupoid hepatitis'. Tissue antibodies are found in a high proportion of patients.

Chronic (lupoid) hepatitis is not the same as classical systemic lupus erythematosus [16] for the liver rarely shows any lesions in classical lupus. Moreover, the

smooth muscle antibody and the mitochondrial antibody are not present in the blood of patients with systemic lupus erythematosus.

Immunological mechanisms and autoantibodies [28]

Autoimmune chronic hepatitis is a disease of disordered immunoregulation marked by a defect in suppressor (regulatory) T-cells. This results in the production of autoantibodies against hepatocyte surface antigens. It is uncertain whether the defect in the immune regulatory apparatus is primary or secondary to an acquired change in the antigenicity of the tissues.

The mononuclear infiltrate in the portal zones consists of B-lymphocytes and helper T-cells with relatively fewer cytotoxic/suppressor cells. This is consistent with the view that antibody-dependent cytotoxicity is the main effector mechanism (fig. 19.9).

Patients have persistently high titres of circulating measles antibodies. This is likely to be due to hyperfunction of the immune system and not to reactivation of persistent virus [24].

The nature of the target antigens on the hepatocyte membrane is unknown. Cell-mediated immunity to membrane proteins has been shown. Liver membrane-specific activated T-cells in peripheral blood may be important in the autoimmune attack of chronic hepatitis.

Patients show many serum autoantibodies. Their role in pathogenesis is not known but they are of great diagnostic value. There is no evidence that antibodies against cellular antigens can themselves mediate the autoimmune attack.

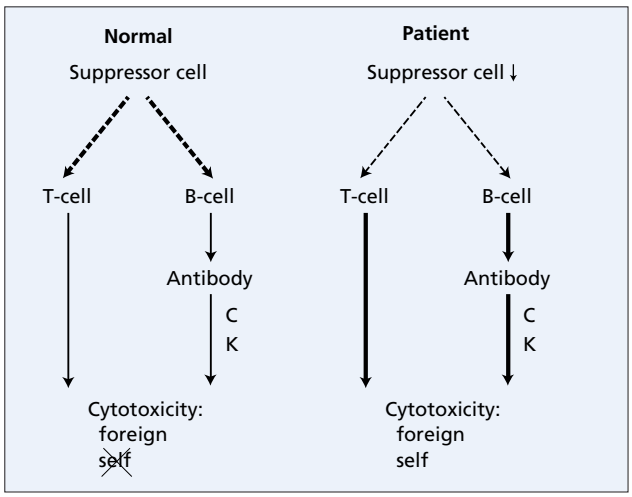


Fig. 19.9. The mechanism of immunological hepatocyte injury in autoimmune chronic hepatitis. In the patient, related to a defect in T-suppressor (regulatory) cells, cytotoxicity is directed not only against foreign antigens but also against self. C, cytotoxic T-cell; K, killer T-cell.

Antinuclear antibody is present in the serum of about 80% of patients. The homogeneous (diffuse) and speckled patterns of immunofluorescence are equal. The speckled form is more frequent in younger patients with higher serum transaminase values [10].

Smooth muscle (*actin*) *antibody* is present in about 70% of patients, and in about 50% of patients with primary biliary cirrhosis. It is also present in low titre in patients with acute type A or B viral hepatitis or with infectious mononucleosis. Titres exceeding 1:40 are rare except in autoimmune chronic hepatitis type 1. The antigen is related to the S-actin of smooth and skeletal muscle. It is also present in cell membranes and in the cytoskeleton of the liver cell. SMA can therefore be regarded as a result of liver cell injury.

Human asialo-glycoprotein receptor autoantibodies. The antigen is a component of liver-specific protein (LSP). The presence is closely linked to inflammation and activity [37].

Mitochondrial antibody. This is usually absent or in only low titre.

Genetics [11, 15]

The female sex predominance (8:1) is similar to other autoimmune diseases. The disease can be familial [19].

Effector T-lymphocytes recognize antigen only if presented on the surface of the damaged hepatocyte by autologous HLA molecules (fig. 19.10) [15]. The interac-

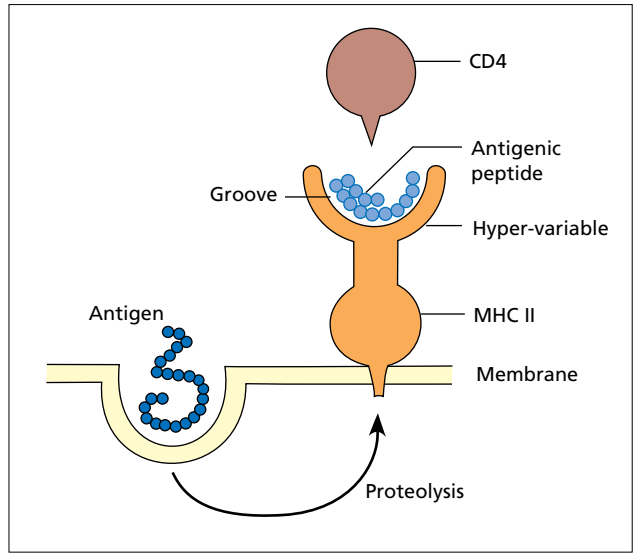


Fig. 19.10. Immunogenetics of autoimmune liver disease: the postulated antigen enters the liver cell by endocytosis. The HLA class II molecule fuses with the antigen-containing endosome. The antigen is broken down to peptides by proteolysis. The HLA class II peptide–complex is transported to the plasma membrane expressed in a groove and presented to the CD4 lymphocyte. The hyper-variability of HLA class II in the groove may predispose to autoimmune chronic hepatitis.

tion between the HLA molecule, the antigenic peptide presented in its groove and the T-cell receptor are crucial. Certain alleles at the HLA loci predispose individuals to related disease. Only the predisposition is inherited not the disease itself which must be triggered by an antigen.

The major histocompatibility complex (MHC) is located on the short arm of chromosome 6. MHC class I and II genes are highly polymorphic. In autoimmune hepatitis type 1, there is a dual association for white people with either HLA-A1-B8-DR3 or HLA-DR4. In Japanese patients the association is predominantly with HLA-DR4. Only limited data are available for autoimmune hepatitis type 2. Analysis of the hyper-variable region of HLA class II indicates that lysine at position 71 is crucial for autoimmune hepatitis type 1 in white people, whereas position 13 is important for Japanese.

The complement genes are also polymorphic and are known as HLA class III genes. The MHC class III allele, C4A-QO, is significantly increased in autoimmune hepatitis type 1 and 2. In the future, HLA typing may be used to identify susceptibility to autoimmune chronic hepatitis. However, recognition of the nature of the antigenic peptide in the HLA groove which is presented to the lymphocyte is essential for further progress.

Hepatic pathology

The lesion is a severe chronic hepatitis. Activity is variable and some areas may be near normal.

Cellular infiltrates, largely lymphocytes and plasma cells, are seen in zone 1 and infiltrating between the liver cells. Aggressive septum formation isolates groups of liver cells as rosettes. Fatty change is inconspicuous. Areas of collapse may be seen. The connective tissue encroaches on the parenchyma. Cirrhosis develops rapidly and is usually of the large nodular type. The chronic hepatitis and the cirrhosis seem to develop almost simultaneously.

As time passes the activity subsides, the cellularity decreases, the necrosis lessens and the fibrosis becomes denser. At necropsy in the long-standing case, the lesion is an inactive cirrhosis. In most cases, however, careful search will reveal areas of interface necrosis and rosette formation.

During remissions, the disease remains inactive, regeneration appears inadequate as the architecture is not restored to normal and the pattern of injury remains detectable.

Cirrhosis is present early in only one-third of patients but is usually present 2 years after the onset [33]. Repeated episodes of necrosis with further stromal collapse and fibrosis lead to a more severe cirrhosis. Eventually the liver becomes small and grossly cirrhotic.

Clinical features (table 19.10)

The condition is predominantly, but not exclusively, one of young people with a peri-pubertal peak and a further increase between the fourth and sixth decades. Three-quarters are female.

The onset is usually insidious, the patient feels generally unwell and is noticed to be jaundiced. In about a quarter of cases the disease seems to present as a typical attack of acute viral hepatitis. It is only when the jaundice persists that the physician is alerted to the possibility of a more chronic liver disorder. It is unclear whether the disease can be initiated by acute viral hepatitis, or whether this is simply an intercurrent infection in a patient with long-standing chronic hepatitis.

In most instances, the hepatic lesion on presentation does not agree with the stated duration of symptoms. Chronic hepatitis must remain asymptomatic for some months or possibly years before jaundice becomes overt and the diagnosis is made. Patients may be recognized sooner if a routine examination reveals stigmata of liver disease or if biochemical tests of liver function are found to be abnormal.

Although the serum bilirubin level is usually increased, some are anicteric. Frank jaundice is often episodic. Rarely, deep cholestatic jaundice is seen.

Amenorrhoea is usual and regular menses is a good sign. However, if a period does occur it may be associated with an increase of symptoms and deepening of jaundice. Epistaxis, bleeding gums and bruising with minimal trauma are other complaints.

Examination shows a tall girl, often above normal stature, and generally looking healthy (fig. 19.11). Spider naevi are virtually constant. They tend to be small and to come and go with changes in the activity of the disease. Livid cutaneous striae may sometimes be found on the thighs, lateral aspect of the abdominal wall, and also, in severe cases, on the upper arms, breasts and back (fig. 19.12). The face may be rounded even before the administration of corticosteroids. Acne is prominent and hirsutism may be seen.

Table 19.10. Typical features of autommune chronic active hepatitis

Usually female
Age 15–25 years or menopause
Serum
transaminases × 10
γ-globulin × 2
Liver biopsy: active, non-diagnostic
ANA > 1 : 40 diffuse
Anti-actin > 1 : 40
Dramatic response to corticosteroids

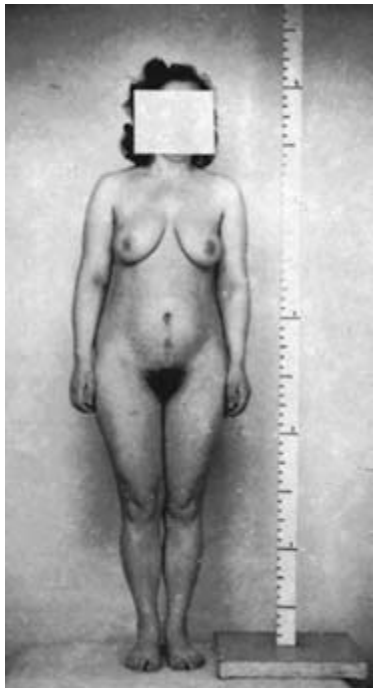


Fig. 19.11. Active juvenile cirrhosis. Well-developed girl with good nutrition.

Abdominal examination in the early stages shows a firm liver edge some 4 cm below the right costal margin. The left lobe may be disproportionately enlarged. In the later stages the liver becomes impalpable. The spleen is usually enlarged. Ascites, oedema and hepatic encephalopathy are late features.

Recurrent episodes of active liver disease punctuate the course.

Associated conditions

Chronic autoimmune active hepatitis is not a condition confined to the liver (table 19.11).

In those who are particularly ill, there may be sustained pyrexia [33]. Such patients may also have an acute, recurrent, non-deforming, migrating polyarthritis of the large joints. In most cases, pain and stiffness are present without marked swelling. The changes usually resolve completely.

Associated skin conditions include allergic capillaritis, acne, erythema, LE-type changes and purpura.

Splenomegaly may be present, often with generalized lymphadenopathy, presumably related to lymphoid hyperplasia.

Renal biopsy often shows mild glomerulitis. Immune complexes in the glomeruli are restricted to those with kidney disease. Glomerular antibodies in about half the patients are unrelated to the extent of renal damage.

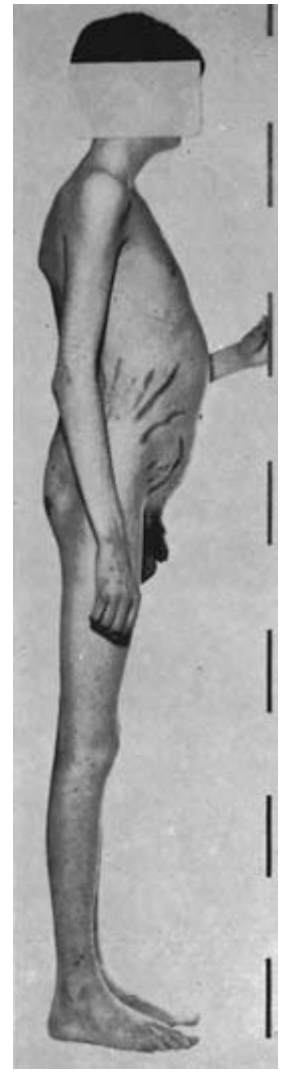


Fig. 19.12. Active chronic 'lupoid' hepatitis. Note the appearance of a tall boy with ascites and striae on the abdominal wall and upper arms.

Table 19.11. Associated lesions in 81 cases of autoimmune chronic hepatitis [33]

Purpura	2
Erythemas	4
Arthralgia	9
Lymphadenopathy	2
Pulmonary infiltrates	7
Pleurisy	2
Rheumatic heart disease	4
Ulcerative colitis	5
Diabetes	3
Hashimoto's thyroiditis	2
Renal tubular defects	3
Lupus kidney	3
Haemolytic anaemia	1

Pulmonary changes include pleurisy, transitory pulmonary infiltrations and collapse. A mottled chest radiograph may be related to dilated precapillary blood vessels. Multiple pulmonary arteriovenous anastomoses are also found (Chapter 6). Fibrosing alveolitis is another possibility.

Primary pulmonary hypertension has been described in one patient with multi-system involvement [5].

Endocrine changes include a cushingoid appearance, acne, hirsutism and cutaneous striae. Boys may develop gynaecomastia. Hashimoto's thyroiditis may be seen and other thyroid abnormalities include myxoedema and thyrotoxicosis. Patients develop diabetes mellitus, before and after diagnosis of the chronic hepatitis.

Mild anaemia, leucopenia and thrombocytopenia are associated with the enlarged spleen. A positive Coombs' test with haemolytic anaemia is another rare complication. Rarely, a hypereosinophilic syndrome is associated [7].

Ulcerative colitis presents either with the chronic active hepatitis or after it.

Hepato-cellular cancer is reported but is very rare [4].

Biochemistry

This picture is of very active disease (see table 19.10). Apart from the hyperbilirubinaemia of about 2–10 mg/dl (35–170 µmol/l), the serum γ-globulin levels are more than twice the upper limit of normal (fig. 19.13). Electrophoresis shows a polyclonal gammopathy, rarely monoclonal. Serum transaminases are usually more than 10 times increased. Serum albumin is maintained until the later stages of liver failure. During the course transaminases and γ-globulin levels fall spontaneously.

Serum α-fetoprotein levels may be increased to greater than twice the upper limit of normal. Levels fall with corticosteroid therapy.

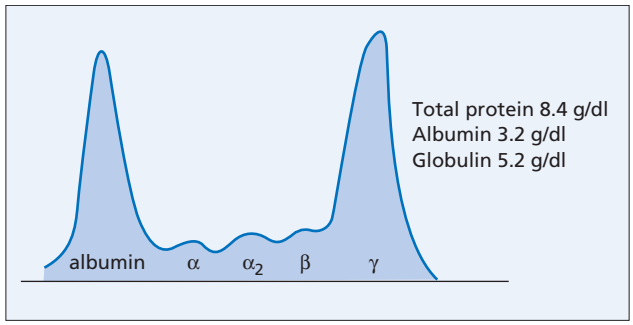


Fig. 19.13. Electrophoresis of the serum proteins. Note the very high γ-globulin.

Haematology

Thrombocytopenia and leucopenia are frequent even before the late stage of portal hypertension and very large spleen. A mild anaemia is also usual. Prothrombin time is often prolonged even in the early stages when hepato-cellular function seems preserved.

Needle biopsy of the liver

This is very valuable, but may prove difficult to perform because of the coagulation defect. Transjugular liver biopsy may be needed. If biopsy is possible, classic severe chronic hepatitis is seen.

Differential diagnosis (fig. 19.14)

Needle liver biopsy may be required to determine whether *cirrhosis* is present.

The distinction from *hepatitis B positive chronic hepatitis* is made by testing for hepatitis B markers.

Patients with *hepatitis C* may have circulating autoantibodies. Using first-generation HCV-antibody testing, some are false positive related to high serum globulin values, but even second-generation tests sometimes read positive. Patients with HCV may have circulating autoantibodies to LKM-1 (see table 19.9).

The distinction from *Wilson's disease* is vital. A family history of liver disease is important. Presentation is often with haemolysis and ascites. Slit lamp examination of the cornea should be performed to look for Kayser–Fleischer rings. Confirmation of the diagnosis is made by finding a reduced serum copper and caeruloplasmin and increased urinary copper values. Liver copper is increased.

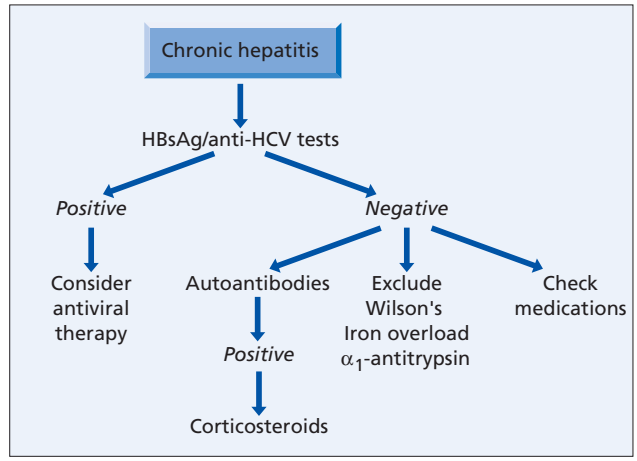


Fig. 19.14. The differential diagnosis and management of chronic hepatitis.

Ingestion of *drugs*, such as nitrofurantoin, methyl dopa or isoniazid, must be excluded.

Chronic hepatitis may coexist with *ulcerative colitis*. A distinction must be made between this combination and *sclerosing cholangitis* where serum alkaline phosphatase values are usually increased and serum smooth muscle antibodies are absent. ERCP is diagnostic.

Alcoholic liver disease. The history, stigmata of chronic alcoholism and large tender liver are helpful diagnostic points. Liver histology shows fat (a rare association of autoimmune hepatitis), alcoholic hyaline, focal polymorphs infiltration and maximal liver damage in zone 3.

Haemochromatosis should be excluded by serum transferrin saturation and ferritin determination.

Treatment

Clinical trials have shown that corticosteroid treatment prolongs life in severe chronic autoimmune type 1 hepatitis [6, 29, 36].

Benefit is greatest in the first 2 years (figs 19.15, 19.16) [25]. Fatigue lessens, appetite improves, fever and arthralgias are controlled. The menses return. Serum bilirubin, transaminase and γ-globulin levels usually fall. The changes are so dramatic as to be virtually diagnostic of autoimmune chronic hepatitis. Hepatic histology shows decreased inflammatory activity but the progression from chronic hepatitis to cirrhosis is not prevented.

Liver biopsy must precede therapy. If coagulation defects prohibit this procedure the biopsy must be done as soon as possible after a remission has been induced by corticosteroids.

The usual dose is 30 mg/day prednisolone (or 40 mg prednisone) for 1 week reducing to a maintenance dose of 10–15 mg daily (table 19.12).

Biochemical and histological remission can usually be achieved within 6 months. Prednisolone therapy usually extends over 2–3 years or longer, usually for life (table 19.13). Premature withdrawal leads to relapse [18]. Although control is usually re-established within 1 or 2 months, there are occasional fatalities.

Prednisone may be used but in a slightly higher dose. Alternate day prednisolone is not recommended as the incidence of serious complications is higher and histological remission less frequent.

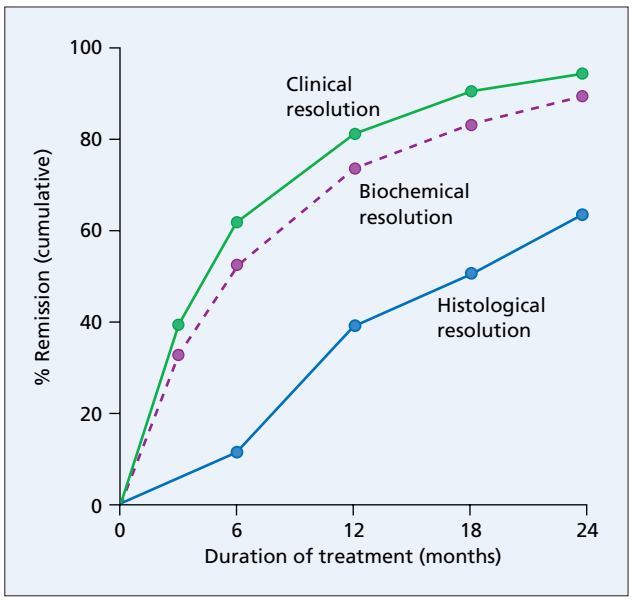


Fig. 19.15. The effect of prednisolone treatment in severe chronic autoimmune hepatitis.

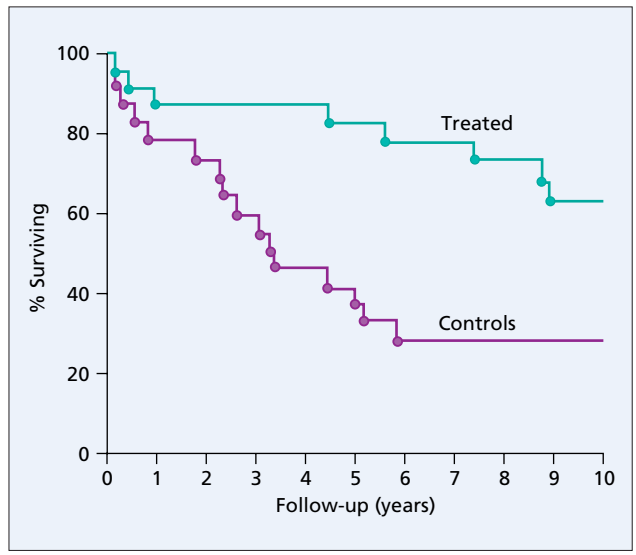


Fig. 19.16. Later results of the Royal Free Hospital trial of prednisolone in chronic autoimmune hepatitis. Note the improved survival in the treated group [25].

Table 19.12. Prednisolone in autoimmune chronic hepatitis

First week
10 mg prednisolone three times a day (30 mg/day)
Second and third weeks
Reduce prednisolone to maintenance dose (10–15 mg/day)
Every month
Clinical check—liver tests
At 6 months
Full check—clinical and biochemical
No remission
Continue maintenance dose for 6 more months, consider adding azathioprine (50–100 mg/day)
Maximum dose—20 mg prednisolone with 100 mg azathioprine

Table 19.13. Autoimmune chronic hepatitis: duration of prednisolone treatment

At least 2 years until
Serum
ANA is negative
bilirubin
γ-globulin normal
transaminase
Liver biopsy inactive (usually more than 2 years)

Patients with milder forms, usually middle-aged or elderly men and women, may be maintained with lower doses of prednisolone as steroid side-effects are particularly undesirable in these patients.

Complications of treatment include facial mooning, acne, obesity, hirsutism and striae. These are particularly unwanted by female patients. More serious complications include growth retardation in those younger than 10 years, with diabetes and serious infections.

Bone loss is found even with only 10 mg prednisolone daily and is related to duration of therapy. Calcium supplementation may be indicated and physical activity encouraged. Bone density scans are done every 1–2 years. Post-menapausal women are given hormone replacement therapy.

Side-effects are rare if the dose of prednisolone is not more than 15 mg daily. If this is exceeded or serious complications have arisen, alternative measures must be considered.

If 20 mg prednisolone daily has not produced a remission, azathioprine 50–100 mg daily may be added. It is not given as routine. Continual use of such a drug over many months or even years has obvious disadvantages. Other indications for azathioprine include gross cushingoid features, associated diseases such as diabetes and other side-effects at doses required to induce remission.

Azathioprine in a higher dose (2 mg/kg body weight) has been given alone to those who have been in complete remission for at least 1 year on the combination [23]. Side-effects include arthralgias, myelosuppression and an increased risk of cancer.

Cyclosporine has been used in a patient resistant to corticosteroid therapy [17]. This toxic drug should not be given except as a last resort when conventional therapy has failed.

Hepatic transplantation is considered when corticosteroids have failed to induce a remission or in the late stages where the complications of cirrhosis have developed. The survival rate is comparable to that of patients who enter a remission after corticosteroids [34]. Autoimmune chronic hepatitis may recur after the transplant [14].

Course and prognosis

This is extremely variable. The course is a fluctuant one marked by episodes of deterioration when jaundice and malaise are increased. The ultimate effect is inevitably cirrhosis with very few exceptions.

The 10-year survival is 63% [25]. After an initial remission following 2 years of corticosteroid therapy, one-third achieve a 5-year remission while two-thirds relapse and have to be re-treated. Further corticosteroids have more side-effects. The mean survival is 12.2 years. Mortality is greatest during the first 2 years when the disease is most active. Sustained remission is more likely if the patient is diagnosed early and if immunosuppression is adequate. Corticosteroid therapy prolongs life, but most patients eventually reach the end-stage of cirrhosis.

Post-menopausal women respond to initial corticosteroid therapy but have more long-term complications.

Patients who are DR3 allotypes present earlier than DR4, they enter remission less frequently and tend to relapse. They need more transplants [11].

Oesophageal varices are an uncommon initial finding. Nevertheless, bleeding from oesophageal varices and hepato-cellular failure are the usual causes of death.

Pregnancy in patients with chronic active hepatitis is discussed later (Chapter 27).

Syncytial giant-cell hepatitis

This chronic hepatitis was once considered to be related to paramyxoma infection [32]. However, this could not be confirmed. The condition is probably related to many forms of liver disease including autoimmune chronic hepatitis, primary sclerosing cholangitis and hepatitis C virus infection [13, 27].

References

1 Bearn AG, Kunkel HG, Slater RJ. The problem of chronic liver disease in young women. *Am. J. Med*. 1956; **21**: 3.
2 Ben-Ari Z, Dhillon AP, Sherlock S. Autoimmune cholangiopathy: part of the spectrum of autoimmune chronic active hepatitis. *Hepatology* 1993; **18**: 10.
3 Brunt EM. Grading and staging: the histopathological lesions of chronic hepatitis: the Knodell histology activity index and beyond. *Hepatology* 2000; **31**: 241.
4 Burroughs AK, Bassendine MF, Thomas HC et al. Primary liver cell cancer in autoimmune chronic liver disease. *Br. Med. J*. 1981; **282**: 273.
5 Cohen N, Mendelow H. Concurrent 'active juvenile cirrhosis' and 'primary pulmonary hypertension'. *Am. J. Med*. 1965; **39**: 127.
6 Cook GC, Mulligan R, Sherlock S. Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. *Q. J. Med*. 1971; **40**: 159.
7 Croffy B, Kopelman R, Kaplan M. Hypereosinophilic

syndrome. Association with chronic active hepatitis. *Dig. Dis. Sci*. 1988; **33**: 233.
8 Czaja AJ. Chronic active hepatitis: the challenge for a new nomenclature. *Ann. Intern. Med*. 1993; **119**: 510.
9 Czaja AJ, Manns MP, McFarlane IG *et al*. Autoimmune hepatitis: the investigational and clinical challenges. *Hepatology* 2000; **31**: 1194.
10 Czaja AJ, Nishioka M, Morshed SA *et al*. Patterns of nuclear immunofluorescence and reactivities to recombinant nuclear antigens in autoimmune hepatitis. *Gastroenterology* 1994; **107**: 200.
11 Czaja AJ, Strettel MDJ, Thomson LJ et al. Associations between alleles of the major histocompatibility complex and type 1 autoimmune hepatitis. *Hepatology* 1997; **25**: 317.
12 Desmet VJ, Gerber M, Hoofnagle JH *et al*. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* 1994; **19**: 1513.
13 Devaney K, Goodman ZD, Ishak KG. Post infantile giant-cell transformation in hepatitis. *Hepatology* 1992; **16**: 327.
14 Devlin J, Donaldson P, Portmann B *et al*. Recurrence of autoimmune hepatitis following liver transplantation. *Liver Transplant Surg*. 1995; **1**: 162.
15 Donaldson P, Doherty D, Underhill J *et al*. The molecular genetics of autoimmune liver disease. *Hepatology* 1994; **20**: 225.
16 Gurian LE, Rogoff TM, Ware AJ *et al*. The immunological diagnosis of chronic active 'auto-immune' hepatitis: distinction from systemic lupus erythematosus. *Hepatology* 1985; **5**: 397.
17 Hayams JS, Ballows M, Leichtner AM. Cyclosporin treatment of autoimmune chronic active hepatitis. *Gastroenterology* 1987; **93**: 890.
18 Hegarty JE, Nouri Aria KT, Portmann B *et al*. Relapse following treatment withdrawal in patients with autoimmune chronic active hepatitis. *Hepatology* 1983; **3**: 685.
19 Hodges S, Loboyeo A, Donaldson P *et al.* Autoimmune chronic active hepatitis in a family. *Gut* 1991; **32**: 299.
20 Homberg JC, Abuaf N, Bernard O *et al*. Chronic active hepatitis associated with antiliver/kidney microsome antibody type 1: a second type of 'autoimmune' hepatitis. *Hepatology* 1987; **7**: 1333.
21 International Autoimmune Hepatitis Group. Report: review of criteria for diagnosis of autoimmune hepatitis. *J. Hepatol*. 1999; **31**: 929.
22 Ishak KG. Pathologic features of chronic hepatitis: a review and update. *Am. J. Clin. Pathol*. 2000; **113**: 40.
23 Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. *N. Engl. J. Med*. 1995; **333**: 958.
24 Kalland K-H, Endresen C, Haukenes G *et al*. Measles-specific nucleotide sequences and autoimmune chronic active hepatitis. *Lancet* 1989; **1**: 1390 (letter).
25 Kirk AP, Jain S, Pocock S *et al*. Late results of Royal Free Hospital controlled trial of prednisolone therapy in hepatitis B surface antigen-negative chronic active hepatitis. *Gut* 1980; **21**: 78.
26 Knodell RG, Ishak KG, Black WC *et al*. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981; **4**: 431.
27 Lau JYN, Konkoulis G, Mieli-Vergano G *et al*. Syncytial giant-cell hepatitis: a specific disease entity? *J. Hepatol*. 1992; **15**: 216.
28 Manns MP, Strassburg CP. Autoimmune hepatitis: clinical challenges. *Gastroenterology* 2001; **120**: 1502.
29 Murray-Lyon IM, Stern RB, Williams R. Controlled trial of prednisone and azathioprine in active chronic hepatitis. *Lancet* 1973; **i**: 735.
30 Obermayer-Straub P, Strassburg CP, Manns MP. Autoimmune hepatitis. *J. Hepatol*. 2000; **32 (**suppl. 1); 181.
31 Philipp T, Durazzo M, Trautwein C *et al*. Recognition of uridine diphosphate glucuronyl transferases by LKM-3 antibodies in chronic hepatitis D. *Lancet* 1994; **344**: 578.
32 Phillips MJ, Blendis LM, Paucell S *et al*. Syncytial giant-cell hepatitis. Sporadic hepatitis with distinctive pathologic features, a severe clinical course and paramyxoviral features. *N. Engl. J. Med*. 1991; **324**: 455.
33 Read AE, Harrison CV, Sherlock S. 'Juvenile cirrhosis'; part of a system disease. The effect of corticosteroid therapy. *Gut* 1963; **4**: 378.
34 Sanchez-Urdazpal L, Czaja AJ, Van Hock B *et al*. Prognostic features and role of liver transplantation in severe corticosteroid-treated autoimmune chronic active hepatitis. *Hepatology* 1991; **15**: 215.
35 Sherlock S. Chronic hepatitis and cirrhosis. *Hepatology* 1984; **4**: 25S.
36 Soloway RD, Summerskill WH, Baggenstoss AH *et al*. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. *Gastroenterology* 1972; **63**: 820.
37 Treichel U, Poralla T, Hess G *et al*. Autoantibodies to human asialoglycoprotein receptor in autoimmune-type chronic hepatitis. *Hepatology* 1990; **11**: 606.
38 Waldenström J. *Leber, Blutproteine und Nahrungsweiss Stoffwechs Krh*, Sonderband: XV, p. 8. Tagung, Bad Kissingen, 1950.
39 Wies I, Brunner S, Henninger J *et al*. Identification of target antigen for SLA/LP autoantibodies in autoimmune hepatitis. *Lancet* 2000; **355**: 1510.
40 Yamamoto AM, Cresteil D, Homberg JC *et al*. Characterization of antiliver–kidney microsome antibody (anti-LKM I) from hepatitis C virus-positive and virus-negative sera. *Gastroenterology* 1993; **104**: 1762.

Chapter 20
Drugs and the Liver

The liver is particularly concerned with drug metabolism, and especially of drugs given orally (fig. 20.1). These must be lipid soluble to have passed the membrane of the intestinal cell. They must then be presented to the liver and converted to water-soluble (more polar) compounds for excretion via the urine or bile.

Drugs can cause toxic effects which can mimic almost every naturally occurring liver disease in man (table 20.1). About 2% of all cases of jaundice in hospitalized patients are drug induced. About one-quarter of cases of fulminant hepatic failure in the USA are thought to be medicament-related. In any patient with liver disease it is essential to know all drugs that have been taken over the last 3 months. The physician may have to be a detective to identify them all.

Early suspicion of a drug-related hepatic reaction, and, if possible, accurate diagnosis, are essential. Severity is greatly increased if the drug is continued after symptoms develop or after serum transaminases rise. This provides grounds for negligence claims.

The response of the liver to drugs depends on an interplay between absorption, environmental factors and genetics (fig. 20.2).

An individual drug may cause more than one type of reaction. There may be an overlap between hepatitic, cholestatic and hypersensitivity reactions. Halothane, for instance, can cause zone 3 necrosis and also an acute hepatitis-like picture. The promazines overlap between the hepatitic and cholestatic types. Methyl dopa can cause acute or chronic hepatitis, cirrhosis, hepatic granulomas or cholestasis.

Pharmacokinetics [60, 70]

The hepatic clearance of drugs given by mouth depends on the efficiency of the drug-metabolizing enzymes, the intrinsic clearance, the liver blood flow and the extent of plasma protein binding (fig. 20.3). Drugs vary in their pharmacological effects according to the relative importance of these different pharmacokinetic factors (table 20.2) [127].

Drugs which are avidly taken up by the liver (high intrinsic clearance) are said to have a high *first-pass metabolism*. The rate-limiting factor in their hepatic uptake is liver blood flow and, indeed, their clearance can be used to measure liver blood flow. Indocyanine

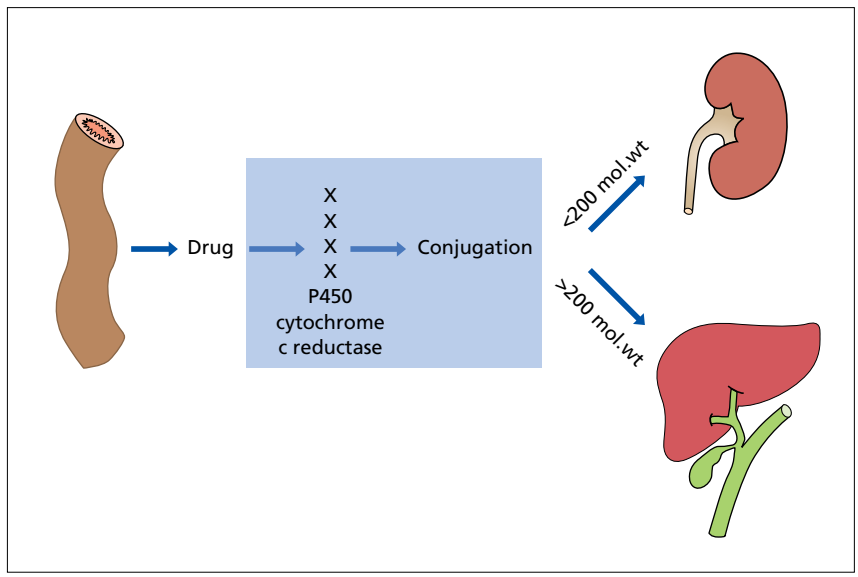


Fig. 20.1. Hepatic drug metabolism.

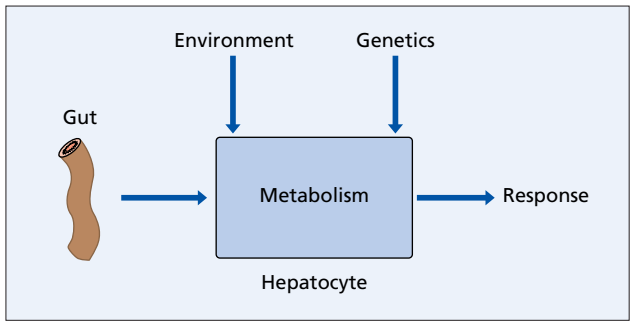


Fig. 20.2. The response of the liver to drugs depends on an interplay between absorption, environmental factors and genetics.

$$CLH = QH \left[\frac{CLint.fb}{QH + CLint.fb} \right]$$

Fig. 20.3. Formula for calculating clearance (CLH) of a drug by the liver. CLint, intrinsic clearance; fb, plasma protein binding; QH, liver blood flow [10].

Table 20.1. Classification of hepatic drug reactions

Type	Features	Examples
Zone 3 necrosis	Dose dependent, multi-organ failure	Carbon tetrachloride Paracetamol Halothane
Mitochondrial cytopathies	Affects children Reye's-like syndrome Cirrhosis	Valproate
Steato-hepatitis	Long half-life Cirrhosis	Perhexiline Amiodarone
Acute hepatitis	Bridging necrosis Short term, acute Long term, chronic	Methyl dopa Isoniazid Halothane Ketoconazole
General hypersensitivity	Often with granulomas	Sulphonamides Quinidine Allopurinol
Fibrosis	Portal hypertension Cirrhosis	Methotrexate Vinyl chloride Vitamin A
Cholestasis		
canalicular	Dose dependent, reversible	Sex hormones
hepato-canalicular	Reversible 'obstructive' jaundice	Chlorpromazine Erythromycin Nitrofurantoin Azathioprine
ductular	Age-related. Renal failure	Benoxyprofen
Vascular		
Veno-occlusive disease	Dose dependent	Irradiation Cytotoxics
Sinusoidal dilatation and peliosis		Azathioprine Sex hormones
Hepatic vein obstruction	Thrombotic effect	Sex hormones
Portal vein obstruction	Thrombotic effect	Sex hormones
Biliary		
Sclerosing cholangitis	Cholestasis	Hepatic arterial FUDR
Gallbladder sludge	Biliary colic	Ceftriaxone
Neoplastic		
Focal nodular hyperplasia	Benign. Presents space-occupying lesion	Sex hormones
Adenoma	May rupture. Usually regress	Sex hormones
Hepato-cellular carcinoma	Very rare Relatively benign	Danazol Sex and anabolic hormones

FUDR, 5-fluoro-2'-deoxyuridine.

Table 20.2. Classification of drugs based on pharmacokinetic parameters obtained in normal subjects [70]

	Hepatic extraction	Protein binding	Effect of shunting on systemic availability	Examples
Enzyme limited, binding insensitive	Low	Low (<90%)	0	Antipyrine Amobarbital Caffeine Theophylline Aminopyrine
Enzyme limited, binding sensitive	Low	High (>90%)	0	Chlordiazepoxide Diazepam Diphenylhydantoin Indomethacin Phenylbutazone Rifampicin Tolbutamide Warfarin
Flow and enzyme sensitive	Medium	No effect	+	Acetaminophen Chlorpromazine Isoniazid Merperidine Metoprolol Nortriptyline Quinidine
Flow limited	High	No effect	+++	Galactose Indocyanine green Labetalol Lidocaine Morphine Pentazocine Propoxyphene Propranolol Verapamil

green is one such drug. These drugs are usually highly lipid soluble. If liver blood flow falls, for instance due to cirrhosis or heart failure, the systemic effect of the high first-pass rate drug will be enhanced. Administration of drugs such as propranolol or cimetidine which lower hepatic blood flow will have a similar effect.

Because of its high first-pass uptake, a drug such as glyceryl trinitrate has to be given sublingually to avoid entry into the portal vein. Similarly, lignocaine has to be given intravenously.

Drugs with a low intrinsic clearance, such as theophylline, depend on enzyme function. Changes in hepatic blood flow have little effect.

Plasma protein binding limits the presentation of the drug to hepatic enzymes. This will be affected by changes in the synthesis and degradation of plasma proteins.

Hepatic drug metabolism

Phase 1. The main drug-metabolizing system resides in the microsomal fraction of the liver cell (smooth endoplasmic reticulum). The enzymes concerned are mixed function mono-cytochrome C reductase and cytochrome P450. Reduced NADPH in the cytosol is a co-factor. The drug is rendered more polar by hydroxylation or oxidation. Alternative phase 1 drug-metabolizing reactions include the conversion of alcohol to acetaldehyde by alcohol dihydrogenases found mainly in the cytosolic fraction.

Enzyme inducers include barbiturates, alcohol, anaesthetics, hypoglycaemic and anti-convulsant agents, griseofulvin, rifampicin, phenylbutazone and meprobamate. Enlargement of the liver following the introduction of drug therapy can be related to enzyme induction.

Phase 2. These biotransformations involve conjugation of the drug or drug metabolite with a small endogenous molecule. The enzymes concerned are usually

not confined to the liver, but are present there in high concentration.

Active transport. This system is located at the biliary pole of the hepatocyte. The mechanism is energy dependent and can be saturated.

Biliary and urinary excretion. Factors determining whether the metabolized drug will be excreted ultimately in bile or urine are multiple and many are unclear. Highly polar substances are excreted unaltered in the bile and also those which become more polar after conjugation. Those with a molecular weight exceeding 200 tend to be excreted in the bile. As the molecular weight falls, the urinary route becomes more important (fig. 20.1).

The P450 system

Drugs are metabolised, and toxic metabolites produced, by the P450 system of haemoproteins situated in the endoplasmic reticulum of the hepatocyte. At least 50 P450s have been identified and there are undoubtedly more. Each P450 protein is encoded by a unique gene [158]. The human P450s concerned with drug metabolism are members of the three families, P450-I, P450-II and P450-III (fig. 20.4, table 20.3). Each P450 has a unique 'substrate' binding site, capable of binding some, but not all, drugs. Each P450 can metabolize many drugs. Genetic differences in the catalytic activity of the P450s may determine idiosyncratic, untoward reactions to drugs. This is exemplified by the poor metabolism of debrisoquine (an anti-arrhythmic drug) due to abnormal expression of P450-II-D6 [46]. This enzyme system also metabolizes most β-blockers and neuroleptics. Poor metabolism of debrisoquine can be identified by PCR amplification of parts of the mutant genes for cytochrome P450-II-D6. This raises the possibility that in the future patients who will react abnormally to a drug can be identified.

P450-II-E1 is involved in the production of electrophilic metabolites of acetaminophen.

Table 20.3. Characteristics of some human liver P450s [158]

P450	Drug substrates	Probable inducers
I-A1	Carcinogens	Omeprazole
I-A2	Caffeine Theophylline	Cigarette smoke Acetaminophen
II-C*	Mephenytoin Tienylic acid Diazepam Tolbutamide Phenylbutazone	None identified
II-D*	Debrisoquine Most β-blockers Many neuroleptics Encainide Codeine	None identified
II-E1	Acetaminophen Ethanol	Ethanol Isoniazid
III*	Cyclosporin A Erythromycin Ketoconazole Nifedipine Oestrogens Midazolam/triazolam Lidocaine	Anti-seizure medications Rifampicin Glucocorticoids

*Multiple subfamily members exist which may have differing catalytic properties and regulation.

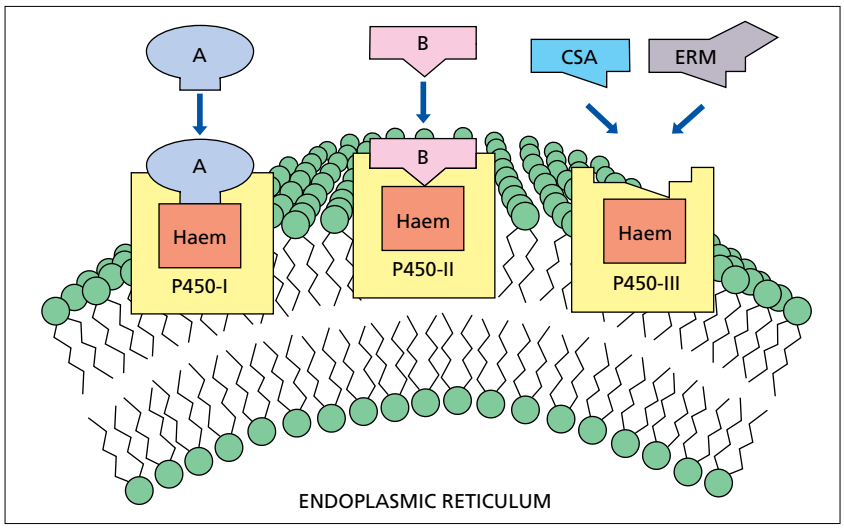


Fig. 20.4. P450s involved in drug metabolism are members of three gene families: P450-I, P450-II and P450-III. Individual P450s have distinct catalytic properties. Cyclosporin (CSA) and erythromycin (ERM) bind to and are metabolized by P450s within the P450-III family [158].

P450-III-A is concerned with the metabolism of cyclosporin and other drugs, especially erythromycin, steroids and ketoconazole. P450-II-C polymorphism affects the metabolism of mephenytoin, diazepam and many other drugs.

Enzyme induction and drug interactions

Enzyme induction (table 20.3), by increasing the P450 enzymes, leads to enhanced production of toxic metabolites. Expression of P450s and induction by phenobarbitone are maintained in transplanted hepatocytes without reference to acinar position or zonal/sinusoidal microenvironment [86].

Two active drugs competing for an enzyme-binding site may lead to the drug with the lower affinity being metabolized more slowly and thus having a more prolonged action.

Ethanol induces P450-II-E1 and so enhances the toxicity of acetaminophen (see fig. 20.10). Similarly, patients treated with isoniazid which also induces P450-II-E1, have increased acetaminophen toxicity [94].

P450-III-A which metabolizes cyclosporin is induced by rifampicin and steroids. This explains the reduced blood cyclosporin levels when these drugs are given. Cyclosporin, tacrolimus (FK506), erythromycin and ketoconazole compete for binding and metabolism by P450-III-A and cyclosporin levels rise after they are given.

Omeprazole induces P450-I-A [31]. This is important in the biotransformation of pro-carcinogens, carcinogens and many drugs. An increased tendency to malignancy after omeprazole is possible.

In the future, it should be possible to determine P450 profiles and detect those likely to develop an adverse drug reaction. Selective inhibitors or inducers may be used to alter the P450 profile [158].

Immunological hepato-toxicity

The metabolite may act as a hapten with cell protein so inducing immunological liver injury (fig. 20.5). The P450s can be involved. Several P450 isoenzymes are present and inducible on the membranes of hepatocytes and immunization against them might lead to immunological destruction of the liver cell [82].

Risk factors for hepatic drug injury [77]

Liver disease [128]

The impaired metabolism is proportional to the extent of hepato-cellular failure and is greatest in cirrhosis. A correlation exists between the half-life of a drug and the prothrombin time, serum albumin level, hepatic encephalopathy and ascites [38].

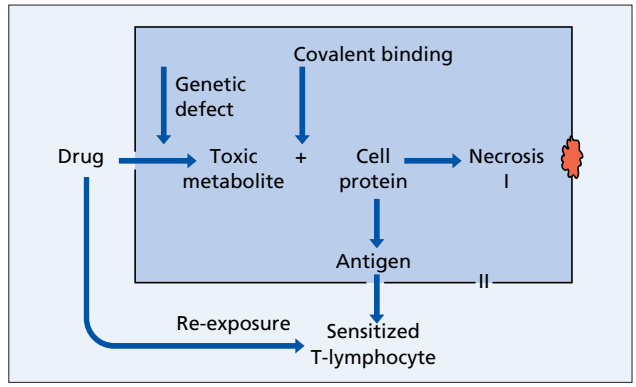


Fig. 20.5. The mechanisms of hepato-toxicity, direct metabolite-related and immunological hypersensitivity.

The causes of the impaired drug metabolism are multiple. Reduced hepatic blood flow leads to impaired metabolism particularly of high first-pass drugs [17]. Impaired oxidative metabolism is seen particularly with barbiturates and with chlordiazepoxide. Glucuronidation is preserved so that morphine, which is a high-clearance drug normally inactivated in this way, is eliminated normally. However, glucuronidation of some drugs may be impaired in patients with liver disease [54].

Reduced plasma protein binding follows failure of hepatic albumin synthesis. Benzodiazepines, for instance, are eliminated almost solely by hepatic biotransformation, highly protein bound, and this restricts their elimination. In hepato-cellular disease there is a decrease in drug clearance from plasma, and an increase in its volume of distribution which is accounted for by decreased protein binding.

Increased cerebral sensitivity, particularly to sedatives, may be related to an increase in cerebral receptors in liver disease.

Age and sex

Hepatic drug reactions are rare in children, apart from accidental overdose. They may even be resistant, since children with paracetamol overdose have much less liver damage than an adult with an equivalent paracetamol serum concentration. Valproate hepato-toxicity, however, does affect children, as rarely does halothane and salazopyrine.

Old age is associated with decreased disposition of drugs undergoing phase 1 but not phase 2 biotransformation [127]. This is not related to a fall in cytochrome P450 activities but rather to diminished hepatic volume and liver blood flow.

Hepatic drug reactions are more frequent in females.

In the fetus, P450 enzymes are very low, if present at all. After birth, they increase and their intra-lobular distribution changes [117].

Drugs causing interference with bilirubin metabolism

Drugs can affect bilirubin metabolism at any stage. The reactions are predictable, reversible and not serious in the adult. In the neonate, however, a rise in unconjugated bilirubin in the brain potentiates bilirubin encephalopathy (*kernicterus*). This is enhanced by drugs such as salicylates or sulphonamides which compete with bilirubin for its attachment to albumin. In adults, with such conditions as Gilbert's syndrome, chronic hepatitis or primary biliary cirrhosis, bilirubinaemia is enhanced by drugs which interfere with bilirubin metabolism.

Haemolytic reactions increase the bilirubin load on the liver cell. This is rare as a single defect and is usually combined with a hypersensitivity reaction which decreases hepato-cellular function. Sulphonamides, phenacetin, ribavirin or quinine can cause such reactions. Such drugs may also precipitate haemolysis in those with glucose-6-phosphate dehydrogenase deficiency.

The offending drug may be transmitted in the mother's milk. The toxic effects of synthetic vitamin K preparations in neonates may be partially due to increased haemolysis.

Certain drugs interfere with the uptake and transport of bilirubin in the hepatocyte. They include cholecystographic media and rifampicin. Transport proteins may be decreased in neonates, making them susceptible to drugs that compete with bilirubin for transport. These drugs would potentiate kernicterus.

Cholestasis follows interference by drugs, such as sex hormones, with bilirubin canalicular excretion.

Diagnosis of drug-induced liver disease (table 20.4)

Common causes of drug-related hepatic reactions are antibiotics, non-steroidal anti-inflammatory drugs, cardio-vascular drugs and central nervous system modifiers—in fact the whole range of modern pharmacotherapeutics. Every drug should be suspected and the manufacturer and the Safety of Medicines Organization should be contacted.

History must include dose, route of administration, duration, previous administration and any concomitant drugs.

The onset (*challenge*) is usually within 5–90 days of starting. A positive *de-challenge* is a 50% fall in serum transaminases within 8 days of stopping the drug. Deliberate *re-challenge* is usually ethically impossible. However, *inadvertent re-challenge* gives valuable evidence that the drug was indeed hepato-toxic.

Table 20.4. Investigation of drug-related liver disease

	Notes
Suspect any drug	Contact manufacturer and Safety of Medicines Organization
Drug history	All medicines, dose, duration, previous administration
De-challenge	Rapid fall in transaminases
Re-challenge	Inadvertent. Deliberate usually impossible
Exclude other liver diseases	Hepatitis A, B and C; autoimmune; biliary obstruction
Liver biopsy	If necessary: fat, granulomas, zonal hepatitis, bile duct lesions

Other causes of a hepatic reaction such as hepatitis A, B or C, autoimmune liver disease or biliary obstruction must be excluded.

In difficult cases, liver biopsy can be valuable. A drug-related reaction is suggested by fatty change, granulomas, bile duct lesions, zonal hepatic necrosis and general hepato-cellular unrest.

Hepato-cellular zone 3 necrosis

Hepato-cellular injury is rarely due to the drug itself and a toxic metabolite is usually responsible (fig. 20.6). The drug-metabolizing enzymes activate chemically stable drugs to produce electrophilic metabolites. These potent alkylating, arylating or acylating agents bind covalently to liver molecules which are essential to the life of the hepatocyte, and necrosis ensues (figs 20.6, 20.7). This follows exhaustion of intra-cellular substances such as glutathione which are capable of preferentially conjugating with the toxic metabolite. In addition, metabolites with an unpaired electron are produced by oxidative reactions of cytochrome P450. These *free radicals* can also bind covalently to proteins and to unsaturated fatty acids of cell membranes. This results in *lipid peroxidation* and membrane damage. The end result is hepatocyte death related to failure to pump calcium from the cytosol and to depressed mitochondrial function (figs 20.6, 20.7). Necrosis is greatest in zone 3, where drug-metabolizing enzymes are found in the highest concentration and where the oxygen tension is lowest in sinusoidal blood. Fatty change is also seen but the inflammatory reaction is slight.

The hepatic necrosis is dose dependent. Animal models exist. Other organs also suffer and renal damage is often the most important. In mild cases, jaundice may be mild, slight and transient. Serum biochemical tests show marked rises in transaminases. Prothrombin time

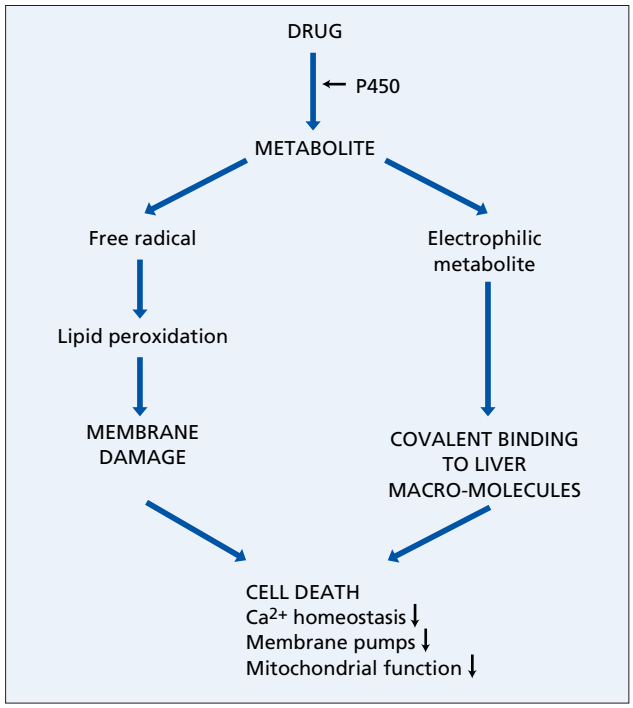


Fig. 20.6. The mechanism of metabolite-related direct hepatocellular necrosis.

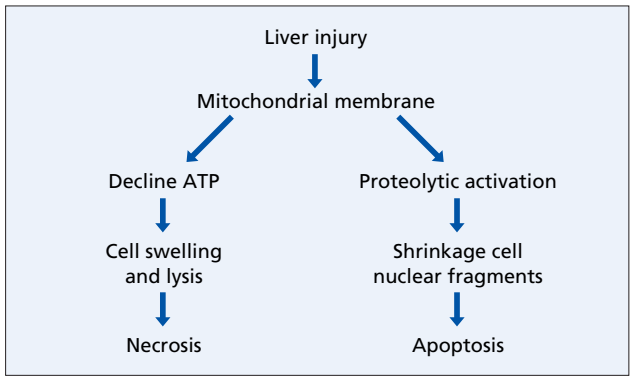


Fig. 20.7. Mechanism of hepatocyte death.

increases rapidly. Light microscopy shows clear-cut zone 3 necrosis, with scattered fatty change and little inflammatory reaction (fig. 20.8). Peri-portal fibrosis may sometimes be marked. Paracetamol (acetaminophen) is a good example of a drug producing this type of necrosis.

Some drugs cause zone 3 hepatic necrosis, but in only a small proportion of those exposed. The mechanism cannot be straightforward dose-dependent toxicity, and metabolic idiosyncrasy is postulated. Halothane occasionally causes confluent zonal or massive necrosis as well as a hepatitic reaction. The products of reductive metabolism are reactive, as are the oxidative ones. The

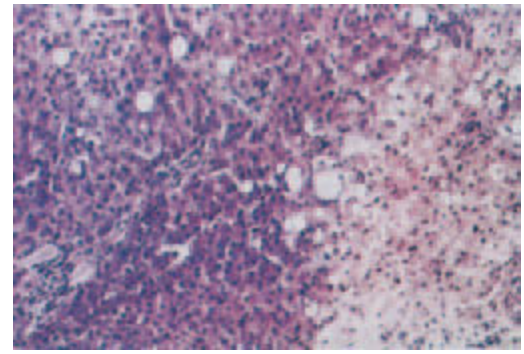


Fig. 20.8. Accidental carbon tetrachloride poisoning. To the right of the section, liver cells are necrotic and show hydropic degeneration and fatty change. Surviving liver cells to the left of the section show occasional fatty change. The portal zones are unaffected.

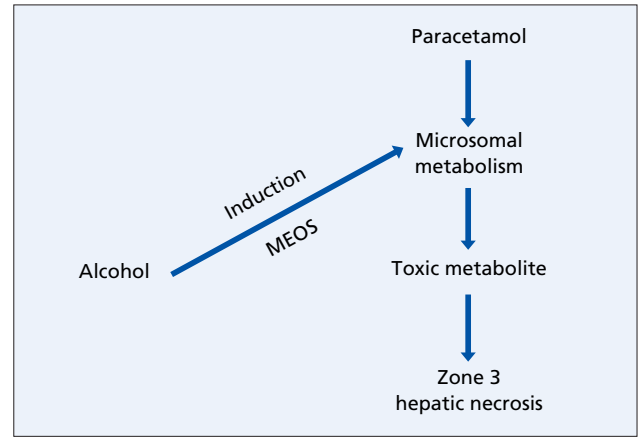


Fig. 20.9. Alcohol, as an enzyme-inducing agent, increases the production of toxic metabolites of paracetamol, so potentiating hepatic necrosis. MEOS, microsomal enzyme oxidizing system.

metabolites produced by either mechanism could bind to cellular macro-molecules and cause lipid peroxidation and inactivation of drug-metabolizing and other enzymes.

Effects of enzyme induction and inhibition

Due to enzyme induction, rats pre-treated with phenobarbital show increased zone 3 necrosis following carbon tetrachloride.

Alcohol ingestion considerably enhances paracetamol toxicity so that as little as 4–8 g can cause serious liver damage (fig. 20.9) [131, 170]. This is apparently due to the induction by alcohol of P450-3a (P450-II-E1) which is important in generating toxic metabolites. It is also concerned in oxygenation of nitrosamines at the α-carbon (fig. 20.10). Theoretically, this could increase the risk of

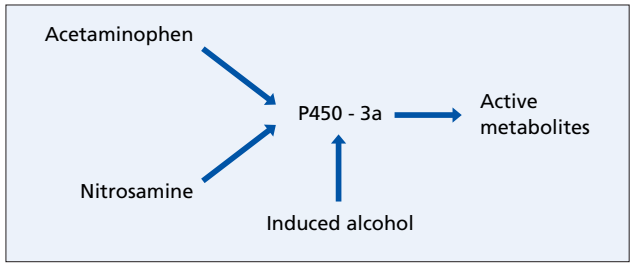


Fig. 20.10. Alcohol, by inducing P450-3a (P450-II-E1) drug-metabolizing enzymes, enhances the toxicity of paracetamol (acetaminophen) and the carcinogen nitrosamine.

cancer in alcoholics. Cimetidine inhibits P450 mixed-function oxidase activities and modifies the hepato-toxic effects of paracetamol.

The administration of drugs which induce microsomal enzymes, for instance phenytoin, results in increases in serum γ-glutamyl transpeptidase (γ-GT) [59].

Carbon tetrachloride

This may be taken accidentally or suicidally. It may be inhaled, for instance in dry-cleaning or in filling fire extinguishers, or mixed in drinks.

The liver injury is induced by a toxic metabolite. This depends on a cytochrome P450-dependent mono-oxygenase which is located in the smooth endoplasmic reticulum of peri-venular hepatocytes. The effect is enhanced by enzyme-inducers such as alcohol and barbiturates, and reduced by protein malnutrition which depresses drug-metabolizing enzymes.

Clinical features

Vomiting, abdominal pain and diarrhoea are followed within 48 h by jaundice. The liver may be enlarged and tender. Spontaneous haemorrhages reflect the profound hypoprothrombinaemia. Serum transaminase values are very high (fig. 20.11); the serum albumin level falls.

In severe cases acute renal failure overshadows hepatic destruction. Acute haemorrhagic gastritis is prominent. Since carbon tetrachloride is an anaesthetic the patient becomes increasingly drowsy.

Pathology

Zone 3 cells show hydropic degeneration marked by clear cytoplasm and pyknotic nuclei (see fig. 20.8). Fatty change varies from a few droplets to diffuse involvement of liver cells. Polymorphonuclear infiltration of the portal zones is slight and fibrosis is uncommon. With recovery the liver pattern returns to normal.

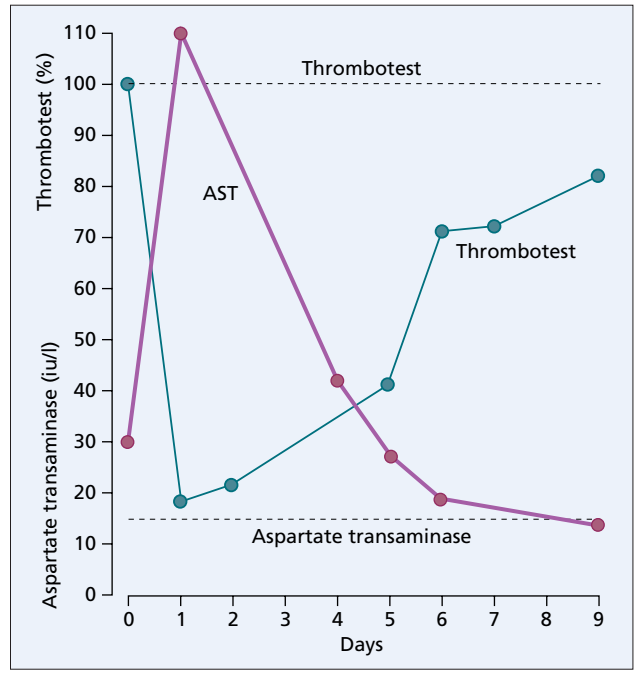


Fig. 20.11. Suicidal inhalation of carbon tetrachloride in a young male. Note the rapid fall in thrombotest with rise in transaminase (AST) values. At 6 days they have virtually returned to normal.

Prognosis

Death in the acute stage is due to kidney failure. If the patient survives the acute episode there are no late hepatic sequelae. In rats, repeated administration leads to cirrhosis. This sequence is not seen in man. Liver cells may even be more resistant with prolonged exposure. Carbon tetrachloride is not an aetiological factor in hepatic cirrhosis in man.

Treatment

Screening tests in workers should include routine examination for liver enlargement and tenderness, urine testing for urobilinogen and serum transaminase, and γ-GT estimations.

Acute poisoning is treated by a high-calorie, high-carbohydrate diet and along the usual lines for acute hepato-renal failure including dialysis. Prompt treatment with acetyl cysteine may minimize hepato-renal damage.

Related compounds

Teenagers sniffing cleaning fluid, which contains trichlorethylene, or glue containing toluene, suffer jaundice with liver necrosis and renal failure.

Industrial exposure to the solvent, 1,1,1-

trichlorethane, can cause a somewhat similar picture to carbon tetrachloride.

Benzene derivatives include trinitrotoluene (TNT), dinitrophenol and toluene. The maximum effect is on the bone marrow with aplasia. The liver may be involved acutely, but chronic sequelae are rare.

Industrial exposure to organic solvents can lead to abnormal transminase values. Short exposure (less than 3 months) to the solvent dimethylformamide results in digestive symptoms, marked rise in transaminases, focal hepato-cellular necrosis and microvesicular steatosis [119]. With longer exposure (greater than 1 year) symptoms are minimal and transaminase elevations modest. Liver biopsies show microvesicular steatosis and prominent smooth endoplasmic reticulum. Electron microscopy shows PAS-positive inclusions and abnormal mitochondria.

Industrial liver injury may be under-diagnosed. The prognosis of those exposed chronically remains uncertain.

Amanita mushrooms

Acute liver failure follows the ingestion of various *Amanita* mushrooms, including *A. phalloides* and *A. verna*. Three stages of illness can be recognized. The first, starting 8–12 h after ingestion, consists of nausea, cramping abdominal pain and rice-water diarrhoea and lasts for 3–4 days. The second phase is characterized by apparent improvement. The third stage includes hepato-renal and central nervous system degeneration with massive cell destruction. The liver shows zone 3 necrosis without much inflammation. Fatty change is seen in fatal cases. The condition is life-threatening although recovery can occur.

The mushroom toxin, phalloidin, inhibits actin polymerization and causes cholestasis. Amanitine inhibits protein synthesis by RNA inhibition.

Supportive measures are all that can be offered. Haemodialysis may be helpful. Hepatic transplantation has been successfully employed [19].

Paracetamol (acetaminophen)

Hepato-toxity is not directly due to paracetamol, but to an unstable toxic metabolite, *N*-acetyl-*p*-benzoquininemine (NAP Q1) (fig. 20.12). This metabolite is generated by cytochrome P450-II-E1. The toxic metabolite is inactivated by glutathione and cell damage follows when this is depleted. Induction of P450-II-E1 enhances cytotoxicity. This may be by alcohol, other drugs such as isoniazid or anti-convulsants, or malnutrition. In the adult, a minimum of 7.5–10 g produces hepatic necrosis, but the dose is difficult to assess because of early vomiting and unreliable histories. It may be considerably less [16]; as little as 4–8 g/day may produce liver damage in an alcoholic and even less if there is underlying liver disease [170].

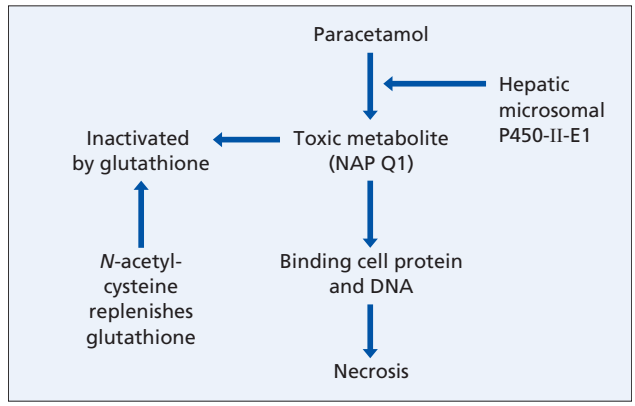


Fig. 20.12. The mechanism of paracetamol (acetaminophen) liver injury and of *N*-acetylcysteine treatment.

In the UK, paracetamol toxicity usually follows suicidal overdose. In the USA, however, in an urban county hospital, accidental misuse had higher rates of mortality and morbidity, perhaps due to the higher frequency of chronic alcohol abuse [129].

Clinical features

Within a few hours of ingestion, the patient becomes nauseated and vomits. Consciousness is preserved. After about 48 h recovery seems in progress; then on about the third or fourth day the patient deteriorates and becomes jaundiced when the liver is tender. Serum transaminase and prothrombin levels are enormous—even higher than those recorded in viral hepatitis or acute alcoholic hepatitis (fig. 20.13). In the more seriously affected, deterioration is then rapid with the signs of acute hepatic necrosis. Acute tubular necrosis develops in 25–30% of those untreated. Myocardial damage and hypoglycaemia are prominent.

Hepatic histology shows zone 3 necrosis, some fatty change and very little inflammation. Reticulin collapse may be confluent and massive, but cirrhosis is not a sequel.

Prognosis

The overall mortality for 201 patients admitted to a general hospital was 3.5% [95]. The development of metabolic acidosis, a severe or progressive coagulopathy, encephalopathy of any grade or renal failure indicates transfer of the patient to a specialist centre without delay [103].

Death usually occurs between 4 and 18 days after ingestion. Cardio-pulmonary and renal insufficiency in

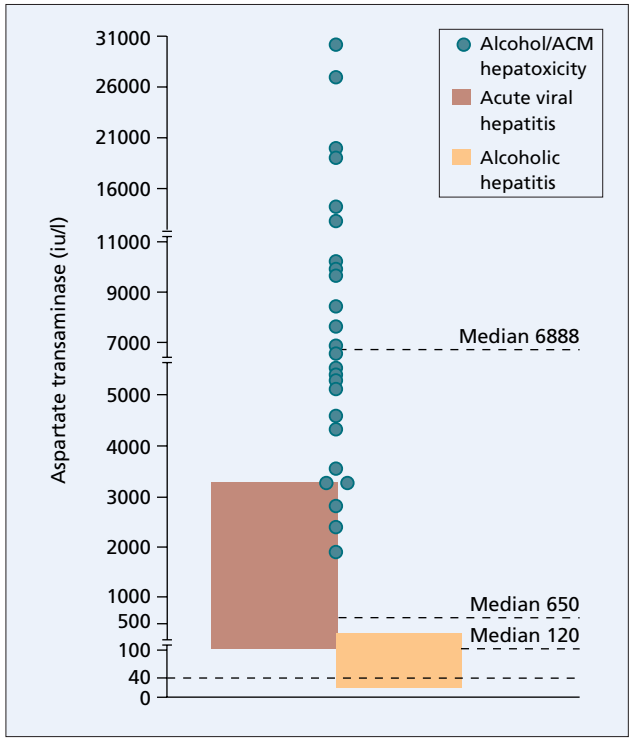


Fig. 20.13. Serum aspartate transaminase levels in patients with acute viral hepatitis, alcoholic hepatitis and a combination of alcohol and acetaminophen (ACM) (paracetamol) [131].

elderly patients increases the risk of damage after modest doses of paracetamol [14].

Treatment

The stomach is washed out. The patient is admitted to hospital. Features of hepatic necrosis are delayed and early improvement should not give a false sense of security.

The treatment of acute liver failure is outlined in Chapter 8. Renal failure may be early and dominant. Intravenous fluids are commenced immediately.

All patients presenting with a serum paracetamol concentration greater than 150 mg/l should be treated with acetylcysteine with a treatment threshold of 100 mg/l for those patients with known risk factors. Diagrams are constructed, plotting a line joining 200 mg/l at 4 h and 50 mg/l at 12 h on a semilog graft concentration vs. time. Values below this line indicate a clinically insignificant chance of liver damage. However, the treatment line of 150 mg/ml is better and acetylcysteine should be given to all patients with hepatic damage due to paracetamol, even if delayed more than 15 h from ingestion.

Treatment is aimed at replenishing the glutathione reserves of the liver cell. Unfortunately, glutathione itself penetrates poorly into the liver. Precursors have therefore been used. Intravenous acetylcysteine (mucomist, parvolex) is rapidly hydrolysed to cysteine and this is the treatment of choice [48]. If given within 16 h of ingestion, *N*-acetylcysteine is so effective that liver injury is now rare after paracetamol self-poisoning [88].

In fulminant cases, liver transplantation is effective. However, very few patients need this option [8]. Survival is good and psychological rehabilitation has not proved difficult [95].

Salicylates

Patients on salicylate therapy for acute rheumatic fever, juvenile and adult rheumatoid arthritis, and systemic lupus erythematosus, may develop acute hepatic injury and even chronic hepatitis. This may develop even with serum salicylate levels below 25 mg/100 ml.

Hyperthermia [49]

Heat stroke is accompanied by hepato-cellular damage, in 10% severe and contributing to death. Pathologically it is marked by microvesicular fat, congestion, cholestasis (sometimes ductal), haemosiderosis and sinusoidal infiltration with primitive cells. Dilatation of portal venules is prominent in fatal cases. Biochemically there may be jaundice, increased transaminase levels and a fall in prothrombin and albumin levels. The damage is due to hypoxia and to direct thermal injury. Some of the changes may be related to endotoxaemia. Obesity is a risk factor.

Exertional heat stroke is marked by collapse, convulsions, hypotension and hyperpyrexia. Rhabdomyolysis and neuronal cerebellar damage are complications. Treatment is by core cooling and rehydration. Liver transplant may have to be considered.

Hypothermia

Although the changes in experimental animals are impressive, in man they are inconspicuous. The effect of low temperatures on the liver is unlikely to be of serious consequence.

Burns

Within 36–48 h of burning, the liver shows changes very similar to those seen in carbon tetrachloride poisoning. These are reflected in minor changes in liver function tests.

Hepato-cellular zone 1 necrosis

This type of injury resembles that of zone 3 but is maximal in zone 1 (peri-portal) areas.

Ferrous sulphate

Accidental ingestion of large quantities of ferrous sulphate is followed by zone 1 coagulative degeneration with nuclear pyknosis and fragmentation with little or no inflammation.

Phosphorus

The red form is relatively non-toxic but the yellow form is extremely lethal—as little as 60 mg being fatal. It is usually taken accidentally or suicidally as rat poison or in fire crackers.

Poisoning causes acute gastric irritation. Phosphorus may be found by gastric lavage. The patient's breath has a characteristic garlic odour and the faeces are frequently phosphorescent. Jaundice appears on the third or fourth day. The course may be fulminating with coma and death within 24 h or, more usually, within the first 4 days.

The liver biopsy shows zone 1 necrosis with macro- and medium-sized fat droplets. Inflammation is minimal.

About one-half of patients recover, and ultimate recovery will probably be complete. There is no specific treatment.

Mitochondrial cytopathies

Some drugs seem to have a predominant effect on mitochondrial function causing inhibition of respiratory chain enzymes. Clinically they are marked by vomiting and apathy. Lactic acidosis, hypoglycaemia and metabolic acidosis are seen. Mitochondrial β-oxidation of fatty acids is associated with microvesicular fatty liver. Electron microscopy shows mitochondrial damage. The diseases are multi-system.

Sodium valproate

Asymptomatic rises in serum transaminases, which subside on withdrawing the drug or reducing the dose, are reported in about 11% of patients receiving valproate. However, a more severe, even fatal, hepatic reaction may develop [113]. The patients are usually young, between 2.5 months and 34 years with 69% being 10 years old or less. Males are particularly affected. Presentation is usually within 1–2 months of starting the drug and is not seen after 6–12 months of therapy. Vomiting and disturbed consciousness are seen with hypoglycaemia and clotting defects. Other features of the microvesicular fat syndrome are also found.

Liver biopsy shows microvesicular fat mainly in zone 1. Variable hepato-cellular necrosis is seen in zone 3. Electron microscopy shows obvious mitochondrial changes.

Valproate or one of its metabolites, particularly 2-propyl-pentanoic acid, interferes with mitochondrial function, particularly β-oxidation of fatty acids. Polypharmacy, such as with anti-epileptic drugs, may be a risk factor for fatal hepato-toxicity in young children. Blood ammonia levels rise, indicating inhibition of mitochondrial urea-cycle enzymes. Even in healthy subjects valproate induces inhibition of urea synthesis with hyperammonaemia [52]. Patients having severe reactions to valproate might have an inborn deficiency of urea-cycle enzymes, but this has not been proved, although one patient with inherited carbamoyl transferase deficiency died when receiving valproate [52].

Tetracyclines

Tetracycline inhibits production of the transport proteins which excrete phospholipids from the hepatocyte, so resulting in fatty liver.

Deaths due to hepato-renal failure have followed large doses of intravenous tetracycline given to pregnant women with pyelonephritis [130]. Tetracyclines also have been associated with acute fatty liver of pregnancy. Tetracyclines should be avoided during pregnancy although large intravenous doses are probably necessary for significant hepato-toxicity.

Tacrine

Tacrine, a cholinesterase inhibitor, is associated with rises in serum transaminases in 50%. These achieve three times the upper limit of normal in 25% and 20 times in 2% [159]. The increases are seen after 4–6 weeks of therapy. They are usually asymptomatic and only a few cases of jaundice have been reported. Discontinuation reverses the transaminase increases and a challenge in mild cases is usually negative.

The drug is probably directly hepato-toxic and the reaction is not immuno-allergic but is due to a toxic metabolite. Weak base tacrine exerts an effect on human and animal mitochondria [9]. This increases the energy expenditure of the cell without concomitant ATP formation and leads to cell dysfunction at low doses and cell demise at higher doses [9].

Antiviral nucleoside analogues

Clinical trials of fialuridine (FIAU), a fluorinated pyridine nucleoside analogue, had disastrous consequences when used to treat chronic hepatitis B infection [85]. After 8–12 weeks, volunteers developed hepatic failure, lactic acidosis, hypoglycaemia, coagulopathy, neuropathy and renal failure, sometimes fatal. Liver biopsies showed microvesicular steatosis and abnormal mitochondria. The mechanism is probably the incorporation

of FIAU into the mitochondrial genome in place of thymidine [107].

Fulminant hepatitis with severe lactate acidosis has been reported in HIV-infected patients on *didanosine* (ddI) [10]. Some of the side-effects of *azidothymidine* (AZT) and *23-dideoxycitidine* (ddC) are probably due to inhibition of mitochondrial DNA synthesis.

Lamivudine has not resulted in serious liver damage. It does not inhibit mitochondrial DNA replication in intact cells [148].

Bacillus cereus

Emetic toxin in contaminated food can cause fulminant liver failure due to mitochondrial toxicity [87].

Steato-hepatitis

The reaction termed *non-alcoholic steato-hepatitis* (NASH) histologically resembles acute alcoholic hepatitis with sometimes, in addition, electron microscopic evidence of lysosomal phospholipidosis. Mallory's hyaline is found in zone 3 in distinction to true alcoholic hepatitis.

Perhexiline maleate

Perhexiline maleate, an anti-anginal drug now withdrawn, has been associated with hepatic histology resembling acute alcoholic hepatitis. Patients with this reaction lack a gene concerned with the oxidation of debrisoquine. The defect leads to a deficiency of a monoxygenase reaction in liver microsomes.

Amiodarone

This anticardiac–dysrhythmia drug has caused toxic damage to lung, cornea, thyroid, peripheral nerves and liver [155]. Abnormal biochemical tests of liver function are found in 15–50% of patients receiving it [121].

Hepato-toxicity usually develops more than 1 year after starting therapy but can occur within 1 month. The spectrum is wide, from isolated asymptomatic transaminase elevations to a fulminant fatal disorder. Hepatotoxicity is usually marked by an increase in serum transaminases and rarely by jaundice. Symptoms may be absent and toxicity detected only by routine monitoring; hepatomegaly is not constant. Severe cholestasis may be a feature. Fatal cirrhosis can develop. Children can be affected.

Amiodarone has a very large volume of distribution and a very long half-life, so that blood levels may remain raised for many months after withdrawal of therapy (fig. 20.14). Amiodarone and its major metabolite, *N*-desethylamiodarone, are present in the liver for several months after stopping the drug [138]. The incidence and severity

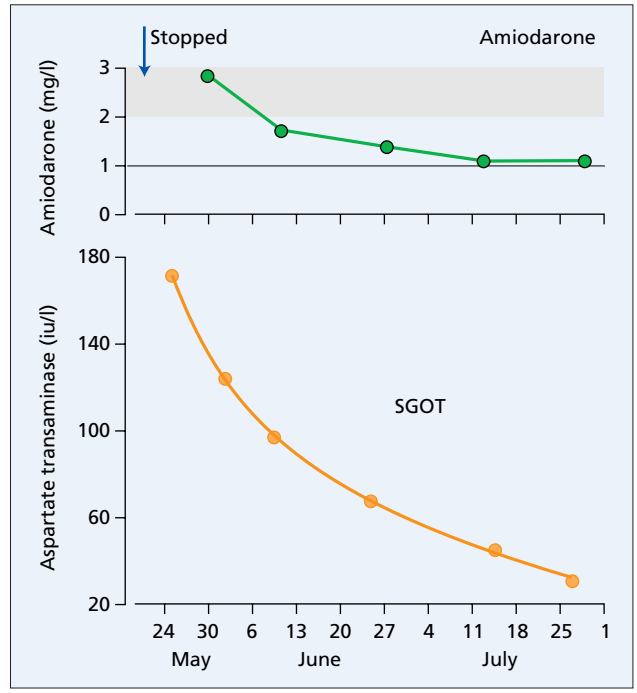


Fig. 20.14. Aspartate transaminase (SGOT) and blood amiodarone levels in a 63-year-old physician. Note the persistence of blood amiodarone levels 2 months after stopping therapy.

of side-effects correlates with the serum concentration, and the dose must be kept between 210 and 600 mg daily.

Amiodarone is iodinated and this results in an increased density on a CT scan. This does not correlate with hepatic injury.

Hepatic histology shows an acute alcoholic hepatitis-like picture with fibrosis and, sometimes, pronounced bile ductular proliferation. Electron microscopy shows phospholipid-laden lysosomal lamellar bodies containing myelin figures (fig. 20.15) [78]. These are constantly found in amiodarone-treated patients and signify drug exposure, not drug toxicity. Swollen granular zone 3 macrophages, presumably iodine-laden lysosomal bodies, may be an early marker of amiodarone hepatotoxicity. Either the drug itself or its main metabolite probably inhibit lysosomal phospholipases responsible for catabolizing phospholipids.

A similar phospholipidosis can be found with *parenteral nutrition* and complicating *trimethoprim–co-trimoxazole* therapy (Septrin, Bactrim) [93].

Synthetic oestrogens

A picture of 'alcoholic hepatitis' has been associated with massive doses of synthetic oestrogen used to treat prostatic cancer [132].

Calcium channel blockers

Nifedipine has been associated with steato-hepatitis but more evidence is required. Diltiazem has been associated with fevers, headache and abnormal transaminases within 18 days of starting treatment. Liver biopsy shows many well-defined granulomas [125].

Fibrosis

Fibrosis forms part of most drug reactions, but in some it may be the predominant feature. The fibrous tissue is deposited in the Disse space, where it obstructs sinusoidal blood flow, causing non-cirrhotic portal hypertension and hepato-cellular dysfunction. The lesion is related to toxic drug metabolites and is usually in zone 3, an exception being methotrexate where the damage is in zone 1.

Methotrexate

Hepato-toxicity results from a toxic metabolite of microsomal origin which induces fibrosis and ultimately cirrhosis (fig. 20.16). Primary liver cancer can develop. Hepato-toxicity is likely to follow long-term therapy, usually for psoriasis, rheumatoid arthritis or leukaemia. The risk seems to be lower in rheumatoid patients than in those with psoriasis [161]. Symptomatic liver disease is rare. Serial liver biopsies usually show benign appearances but three of 45 patients with rheumatoid arthritis developed serious liver disease [109]. Fibrosis may be graded from mild, which is probably insignificant, to significant and even to cirrhosis when the drug should be stopped.

Fibrosis is dose and duration dependent. When given in three 5-mg doses at 12-h intervals each week (i.e. 15 mg/week), it seems safe. Baseline liver biopsies are only indicated in those at particular risk, having significant alcohol intake or a history of liver disease. Serum transaminases are a poor reflection of underlying liver disease but should be monitored monthly; increases indicate that a liver biopsy should be done. In all cases a routine liver biopsy should be performed at 2 years or when the cumulative dose of methotrexate exceeds 1.5 g.

Ultrasound may be useful in detecting fibrosis and indicating stopping therapy. Hepatic transplantation has been performed for severe methotrexate hepato-toxicity [44].

Other cytotoxic drugs

These have a wide range of hepato-toxicity. The liver, however, is surprisingly resistant to injury by cytotoxic drugs, perhaps due to its low proliferative rate and extensive detoxifying capabilities.

Cytotoxic drugs cause rises in serum transaminases if large amounts are given. Drugs such as methotrexate, azathioprine and cyclophosphamide cause zone 3 necrosis, fibrosis and cirrhosis. Mild sclerosis of some portal zones results in the picture of idiopathic portal hypertension after cytotoxic therapy for leukaemia [134].

Veno-occlusive disease (VOD) is associated with cyclophosphamide, busulphan and irradiation. *Cholestasis* may be dose-related due to such drugs as cytosine arabinoside, or *hepato-canalicular* due to azathioprine. *Sinusoidal dilatation*, *peliosis* and *tumours* are associated with sex and anabolic hormone therapy. One drug

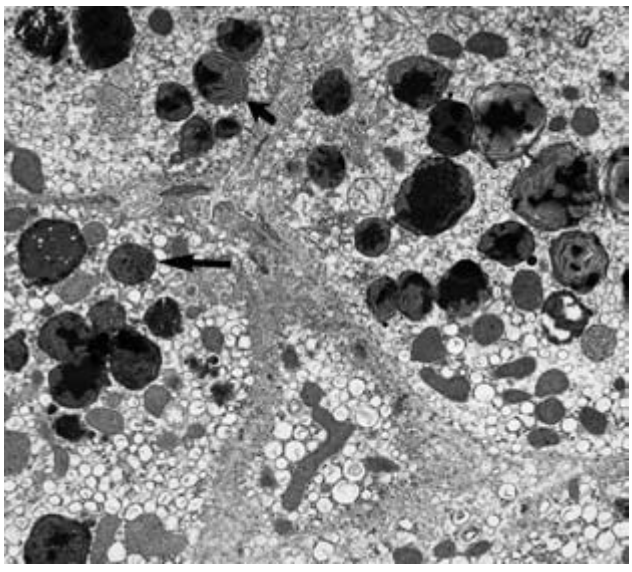


Fig. 20.15. Amiodarone hepato-toxicity: electron microscopy of the liver showing lysosomal lamellar bodies containing myelin figures (arrows).

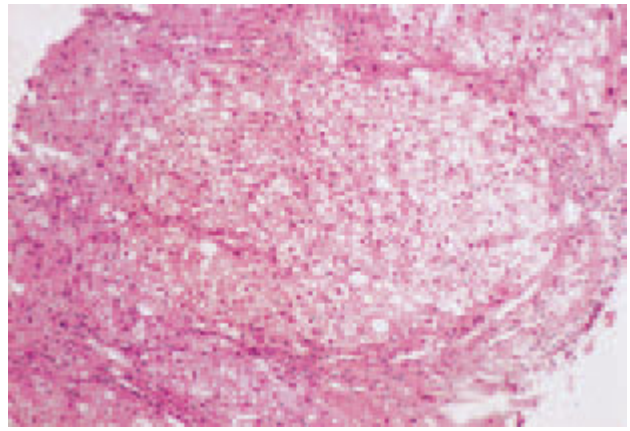


Fig. 20.16. Methotrexate liver injury. The zonal architecture is maintained. The portal zones are expanded with fibrous tissue and mononuclear cells. The hepatocytes show fatty change. (H & E,×65.)

may enhance the toxicity of another, for instance 6-mercaptopurine effects are worsened by doxorubicin.

Long-term use of cytotoxic agents in recipients of renal transplants or in children with acute lymphatic leukaemia leads to chronic hepatitis, fibrosis and portal hypertension.

Arsenic

The organic, trivalent compounds are particularly poisonous. Arsenic trioxide 1% (Fowler's solution) given for long periods for the treatment of psoriasis has resulted in non-cirrhotic portal hypertension [100]. Acute, probably homicidal, arsenic poisoning can cause perisinusoidal fibrosis and VOD [66].

Arsenic in drinking water and native drugs in India may be related to 'idiopathic' portal hypertension. The liver shows portal tract fibrosis and sclerosis of the portal vein branches (fig. 20.17). Angiosarcoma is a complication.

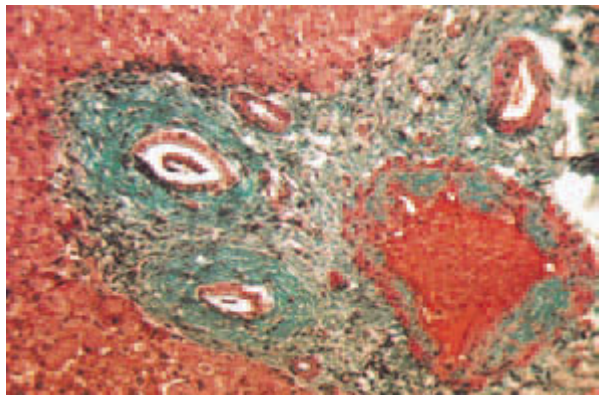


Fig. 20.17. Arsenic hepato-toxicity following treatment of psoriasis. Zone 1 is expanded by fibrosis and sclerosis of portal vein radicles. (Mallory's trichrome stain.)

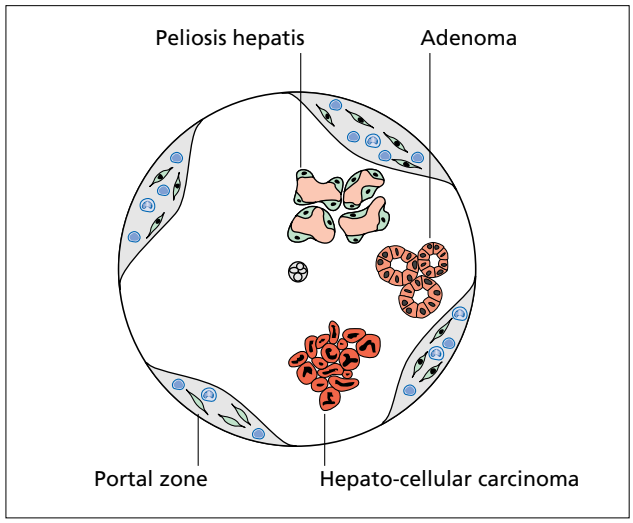


Fig. 20.18. Toxic effects of vinyl chloride, arsenic and thorotrast on the liver.

Vinyl chloride

Workers exposed to vinyl chloride monomer over many years develop hepato-toxicity (fig. 20.18). The earliest change is a sclerosis of portal venules in zone 1 of the liver with the clinical changes of splenomegaly and portal hypertension. Later associations include angiosarcoma of the liver and peliosis hepatis. Early histological alterations indicative of vinyl monomer exposure are focal hepato-cellular and focal mixed hepatocyte and sinusoidal cell hyperplasia. These are followed by subcapsular portal and perisinusoidal fibrosis.

Vitamin A

Vitamin A is being increasingly used in dermatology, by food faddists, in cancer prevention and for hypogonadism. Toxicity develops with as little as 25 000 iu daily over 6 years or 50 000 iu daily for 2 years [42]. It is potentiated by alcohol abuse.

The patient presents with nausea, vomiting, hepatomegaly, abnormal biochemical tests and portal hypertension. Ascites, either exudate or transudate, may develop. Histology shows hyperplasia of fat-storing (Ito) cells with vacuoles which fluoresce under ultraviolet light. Fibrosis and cirrhosis may develop [42].

Vitamin A is slowly metabolized from the hepatic stores and may be identified in the liver months after stopping treatment.

Retinoids

These vitamin A derivatives are used largely in dermatology. Etretinate, which is structurally similar to retinol, has caused severe hepatic reactions. Hepato-toxicity has also been reported with its metabolite, acitretin [151], and with isotretinoin.

Vascular changes

Sinusoidal dilatation

Focal dilatation of zone 1 sinusoids may complicate contraceptive or anabolic steroid therapy. This can cause hepatomegaly and abdominal pain with rises in serum enzymes. Hepatic arteriography shows stretched, attenuated branches of the hepatic artery with a patchy parenchymal pattern where areas of contrast alternate with areas which are not well filled.

The condition regresses on stopping the hormone.

A similar change may complicate azathioprine given after renal transplantation and this may be followed 1–3 years later by fibrosis and cirrhosis.

Peliosis hepatis

The large blood-filled cavities may or may not be lined with sinusoidal cells (fig. 20.19). They are distributed randomly, the diameter varying from 1 mm to several centimetres [168]. Electron microscopy shows the passage of red blood cells through the endothelial barrier and perisinusoidal fibrosis may develop. These alterations might constitute the primary event [167].

Peliosis has been described in patients taking oral contraceptives, in men having androgenic and anabolic steroids, and following tamoxifen. Peliosis has been reported in recipients of renal transplants. It has also complicated danazol therapy.

Veno-occlusive disease (VOD)

Small, zone 3 hepatic veins are particularly sensitive to toxic damage, reacting by sub-endothelial oedema and subsequent collagenization. The disease was originally described from Jamaica due to toxic injury to the minute hepatic veins by pyrrolizidine alkaloids taken as *Senecio* in medicinal bush teas. It has since been described from India [146], Israel, Egypt and even Arizona. It has been related to contamination of wheat [146].

The disease is marked by an acute stage with painful hepatomegaly, ascites and inconspicuous jaundice. The patient may recover, die or pass into a sub-acute stage of hepatomegaly and recurrent ascites. The chronic type resembles any other cirrhosis. Diagnosis is made by liver biopsy.

Azathioprine induces endotheliitis. Its long-term use in kidney and liver transplant recipients is associated with sinusoidal dilatation, peliosis, VOD and nodular regenerative hyperplasia [141].

Cytotoxic therapy especially with cyclophosphamide BNCU, azathioprine, busulphan, VP-16 and total body irradiation exceeding 12 Gy are associated with VOD. VOD follows high-dose cytoreductive therapy in bone marrow recipients [136]. There is widespread damage to zone 3 structures including hepatocytes, sinusoids and particularly small hepatic venules. It is marked by jaundice, painful hepatomegaly and weight gain (ascites). In 25% of patients it is severe with death occurring within 100 days.

Hepatic irradiation. The liver has a low tolerance to radiotherapy. Radiation hepatitis increases when doses reach or exceed 35 Gy to the whole organ delivered as 10 Gy/week. VOD appears 1–3 months after completion of therapy. It may be transient or death may ensue from liver failure. Histologically, zone 3 haemorrhage is seen with hepatic venules showing fibrosis and obliteration.

Hepatic vein occlusion (Budd–Chiari syndrome) has been reported following oral contraceptives, and after azathioprine in a renal transplant patient (Chapter 11) [150].

Acute hepatitis

The reaction is immuno-allergic. A drug metabolite binds covalently to a particular membrane P450. This metabolite–P450 acts as neoantigen and stimulates the immune system to form autoantibodies (fig. 20.20) [122]. In metabolically and immunologically susceptible subjects, the immune reaction is severe enough to destroy the hepatocyte.

Only a very small proportion of patients taking the drug will have this reaction. There is usually no method of predicting who will be susceptible. The reaction is unrelated to dose, but is commoner after multiple exposures. The onset is delayed until about 1 week after exposure, and it usually appears within 12 weeks of starting therapy.

The reaction is usually hepatic, the clinical picture resembling acute viral hepatitis. Biochemical tests indicate hepato-cellular damage. Serum γ-globulins are increased.

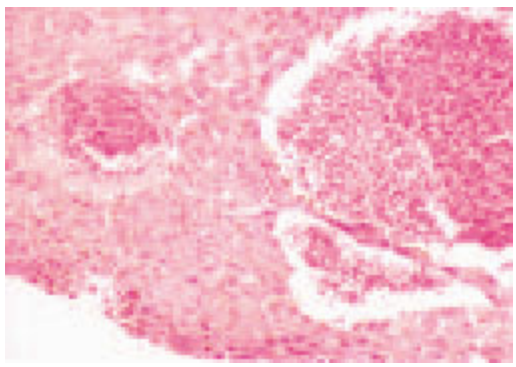


Fig. 20.19. Peliosis hepatis. A dilated blood space is seen with no clear-cut wall.

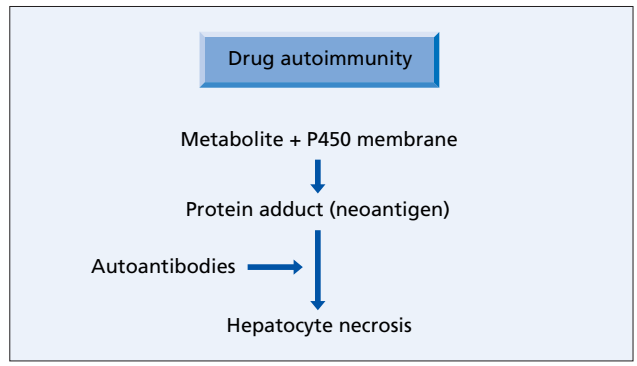


Fig. 20.20. Possible mechanism of drug-related autoimmune hepatocyte necrosis.

In those who recover, maximum serum bilirubin levels are reached after 2–3 weeks. The more seriously affected die of hepatic failure. The mortality is high for those who are clinically recognized—higher than for viral hepatitis. If hepatic encephalopathy is reached, the mortality is 70%.

An enormous number of drugs cause this hepatic reaction. They may be recognized only after the drug has been released on the general market. Specialist text books should be consulted for individual drugs [18, 38, 144, 169]. Any drug should be suspected. An individual drug can cause more than one reaction and there may be an overlap between the acute hepatitic, cholestatic and hypersensitivity reactions.

Hepatic histology may be virtually indistinguishable from acute viral hepatitis [55]. Milder cases show spotty necrosis, becoming more extensive and reaching a stage of diffuse liver injury and collapse. Bridging is frequent; inflammatory infiltration is variable. Chronic hepatitis may sometimes be a sequel.

The reactions tend to be severe, particularly if the drug is continued after liver damage has started. Patients with acute, fulminant drug-related liver failure must be considered for hepatic transplantation (Chapter 8). Corticosteroids are of doubtful benefit.

Older women are at particular risk, whereas the reactions are unusual in children.

Isoniazid

Between 10 and 36% of individuals taking isoniazid will show raised transaminase values during the first 10 weeks and about 1% will develop hepatitis. This will rise to 2% in those aged more than 50 years. Females are at particular risk.

After acetylation the isoniazid is converted to a hydrazine which is changed by drug-metabolizing enzymes to a potent acylating agent which produces liver necrosis (fig. 20.21) [91]. This has not been identified.

Combination of the isoniazid with an enzyme-inducer such as rifampicin increases the risk [139]. Anaesthetic drugs, paracetamol and alcohol enhance toxicity. Para-aminosalicylate, on the other hand, is an enzyme-retarder, and this may account for the relative safety of the para-aminosalicylate–isoniazid combination formerly used in the treatment of tuberculosis. The addition of pyrazinamide markedly increases the mortality [33].

The slow acetylator phenotype is caused by decreased or absent *N*-acetyltransferase. The relation of hepatotoxicity to acetylator status remains uncertain, although in Japanese patients fast acetylators are more susceptible [165].

Immunological liver injury is possible. However, 'allergic' manifestations are absent and the number developing sub-clinical liver injury is very high.

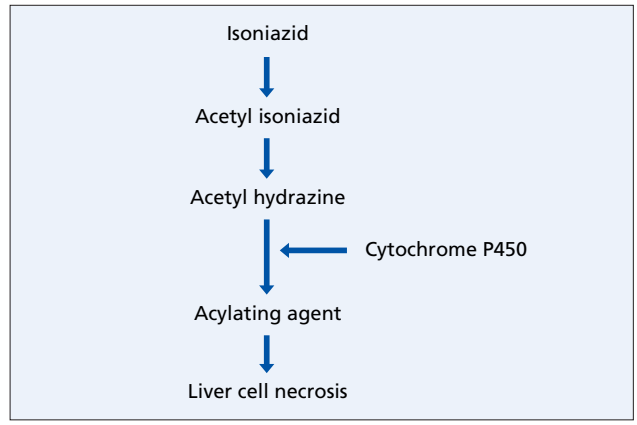


Fig. 20.21. The possible mechanism of isoniazid liver injury.

Elevated serum transaminase values are frequent during the first 8 weeks of therapy. There are usually no symptoms and the transaminases subside despite continuing isoniazid. Nevertheless, transaminases should be monitored before treatment is started and 4 weeks later. If increases are found they should be repeated at weekly intervals. Rising levels indicate that treatment must be stopped.

Clinical features

After treatment for 2–3 months, non-specific symptoms include anorexia and weight loss. These continue for 1–4 weeks before the onset of jaundice.

The hepatitis usually resolves rapidly on stopping the drug, but if jaundice develops there is a 10% mortality [11].

Severity is greatly increased if the drug is continued after symptoms develop or serum transaminases rise. The reactions are more serious if the patient presents after more than 2 months on the drug [11]. Malnutrition and alcoholism increase the risk [105].

The *liver biopsy* may show acute hepatitis. Continued administration leads to chronic hepatitis which is probably non-progressive if the drug is withdrawn.

Rifampicin

This has usually been given with isoniazid. Rifampicin on its own may cause a mild hepatitis, but this is usually in the context of a general hypersensitivity reaction.

Pyrazinamide

This is one of the most hepato-toxic of the anti-tuberculosis drugs. A hypersensitivity reaction seems most likely [25]. Hepato-toxicity is increased when given in combination with isoniazid and rifampicin.

Methyl dopa

Increases in serum transaminases, which generally subside despite continued drug administration, are reported in 5%. These may be metabolite-related, since human microsomes can convert methyl dopa to a potent arylating agent.

Methyl dopa hepato-toxicity may also be immunologically related to metabolic activation and the production of a drug-associated antigen.

The patient is often post-menopausal and has been on methyl dopa for 1–4 weeks. The reaction usually appears within the first 3 months. Prodromes include pyrexia and are short. Liver biopsy shows bridging and multilobular necrosis. Death may occur in the acute stage, but clinical improvement usually follows stopping the drug.

Other anti-hypertensives

These are subject to the same genetic polymorphism as debrisoquine (P450-II-D6). Hepato-toxicity has been reported with metoprolol, atenolol, labetalol [24], acebutalol and hydralazine derivatives.

Enalapril, an angiotensin-converting enzyme inhibitor, is a cause of hepatitis with eosinophilia [123]. Verapamil can also cause an acute hepatitis-like reaction.

Halothane

Halothane-associated liver damage is very rare. It seems to be of two types: mild, evidenced by raised serum transaminase, and fulminant in a few patients who have usually been exposed previously to halothane.

Mechanisms

Products of reductive metabolism are particularly hepato-toxic in the presence of hypoxaemia. Active metabolites could cause lipid peroxidation and inactivation of drug-metabolizing enzymes.

Halothane is stored in adipose tissue and may be released slowly; obesity is frequently associated with halothane hepatitis.

Lymphocytes show increased cytotoxicity and this is also found in family members.

The association with multiple exposures (fig. 20.22), the pattern of fever, and the occasional eosinophilia and skin rash suggest an immuno-allergic mechanism. Approximately 20% of halothane is biotransformed by cytochrome P450s, primarily CYP 2E1, to an unstable intermediate trifluoro-acetyl chloride [62]. This binds covalently to liver proteins causing cellular injury. In some individuals, these trifluoro-acetylated proteins are immunogenic and lead to fulminant hepatic necrosis.

Clinical features

Halothane hepatitis is much more frequent after multiple anaesthetics. Obese, elderly females seem particularly at risk. Children can be affected.

Fever, usually with rigors, develops more than 7 days (range 8–13 days) after the first operation and is usually accompanied by malaise and non-specific gastrointestinal symptoms, including right upper abdominal pain. After several exposures the temperature is noted 1–11 days post-operatively (fig. 20.22). Jaundice appears rapidly after the pyrexia, about 10–28 days after a *single* exposure and 3–17 days after *multiple* anaesthetics. This delay before jaundice, usually of about 1 week, is helpful in excluding other causes of post-operative icterus.

The total white cell count is usually normal, occasionally with eosinophilia. Serum bilirubin levels may be very high, particularly in fatal cases, but are under 170 µmol/l (10 mg/dl) in 40%. The condition may be anicteric. Serum transaminases are in the range found in viral hepatitis. An occasionally high serum alkaline phosphatase level may be seen. If the patient becomes icteric the mortality is very high. Altogether, 139 of 310 patients in one series died (46%). If coma ensues and the one-stage prothrombin time rises markedly, the condition is virtually hopeless.

Hepatic changes

These may be virtually indistinguishable from those of acute viral hepatitis (fig. 20.23). Leucocytic infiltration in the sinusoids, granulomas and fatty change may suggest a drug aetiology. Necrosis may be sub-massive and confluent or massive.

Alternatively, the picture in the first week may be that of direct metabolite-related liver injury with zone 3

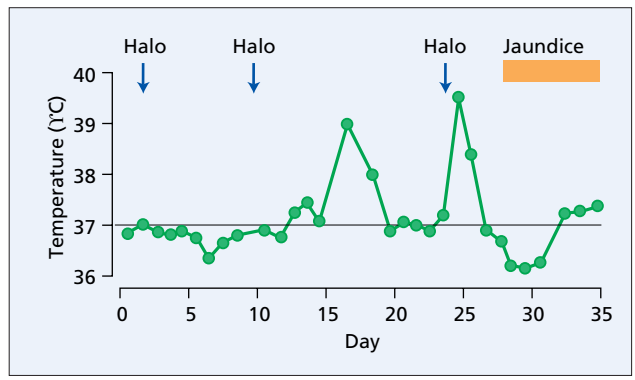


Fig. 20.22. Hepatitis associated with multiple exposures to halothane (Halo). Note the febrile response to the halothane anaesthetics. The patient became jaundiced after the third anaesthetic and rapidly became pre-comatose, developing deep coma on the fourth day and dying on the seventh day.

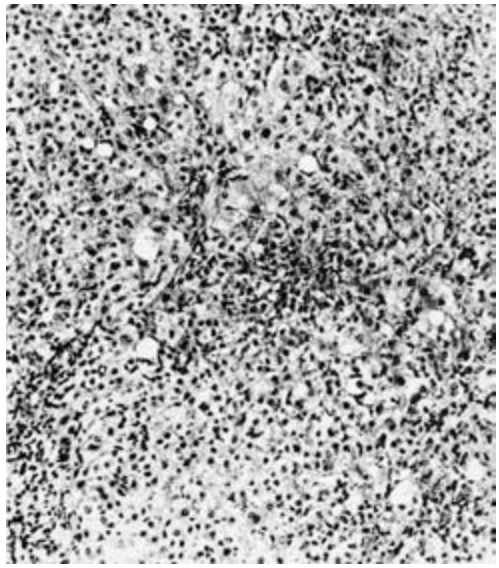


Fig. 20.23. Halothane-associated hepatitis. Hepatic histology shows cellular infiltration largely with mononuclear cells. Zone 3 areas show necrosis and cell swelling. Liver cell columns are disorganized. The appearances are virtually identical to those of acute viral hepatitis. (H & E,×96.)

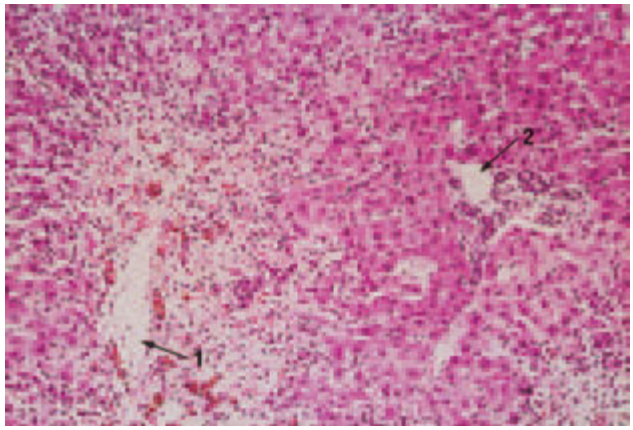


Fig. 20.24. Halothane liver injury. The zone 3 area (1) shows well-defined necrosis without an inflammatory reaction in the portal area (2). (H & E,×220.)

massive necrosis involving two-thirds or more of each acinus (fig. 20.24).

Conclusion

Halothane administration should not be repeated if there is the slightest suspicion of even a mild reaction after the first anaesthetic. All case records should be scrutinized carefully before *any* second anaesthetic is given.

Underlying liver disease is not a risk factor.

Those requiring multiple anaesthetics during a short period should not be given halothane. A second anaesthetic with halothane should not be repeated within 6 months of the first.

Although the danger of halothane anaesthetics, particularly if repeated, are well known, economic constraints mean use continues in developing countries.

Other halogenated anaesthetics

These are metabolized less and are more rapidly excreted and so are much less hepato-toxic than halothane. Nevertheless, they do form trifluoro-acyl adducts in proportion to the rate of metabolism [101]. Hepatitis has been reported following enflurane [79], isoflurane [126] and desflurane [90]. They are all exceedingly rare. Despite increased cost, enflurane or isoflurane should replace halothane, but should probably not be administered at short intervals. Enflurane metabolites are recognized by antibodies from patients with halothane hepatitis. Thus changing from one agent to another for multiple anaesthetics will not necessarily reduce the risk of liver injury in a susceptible individual.

Hydrofluorocarbons

Hydrofluorocarbons used in industry as ozone-sparing substitutes for chlorofluorocarbons can cause liver injury. The mechanism is similar to that suggested for halothane [53].

Systemic antifungals

Ketoconazole. Asymptomatic rises in transaminases are seen in 17.5% of patients given the drug for onychomycosis [21]; 2.9% develop overt hepatitis. Older patients, often female, are usually affected. The drug has usually been taken for longer than 4 weeks and for not less than 10 days [143]. Serum transaminases usually subside spontaneously but if the level exceeds three times the upper limit, the drug must be stopped immediately. The reaction can, rarely, be fatal and indicate liver transplantation [68].

Fluconazole. If used long-term, this drug must be carefully monitored for hepato-toxicity.

Itraconazole. This rarely causes liver damage after about 6 weeks of therapy [75].

Terbinafine. This has been reported to cause predominantly cholestatic liver damage in about 1:50000 cases [154]. The reaction usually resolves, but persistent cholestasis has been reported [76].

Oncology drugs

Hepato-toxicity and VOD are discussed above.

Flutamide. This is an anti-androgen used to treat

prostatic cancer, which can cause both hepatitis and cholestatic jaundice [23, 163].

Cytoproterone [13] and *etoposide* can cause acute hepatitis.

Nervous system modifiers

Pemoline is a central nervous system stimulant used in children. It causes acute hepatitis, probably metabolite-related, which can be fatal [98]. It can also cause an autoimmune-type chronic hepatitis [140].

Disulfiram, used to treat chronic alcoholism, has been associated with an acute hepatitis picture which is sometimes fatal and an indication for liver transplantation [115]. Autoantibodies against specific P450 cytochromes have been shown [35].

Clozapine. This drug, used to treat schizophrenia, causes asymptomatic rises in transaminases in 30–50% and an icteric hepatitis in 84 of 136 000 (0.06%) treated [84]. Fulminant hepatitis is exceedingly rare (0.001%).

Tolcapone (Tasmar). This drug is used to treat Parkinson's disease. It acts by blocking the enzyme which breaks down levadopa, so potentiating the action of levodopa drugs. It causes rises in transaminases in 1.7% of those taking it [4]. The hepatic reaction may be fatal. Liver function tests must be monitored during treatment. The European Commission has recommended suspension of its use. The USA has allowed continued use, but with careful monitoring.

Tizanidine. This centrally acting muscle relaxant has caused serious liver injury [28].

Sustained-release nicotinic acid (niacin)

Hepato-toxicity is related to the time-release form and not the crystalline form.

The reaction develops 1–4 weeks after taking 2–4 g/day. It is hepato-cellular and cholestatic and can be fatal [27].

Sulphonamides and derivatives

Sulfasalazine. The hepatic reaction is usually part of a systemic reaction including a serum sickness picture. The patient has usually been taking the drug for less than 1 month. Re-challenge is positive. There is an association with HLA-B8-DR3. The reaction can be fatal. Children can be affected.

Co-trimoxazole (Septrin)—see p. 357.

Pyrimethamine–sulfadoxine (Fansidar). The reaction is associated with severe cutaneous reactions and transient liver damage. Occasionally the reaction may be fatal. The sulfadoxine is the likely hepato-toxin.

Non-steroidal anti-inflammatory drugs

Most NSAIDs are hepato-toxic, usually through an idiosyncratic or hypersensitivity reaction [114]. The mildest reaction is simply a rise in serum transaminases but fatal liver failure can occur. Acute symptomatic liver disease is not a frequent problem, but transaminases should be monitored during the first 6 months of therapy.

Salicylate toxicity is related to dose, duration and age—younger persons are a particular risk.

Sulindac (*Clinoril*). The reaction may be hepato-cellular, cholestatic or mixed [147]. There are usually hallmarks of hypersensitivity including onset 8 weeks after starting the drug, fever, rash, nausea, vomiting and occasional eosinophilia.

Diclofenac [6]. Significant hepatitis is seen in 1–5 per 100 000 patients treated. The sufferer is usually an elderly female and presents with acute hepatitis. The reaction may be severe. Antinuclear antibodies may be positive.

Liver damage is immunological metabolite-related. Liver/protein diclofenac adducts have been detected [43]. Antibody cell-mediated injury of diclofenac-treated hepatocytes has been shown [65].

Liver function should be monitored during the first 8 weeks of therapy. The reaction can be fatal. Drug challenge is positive.

Nimesulide. The reaction is cholestatic or immuno-metabolic. The drug inhibits cyclo-oxygenase type 2 [152].

Piroxicam hepato-toxicity. The onset is after 1.5–15 months and the reaction can be fatal [108].

Allopurinol can cause a hepatic reaction which can include fibrin ring granulomas [142].

Propafenone can cause an acute hepatic reaction which can be fatal [92].

Hydroxychloroquine has been related to fulminant liver disease.

Naproxen is a rare cause of hepatic dysfunction.

Anti-thyroid drugs

Propylthiouracil. Elevations in transaminases are common in the first 2 months but are usually transient and asymptomatic. The drug may be continued with caution if there are no symptoms and the serum bilirubin is not increased [80].

Carbimazole has induced cholestasis [104], as has methimazole [102].

Quinidine and quinine

This reaction is marked by rash and fever 6–12 days after starting treatment. Liver biopsy shows inflammatory infiltrates and granulomas. Prompt withdrawal leads

to resolution; continued use may cause chronic liver damage.

Troglitazone

This drug reduced peripheral insulin resistance in type 2 diabetes. Unfortunately patients show hepatic dysfunction and deaths have been reported [5, 63, 99]. The drug has now been withdrawn.

Anti-convulsants

Protracted seizures in children can lead to acute zone 3 ischaemic injury [149]. Serum enzyme levels rise dramatically and fall over the following 2 weeks.

Phenytoin (*dilantin*). The reaction usually affects adults 2–4 weeks after starting treatment. The picture closely resembles infectious mononucleosis. Eosinophilia is usual.

Mortality is 50% in those who develop jaundice. It is usually due to streptococcal skin infections. Sufferers may have a genetic defect allowing accumulation of a toxic metabolite. Corticosteroids may be of value.

Dantrolene. This can induce severe, often fatal hepatotoxicity. Hepatic changes include hepatitis, cholangitis, chronic hepatitis and cirrhosis. Use has been severely restricted.

Carbamazepine. This drug has a wide spectrum of hepatic side-effects, the most usual being hepatocellular necrosis with granulomas (fig. 20.25). Sometimes, however, itching, fever and right upper quadrant pain may suggest cholangitis and hepatic histology may show marked cholestasis [72].

Chronic hepatitis

The picture strikingly resembles 'autoimmune' chronic hepatitis in clinical, biochemical, serological and histological features. The patients recover when the drug is withdrawn. Anti-organelle antibodies have been found in a number of patients.

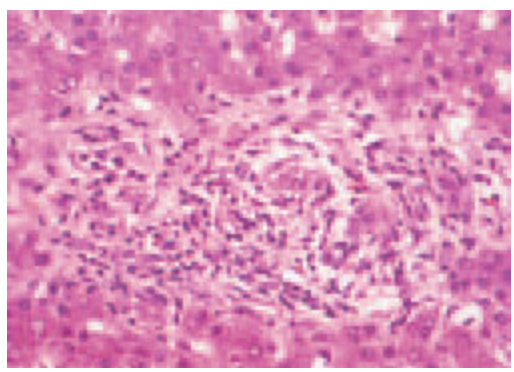


Fig. 20.25. Carbamazepine granulomatous hepatitis.

Chronic hepatitis was first described following the laxative *oxyphenisatin* and this has now been withdrawn from most parts of the world [120].

Chronic hepatitis can develop insidiously after many years of *methyl dopa* therapy, without an acute episode. Improvement follows withdrawal of the drug.

Alverine is a smooth muscle relaxant with papaverine-like effects. It can cause hepatitis with the presence of anti-nuclear (anti-lamin A and C) antibodies [89].

Nitrofurantoin has been related to chronic hepatitis, usually in women, 4 weeks to 11 years after starting treatment [12]. Pulmonary fibrosis is another complication. Hepato-toxicity is related to an active metabolite and may be mediated by CD8+ T-cells [61].

Other causes include clometacin, fenofibrate, isoniazid, papaverine and dantrolene.

Minocyclin can cause a systemic lupus erythematosus-like syndrome and a picture closely resembling autoimmune chronic hepatitis [45, 47].

Herbal remedies

Increasing use of alternative medicine has led to many reports of associated toxicity [69]. Unfortunately, in many instances, the nature of the hepato-toxin remains unknown. Moreover, many of the herbs contain more than one ingredient and may be contaminated by chemicals, heavy metals and micro-organisms. Self-medication is frequent and clinical histories may be unreliable. The spectrum of liver injury is very wide and ranges from acute hepatitis, chronic hepatitis and cirrhosis to cholestasis and VOD.

Pyrrolizidine alkaloids such as *Senecio* and crotolaria, often associated with bush teas, can cause VOD (see p. 349).

Germander is used in teas for anti-choleretic and antiseptic properties. Jaundice, with very high transaminase values, may follow after about 2 months' use. This disappears when the drug is stopped [74]. A toxic metabolite is produced through P453-A [81].

Chaparral is used to treat a variety of conditions, including weight loss, debility, cancer and skin conditions. Jaundice appears 3–52 weeks after ingestion [133]. It usually subsides on stopping the drug. However, acute fulminant failure may indicate liver transplant. Cirrhosis may be a sequel.

Chinese herbs may be used to treat eczema, insomnia and asthma. Preparations associated with hepatotoxicity include Jin Bu Huan [111, 162], Inchin-Ko-To [164] and Ma-Huang [97].

Other hepato-toxic herbal remedies include comfrey, mistletoe, valerian and skullcap. Many more will be recognized.

Recreational drugs

Ecstasy is a synthetic amphetamine derivative used as a stimulant, for instance during all-night rave parties. It has been associated with a picture resembling acute viral hepatitis [3, 34]. The timing of presentation is unpredictable, usually 1–3 weeks after starting, but may be delayed with continued use. Transaminases are exceedingly high. Hepatic histology is an acute hepatitis which may have autoimmune features [40].

The hepatitis may be so severe that hepatic transplantation is necessary [36]. Recovery is usual, but continued use can cause insidious chronic hepatitis and even cirrhosis [40]. Hepatitis may recur on resuming the drug.

Cocaine abuse. Patients with acute cocaine intoxication and rhabdomyolysis usually have biochemical evidence of liver damage [137]. Liver histology shows predominant zone 3 necrosis with zone 1 microvesicular fat [156]. The reactive metabolite is norcocaine nitroxide produced by *N*-methylation and catalysed by P450. The liver injury is caused by peroxidation, free radical formation and covalent binding to hepatic proteins. Reduction by phenobarbitone or other inducers such as alcohol enhance the effect. Shock and hypertension contribute to the zone 3 necrosis.

Canalicular cholestasis

Various *androgens* and *oestrogen* steroids can cause canalicular cholestasis. Oestrogens contained in contraceptive pills are good examples, but cholestasis is decreasing with the reduction in the content of active ingredients. The oestrogen is the important agent, although the progestin may augment the effect.

The drugs interact with the biliary apparatus. Bile salt independent bile flow is reduced by suppression of sodium potassium ATPase activity. Susceptibility may be related to genetic variations in biliary transporters, and an effect of sex steroids on canalicular multi-specific organic anion transporter (cMOAT) has been shown [15].

Sinusoidal membranes become less fluid. Pericellular permeability (tight junctions) may be increased. Cytoskeleton is affected with failure of the pericanalicular micro-filaments to contract [110].

Patients with genetic predisposition to cholestasis of pregnancy are at risk (Chapter 27). An enhanced effect is also seen in those with pre-symptomatic primary biliary cirrhosis. Theoretically, patients with acute hepatitis should be at risk but women convalescent from hepatitis may resume the use of all contraceptives without causing liver damage.

The cause is usually, but not always, a C17-alkylated testosterone. The reaction is dose dependent and reversible.

The patient suffers from itching with variable bilirubinaemia. Serum transaminase values are variable but in about one-third may exceed five times normal. Serum alkaline phosphatase may be disproportionately low.

Liver biopsy shows normal architecture and zone 3 cholestasis with surrounding reaction. *Electron microscopy* shows cholestasis and mild hepato-cellular damage.

The *prognosis* is excellent. Rarely, jaundice is severe and prolonged but usually the patient recovers when the drug is stopped. Recurrence is liable to follow resumption.

Cyclosporin A

Cyclosporin inhibits ATP-dependent bile salt transport [56]. There is dose-dependent inhibition of canalicular MOAT. In man, clinical cholestasis is rare, but hyperbilirubinaemia with or without mild biochemical cholestasis can be seen.

Cyclosporin is metabolized by P450-III-A enzymes (see fig. 20.4). Enzyme induction and competitive inhibition explains interactions with drugs such as ketoconazole and erythromycin [157].

Ciprofloxacin

Quinolones, including ciprofloxacin and ofloxacin can cause intense centrizonal cholestasis with little inflammatory cell infiltrate. Jaundice is transient and enzymes return to normal [50, 67].

Hepato-canalicular cholestasis

The reaction is predominantly cholestatic, but, in addition, hepato-cellular features are present. There is overlap with hypersensitivity and hepatic drug reactions. An immuno-destructive process is focused on the bile ducts interfering with biliary secretory pumps and canalicular transporters.

The acute cholestatic reaction is usually mild, lasting less than 3 months. However, the cholestasis can be protracted (table 20.5). This can be minor, marked simply by continued increases in serum alkaline phosphatase and γ-GT levels. However, the protracted cholestasis may be major, lasting longer than 6 months and with continued pruritus. This chronic phase of ductopenia is defined by the absence of interlobular bile ducts in at least 50% of small portal tracts [30]. Recovery is usual, but occasionally hepatic transplantation is indicated.

Many drugs cause cholestasis. The penicillin derivatives (Augmentin, flucloxacillin), sulphonamides (Septrin, Bactrim), erythromycins, promazines and procarbazine (fig. 20.26) are particularly important.

Table 20.5. Drug-induced cholestasis

Acute < 3 months	
Protracted	
Minor	Continued serum phosphatase increase
Major	Jaundice > 6 months Pruritus Recovery *or* Loss of bile ducts → transplant

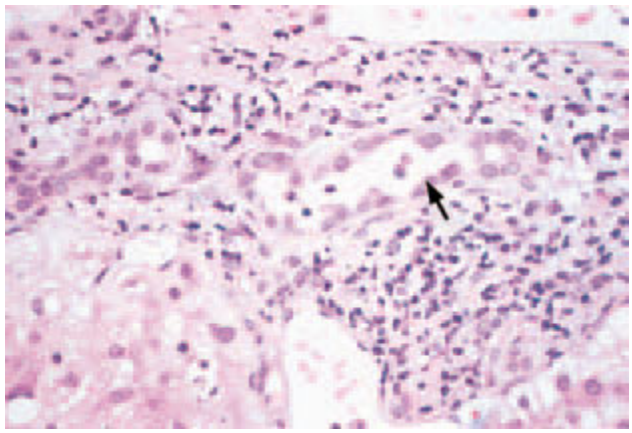


Fig. 20.26. Chronic procarbazine cholestasis: liver biopsy shows a portal area (zone 1) markedly expanded with largely mononuclear cells and some fibrous tissue, and containing a damaged bile duct (arrow). Recovery followed after 6 months jaundice. (H & E, ×100.)

Chlorpromazine

Only 1–2% of those taking the drug develop cholestasis. The reaction is unrelated to dose and in 80–90% the onset is in the first 4 weeks. There may be associated hypersensitivity. Excess eosinophils may be found in the liver (fig. 20.27).

Chlorpromazine decreases canalicular function and reduces bile flow [57]. Free chlorpromazine radicles may be hepato-toxic.

Genetic differences in the bile transformation of chlorpromazine could theoretically lead to the selective accumulation of cholestatic metabolites.

Clinical picture

The onset may simulate viral hepatitis, with a prodrome lasting some 4–5 days. Cholestatic jaundice appears concurrently or within a week and lasts 1–4 weeks. Pruritus may precede jaundice. Recovery is usually complete.

Serum biochemistry shows the features of cholestatic jaundice. A sustained rise in alkaline phosphatase values may be the only change. An eosinophilia may be seen in the peripheral blood in the very early stages.

Hepatic changes

Light microscopy shows cholestasis and, in the portal zones, a marked cellular reaction with mononuclear cells and eosinophils prominent (fig. 20.27). Even in the uncomplicated case some damage to liver cells can be noted. Granulomas may be present.

Prognosis and treatment

Jaundice of the chlorpromazine type is rarely fatal. Occasionally, jaundice lasts more than 3 months and even up to 3 years [118]. The picture is of prolonged cholestatic jaundice with steatorrhoea and weight loss. The clinical picture resembles primary biliary cirrhosis. The onset is, however, much more explosive and, in contrast to primary biliary cirrhosis, which is inevitably progressive, recovery usually ensues. However, the cholestasis can last 6 months or even be permanent with the development of biliary cirrhosis and eventually the need for transplantation.

The mitochondrial antibody test for primary biliary cirrhosis is negative or in low titre.

In the usual case of chlorpromazine jaundice no active treatment is required and recovery is complete. Corticosteroids do not affect the course. Ursodeoxycholic acid may be used to control itching.

Other promazines

An essentially similar picture can complicate therapy with other phenothiazine derivatives such as promazine, prochlorperazine, mepazine or trifluoperazine.

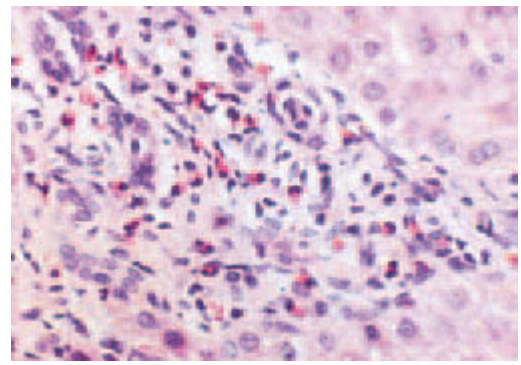


Fig. 20.27. Chlorpromazine hepatitis showing a portal zone reaction with eosinophils prominent.

Penicillins

Amoxycillin is an exceedingly rare cause of liver damage. However, *Augmentin*, a combination of amoxycillin with clavulanic acids, is a frequent cause of cholestasis, predominantly in men on continuous therapy [73, 83]. This is usually, but not always, short-lived. Clavulanic acid is the important hepato-toxic component.

Flucloxacillin causes cholestatic jaundice, usually in older patients taking the drug for more than 2 weeks [37]. Jaundice may appear within 8 weeks, and after the drug has been stopped, making the relationship difficult to establish. Cholestasis can become chronic.

Sulphonomides

Trimethoprim–sulfamethoxazole (*Septrin*, *Bactrim*) can rarely cause cholestatic reactions which usually resolve in 6 months [1]. However, the cholestasis can last 1–2 years [64] and be associated with disappearing bile ducts [166].

Erythromycin

Hepatic reactions are usually with the estolate, but the proprionate, ethylsuccinate and clarithromycin, have also been incriminated.

Two patients reacting to the estolate had a further cholestatic reaction when given the ethylsuccinate 12 and 15 years later [58].

The onset is 1–4 weeks after starting therapy with right upper quadrant pain, which may be severe, simulating biliary disease, fever, itching and jaundice. The blood may show eosinophilia and atypical lymphocytes.

Liver biopsy shows cholestasis, hepato-cellular injury and acidophil bodies. Portal zones show the bile duct wall to be infiltrated with leucocytes and eosinophils and the bile duct cells may show mitoses. At autopsy the gallbladder has been shown to be inflamed.

Haloperidol

This drug may rarely cause a cholestatic reaction resembling that related to chlorpromazine. It may become chronic [32].

Cimetidine and ranitidine [153]

Very rarely, cimetidine or ranitidine can cause a mild, non-fatal cholestatic jaundice, usually developing within 4 weeks of starting the drug.

Oral hypoglycaemics

Cholestasis has been related to chlorpropamide, glibenclamide (glyburide) and acetohexamide.

Tamoxifen

Tamoxifen has been associated with cholestasis and NASH [22, 112].

Other causes

Prolonged cholestasis can follow cyproheptadine (an appetite suppressant) [71] and thiabendazole.

Cholestasis has also been associated with gold, azathioprine, hydralazine [96], captopril [116], propafenone [92], nitrofurantoin (fig. 20.28) and the quinoline enoxacin [2].

Dextropropoxyphene

This analgesic can induce a reaction with recurrent jaundice, upper abdominal pain and rigors, mimicking biliary tract disease [124].

Ductular cholestasis

The bile ducts and canaliculi are filled with dense, inspissated bile casts without any surrounding inflammatory reaction. The plugs contain bilirubin, probably in combination with a drug metabolite. The picture has been particularly associated with *benoxyprofen*, which has a half-life of 30 h in the young, but 111 h in the elderly [145]. Five elderly patients have died with jaundice and renal failure. Generalized poisoning by the drug and its metabolites seems likely. Benoxyprofen has now been withdrawn.

Biliary sludge

This complicates treatment with the antibiotic, *ceftriaxone*. The patient may be symptom-free or suffer reversible biliary colic [106]. It is dose dependent [135]. Sludging is related to sharing a common pathway with bile acids for hepatic transport and also to an interaction with biliary lipid excretion. The sludge consists of a small amount of cholesterol and bilirubin but the major component is the calcium salt of ceftriaxone.

Sclerosing cholangitis (Chapter 15)

Causes include hepatic arterial infusion of cytotoxic drugs such as 5-fluorouridine, thiabendazole, caustics introduced into hydatid cysts and the Spanish toxic oil syndrome.

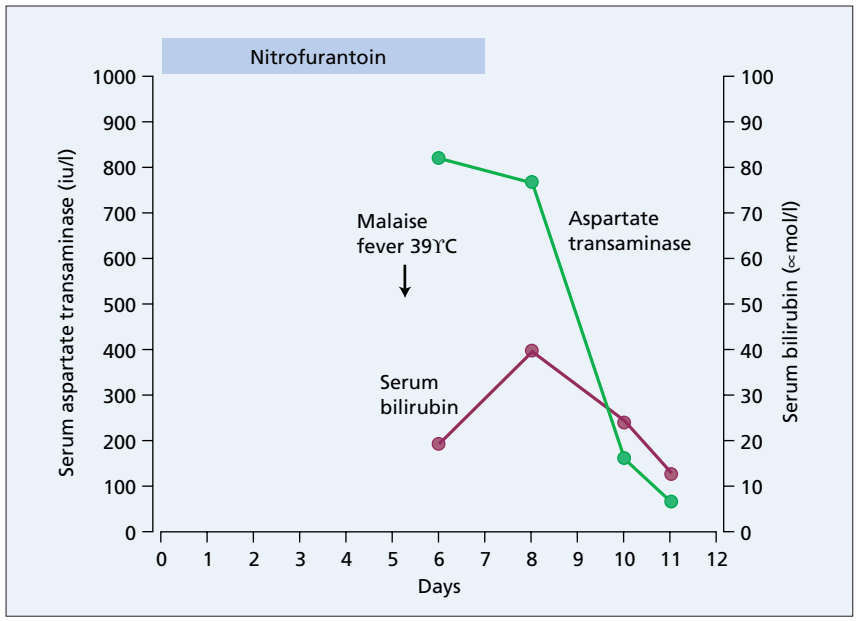


Fig. 20.28. Nitrofurantoin therapy for a urinary tract infection was followed 5 days later by a systemic reaction with jaundice. On stopping the drug the patient recovered rapidly.

Bile duct stricture can follow 10 years after upper abdominal *radiotherapy* [20].

Hepatic nodules and tumours

These are discussed more fully in Chapter 30.

Hepatic adenomas can be associated with sex hormones, particularly oral birth control pills [7]. The incidence is falling as the present pill contains reduced amounts of hormone. If possible, treatment should be conservative as the tumour may show spontaneous regression when hormones are stopped. Pregnancy is avoided.

Women taking hormones, particularly for many years, should be warned of the possibility of adenoma development. If adenoma is diagnosed, the woman must be warned of the possibility of rupture and the significance of any unexplained right upper quadrant pain or swelling in the abdomen. Surgery may be needed for complications, particularly intra-peritoneal or intra-tumour bleeding, severe abdominal pain and anaemia.

Hepato-cellular carcinoma

There is a low, but probably increased, risk of hepato-cellular carcinoma in women receiving oral contraceptives for 8 years or more. The tumour develops in a non-cirrhotic liver, metastases rarely and does not infiltrate [51]. Young women with oral contraceptive exposure tend to survive longer, have fewer symptoms and lower serum α-fetoprotein levels than those developing hepato-cellular carcinoma without exposure to hormones. Tumours are more vascular and haemoperitoneum is commoner.

Adenomas and carcinoma have been associated with *danazol* [39].

Vascular lesions may accompany adenoma or focal nodular hyperplasia. Large arteries and veins are present in excess, sinusoids may be focally dilated and *peliosis* may be present.

Focal nodular hyperplasia does not have such a strong association with hormones as adenoma. It affects both sexes, including children, but especially women in their reproductive years, some of whom may never have taken sex hormones. Asymptomatic patients should be observed regularly. In the symptomatic, stopping the hormones may lead to the lesion regressing. In others, and in particular those with complications, surgical resection is indicated.

Androgenic and *anabolic steroids* can be associated with adenoma, peliosis, nodular regenerative hyperplasia and particularly hepato-cellular carcinoma. Angiosarcoma may be associated. The drugs may be given for aplastic anaemia, hypopituitarism, eunuchoidism, impotency, in female transexuals [160] and in athletes to increase muscle mass [26]. Hepato-cellular cancer is much more frequent with male than female hormone therapy, perhaps due to the much larger doses given. The incidence of hepatic abnormality may be very high, in one series 19 of 60 patients given methyltestosterone showed abnormal liver function tests [160].

Angiosarcoma may follow androgenic anabolic steroids, vinyl chloride, thorotrast and inorganic arsenic.

Epithelioid haemangio-endothelioma is a rare malignant vascular tumour that has been related to oral contraceptive use [29] and to vinyl chloride [41].

Conclusions

Before marketing a new drug, testing must be done on both an acute and chronic basis and on more than one species or strain. Both the drug and its known metabolites must be used. The albumin-binding properties of the drug must be noted. The role of the drug as a hepatic enzyme-inducer must be studied. Clinical trials must include regular pre- and post-treatment estimations of serum bilirubin and transaminase levels. A needle liver biopsy, after informed consent, is particularly helpful in establishing the relation between a drug and liver injury and in determining the type of injury.

The serum transaminases may rise during the first 4 weeks of therapy only to subside despite the drug being continued. When a hepatic reaction is possible, as with isoniazid, it is wise to check serum transaminases 3 and 4 weeks after commencing treatment. If more than three times increased, the drug should be stopped. If less, a further value is taken 1 week later when an increase is an indication for stopping the drug. Continuance of therapy once a hepatic reaction has commenced is the commonest cause of a fatal outcome.

The safety of a drug which causes transient rises in transaminases and apparently no other hepatic effects remains obscure. Many valuable drugs in widespread use fall into this category. In many instances, challenge is the only method of linking a drug with a hepatic reaction, but if its consequence is likely to be serious, this is ethically impossible. However, reporting agencies and drug manufacturers should pay particular attention to the results of inadvertent challenge and to the effects of withdrawing the drug (de-challenge).

Intake of a drug, such as paracetamol, within the therapeutic range, may cause liver injury if the patient is ingesting another drug, such as alcohol, which by enzyme induction increases the production of hepatotoxic metabolites.

An iatrogenic cause must be considered in any patient presenting with any clinical pattern of hepato-biliary disease. This is particularly so with a picture suggesting viral hepatitis in a middle-aged or elderly patient, especially a woman. In the absence of evidence supporting genuine viral hepatitis, the cause is very frequently drug-related.

Widespread recognition of the relation between a drug and a hepatic reaction would follow increased reporting to agencies such as the Committee for Safety of Medicines in the UK, or Medwatch in the USA.

Some catastrophies would be avoided if clinical trials included subjects of all ages, from children to old people, and those with liver disease.

References

1 Altraif I, Lilly L, Wanless IR *et al*. Cholestatic liver disease with ductopenia (vanishing bile duct syndrome) after administration of clindamycin and trimethoprim-sulfamethoxazole. *Am. J. Gastroenterol.* 1994; **89**: 1230.

2 Amitrano L, Gigliotti T, Guardascione MA *et al*. Enoxacin acute liver injury. *J. Hepatol.* 1992; **15**: 270.

3 Andreu V, Mas A, Bruguara M *et al*. Ecstasy: a common cause of severe acute hepatotoxicity. *J. Hepatol.* 1998; **29**: 394.

4 Assal F, Spahr L, Hadangue A *et al*. Tolcapone and fulminant hepatitis. *Lancet* 1998; **352**: 958 (letter).

5 Ault A. Troglitazone may cause irreversible liver damage. *Lancet* 1997; **350**: 1451.

6 Banks AT, Zimmerman HJ, Ishak KG *et al*. Diclofenac-associated hepatotoxicity: analysis of 180 cases reported to the Food and Drug Administration as adverse reactions. *Hepatology* 1995; **22**: 821.

7 Baum JK, Bookstein JJ, Holtz F *et al*. Possible association between benign hepatomas and oral contraceptives. *Lancet* 1973; **ii**: 926.

8 Bernal W, Wendon J, Rela M *et al*. Use and outcome of liver transplantation in acetaminophen-induced acute liver failure. *Hepatology* 1998; **27**: 1050.

9 Berson A, Renault S, Letteron P *et al*. Uncoupling of rat and human mitochondria: a possible explanation for tacrine-induced liver dysfunction. *Gastroenterology* 1996; **110**: 1878.

10 Bissuel F, Bruneel F, Harbersetzer F *et al*. Fulminant hepatitis with severe lactate acidosis in HIV-infected patients on didanosine therapy. *J. Intern. Med.* 1994; **235**: 367.

11 Black M, Mitchell JR, Zimmerman HJ *et al*. Isoniazid-associated hepatitis in 114 patients. *Gastroenterology* 1975; **69**: 289.

12 Black M, Rabin L, Schatz N. Nitrofurantoin-induced chronic active hepatitis. *Ann. Intern. Med.* 1980; **92**: 62.

13 Blake JC, Sawyer AM, Dooley JS *et al*. Severe hepatitis caused by cyproterone acetate. *Gut* 1990; **31**: 556.

14 Bonkovsky HL, Kane RE, Jones DP *et al*. Acute hepatitis and renal toxicity from low doses of acetaminophen in the absence of alcohol abuse or malnutrition: evidence for increased susceptibility to drug toxicity due to cardiopulmonary and renal insufficiency. *Hepatology* 1994; **19**: 1141.

15 Bossard R, Stieger B, O'Neill B *et al*. Ethinylestradiol treatment induces multiple canalicular membrane alterations in rat liver. *J. Clin. Invest.* 1993; **91**: 2714.

16 Bridger S, Henderson K, Glucksman F *et al*. Deaths from low dose paracetamol poisoning. *Br. Med. J.* 1998; **316**: 1724.

17 Callaghan R, Desmond PV, Paull P *et al*. Hepatic enzyme activity is the major factor determining elimination rate of high-clearance drugs in cirrhosis. *Hepatology* 1993; **18**: 54.

18 Cameron RG, Feuer G, de la Iglesia FA, eds. *Drug-induced Hepatotoxicity*. Springer, Berlin, 1996.

19 Castiella A, Lopez Dominguez L, Txoperena G *et al*. Indication for liver transplantation in *Amanita phalloides* poisoning. *Presse Med*. 1993; **22**: 117 (letter).

20 Cherqui D, Palazzo L, Piedbois P *et al*. Common bile duct

stricture as a late complication of upper abdominal radiotherapy. *J. Hepatol.* 1994; **21**: 693.
21 Chien R-N, Yang L-J, Lin P-Y *et al*. Hepatic injury during ketoconazole therapy in patients with onychomycosis: a controlled cohort study. *Hepatology* 1997; **25**: 103.
22 Ching CK, Smith PG, Long RG. Tamoxifen associated hepatocellular damage and agranulocytosis. *Lancet* 1992; **339**: 940 (letter).
23 Cicogani C, Malavolti M, Morselli-Labate AM *et al*. Flutamide-induced toxic hepatitis. Potential utility of ursodeoxycholic acid administration in toxic hepatitis. *Dig. Dis. Sci.* 1996; **41**: 2219.
24 Clark JA, Zimmerman HJ, Tanner LA. Labetalol hepatotoxicity. *Ann. Intern. Med.* 1990; **113**: 210.
25 Corbella X, Vadillo M, Cabellos C *et al*. Hypersensitivity hepatitis due to pyrazinamide. *Scand. J. Infect. Dis.* 1995; **27**: 93.
26 Creagh TM, Rubin A, Evans DJ. Hepatic tumours induced by anabolic steroids in an athlete. *J. Clin. Pathol.* 1988; **41**: 441.
27 Dalton TA, Perry RS. Hepatotoxicity associated with sustained-release niacin. *Am. J. Med.* 1992; **93**: 102.
28 De Graaf EM, Oosterveld M, Tjabbes T *et al*. A case of tizanidine-induced hepatic injury. *J. Hepatol.* 1996; **25**: 772.
29 Dean PJ, Haggitt RC, O'Hara CJ. Malignant epithelioid haemangioendothelioma of the liver in young women: relationship to oral contraceptive use. *Am. J. Surg. Pathol.* 1985; **9**: 695.
30 Degott C, Feldmann G, Larrey D *et al*. Drug-induced prolonged cholestasis in adults: a histological semiquantitative study demonstrating progressive ductopenia. *Hepatology* 1992; **15**: 244.
31 Diaz D, Febre I, Daujat M *et al*. Omeprazole is an aryl hydrocarbon-like inducer of human hepatic cytochrome P-450. *Gastroenterology* 1990; **99**: 737.
32 Dincsoy HP, Saelinger DA. Haloperidol-induced chronic cholestatic liver disease. *Gastroenterology* 1982; **83**: 694.
33 Durand F, Bernuau J, Pessayre D *et al*. Deleterious influence of pyrazinamide on the outcome of patients with fulminant or subfulminant liver failure during antituberculous treatment, including isoniazid. *Hepatology* 1995; **21**: 929.
34 Dykhuizen RS, Brunt PW, Atkinson P *et al*. Ecstasy induced hepatitis mimicking viral hepatitis. *Gut* 1995; **36**: 939.
35 Eliasson E, Stal P, Oksanon A *et al*. Expression of autoantibodies to specific cytochromes P450 in a case of disulfiram hepatitis. *J. Hepatol.* 1998; **29**; 819.
36 Ellis AJ, Wendon JA, Portmann B *et al*. Acute liver damage and ecstasy ingestion. *Gut* 1996; **38**: 454.
37 Fairley CK, McNeil JJ, Desmond P *et al*. Risk factors for development of flucloxacillin associated jaundice. *Br. Med. J.* 1993; **306**: 233.
38 Farrell GC. *Drug-induced Liver Disease*. Churchill Livingstone, Edinburgh, 1994.
39 Fermand JP, Levy Y, Bouscary D *et al*. Danazol-induced hepatocellular adenoma. *Am. J. Med.* 1990; **88**: 529.
40 Fidler H, Dhillon A, Gertner D *et al*. Chronic ecstasy (3, 4-methylenedioxymeta-amphetamine) abuse: a recurrent and unpredictable cause of severe acute hepatitis. *J. Hepatol.* 1996; **25**: 563.
41 Gelin M, Van de Stadt J, Rickaert F *et al*. Epithelioid haemangioendothelioma of the liver following contact with vinyl chloride. *J. Hepatol.* 1989; **8**: 99.
42 Geubel AP, De Galocsy C, Alves N *et al*. Liver damage caused by therapeutic vitamin A administration: estimate of dose-related toxicity in 41 cases. *Gastroenterology* 1991; **100**: 1701.
43 Gil ML, Ramirez MC, Terencio MC *et al*. Immunochemical detection of protein adducts in cultured human hepatocytes exposed to diclofenac. *Biochem. Biophys. Acta* 1995; **1272**: 140.
44 Gilbert SC, Klintmalm G, Menter A *et al*. Methotrexate-induced cirrhosis requiring liver transplantation in three patients with psoriasis. A word of caution in the light of the expanding use of this 'steroid-sparing' agent. *Arch. Intern. Med.* 1990; **150**: 889.
45 Goldstein PE, Deviere J, Cremer M. Acute hepatitis and drug-induced lupus induced by minocycline treatment. *Am. J. Gastroenterol.* 1997; **92**: 143.
46 Gonzalez FJ, Skoda RC, Kimura S *et al*. Characterization of the common genetic defect in humans deficient in debrisoquine metabolism. *Nature* 1988; **331**: 442.
47 Gough A, Chapman S, Wagstaff K *et al*. Minocycline induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. *Br. Med. J.* 1996; **312**: 169.
48 Harrison PM, Keays R, Bray GP *et al*. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. *Lancet* 1990; **335**: 1572.
49 Hassanein T, Razack A, Gavaler JS *et al*. Heatstroke: its clinical and pathological presentation, with particular attention to the liver. *Am. J. Gastroenterol.* 1992; **87**: 1382.
50 Hautekeete ML, Kockx MM, Naegels S *et al*. Cholestatic hepatitis related to quinolones: a report of two cases. *J. Hepatol.* 1995; **23**: 759 (letter).
51 Henderson BE, Preston-Martin S, Edmondson HA *et al*. Hepatocellular carcinoma and oral contraceptives. *Br. J. Cancer* 1983; **48**: 437.
52 Hjelm M, de Silva LVK, Seakins JWT *et al*. Evidence of inherited urea cycle defect in a case of fatal valproate toxicity. *Br. Med. J.* 1986; **292**: 23.
53 Hoet P, Graf MLM, Bourdi M *et al*. Epidemic of liver disease caused by hydrochlorofluorocarbons used as ozone-sparing substitutes of chlorofluorocarbons. *Lancet* 1997; **350**: 556.
54 Hoyumpa AM, Schenker S. Is glucuronidation truly preserved in patients with liver disease? *Hepatology* 1991; **13**: 786.
55 International Group. Guidelines for diagnosis of therapeutic drug-induced liver injury in liver biopsies. *Lancet* 1974; **i**: 854.
56 Kadmon M, Klünemann C, Böhme M *et al*. Inhibition by cyclosporin A of adenosine triphosphate-dependent transport from the hepatocyte into bile. *Gastroenterology* 1993; **104**: 1507.
57 Kawahara H, Marceau N, French SW. Effects of chlorpromazine and low calcium on the cytoskeleton and the secretory function of hepatocytes *in vitro*. *J. Hepatol.* 1990; **10**: 8.
58 Keeffe EB, Reis TC, Berland JE. Hepatotoxicity to both erythromycin estolate and erythromycin ethylsuccinate. *Dig. Dis. Sci.* 1982; **27**: 701.
59 Keeffe EB, Sunderland M, Gabourel JD. Serum gamma-glutamyl transpeptidase activity in patients receiving chronic phenytoin therapy. *Dig. Dis. Sci.* 1986; **31**: 1056.
60 Keiding S. Drug administration to liver patients: aspects of liver pathophysiology. *Semin. Liver Dis.* 1995; **15**: 268.
61 Kelly BD, Heneghan MA, Bennani F *et al*. Nitrofurantoin-

induced hepatotoxicity mediated by CD8+ T-cells. *Am. J. Gastroenterol.* 1998; **93**: 819.
62 Kharasch ED, Hankins D, Mautz D *et al*. Identification of the enzyme responsible for oxidative halothane metabolism: implications for prevention of halothane hepatitis. *Lancet* 1996; **347**: 1367.
63 Kohlroser J, Mathai J, Reichheld J *et al*. Hepatotoxicity due to troglitazone: a report of two cases and review of adverse events reported to the United States Food and Drug Administration. *Am. J. Gastroenterol.* 2000; **95**: 272.
64 Kowdley KV, Keeffe EB, Fawaz KA. Prolonged cholestasis due to trimethoprim sulfamethoxazole. *Gastroenterology* 1992; **102**: 2148.
65 Kretz-Rommel A, Boelsterli UA. Cytotoxic activity of T-cells and non-T-cells from diclofenac-immunized mice against cultured syngeneic hepatocytes exposed to diclofenac. *Hepatology* 1995; **22**: 213.
66 Labadie H, Stoessel P, Callard P *et al*. Hepatic veno-occlusive disease and perisinusoidal fibrosis secondary to arsenic poisoning. *Gastroenterology* 1990; **99**: 1140.
67 Labowitz JK, Silverman WB. Cholestatic jaundice induced by ciprofloxacin. *Dig. Dis. Sci.* 1997; **42**: 192.
68 Lake-Bakkaar G, Scheuer PJ, Sherlock S. Hepatic reactions associated with ketoconazole in the United Kingdom. *Br. Med. J.* 1987; **294**: 419.
69 Larrey D. Hepatotoxicity of herbal remedies. *J. Hepatol.* 1997; **26** (Suppl. 1): 47.
70 Larrey D, Branch RA. Clearance by the liver: current concepts in understanding the hepatic disposition of drugs. *Semin. Liver Dis.* 1983; **3**: 285.
71 Larrey D, Geneve J, Pessayre D *et al*. Prolonged cholestasis after cyproheptadine-induced acute hepatitis. *J. Clin. Gastroenterol.* 1987; **9**: 102.
72 Larrey D, Hadengue A, Pessayre D *et al*. Carbamazepine-induced acute cholangitis. *Dig. Dis. Sci.* 1987; **32**: 554.
73 Larrey D, Vial T, Micaleff A *et al*. Hepatitis associated with amoxycillin-clavulanic acid combination report of 15 cases. *Gut* 1992; **33**: 368.
74 Larrey D, Vial T, Pauwels A *et al*. Hepatitis after germander (*Teucrium chamaedrys*) administration: another instance of herbal medicine hepatotoxicity. *Ann. Intern. Med.* 1992; **117**: 129.
75 Lavrijsen AP, Balmus KJ, Nugteren-Huying WM *et al*. Hepatic injury associated with itraconazole. *Lancet* 1992; **340**: 251 (letter).
76 Lazaros GA, Papatheodonridis GV, Delladatsima JK *et al*. Terbinafine-induced cholestatic liver disease. *J. Hepatol.* 1996; **24**: 753.
77 Lee WM. Drug-induced hepatotoxicity. *N. Engl. J. Med.* 1995; **333**: 1121.
78 Lewis JH, Ranard RC, Caruso A *et al*. Amiodarone hepatotoxicity: prevalence and clinicopathologic correlations among 104 patients. *Hepatology* 1989; **9**: 679.
79 Lewis JH, Zimmerman HJ, Ishak KG *et al*. Enflurane hepatotoxicity: a clinicopathologic study of 24 cases. *Ann. Intern. Med.* 1983; **98**: 984.
80 Liaw Y-F, Huang M-J, Fan K-D *et al*. Hepatic injury during propylthiouracil therapy in patients with hyperthyroidism. A cohort study. *Ann. Intern. Med.* 1993; **118**: 424.
81 Loeper J, Descatoire V, Letteron P *et al*. Hepatotoxicity of germander in mice. *Gastroenterology* 1994; **106**: 464.
82 Loeper J, Descatoire V, Maurice M *et al*. Presence of functional cytochrome P-450 on isolated rat hepatocyte plasma membrane. *Hepatology* 1990; **11**: 850.
83 Luis A, Rodriguez G, Bruno H *et al*. Risk of acute liver injury associated with the combination of amoxycillin and clavulanic acid. *Arch. Intern. Med.* 1996; **156**: 1327.
84 MacFarlane B, Davies S, Mannan K *et al*. Fatal acute fulminant liver failure due to clozapine: a case report and review of clozapine-induced hepatotoxicity. *Gastroenterology* 1997; **112**: 1707.
85 Macilwain C. NIH, FDA seek lessons from hepatitis B drug trial deaths. *Nature* 1993; **364**: 275.
86 Maganto P, Traber PG, Rusnell C *et al*. Long-term maintenance of the adult pattern of liver-specific expression for P-450b, P450e, albumin and α-fetoprotein genes in intrasplenically transplanted hepatocytes. *Hepatology* 1990; **11**: 585.
87 Mahler H, Pasi A, Kramer JM *et al*. Fulminant liver failure in association with the emetic toxin of *Bacillus cereus*. *N. Engl. J. Med.* 1997; **336**: 1142.
88 Makin AJ, Wendon J, Williams R. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987–93). *Gastroenterology* 1995; **109**: 1907.
89 Malka D, Pham B-N, Courvalin J-C *et al*. Acute hepatitis caused by alverine associated with antilamin A and C autoantibodies. *J. Hepatol.* 1997; **27**: 399.
90 Martin JL, Plevak DJ, Flannery KD *et al*. Hepatotoxicity after desflurane anaesthesia. *Anaesthesiology* 1995; **83**: 1125.
91 Mitchell JR, Zimmerman HJ, Ishak KG *et al*. Isoniazid liver injury: clinical spectrum, pathology and probable pathogenesis. *Ann. Intern. Med.* 1976; **84**: 181.
92 Mondardini A, Pasquino P, Bernardi P *et al*. Propafenone-induced liver injury: report of a case and review of the literature. *Gastroenterology* 1993; **104**: 1524.
93 Muñoz SJ, Martinez-Hernandez A, Maddrey WC. Intrahepatic cholestasis and phospholipidosis associated with the use of trimethoprim-sulfamethoxazole. *Hepatology* 1990; **12**: 342.
94 Murphy R, Swartz R, Watkins PB. Severe acetaminophen toxicity in a patient receiving isoniazid. *Ann. Intern. Med.* 1990; **113**: 799.
95 Mutimer DJ, Ayres RCS, Neuberger JM *et al*. Serious paracetamol poisoning and the results of liver transplantation. *Gut* 1994; **35**: 809.
96 Myers JL, Augur NA Jr. Hydralazine-induced cholangitis. *Gastroenterology* 1984; **87**: 1185.
97 Nadir A, Agrawal S, King PD *et al*. Acute hepatitis associated with the use of a Chinese herbal product, Ma-huang. *Am. J. Gastroenterol.* 1996; **91**: 1436.
98 Nehra A, Mullick F, Ishak KG *et al*. Pemoline-associated hepatic injury. *Gastroenterology* 1990; **99**: 1517.
99 Neuschwander-Tetri BA, Isley WL, Oki JC *et al*. Troglitazone-induced hepatic failure leading to liver transplantation. *Ann. Intern. Med.* 1998; **129**: 38.
100 Nevens F, Fevery J, Van Steenbergen W *et al*. Arsenic and noncirrhotic portal hypertension. A report of eight cases. *J. Hepatol.* 1990; **11**: 80.
101 Njoku D, Laster MJ, Gong DH *et al*. Biotransformation of halothane, enflurane, isoflurane and desflurane to trifluoroacetylated liver proteins: association between protein acylation and hepatic injury. *Anaesth. Analg.* 1997; **84**: 173.
102 Noseda A, Borsch G, Muller K-M *et al*. Methimazole-associated cholestatic liver injury: case report and brief literative review. *Hepatogastroenterology* 1986: **33**: 244.
103 O'Grady JG. Paracetamol-induced acute liver failure: prevention and management. *J. Hepatol.* 1997; **26** (Suppl. 1): 41.

104 Ozenne G, Manchon ND, Doucet J *et al*. Carbimazole-induced acute cholestatic hepatitis. *J. Clin. Gastroenterol.* 1989; **11**: 95.

105 Pande JN, Singh SPN, Khilnani GC *et al*. Risk factors for hepatotoxicity from antituberculosis drugs: a case–control study. *Thorax* 1996; **51**: 132.

106 Park HZ, Lee SP, Schy AL. Ceftriaxone-associated gallbladder sludge. Indentification of calcium-ceftriaxone salt as a major component of gallbladder precipitate. *Gastroenterology* 1991; **100**: 1665.

107 Parker WB, Cheng YC. Mitochondrial toxicity of antiviral nucleoside analogs. *J. NIH Res.* 1994; **6**: 57.

108 Paterson D, Kerlin P, Walker N *et al*. Piroxicam-induced submassive necrosis of the liver. *Gut* 1992; **33**: 1436.

109 Phillips CA, Cera PJ, Mangan TF *et al*. Clinical liver disease in patients with rheumatoid arthritis taking methotrexate. *J. Rheumatol.* 1992; **19**: 229.

110 Phillips MJ, Oda M, Mak E *et al*. Microfilament dysfunction as a possible cause of intrahepatic cholestasis. *Gastroenterology* 1975; **69**: 48.

111 Picciotto A, Campo N, Brizzolara R *et al*. Chronic hepatitis induced by Jin Bu Huan. *J. Hepatol.* 1998; **28**: 165.

112 Pinto HC, Baptista A, Camilo ME *et al*. Tamoxifen-associated steatohepatitis—report of three cases. *J. Hepatol.* 1995; **23**: 95.

113 Powell-Jackson PR, Tredger JM, Williams R. Progress report, hepatotoxicity to valproate: a review. *Gut* 1984; **25**: 673.

114 Rabinovitz M, Van Thiel DH. Hepatotoxicity of non-steroidal anti-inflammatory drugs. *Am. J. Gastroenterol.* 1992; **87**: 1696.

115 Rabkin MJ, Corless CL, Orloff SL *et al*. Liver transplantation for disulfiran-induced hepatic failure. *Am. J. Gastroenterol.* 1998; **93**: 830.

116 Rahmat J, Gelfand RL, Gelfand MC *et al*. Captopril-associated cholestatic jaundice. *Ann. Intern. Med.* 1985; **102**: 56.

117 Ratanasavanh D, Beaune P, Morel F *et al*. Intralobular distribution and quantification of cytochrome P-450 enzymes in human liver as a function of age. *Hepatology* 1991; **13**: 1142.

118 Read AE, Harrison CV, Sherlock S. Chronic chlorpromazine jaundice: with particular reference to its relationship to primary biliary cirrhosis. *Am. J. Med.* 1961; **31**: 249.

119 Redlich CA, West AB, Fleming L *et al*. Clinical and pathological characteristics of hepatotoxicity associated with occupational exposure to dimethylformamide. *Gastroenterology* 1990; **99**: 748.

120 Reynolds TB, Lapin AC, Peters RL *et al*. Puzzling jaundice. Probable relationship to laxative ingestion. *JAMA* 1970; **211**: 86.

121 Rinder HM, Love JC, Wexler R. Amiodarone hepatotoxicity. *N. Engl. J. Med.* 1986; **314**: 321.

122 Robin MA, Le Roy M, Descatoire V *et al*. Plasma membrane cytochromes P450 as neoantigens and autoimmune targets in drug-induced hepatitis. *J. Hepatol.* 1997; **26** (Suppl. 1): 23.

123 Rosellini SR, Costa PL, Gaudio M *et al*. Hepatic injury related to enalapril. *Gastroenterology* 1989; **97**: 810.

124 Rosenberg WMC, Ryley NG, Trowell JM *et al*. Dextropropoxyphene-induced hepatotoxicity: a report of nine cases. *J. Hepatol.* 1993; **19**: 470.

125 Sarachek NS, London RL, Matulewicz TJ. Diltiazem and granulomatous hepatitis. *Gastroenterology* 1985; **88**: 1260.

126 Scheider DM, Klygis LM, Tsang T-K *et al*. Hepatic dysfunction after repeated isoflurane administration. *J. Clin. Gastroenterol.* 1993; **17**: 168.

127 Schenker S, Bay M. Drug disposition and hepatotoxicity in the elderly. *J. Clin. Gastroenterol.* 1994; **18**: 232.

128 Schenker S, Martin RR, Hoyumpa AM. Antecedent liver disease and drug toxicity. *J. Hepatol.* 1999; **31**: 1098.

129 Schidt FV, Rochling FA, Casey DL *et al*. Acetaminophen toxicity in an urban country hospital. *N. Engl. J. Med.* 1997; **337**: 1112.

130 Schultz JC, Adamson JS Jr, Workman WW *et al*. Fatal liver disease after intravenous administration of tetracycline in high dosage. *N. Engl. J. Med.* 1963; **269**: 999.

131 Seeff LB, Cuccherini BA, Zimmerman HJ *et al*. Acetaminophen hepatotoxicity in alcoholics: a therapeutic misadventure. *Ann. Intern. Med.* 1986; **104**: 399.

132 Seki K, Minami Y, Nishikawa M *et al*. 'Non-alcoholic steatohepatitis' induced by massive doses of synthetic oestrogen. *Gastroenterol. Jpn* 1983; **18**: 197.

133 Sheikh NM, Philen RM, Love LA. Chaparral-associated hepatotoxicity. *Arch. Intern. Med.* 1997; **157**: 913.

134 Shepherd P, Harrison DJ. Idiopathic portal hypertension associated with cytotoxic drugs. *J. Clin. Pathol.* 1990; **43**: 216.

135 Shiffman ML, Keith FB, Moore EW. Pathogenesis of ceftriaxone-associated biliary sludge. *In vitro* studies of calcium-ceftriaxone binding and solubility. *Gastroenterology* 1990; **99**: 1772.

136 Shulman HM, Fisher LB, Schoch G *et al*. Venoocclusive disease of the liver after marrow transplantation: histological correlates of clinical signs and symptoms. *Hepatology* 1994; **19**: 1171.

137 Silva MO, Roth D, Reddy KR et al. Hepatic dysfunction accompanying acute cocaine intoxication. *J. Hepatol.* 1991; **12**: 312.

138 Simon JB, Manley PN, Brien JF *et al*. Amiodarone hepatotoxicity simulating alcoholic liver disease. *N. Engl. J. Med.* 1984; **311**: 167.

139 Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampicin. A meta-analysis. *Chest* 1991; **99**: 465.

140 Sterling MJ, Kane M, Grace ND. Pemoline-induced autoimmune hepatitis. *Am. J. Gastroenterol.* 1996; **91**: 2233.

141 Sterneck M, Wiesner R, Ascher N *et al*. Azathioprine hepatotoxicity after liver transplantation. *Hepatology* 1991; **14**: 806.

142 Stricker BHCh, Blok APR, Babany G *et al*. Fibrin ring granulomas and allopurinol. *Gastroenterology* 1989; **96**: 1199.

143 Stricker BHC, Blok APR, Bronkhorst FB *et al*. Ketoconazole-associated hepatic injury: a clinicopathological study of 55 cases. *J. Hepatol*. 1986; **3**: 399.

144 Stricker BHC, Spoelstra P. *Drug-induced Hepatic Injury*. Elsevier, Amsterdam, 1985.

145 Taggart HMcA, Alderdice JM. Fatal cholestatic jaundice in elderly persons taking benoxaprofen. *Br. Med. J.* 1982; **284**: 1372.

146 Tameda Y, Hamada M, Takase K *et al*. Fulminant hepatic failure caused by ecarazine hydrochloride (a hydralazine) derivative. *Hepatology* 1996; **23**: 465.

147 Tarazi EM, Harter JG, Zimmerman HJ *et al*. Sulindac-associated hepatic injury: analysis of 91 cases reported to the Food and Drug Administration. *Gastroenterology* 1993; **104**: 569.

148 Tyrrell DLJ, Mitchell MC, De Man RA *et al*. Phase II trial of

lamivudine for chronic hepatitis B. *Hepatology* 1993; **18**: 112 A.

149 Ussery XT, Henar EL, Black DD *et al*. Acute liver injury after protracted seizures in children. *J. Paediatr. Gastroenterol. Nutr.* 1989; **9**: 421.

150 Valla D, Le MG, Poynard T *et al*. Risk of hepatic vein thrombosis in relation to recent use of oral contraceptives: a case–control study. *Gastroenterology* 1986; **90**: 807

151 Van Ditzhuijsen TJM, van Haelst UJGM, van Dooren-Greebe RJ. Severe hepatotoxic reaction with progression to cirrhosis after use of a novel retinoid (acitretin). *J. Hepatol*. 1990; **11**: 185.

152 Van Steenbergen W, Peeters P, De Bondt J *et al*. Nimesulide-induced acute hepatitis: evidence from six cases. *J. Hepatol.* 1998; **29**: 135.

153 Van Steenbergen W, Vanstapel MJ, Desmet V *et al*. Cimetidine-induced liver injury. Report of three cases. *J. Hepatol*. 1985; **1**: 359.

154 Van't Wout JW, Herrmann WA, de Vries RA *et al*. Terbinafine-associated hepatic injury. *J. Hepatol.* 1994; **21**: 115.

155 Vorperian VR, Havighurst TC, Miller S *et al*. Adverse effects of low dose amiodarone: a meta-analysis. *J. Am. Coll. Cardiol.* 1997; **30**: 791.

156 Wanless IR, Dore S, Gopinath N *et al*. Histopathology of cocaine hepatotoxicity. Report of four patients. *Gastroenterology* 1990; **98**: 497.

157 Watkins PB. The role of cytochromes P-450 in cyclosporin metabolism. *J. Am. Acad. Dermatol.* 1990; **23**: 1301**.**

158 Watkins PB. Role of cytochromes P-450 in drug metabolism and hepatotoxicity. *Semin. Liver Dis*. 1990; **10**: 235.

159 Watkins PB, Zimmerman HJ, Knapp MJ *et al*. Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. *JAMA* 1994; **271**: 992.

160 Westaby D, Ogle SJ, Paradinas FJ *et al*. Liver damage from long-term methyltestosterone. *Lancet* 1977; **ii**: 261.

161 Whiting-O'Keefe QE, Fye KH, Sack KD. Methotrexate and histological hepatic abnormalities: a meta-analysis. *Am. J. Med.* 1991; **90**: 711.

162 Woolf GM, Petrovic LM, Rojter SE *et al*. Acute hepatitis associated with the Chinese herbal product Jin Bu Huan. *Ann. Intern. Med.* 1994; **121**: 729.

163 Wysowski DK, Freiman JP, Tourtelot JB *et al*. Fatal and non-fatal hepatotoxicity associated with flutamide. *Ann. Intern. Med.* 1993; **118**: 860.

164 Yamamoto M, Ogawa K, Morita M *et al*. The herbal medicine Inchin-ko-to inhibits liver cell apoptosis induced by transforming growth factor B1. *Hepatology* 1996; **23**: 552.

165 Yamamoto T, Suou T, Hirayama C. Elevated serum aminotransferase induced by isoniazid in relation to isoniazid acetylator phenotype. *Hepatology* 1986; **6**: 295.

166 Yao F, Behling CA, Saab S *et al*. Trimethoprim-sulfamethoxazole-induced vanishing bile duct syndrome. *Am. J. Gastroenterol.* 1997; **92**: 167.

167 Zafrani ES, Cazier A, Baudelot A-M *et al*. Ultra-structural lesions of the liver in human peliosis: a report of 12 cases. *Am. J. Pathol.* 1984; **114**: 349.

168 Zafrani ES, Pinaudeau Y, Dhumeaux D. Drug-induced vascular lesions of the liver. *Arch. Intern. Med.* 1983; **143**: 495.

169 Zimmerman HJ. *The Adverse Effects of Drugs and Other Chemicals on the Liver*, 2nd edn. Raven Press, New York, 1999.

170 Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. *Hepatology* 1995; **22**: 767.

Chapter 21
Hepatic Cirrhosis

Definition

Cirrhosis is defined anatomically as a diffuse process with fibrosis and nodule formation. Although the causes are many, the end result is the same.

Fibrosis is not synonymous with cirrhosis. Fibrosis may be in acinar zone 3 in heart failure, or in zone 1 in bile duct obstruction and congenital hepatic fibrosis (fig. 21.1) or interlobular in granulomatous liver disease, but without a true cirrhosis.

Nodule formation without fibrosis, as in partial nodular transformation (fig. 21.1), is not cirrhosis.

The relation of chronic hepatitis to cirrhosis is discussed in Chapter 19.

Production of cirrhosis

The responses of the liver to necrosis are limited; the most important are collapse of hepatic lobules, formation of diffuse fibrous septa and nodular regrowth of liver cells. Thus, irrespective of the aetiology, the ultimate histological pattern of the liver is the same, or nearly the same. Necrosis may no longer be apparent at autopsy.

Fibrosis follows hepato-cellular necrosis (fig. 21.2). This may follow interface hepatitis in zone 1 leading to portal–portal fibrous bridges. Confluent necrosis in zone 3 leads to central–portal bridging and fibrosis. Focal necrosis is followed by focal fibrosis. The cell death is fol-

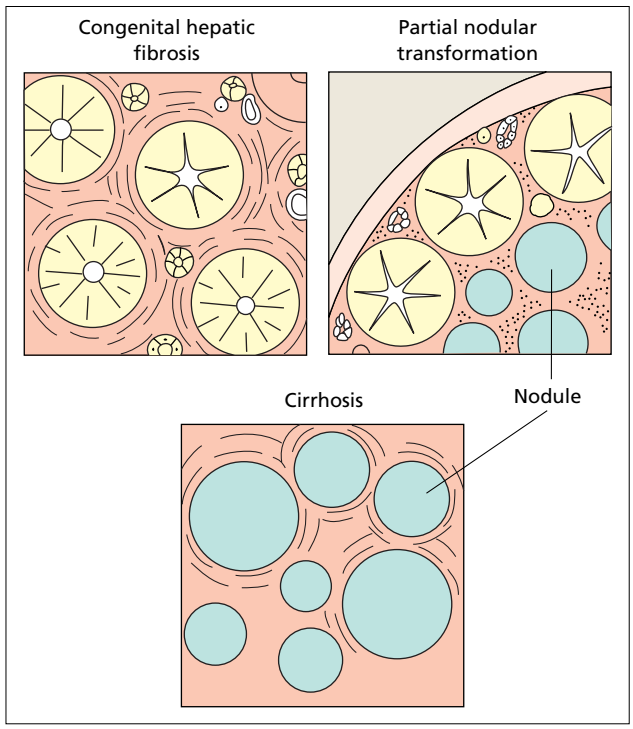


Fig. 21.1. Cirrhosis is defined as widespread fibrosis and nodule formation. Congenital hepatic fibrosis consists of fibrosis without nodules. Partial nodular transformation consists of nodules without fibrosis.

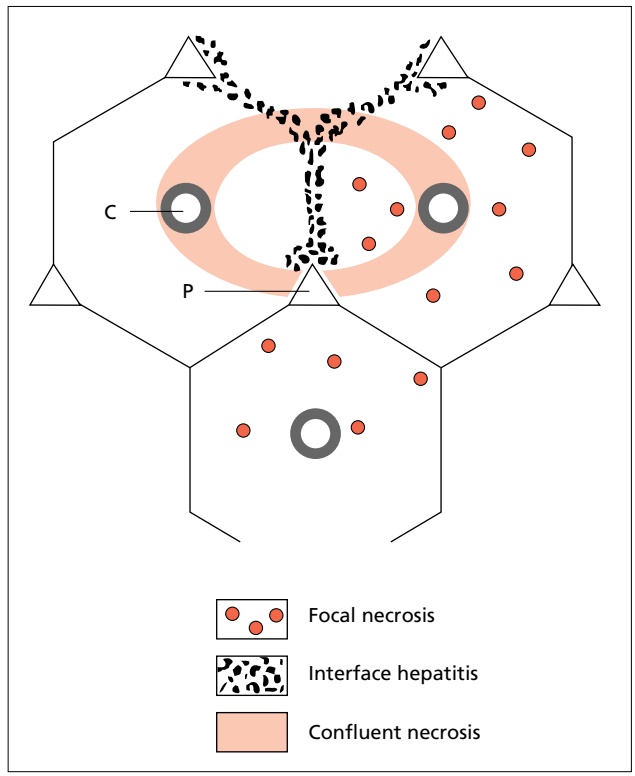


Fig. 21.2. Focal necrosis, interface hepatitis and confluent necrosis and their relationship to portal–portal and portal–central fibrosis C, central vein; P, portal tract. (Courtesy of L. Bianchi.)

lowed by nodules which disturb the hepatic architecture and a full cirrhosis develops.

Sinusoids persist at the periphery of the regenerating nodules at the site of the portal–central bridges. Portal blood is diverted past functioning liver tissue leading to vascular insufficiency at the centre of the nodules (zone 3) and even to persistence of the cirrhosis after the cause has been controlled. Abnormal connective tissue matrix is laid down in the space of Disse, so impeding metabolic exchange with the liver cells.

New fibroblasts form around necrotic liver cells and proliferated ductules. The fibrosis (collagen) progresses from a reversible to an irreversible state where acellular permanent septa have developed in zone 1 and in the lobule. The distribution of the fibrous septa varies with the causative agent. In haemochromatosis, the iron excites portal zone fibrosis. In alcoholism, the fibrosis is predominantly in zone 3.

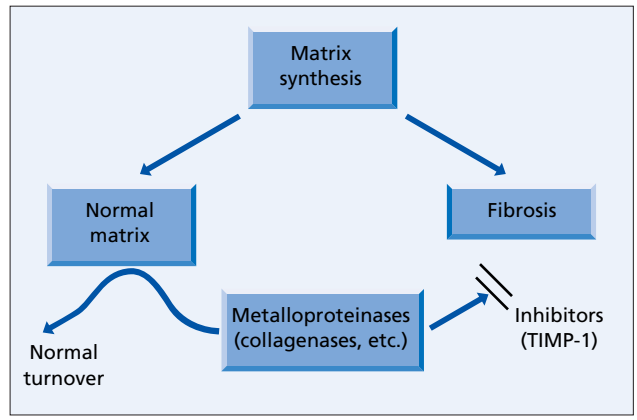


Fig. 21.3. Mechanism of normal and abnormal connective tissue production. TIMP, tissue inhibitor of matrix metalloproteinases.

Fibrogenesis [9, 41]

The transformation of normal liver to fibrotic liver and eventually cirrhosis is a complex process involving several key components in particular stellate cells, cytokines, and proteinases and their inhibitors.

The amount and composition of the extra-cellular matrix changes. The normal low density basement membrane is replaced by high density interstitial-type connective tissue, containing fibrillary collagens. This change owes as much to reduced degradation as to increased synthesis of connective tissue.

There is interaction between stellate cells and adjacent sinusoidal and parenchymal cells, cytokines and growth factors, proteases and their inhibitors, and the extra-cellular matrix. The formation of fibrous tissue depends not only on the synthesis of excess matrix but also changes in its removal. This depends upon the balance between enzymes that degrade the matrix and their inhibitors (fig. 21.3).

An understanding of both fibrogenic and fibrolytic processes in the liver may eventually allow therapeutic measures to prevent or remove fibrosis.

Normal liver has a connective tissue matrix which includes type IV (non-fibrillary) collagen, glycoproteins (including fibronectin and laminin) and proteoglycans (including heparan sulphate). These comprise the low density basement membrane in the space of Disse. Following hepatic injury there is a three- to eight-fold increase in the extra-cellular matrix which is of a high density interstitial type, containing fibril-forming collagens (types I and III) as well as cellular fibronectin, hyaluronic acid and other matrix proteoglycans and glycoconjugates. There is loss of endothelial cell fenestrations and hepatocyte microvilli, and capillarization of sinusoids, which impedes the metabolic exchange between blood and liver cells.

The *hepatic stellate cell* (also called lipocyte, fat-storing cell, Ito cell, pericyte) is the principle cell involved in fibrogenesis. It lies in the space of Disse and makes surface contact with hepatocytes, endothelial cells and nerves fibres. In the resting state these cells have intra-cellular droplets containing vitamin A. They contain 40–70% of the body stores of retinoids. The population of stellate cells appears to be heterogeneous with differences in the expression of cytoskeletal filaments, retinoid content and the potential for activation.

Stellate cells are activated by factors released when adjacent cells are injured (fig. 21.4). Such factors include TGF-β1 from endothelial, Kupffer cells and platelets, lipid peroxides from hepatocytes, and PDGF and EGF from platelets. Activation is therefore a paracrine effect—in distinction to the perpetuation of activation (see below) which is mainly autocrine due to factors derived from the stellate cell itself. Transcription factors, including NFκB, and STAT1, regulate activation.

Stellate cell activation is accompanied by loss of retinoid droplets, cellular proliferation and enlargement, increased endoplasmic reticulum, and expression of smooth muscle specific α-actin. The cells become contractile. They release cytokines, chemotactic factors, extra-cellular matrix and enzymes that degrade matrix. During hepatic stellate cell activation, prion protein gene expression and synthesis of the benign cellular form of prion protein (PrP^c) are induced. PrP^c expression is absent in normal liver but in chronic liver disease correlates with the degree of inflammation rather than fibrosis [37].

Extra-cellular matrix is not a passive product. The individual proteins have domains that interact with stellate and other cells through membrane receptors including integrins. These mediate their effects through cytoplasmic signalling pathways which can influence collagen synthesis and metalloprotease activity [26].

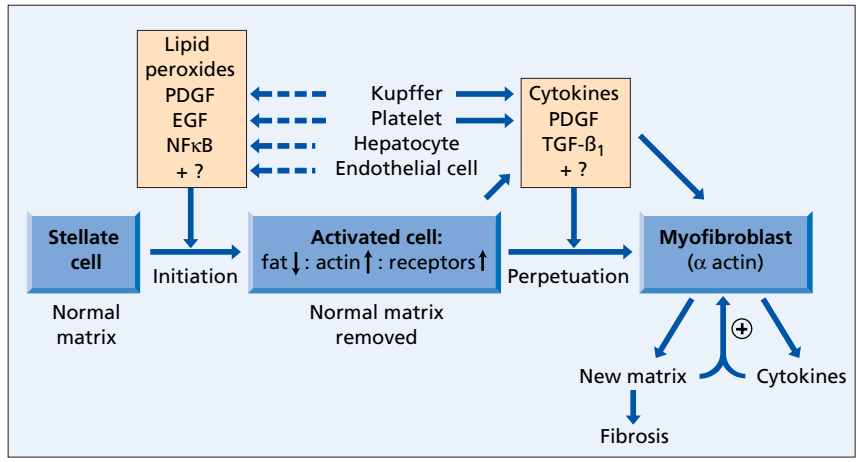


Fig. 21.4. Activation of hepatic stellate cells in fibrogenesis. Myofibroblasts probably also produce inhibitors of collagenases, enhancing fibrogenesis.

Proliferation of stellate cells is well documented in liver injury. PDGF is the most potent mitogen. Other proliferative stimulants include endothelin 1 (ET-1), thrombin and insulin-like growth factor.

Stellate cells congregate in the area of injury, through proliferation and migration from elsewhere, in response to the release of PDGF and monocyte chemotactic peptide 1 (MCP-1).

Although endothelial cells produce several components of extra-cellular matrix after liver injury including fibronectin and type IV collagen, there is preferential expression of matrix genes in stellate cells and these cells are the predominant source of the increased extracellular matrix. The production of fibrous matrix by stellate cells is stimulated by TGF-β1, IL1β, TNF, products of lipid peroxidation, and acetaldehyde from the metabolism of alcohol.

The increase in interstitial matrix is a further stimulus to stellate cell activation.

Imbalance between matrix synthesis and degradation plays a major role in hepatic fibrogenesis [9]. Matrix degradation depends upon the balance between matrix metalloproteinases (MMPs), tissue inhibitors of MMPs (TIMPs) and converting enzymes (MT1-MMP and stromelysin). It is not clear where all these come from, but activated stellate cells are the main source of MMP-2 and stromelysin, express RNA for TIMP-1 and TIMP-2 and produce TIMP-1 and MT1-MMP [41]. Kupffer cells secrete type IV collagenase (MMP-9). The net result of the changes during hepatic injury is increased degradation of the normal basement membrane collagen, and reduced degradation of interstitial-type collagen. The latter may be explained by increased TIMP-1 and TIMP-2 expression relative to MMP-1 (interstitial collagenase). Overexpression of human TIMP-1 in a transgenic mouse model increased CCl_4-induced hepatic fibrosis sevenfold [83]. During the resolution of experimental liver injury, TIMP-1 and TIMP-2 expression is reduced, and net collagenase activity is increased with removal of fibrotic matrix [31].

In experimental studies of telomerase-deficient animals, where there is shortening of chromosomal telomeres, progression to cirrhosis following CCl_4 injury is accelerated [70]. Maintenance of chromosomal telomeres is central to the capacity of hepatocytes to proliferate normally.

Activated stellate cells (myofibroblasts) show features of smooth muscle and are contractile. They may constrict sinusoids locally and thus have a role in the regulation of blood flow. Stimuli for contraction include ET-1, arginine vasopressin and adrenomedullin. Stellate cells produce nitric oxide, a physiological antagonist to ET-1. Contraction could therefore be due to reduced nitric oxide as well as increased ET-1.

The degree of hepatic fibrosis following hepatocellular injury varies according to the cause and the balance between the response of stellate and Kupffer cells to the cytokines and growth factors produced. The spectrum ranges from mild fibrosis that resolves with removal of the insult to severe scarring and nodule formation (cirrhosis) that is irreversible. Similarly, portal hypertension may have a reversible element (stellate cell contraction) or be irreversible due to capillarization of sinusoids and sinusoidal stenosis due to fibrosis.

Treatment may be directed at removing the aetiological agent or suppressing hepatic inflammation, both currently the focus of clinicians, or inhibiting stellate cell activation or activated stellate cells, an area of intense research. During recovery apoptosis of activated stellate cells appears important in removing the source of increased extra-cellular matrix [10, 31].

Cytokines and hepatic growth factors [74]

Apart from their role in fibrogenesis, cytokines have a wide range of other effects. They are hormone-like proteins which co-ordinate differentiating cells, and maintain or restore physiological homeostasis through interaction with membrane receptors. They are essential for communication not only within the liver itself but also between the liver and extra-hepatic sites. Cytokines

regulate the intermediate metabolism of amino acids, proteins, carbohydrates, lipids and minerals. They interact with classical hormones such as glucocorticoids. Since many cytokines exert growth factor like activity, in addition to their specific pro-inflammatory effects, the distinction between cytokines and growth factors is somewhat artificial. No growth factor or cytokine acts independently.

The liver, predominantly the Kupffer cells, produces pro-inflammatory cytokines such as TNF-α, IL1 and IL6 (fig. 6.9). The liver also clears circulating cytokines, so limiting their systemic action. Failure of clearance may account for some of the immunological changes in cirrhosis. Cytokines may also inhibit hepatic regeneration.

Cytokine production is mediated through activation of monocytes and macrophages by endotoxin of gut origin. In cirrhosis, endotoxaemia is enhanced by increased gut permeability and depressed Kupffer cells which normally prevent uptake of endotoxin by the hepatocyte for detoxification and elimination. Cytokine overproduction mediates some of the systemic changes of cirrhosis, such as fever and anorexia. Fatty acid synthesis is increased by TNF-α, IL1, and interferon-α (IFN-α) with resultant fatty liver.

IL6, IL1 and TNF-α induce hepatic acute-phase protein synthesis with production, amongst others, of C-reactive protein, amyloid A, haptoglobin, complement B and α_1-antitrypsin.

The remarkable hepatocyte regenerative capacity after such insults as viral hepatitis or hepatic resection is probably initiated by growth factors interacting with specific receptors on cell surfaces.

Hepatocyte growth factor (HGF) is the most potent stimulator of DNA synthesis in mature hepatocytes, and triggers liver regeneration after injury. It is produced not only by liver cells (including stellate cells) but also in other tissues and by tumours [13]. Production is regulated by several factors including IL1α and IL1β, as well as TGF-β1 and glucocorticoids. It stimulates the growth of other cell types including melanocytes and haemopoietic cells.

Epidermal growth factor (EGF) is formed in regenerating hepatocytes. EGF receptors have a high density on hepatocyte membranes and are also found in the nucleus. EGF uptake is greatest in zone 1 (peri-portal) where regeneration is most active.

TGF-α has a 30–40% sequence homology with EGF and can bind to EGF receptors so initiating hepatocyte replication.

TGF-β1 is probably the major inhibitor of hepatocyte proliferation and is strongly expressed in non-parenchymal cells during liver regeneration. Experimentally TGF-β1 exerts both positive and negative effects, depending on the cell type and culture conditions.

TGF-β inhibits and EGF stimulates amino acid uptake by cultured hepatocytes.

Monitoring fibrogenesis

The proteins and metabolites of connective tissue metabolism spill over into the plasma where they can be measured. Unfortunately, results reflect fibrosis generally and may not give information specifically about hepatic fibrosis.

Aminoterminal *procollagen type III peptide* (PIII-P) is cleaved off the procollagen molecule in the synthesis of a collagen type III fibril. In studies of patients with chronic liver disease there is a relationship between the serum concentration and the degree of hepatic fibrosis [2, 35]. However, because of overlap the value of a single measurement in an individual patient is not of practical diagnostic value. Serum levels may be useful in monitoring hepatic fibrosis particularly in the alcoholic [59]. However increased levels may reflect inflammation and necrosis rather than fibrosis alone.

Many other assays have been studied—the number reflecting the absence of a reliable marker of fibrosis—including hyaluronan, TIMP-1 [42], integrin-β1, YKL-40 [35] and MMP-2 [55]. Urinary desmosine and hydroxylysylpyridinoline, markers of elastin and collagen breakdown, also correlate with hepatic fibrosis [2]. In general, however, these serum and urinary estimations are largely of experimental interest and are infrequently used clinically. Liver biopsy cannot currently be replaced by these markers to assess the degree of fibrosis in the individual patient.

Classification of cirrhosis

Morphological classification

Three anatomical types of cirrhosis are recognized: micronodular, macronodular and mixed.

Micronodular cirrhosis is characterized by thick, regular septa, by regenerating small nodules varying little in size, and by involvement of every lobule (figs 21.5, 21.6). The micronodular liver may represent impaired capacity for regrowth as in alcoholism, malnutrition, old age or anaemia.

Macronodular cirrhosis is characterized by septa and nodules of variable sizes and by normal lobules in larger nodules (figs 21.7, 21.8). Previous collapse is shown by juxtaposition in the fibrous scars of three or more portal tracts. Regeneration is reflected by large cells with large nuclei and by cell plates of varying thickness.

Regeneration in a micronodular cirrhosis results in a macronodular or *mixed* appearance. With time, micronodular cirrhosis often converts to macronodular.

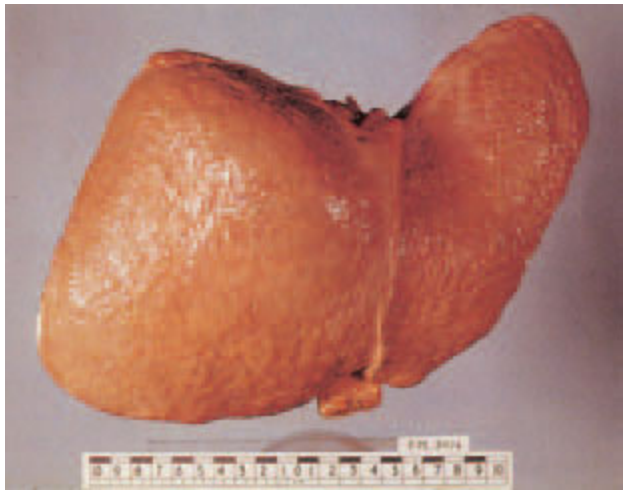


Fig. 21.5. The small finely nodular liver of micronodular cirrhosis.

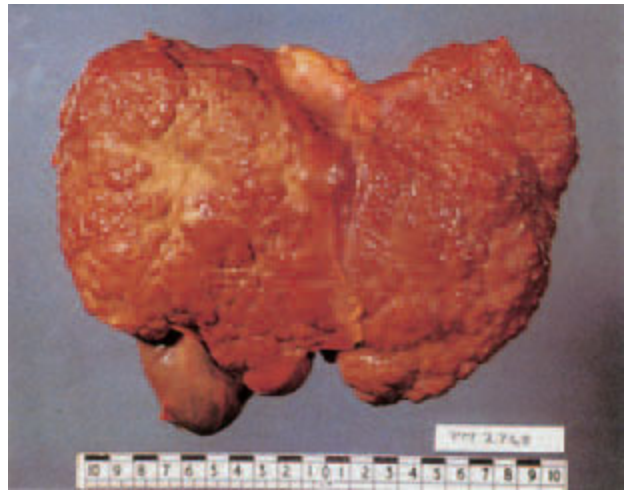


Fig. 21.7. The grossly distorted coarsely nodular liver of macronodular cirrhosis.

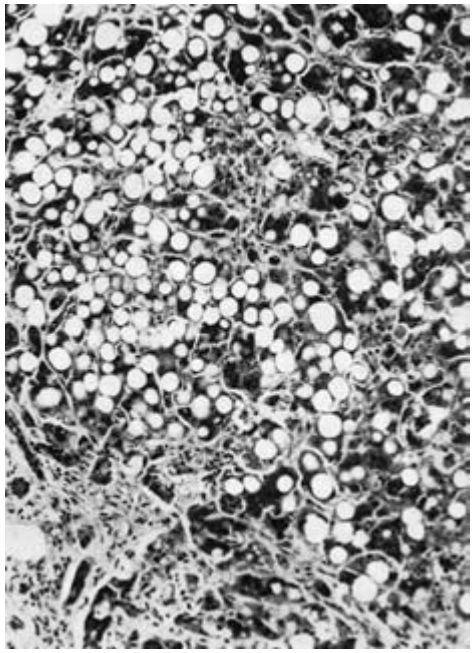


Fig. 21.6. Micronodular cirrhosis. Gross fatty change. The liver cells are often necrotic. Fibrous septa dissect the liver. (H & E, ×135.)

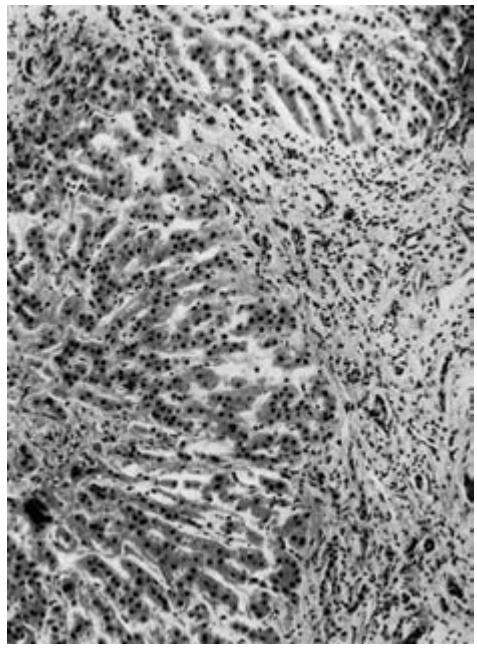


Fig. 21.8. Macronodular cirrhosis. Nodules of regenerating liver cells of different sizes are intersected by fibrous bands of various widths containing proliferating bile ducts. Fatty change is not seen. (H & E, ×135.)

Aetiology (table 21.1)

1 Viral hepatitis types B ± delta; C.
2 Alcohol.
3 Metabolic, e.g. haemochromatosis, Wilson's disease, α_1-antitrypsin deficiency, type IV glycogenosis, galactosaemia, congenital tyrosinosis, non-alcoholic steatohepatitis, intestinal bypass.
4 Prolonged cholestasis, intra- and extra-hepatic.
5 Hepatic venous outflow obstruction, e.g. veno-occlusive disease, Budd–Chiari syndrome, constrictive pericarditis.
6 Disturbed immunity (autoimmune hepatitis).
7 Toxins and therapeutic agents, e.g. methotrexate, amiodarone.
8 Indian childhood cirrhosis.

Other possible factors to be considered include the following.

Table 21.1. Aetiology and definitive treatment of cirrhosis

Aetiology	Treatment
Viral hepatitis (B, C and D)	?Antivirals
Alcohol	Abstention
Metabolic	
iron overload	Venesection. Desferrioxamine
copper overload (Wilson's disease)	Copper chelator
α_1-antitrypsin deficiency	?Transplant
type IV glycogenesis	?Transplant
galactosaemia	Withdraw milk and milk products
tyrosinaemia	Withdraw dietary tyrosine. ?Transplant
Cholestatic (biliary)	Relieve biliary obstruction. ?Transplant
Hepatic venous outflow block	
Budd–Chiari syndrome	Relieve main vein block. ?Transplant
heart failure	Treat cardiac cause
Autoimmune hepatitis	Prednisolone
Toxins and drugs, e.g. methotrexate, amiodarone	Identify and stop
Indian childhood cirrhosis	?Penicillamine
Cryptogenic	—

Malnutrition (Chapter 25).

Infections. Malarial parasites do not cause cirrhosis. The coexistence of malaria and cirrhosis probably reflects malnutrition and viral hepatitis in the community.

Syphilis causes cirrhosis in neonates but not in adults.

In schistosomiasis, the ova excite a fibrous tissue reaction in the portal zones. The association with cirrhosis in certain countries is probably related to other aetiological factors, for example hepatitis C.

Granulomatous lesions. Focal granuloma in such conditions as brucellosis, tuberculosis and sarcoidosis heal with fibrosis, but the liver does not show nodular regrowth.

Cryptogenic cirrhosis. The aetiology is unknown and this is clearly a heterogeneous group. Frequency varies in different parts of the world; in the UK it is about 5–10%, whereas in other areas such as France or in urban parts of the USA where alcoholism is prevalent the proportion is lower. As specific diagnostic criteria appear, so the percentage falls. The advent of testing for hepatitis B and C transferred many previously designated cryptogenic cirrhotics to the post-hepatitic group. Estimations of serum smooth muscle and mitochondrial antibodies and better interpretation of liver histology separate others into the autoimmune chronic hepatitis–primary biliary cirrhosis category. Some of the remainder may be alcoholics who deny alcoholism or have forgotten that they ever consumed alcohol. There remains a hard core of patients in whom the cirrhosis remains cryptogenic. Some of these have features suggesting that non-alcoholic steatohepatitis is responsible [15, 67].

Mechanisms are discussed in individual chapters. The clinical and pathological picture may be that of a 'chronic hepatitis' which has proceeded to cirrhosis.

Anatomical diagnosis

The diagnosis of cirrhosis depends on demonstrating widespread nodules in the liver combined with fibrosis. This may be done by *direct visualization*, for instance at laparotomy or laparoscopy. However, laparotomy should never be used to diagnose cirrhosis because it may precipitate liver failure even in those with very well-compensated disease.

Laparoscopy visualizes the nodular liver and allows directed liver biopsy (fig. 21.9).

Radio-isotope scanning may show decreased hepatic uptake, an irregular pattern and uptake by spleen and bone marrow. Nodules are not identified.

Using *ultrasound*, cirrhosis is suggested by liver surface nodularity (fig. 5.5) and portal vein mean flow velocity [27]. The caudate lobe is enlarged relative to the right lobe. However, ultrasound is not reliable for the diagnosis of cirrhosis. Regenerating nodules may be shown as focal lesions [39]. These should be considered malignant unless proved otherwise by serial imaging and α-fetoprotein levels.

CT scan is cost-effective for the diagnosis of cirrhosis and its complications (fig. 21.10). Liver size can be assessed and the irregular nodular surface seen. Benign regenerative nodules are not visualized by CT. Fatty change, increased density due to iron and a space-occupying lesion can be recognized. After intravenous contrast, the portal vein and hepatic veins can be identified in the liver, and a collateral circulation with splenomegaly may give confirmation to the diagnosis of

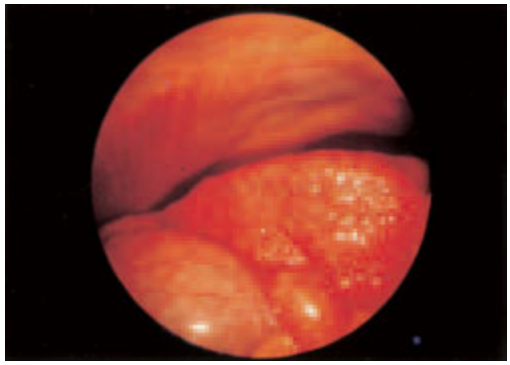


Fig. 21.9. Laparoscopy showing the nodular liver of cirrhosis. Note gallbladder to the left.

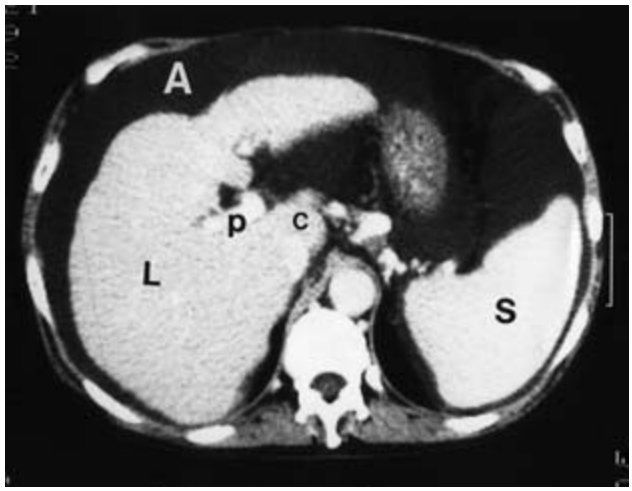


Fig. 21.10. CT scan, after intravenous contrast, in cirrhosis shows ascites (A), small liver with irregular surface (L), enlarged caudate lobe (c), patent portal vein (p) and splenomegaly (S).

portal hypertension. Large collateral vessels, usually peri-splenic or para-oesophageal, may add confirmation to a clinical diagnosis of chronic porto-systemic encephalopathy. Ascites can be seen. The CT scan provides an objective record useful for following the course. Directed biopsy of a selected area can be performed safely.

Biopsy diagnosis of cirrhosis may be difficult. Reticulin and collagen stains are essential for the demonstration of a rim of fibrosis around the nodule (fig. 21.11, table 21.2) .

Helpful diagnostic points include absence of portal tracts, abnormal vascular arrangements, hepatic arterioles not accompanied by portal veins, the presence of nodules with fibrous septa, variability in liver cell size and appearance in different areas, and thickened liver cell plates [72].

Since neither liver biopsy nor scanning have a diagnostic sensitivity greater than 90% (ultrasound, 87%; liver biopsy, 62%) [27], it has been proposed that ultrasound be done before liver biopsy is performed [71]. If cirrhosis is suspected on ultrasound (or clinical findings) at least two separate liver biopsy specimens should be taken for histology. If histology does not show cirrhosis but the specimen shows fragmentation, fibrosis or architectural disruption, this together with the ultrasound result should allow a diagnosis of cirrhosis to be made [71].

Table 21.2. Staining of connective tissue collagen in biopsies

Type	Site	Stained by
I	Portal zones, central zones, broad scars	Van Giesen
II	Sinusoids (elastic tissue)	Elastin
III	Reticulin fibres (sinusoids, portal zones)	Silver
IV	Basement membranes	PAS

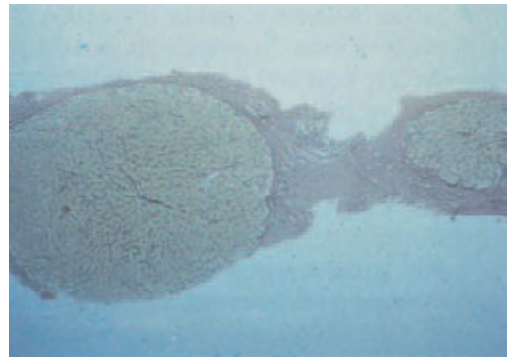


Fig. 21.11. Liver biopsy in cirrhosis: the specimen is small but nodules are shown outlined by reticulin. (Reticulin stain, ×40.)

Functional assessment

Liver failure is assessed by such features as jaundice, ascites (Chapter 9), encephalopathy (Chapter 7), low serum albumin, and a prothrombin deficiency not corrected by vitamin K.

Portal hypertension (Chapter 10) is shown by splenomegaly, oesophageal varices and by the newer methods of measuring portal pressure.

Evolution is monitored by serial clinical, biochemical and histological observations, and classified as progressing, regressing or stationary.

Clinical cirrhosis (table 21.3)

Cirrhosis, apart from other features peculiar to the cause, results in two major events: hepato-cellular failure (Chapters 6, 7 and 9) and portal hypertension (Chapter

Table 21.3. General investigations in the patient with cirrhosis (see also table 10.1)

Occupation, age, sex, domicile

Clinical history
Fatigue and weight loss
Anorexia and flatulent dyspepsia
Abdominal pain
Jaundice. Colour of urine and faeces
Swelling of legs or abdomen
Haemorrhage—nose, gums, skin, alimentary tract
Loss of libido
Past health: jaundice, hepatitis, drugs ingested, blood transfusion
Social: alcohol consumption
Hereditary

Examination
Nutrition, fever, fetor hepaticus, jaundice, pigmentation, purpura, finger clubbing, white nails, vascular spiders, palmar erythema, gynaecomastia, testicular atrophy, distribution of body hair. Parotid enlargement. Dupuytren's contracture. Blood pressure
Abdomen: ascites, abdominal wall veins, liver, spleen
Peripheral oedema
Neurological changes: mental functions, stupor, tremor

Investigations
Haematology
- haemoglobin, leucocyte and platelet count, prothrombin time (INR)

Serum biochemistry
- bilirubin
- transaminase
- alkaline phosphatase
- γ-glutamyl-transpeptidase
- albumin and globulin
- immunoglobulins

If ascites present
- serum sodium, potassium, bicarbonate, chloride, urea and creatinine levels
- weigh daily
- 24-h urine volume and sodium excretion

Serum immunological
- smooth muscle, mitochondrial and nuclear antibodies
- hepatitis B antigen (HBsAg), anti-HCV (other markers of hepatitis, see Chapters 17 and 18)
- α-fetoprotein

Endoscopy
Hepatic CT scan or ultrasound
Needle liver biopsy if blood coagulation permits
EEG if neuropsychiatric changes

10). Prognosis and treatment depend on the magnitude of these two factors. In clinical terms, the types are either 'compensated' or 'decompensated'. In addition, cirrhosis, whatever its type, has certain clinico-pathological associations.

It is difficult to relate the clinical picture to the underlying pathology although there are certain similarities. In Europe and the USA, cirrhosis of the alcoholic, chronic hepatitis B and C and cryptogenic cirrhosis account for the majority. In developing countries, the predominant causes are hepatitis virus B and C. The age and sex distribution of the various types differ.

The terminal stages of the various types may be identical. The aetiological distinction is important both for prognosis and for specific treatment, such as alcohol withdrawal, venesection in haemochromatosis or prednisolone in autoimmune chronic hepatitis (table 21.1). Finally, comparison of cirrhosis in different parts of the world must allow for different aetiologies, although the basic pattern of liver cell failure and portal hypertension may be similar.

Clinical and pathological associations

1 *Nutrition.* Protein-calorie malnutrition is a common complication of chronic liver disease, present in 20% of patients with compensated cirrhosis and more than 60% of those with severe hepatic dysfunction [44, 66]. The cause appears to be multifactorial, but inadequate intake of protein and energy-producing food and an increased resting energy expenditure (REE) contribute. Although gustatory and olfactory acuity (taste and smell) is impaired subjectively in cirrhotic patients, their selection of food does not differ from healthy controls [48]. The reduced intake of food may relate to humoral factors, such as hyperinsulinaemia [69]. Dental and peridontal disease reflects poor oral hygiene and dental care rather than cirrhosis *per se*.

Several methods exist for estimating the REE, including composite scores of clinical observation such as skinfold thickness. However, there is no consensus as to which should be used [66]. Measurement by indirect calorimetry, recommended to reduce the error likely from estimates using formulae, shows an REE of 23.2 ± 3.8 kcal/kg/24 h in cirrhotics compared with 21.9 ± 2.9 in healthy volunteers [49]. Patients with chronic hepatitis C have an increased energy expenditure that returns to normal in those responding to interferon therapy [65].

Fat stores and muscle mass are reduced in many cirrhotics, particularly the alcoholic and those who are Child's grade C (table 10.4) [32]. Alcoholic cirrhotic patients have muscle weakness that appears to be related to the severity of malnutrition rather than the severity of liver disease [5]. Muscle wasting is related to reduced muscle protein synthesis [53].

Prognosis in cirrhotics is related to nutritional status [44]. Malnutrition also is an independent predictor for the first variceal bleed and survival in patients with oesophageal varices. Increased REE persists after transplantation with associated poor nutrition [54].

2 *Eye signs*. Lid retraction and lid lag is significantly increased in patients with cirrhosis compared with a

control population [78]. There is no evidence of thyroid disease. Serum-free thyroxine is not increased.

3 *Parotid gland enlargement* and *Dupuytren's contracture* are seen in some alcoholic patients with cirrhosis.

4 *Digital clubbing* and *hypertrophic osteoarthropathy* may complicate cirrhosis, especially biliary cirrhosis. These changes may be due to aggregated platelets, passing peripherally through pulmonary arteriovenous shunts, plugging capillaries and releasing PDGF [20].

5 *Muscle cramps* occur significantly more frequently in cirrhotic patients than in patients without liver disease, and correlate with the presence of ascites, low mean arterial pressure and plasma renin activity [6]. Cramps often respond to oral quinine sulphate. Weekly infusion of human albumin is beneficial by improving effective circulating volume [6].

6 *Steatorrhoea* is frequent even in the absence of pancreatitis or alcoholism. It can be related to reduced hepatic bile salt secretion (fig. 13.11).

7 Splenomegaly and abdominal wall venous collaterals usually indicate portal hypertension.

8 *Abdominal herniae* are common with ascites. They should not be repaired unless endangering life or unless the cirrhosis is very well compensated.

9 *Gastrointestinal*. Varices are visualized by endoscopy. Peptic ulceration has been found in 11% of 324 patients with cirrhosis [75], more frequently those HBsAg positive. Seventy per cent were asymptomatic. Duodenal ulcers were more frequent than gastric ulcers. The prevalence of *Helicobacter pylori* based on serology is significantly greater in patients with cirrhosis than those without liver disease (76 vs. 42%) [76]. This does not seem to correlate with the severity of liver disease, or relate to the development of peptic ulceration.

Small bowel bacterial overgrowth occurs in 30% of patients with alcoholic cirrhosis, being more frequent in those with than without ascites (37 vs. 5%) [52]. It is associated with older age and the administration of H_2-receptor antagonists or proton pump inhibitors. The hydrogen breath test correlates poorly with the results of microbiological culture from jejunal fluid [8]. Experimentally increasing intestinal motility with cisapride reduces jejunal flora and bacterial translocation across the bowel wall [61].

10 *Primary liver cancer* is frequent with all forms of cirrhosis except the biliary and cardiac types with an overall 60-fold increased risk [77]. An increased risk of non-hepatic cancers has been reported, but this may be due to other factors including alcohol and cigarette use [77]. *Metastatic cancer* is said to be rare, due to the reduced frequency of extra-hepatic carcinoma in cirrhosis. However, when groups of patients with cancer and with or without cirrhosis were compared, the incidence of hepatic metastases was the same in each group.

11 *Gallstones*. Ultrasound shows that 18.5% of males and 31.2% of females with chronic liver disease have gallstones, usually of pigment type [73]. This is four to five times higher than the general population. The gallstones do not affect survival [23]. The low bile salt/unconjugated bilirubin ratio with very high biliary monoconjugated bilirubin predisposes to pigment gallstones [4]. Surgery should be avoided unless the clinical indication is clearly strong, and transplantation not imminent, for the patient is a poor operative risk.

12 Chronic relapsing *pancreatitis* and pancreatic calcification are often associated with alcoholic liver disease.

13 *Cardiovascular*. Cirrhotics are less liable to coronary and aortic atheroma than the rest of the population. At autopsy, the incidence of coronary artery disease is about a quarter of that among total cases examined without cirrhosis. Cirrhosis is associated with an increased cardiac output and heart rate, as well as decreased systemic peripheral vascular resistance and blood pressure. Splanchnic arterial vasodilatation and impaired autonomic activity play a role [33, 79]. Cardiac parasympathetic dysfunction is reversed by captopril, suggesting a defect in neuromodulation by centrally acting angiotensin II [21]. The Q–T interval on ECG is frequently prolonged [11]. Vasodilatation is due to many factors including an impaired response to catecholamines, increased vascular synthesis of nitric oxide [51], and elevated circulating adrenomedullin [22, 38] and calcitonin gene-related peptide [28]. Vascular tone is reduced, accounting for blunted systemic and renal effects of volume expansion.

Cirrhotic cardiomyopathy is recognized, with abnormal cardiac contractility, particularly with pharmacological and physiological stress [56]. A reduction in myocardial β-adrenergic receptor signal transduction plays a role, perhaps due to changes in the lipid content of the cardiac plasma membrane or an inhibitory effect of jaundice on adenyl cyclase [45, 46]. Left ventricular wall thickness may be increased [68]. Elevated circulating cardiac troponin I may reflect myocyte injury [62]. Cardiac dysfunction may be subclinical, only presenting after liver transplantation [43].

14 *Pulmonary*. Hypoxaemia may be due to the hepatopulmonary syndrome, and right heart failure to portopulmonary hypertension (Chapter 6) [40]. α_1-Antitrypsin deficiency may cause childhood liver disease, and later emphysema and silent cirrhosis (Chapter 25). Pulmonary atelectasis may follow hydrothorax due to trans-diaphragmatic passage of ascites.

15 *Renal*. Changes in intrarenal circulation, and particularly a redistribution of blood flow away from the cortex, are found in all forms of cirrhosis. This predisposes to the *hepato-renal syndrome* (Chapter 9). Intrinsic renal failure follows periods of hypotension and shock.

Glomerular changes include a thickening of the mesangial stalk and to a lesser degree of the capillary

walls (*cirrhotic glomerular sclerosis*). Deposits of IgA are most frequent (fig. 21.12) [58, 60]. These are particularly found with alcoholic liver disease. The changes are usually latent, but occasionally are associated with proliferative changes and the clinical manifestations of glomerular involvement. Chronic hepatitis C infection is associated with cryoglobulinaemia and membranoproliferative glomerulonephritis [34].

16 *Infections*. Bacterial infections are frequent due to reduced immune defence mechanisms and impaired reticulo-endothelial cell phagocytic activity. Bacteraemia, pneumonia and urinary tract infections are common. Patients with ascites are prone to spontaneous bacterial peritonitis (SBP) (Chapter 9) present in 10–20% of patients with ascites admitted to hospital [57]. Spontaneous bacterial empyaema in a pre-existing hydrothorax may occur in the absence of SBP [82]. In the cirrhotic with febrile coma, bacterial meningitis should be considered [64]. Nasal carriage of *Staphylococcus aureus* is increased in cirrhotic patients [16].

Sepsis should always be suspected in cirrhotic patients with unexplained pyrexia or deterioration. Empirical treatment with a broad-spectrum antibiotic is often necessary after appropriate specimens have been taken for microbiological culture. After gastrointestinal haemorrhage the risk of sepsis is greater in Child C rather than Child A/B grade cirrhotics (53 vs. 18%). Prophylactic antibiotics (ciprofloxacin and augmentin) reduced the incidence of sepsis in Child C cirrhotics to 13% [63].

There has been a resurgence of tuberculosis, and tuberculous peritonitis is therefore still encountered but often not suspected.

17 *Drug metabolism*. In cirrhotics the effect of drugs is generally increased due to reduced elimination [29]. There are two particular causes: reduced hepatocyte mass rather than enzyme activity [50], and the shunting of blood past the liver. For drugs with a high hepatic extraction ratio (high first-pass effect) predicting the therapeutic effect after oral administration is difficult, due to the variation in the degree of shunting (both porto-systemic and intra-hepatic) between patients. The clinical effect of low extraction drugs in cirrhotics is more dependent on hepato-cellular function and therefore more predictable. Overall drug dosage should be reduced according to the severity of liver disease.

Other components of the metabolic pathway may alter drug handling in cirrhosis including absorption, tissue distribution, protein binding, biliary secretion, enterohepatic circulation and target-organ responsiveness.

18 *Diabetes mellitus*. While up to 80% of cirrhotics are glucose intolerant, only 10–20% are truly diabetic. The prevalence of diabetes is greater among those with hepatitis C or alcohol-related cirrhosis compared with those with cholestatic cirrhosis [84].

19 *Sleep disturbance*. Patients with cirrhosis have abnormalities of sleep pattern, unrelated to hepatic encephalopathy. This may be related to a tendency for being active in the evening, and having a delayed bedtime and wake-up time [19]. This seems part of a broader abnormality of circadian rhythm [12].

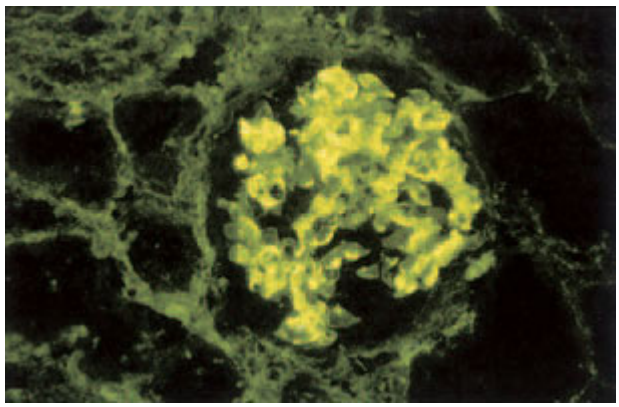


Fig. 21.12. IgA nephropathy: renal biopsy showing IgA deposition in glomerulus of cirrhotic patient (alcohol-related) with creatinine clearance of 20 ml/min and proteinuria (immunostaining with FITC rabbit antihuman IgA).

Hyperglobulinaemia

Elevation of the total serum globulin, and particularly gamma level, is a well-known accompaniment of chronic liver disease. Electrophoresis shows a polyclonal gamma response, but rarely a monoclonal picture may be seen. The increased γ-globulin values may be related in part to increased tissue autoantibodies, such as smooth muscle antibody. However, the major factor seems to be failure of the damaged liver to clear intestinal antigens (fig. 21.13). Patients with cirrhosis show increased serum antibodies to gastrointestinal tract antigens, particularly *Escherichia coli*. Such antigens bypass the liver through portal-systemic channels or through the internal shunts developing around the cirrhotic nodules. Once in the systemic circulation they provoke an increased antibody response from such organs as the spleen. Systemic endotoxaemia may arise similarly. Polymeric IgA and IgA–antigen complexes of gut origin can also reach the systemic circulation. Suppressor T-lymphocyte function is depressed in chronic liver disease and this would reduce the suppression of B-lymphocytes and so favour antibody production.

Compensated cirrhosis

The disease may be discovered at a routine examination or biochemical screen, or at operation undertaken for some other condition (fig. 21.14). Cirrhosis may be suspected if the patient has mild pyrexia, vascular

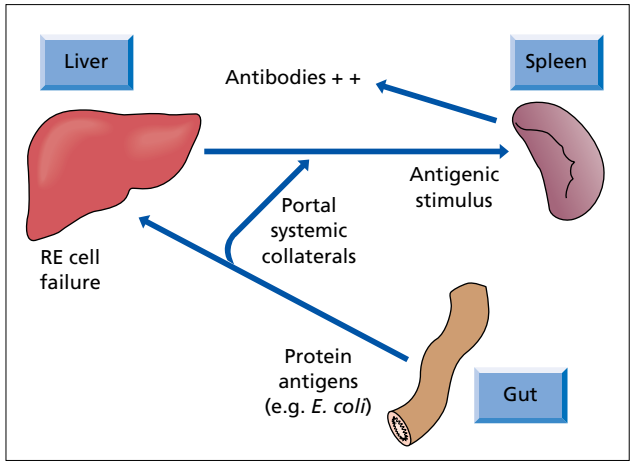


Fig. 21.13. A possible mechanism for the increased serum antibody (and globulin) levels in cirrhosis. Protein antigens from the gut bypass reticulo-endothelial (RE) Kupffer cells in the liver and present an antigenic stimulus to other organs, particularly the spleen, so increasing serum antibodies.

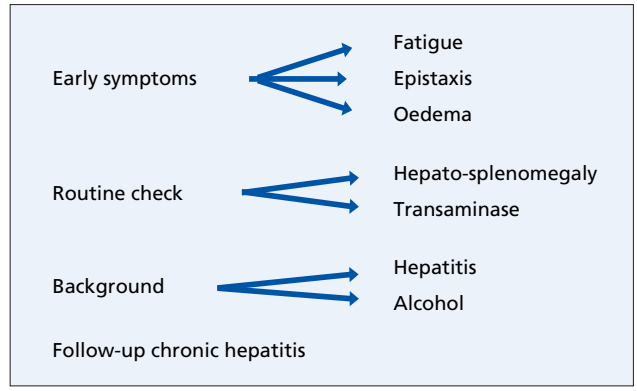


Fig. 21.14. Presentation of 'compensated' hepatic cirrhosis.

spiders, palmar erythema, or unexplained epistaxis or oedema of the ankles. Firm enlargement of the liver and splenomegaly are helpful diagnostic signs. Vague morning indigestion and flatulent dyspepsia may be early features in the alcoholic cirrhotic. Confirmation should be sought by biochemical tests, scanning and, if necessary, by liver biopsy.

Biochemical tests may be quite normal in this group. The most frequent changes are a slight increase in the serum transaminase or γ-GT level.

Diagnosis is confirmed by *needle liver biopsy*.

These patients may remain compensated until they die from another cause. Some proceed, in a period from months to years, to the stage of hepato-cellular failure. In others the problem is of portal hypertension with oesophageal bleeding. Portal hypertension may be present even with normal liver function tests. The course in the individual patient is very difficult to predict.

Decompensated cirrhosis

The patient usually seeks medical advice because of ascites and/or jaundice. General health fails with weakness, muscle wasting and weight loss. Continuous mild fever (37.5–38°C) is often due to Gram-negative bacteraemia, to continuing hepatic cell necrosis or to a complicating liver cell carcinoma. A liver flap may be present. Cirrhosis is the commonest cause of hepatic encephalopathy.

Jaundice implies that liver cell destruction exceeds the capacity for regeneration and is always serious. The deeper the jaundice the greater the inadequacy of liver cell function.

The skin may be pigmented. Clubbing of the fingers is occasionally seen. Purpura over the arms, shoulders and shins may be associated with a low platelet count. Spontaneous bruising and epistaxes reflect a prothrombin deficiency. The circulation is over-active. The blood pressure is low. Sparse body hair, vascular spiders, palmar erythema, white nails and gonadal atrophy are common.

Ascites is usually preceded by abdominal distension. Oedema of the legs is frequently associated.

The liver may be enlarged, with a firm regular edge, or contracted and impalpable. The spleen may be palpable.

The differential diagnosis of hepatic encephalopathy, ascites and jaundice are described in Chapters 7, 9 and 12.

Laboratory findings

Haematology. There is usually a mild normocytic, normochromic anaemia; it is occasionally macrocytic. Gastrointestinal bleeding leads to hypochromic anaemia. The leucocyte and platelet counts are reduced ('hypersplenism'). The prothrombin time is prolonged and does not return to normal with vitamin K therapy. The bone marrow is macronormoblastic. Plasma cells are increased in proportion to the hyperglobulinaemia.

Serum biochemical changes. In addition to the raised serum bilirubin level, albumin is depressed and γ-globulin raised. The serum alkaline phosphatase is usually raised to about twice normal; very high readings are occasionally found, particularly with alcoholic cirrhosis. Serum transaminase values may be increased.

Urine. Urobilinogen is present in excess; bilirubin is also present if the patient is jaundiced. The urinary sodium excretion is diminished in the presence of ascites, and in a severe case less than 5 mmol/l is passed daily.

Table 21.4. Histopathology and aetiology of cirrhosis

Aetiology	Morphological pattern	Fat	Cholestasis	Iron	Copper	Acidophilic bodies	PAS-positive globules	Mallory's hyalin	Ground-glass hepatocytes
Viral hepatitis B	Macro- or micronodular	–	–	–	–	+	–	–	+
Viral hepatitis C	Macro- or micronodular	+	–	±	–	+	–	–	–
Alcohol	Micro- or macronodular	+	±	±	–	±	–	+	–
Haemochromatosis	Micronodular	±	–	+	–	–	–	–	–
Wilson's disease	Macronodular	±	±	–	±	+	–	+	–
α_1-antitrypsin deficiency	Micro- or macronodular	±	±	–	±	±	+	±	–
Primary biliary	Biliary	–	+	–	+	–	–	±	–
Venous outflow obstruction	Reversed	–	–	–	–	–	–	–	–
Intestinal bypass operation	Micronodular	+	–	–	–	±	–	±	–
Indian childhood cirrhosis	Micronodular	–	±	–	+	–	–	+	–

– Usually absent; ± may be present; + usually present.

Needle biopsy diagnosis (table 21.4) [72]

This may give a clue to the aetiology and inflammatory activity. If there are contraindications, such as ascites or a coagulation defect, the transjugular approach should be used. Serial biopsies are valuable in assessing progress.

In cirrhosis, directed biopsies, using ultrasound or CT and a Trucut needle, are particularly helpful in obtaining adequate samples and avoiding other viscera, especially the gallbladder.

Prognosis

Cirrhosis is usually believed to be irreversible, but fibrosis may regress as seen in treated haemochromatosis or Wilson's disease. The concept of irreversibility is not absolute.

Cirrhosis need not be a progressive disease. With therapy the downhill progress may be checked.

The advent of liver transplantation has emphasized the need for an accurate prognosis so that surgery may be performed at the right time.

Child's classification (grades A–C)—which depends on jaundice, ascites, encephalopathy, serum albumin concentration and nutrition (table 10.4)—gives a good short-term prognostic guide. Prothrombin time can be used rather than nutritional status (Child–Pugh modification) and individual features scored by severity. The total score classifies patients into grade A, B or C [30], although published studies often differ in their choice of numerical boundary between one grade and another [47].

Multiple logistic or Cox regression analyses have been applied to cirrhotics [1, 18] to derive a prognostic index. Several chronic liver diseases have been analysed individually including alcohol, chronic hepatitis B and C, primary biliary cirrhosis and primary sclerosing cholangitis. The need for some simplfication and standardization of scoring methods within disease groups has been suggested to supersede the Child–Turcotte and Child–Pugh classifications [17].

Poor prognosis is associated with a prolonged prothrombin time, marked ascites, gastrointestinal bleeding, advanced age, high daily alcohol consumption, high serum bilirubin and alkaline phosphatase, low albumin values, and poor nutrition.

Patients with compensated cirrhosis become decompensated at the rate of 10% per year. Ascites is the usual first sign. Decompensated patients have around a 20% 5-year survival.

The 1-year survival rate of cirrhotic patients following the first episode of spontaneous bacterial peritonitis is 30–45% [3] and following the first episode of acute hepatic encephalopathy is around 40% [14]. Studies of functional liver function tests generally add little to Child's grading, although the aminopyrine breath test has been reported to add prognostic information in Child's grade A and B but not grade C alcoholic cirrhotics [80].

The following points are useful prognostically:

1 *Aetiology*. Alcoholic cirrhotics, if they abstain, respond better than those with 'cryptogenic' cirrhosis.
2 If decompensation has followed haemorrhage, infection or alcoholism, the prognosis is better than if it is spontaneous, because the *precipitating factor* is correctable.
3 The *response to therapy*. If the patient has failed to improve within 1 month of starting hospital treatment, the outlook is poor.
4 *Jaundice*, especially if persistent, is a serious sign.
5 *Neurological complications*. The significance of encephalopathy depends on the clinical circumstances. Developing in the course of progressive hepato-cellular failure, it carries a bad prognosis. Chronic and associated with an extensive portal-systemic collateral circulation, it usually responds well to medical treatment, and the prognosis is better. Overall hepatic encephalopathy is associated with a shortened survival [14]. Autonomic neuropathy is also a poor prognostic indicator [24].
6 *Ascites* worsens the prognosis, particularly if large doses of diuretics are needed for control.
7 *Liver size*. A large liver carries a better prognosis than a small one because it is likely to contain more functioning cells.
8 *Portal venous pressure*. In many studies, prediction of survival by the Child–Pugh score is improved by adding portal pressure, derived from the hepatic venous pressure gradient [7].
9 *Haemorrhage from oesophageal varices*. Portal hypertension must be considered together with the state of the liver cells. If function is good, haemorrhage may be tolerated; if poor, hepatic coma and death are probable.
10 *Biochemical tests*. If the serum albumin is less than 25 g/l the outlook is poor. Hyponatraemia (serum sodium < 120 mmol/l), if unrelated to diuretic therapy, is grave. Serum transaminase and globulin levels give no guide to prognosis.
11 Persistent *hypotension* (systolic BP < 100 mmHg) is serious.
12 *Hepatic histological changes*. Sections are useful in evaluating the extent of necrosis and of inflammatory infiltration. A fatty liver responds well to treatment.

Conclusions

The prognosis is determined by the extent of hepato-cellular failure. Jaundice, spontaneous bruising and ascites resistant to treatment are grave signs. If specific treatment is available the outlook is better.

Treatment

The management of the *well-compensated* cirrhotic is directed towards the maintenance of an adequate balanced diet, the avoidance of alcohol, the early detection of hepato-cellular failure, fluid retention and encephalopathy, and the prevention of variceal haemorhhage.

Nutrition

A diet of 1.0–1.2 g of protein per kilogram of body weight is needed in cirrhotics since the requirement is increased compared to normal individuals. In those with inadequate intake or poor nutrition this is increased to 1.5 g/kg/day [44, 66]. During the acute phase of encephalopathy the intake may have to be reduced temporarily, but intake should be increased again as soon as clinically appropriate. Additional branched-chain amino acids are not indicated in stable cirrhotic patients [81].

Energy requirements are similar to normal (25–35 kcal/kg/day) except in those with malnutrition or an inadequate intake, when the target should be 35–40 kcal/kg/day [66]. Sip-feed supplements to the standard kitchen diet are useful. Avoidance of fats, eggs, coffee or chocolate is not of any therapeutic value. The enteral route should be used. If this is not possible, parenteral feeding is used with energy provided by glucose and fat in a ratio of 65–50 : 35–50% of non-protein calories [66].

The onset of hepato-cellular failure with oedema and ascites demands sodium restriction and diuretics (Chapter 9); complicating encephalopathy is an indication for a lowered protein intake and lactulose (Chapter 7).

Portal hypertension may demand special treatment (Chapter 10).

Anti-fibrotic drugs [41]

The treatment of cirrhosis lies in removing the damaging agent, suppressing hepatic inflammation and reducing fibrogenesis. The promotion of matrix degradation remains a theoretical than practical approach at present.

In some hepatic disease, the cause can be removed, as in alcohol, iron and copper, or inhibited as in chronic viral hepatitis B and C.

Hepatic inflammation may be abolished by corticosteroids in autoimmune chronic hepatitis, or antiviral drugs in viral hepatitis B and C.

Several component of the fibrogenic pathway could be blocked or modulated [41]. Downregulation of stellate cells is an attractive target and in experimental models many agents do this effectively, including interferons α and γ and sho-saiko-to, a herbal medicine. Fibrogenesis may also be reduced by anti-oxidants (e.g. vitamin E), cytokine blockade by receptor antagonists, and inhibitors of collagen synthesis. Dietary supplimentation with phosphatidylcholine reduces alcohol-induced fibrosis possibly through a membrane-stabilizing effect. However, these data are predominantly experimental and clinical trials are needed.

Procollagen secretion requires the polymerization of

microtubules, a process that can be inhibited by microtubule disruptive drugs such as *colchicine*. Trials have suggested benefit [36] but evidence is not sufficiently strong to recommend the use of long-term colchicine for patients with cirrhosis.

Surgical procedures [25]

All operations in cirrhotic patients carry a high risk and a high mortality. Surgery in non-bleeding cirrhotic patients has an operative mortality of 30% and an additional morbidity rate of 30%. These are related to Child's grade—mortality being 10% in grade A, 31% in grade B, and 76% in grade C patients. Operations on the biliary tract, for peptic ulcer disease or for colon resection have a particularly bad prognosis. Predictive features of a poor outcome include a low serum albumin, the presence of infection and a prolonged prothrombin time. The surgical risk in patients with chronic liver disease emphasizes the need for a careful pre-operative evaluation.

Upper abdominal surgery increases the difficulty, and should be avoided in potential candidates for liver transplantation (Chapter 38).

References

1 Adler M, Verset D, Bouhdid H *et al*. Prognostic evaluation of patients with parenchymal cirrhosis. *J. Hepatol.* 1997; **26**: 642.
2 Afdhal NH, Keaveny AP, Cohen SB *et al*. Urinary assays for desmosine and hydroxylysylpyridinoline in the detection of cirrhosis. *J. Hepatol*. 1997; **27**: 993.
3 Altman C, Grange J-D, Amiot X *et al*. Survival after a first episode of spontaneous bacterial peritonitis. Prognosis of potential candidates for orthotopic liver transplantation. *J. Gastroenterol. Hepatol.* 1995; **10**: 47.
4 Alvaro D, Angelico M, Gandin C *et al*. Physico-chemical factors predisposing to pigment gallstone formation in liver cirrhosis. *J. Hepatol.* 1990; **10**: 228.
5 Andersen H, Borre M, Jakobsen J *et al*. Decreased muscle strength in patients with alcoholic liver cirrhosis in relation to nutritional status, alcohol abstinence, liver function, and neuropathy. *Hepatology* 1998; **27**: 1200.
6 Angeli P, Albino G, Carraro P *et al*. Cirrhosis and muscle cramps: evidence of a causal relationship. *Hepatology* 1996; **23**: 264.
7 Armonis A, Patch D, Burroughs A. Hepatic venous pressure measurement: an old test as a new prognostic marker in cirrhosis? *Hepatology* 1997; **25**: 245.
8 Bauer TM, Schwacha H, Steinbrückner B *et al*. Diagnosis of small intestinal bacterial overgrowth in patients with cirrhosis of the liver: poor performance of the glucose breath hydrogen test. *J. Hepatol.* 2000; **33**: 382.
9 Benyon RC, Arthur MJP. Extracellular matrix degradation and the role of hepatic stellate cells. *Semin. Liver Dis.* 2000; (in press).
10 Benyon RC, Iredale JP. Is liver fibrosis reversible? *Gut* 2000; **46**: 443.
11 Bernardi M, Calandra S, Colantoni A *et al*. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and aetiology of the disease and possible pathogenic factors. *Hepatology* 1998; **27**: 28.
12 Blei AT, Zee P. Abnormalities of circadian rhythmicity in liver disease. *J. Hepatol.* 1998; **29**: 832–835.
13 Boros P, Miller CM. Hepatocyte growth factor: a multifunctional cytokine. *Lancet* 1995; **345**: 293.
14 Bustamante J, Rimola A, Ventura P-J *et al*. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. *J. Hepatol.* 1999; **30**: 890.
15 Caldwell SH, Oelsner DH, Iezzoni JC *et al*. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. *Hepatology* 1999; **29**: 664.
16 Chapoutot C, Pageaux G-P, Perrigault P-F *et al*. *Staphylococcus aureus* nasal carriage in 104 cirrhotic and control patients: a prospective study. *J. Hepatol.* 1999; **20**: 249.
17 Christensen E. Prognostic models in chronic liver disease: validity, usefulness and future role. *J. Hepatol.* 1997; **26**: 1414.
18 Christensen E, Schlichting P, Anderson PK *et al*. Updating prognosis and therapeutic evaluation in cirrhosis with Cox's multiple regression model for time-dependent variables. *Scand. J. Gastroenterol.* 1986; **21**: 163.
19 Córdoba J, Cabrera J, Lataif L *et al*. High prevalence of sleep disturbance in cirrhosis. *Hepatology* 1998; **27**: 339.
20 Dickinson CJ. The aetiology of clubbing and hypertrophic osteoarthropathy. *Eur. J. Clin. Invest.* 1993; **23**: 330.
21 Dillon JF, Nolan J, Thomas H *et al*. The correction of autonomic dysfunction in cirrhosis by captopril. *J. Hepatol.* 1997; **26**: 331.
22 Fernández-Rodriguez CM, Prada IR, Prieto J *et al*. Circulating adrenomedullin in cirrhosis: relationship to hyperdynamic circulation. *J. Hepatol.* 1998; **29**: 250.
23 Finucci G, Tirelli M, Bellon S *et al*. Clinical significance of cholelithiasis in patients with decompensated cirrhosis. *J. Clin. Gastroenterol.* 1990; **12**: 538.
24 Fleckenstein JF, Frank SM, Thuluvath PJ. Presence of autonomic neuropathy is a poor prognostic indicator in patients with advanced liver disease. *Hepatology* 1996; **23**: 471.
25 Friedman LS. The risk of surgery in patients with liver disease. *Hepatology* 1999; **29**: 1617.
26 Friedman SL, Maher JJ, Bissell DM. Mechanisms and therapy of hepatic fibrosis: report of the AASLD single topic basic research conference. *Hepatology* 2000; **32**: 1401.
27 Gaiani S, Gramantieri L, Venturoli N *et al*. What is the criterion for differentiating chronic hepatitis from compensated cirrhosis? A prospective study comparing ultrasonography and percutaneous liver biopsy. *J. Hepatol.* 1997; **6**: 979.
28 Henriksen JH, Møller S, Schifter S *et al*. Increased arterial compliance in decompensated cirrhosis. *J. Hepatol.* 1999; **31**: 712.
29 Huet P-M, Villeneuve J-P, Fenyves D. Drug elimination in chronic liver diseases. *J. Hepatol.* 1997; **26** (Suppl. 2): 63.
30 Infante-Rivard C, Esnaola S, Villeneuve J-P *et al*. Clinical and statistical validity of conventional prognostic factors in predicting short-term survival among cirrhotics. *Hepatology* 1987; **7**: 660.
31 Iredale JP, Benyon RC, Pickering J *et al*. Mechanisms of spontaneous resolution of rat liver fibrosis: hepatic stellate cell apoptosis and reduced hepatic expression of metalloproteinase inhibitors. *J. Clin. Invest.* 1998; **102**: 538.
32 Italian Multicentre Cooperative Project. Nutritional status in cirrhosis. *J. Hepatol.* 1994; **21**: 317.
33 Iwao T, Oho K, Sakai T *et al*. Splanchnic and extrasplanchnic

arterial haemodynamics in patients with cirrhosis. *J. Hepatol.* 1997; **27**: 817.
34 Jefferson JA, Johnson RJ. Treatment of hepatitis C-associated glomerular disease. *Semin. Nephrol.* 2000; **20**: 286.
35 Johansen JS, Christoffersen P, Møller S *et al*. Serum YKL-40 is increased in patients with hepatic fibrosis. *J. Hepatol.* 2000; **32**: 911.
36 Kershenobich D, Vargas F, Garcia-Tsao G *et al*. Colchicine in the treatment of cirrhosis of the liver. *N. Engl. J. Med.* 1988; **318**: 1709.
37 Kitada T, Seki S, Ikeda K *et al*. Clinicopathological characterization of prion: a novel marker of activated human hepatic stellate cells. *J. Hepatol.* 2000; **33**: 751.
38 Kojima H, Tsujimoto T, Uemura M *et al*. Significance of increased plasma adrenomedullin concentration in patients with cirrhosis. *J. Hepatol.* 1998; **28**: 840.
39 Kondo F, Ebara M, Sugiura N *et al*. Histological features and clinical course of large regenerative nodules: evaluation of their precancerous potential. *Hepatology* 1990; **12**: 592.
40 Krowka MJ. Hepatopulmonary syndromes. *Gut* 2000; **46**: 1.
41 Li D, Friedman SL. Liver fibrogenesis and the role of hepatic stellate cells: new insights and prospects for therapy. *J. Gastroenterol. Hepatol*. 1999; **14**: 618.
42 Li J, Rosman AS, Leo MA *et al*. Tissue inhibitor of metalloproteinase is increased in the serum of precirrhotic and cirrhotic alcoholic patients and can serve as a marker of fibrosis. *Hepatology* 1994; **19**: 1418.
43 Liu H, Lee SS. Cardiopulmonary dysfunction in cirrhosis. *J. Gastroenterol. Hepatol.* 1999; **14**: 600.
44 Lochs H, Plauth M. Liver cirrhosis: rationale and modalities for nutritional support—the European Society of Parenteral and Enteral Nutrition consensus and beyond. *Curr. Opin. Clin. Nutr. Metabol. Care* 1999; **2**: 345.
45 Ma Z, Lee SS. Cirrhotic cardiomyopathy: getting to the heart of the matter. *Hepatology* 1996; **24**: 451.
46 Ma Z, Zhang Y, Huet P-M *et al*. Differential effects of jaundice and cirrhosis on α-adrenoceptor signalling in three rat models of cirrhotic cardiomyopathy. *J. Hepatol.* 1999; **30**: 485.
47 McIntyre N. The Child–Turcotte and Child–Pugh classification. In: Reichen J, Poupon RE, eds. *Surrogate Markers to Assess Efficacy of Treatment in Chronic Liver Disease*. Kluwer Academic Publishers, London, 1996, p. 69.
48 Madden AM, Bradbury W, Morgan MY. Taste perception in cirrhosis: its relationship to circulating micronutrients and food preferences. *Hepatology* 1997; **26**: 40.
49 Madden AM, Morgan MY. Resting energy expenditure should be measured in patients with cirrhosis, not predicted. *Hepatology* 1999; **30**: 655.
50 Meyer B, Luo H, Bargetzi M *et al*. Quantification of intrinsic drug-metabolizing capacity in human liver biopsy specimens: support for the intact-hepatocyte theory. *Hepatology* 1991; **13**: 475.
51 Moreau R, Lebrec D. Endogenous factors involved in the control of arterial tone in cirrhosis. *J. Hepatol.* 1995; **22**: 370.
52 Morencos FC, De Las Heras Castano G, Ramos LM *et al*. Small bowel bacterial overgrowth in patients with alcoholic cirrhosis. *Dig. Dis. Sci.* 1996: **41**: 552.
53 Morrison WL, Bouchier IAD, Gibson JNA *et al*. Skeletal muscle and whole-body protein turnover in cirrhosis. *Clin. Sci.* 1990; **78**: 613.
54 Muller MJ, Boker KHW, Selberg O. Are patients with liver cirrhosis hypermetabolic? *Clin. Nutr.* 1994; **13**: 131.
55 Murawaki Y, Yamada S, Ikuta Y *et al*. Clinical usefulness of serum matrix metalloproteinase-2 concentration in patients with chronic viral liver disease. *J. Hepatol.* 1999; **30**: 1090.
56 Naschitz JE, Slobodin G, Lewis RJ *et al*. Heart diseases affecting the liver and liver diseases affecting the heart. *Am. Heart J.* 2000; **140**: 111.
57 Navasa M, Rimola A, Rods J. Bacterial infections in liver disease. *Semin. Liver Dis.* 1997; **17**: 323.
58 Newell GC. Cirrhotic glomerulonephritis: incidence, morphology, clinical features, and pathogenesis. *Am. J. Kidney Dis.* 1987; **9**: 183.
59 Niemela O, Risteli L, Sotaniemi EA *et al*. Aminoterminal propeptide of type III procollagen in serum in alcoholic liver disease. *Gastroenterology* 1983; **85**: 254.
60 Noble-Jamieson G, Thiru S, Johnston P *et al*. Glomerulonephritis with end-stage liver disease in childhood. *Lancet* 1992; **339**: 706.
61 Pardo A, Bartoli R, Lorenzo-Zúniga V *et al*. Effect of cisapride on intestinal bacterial overgrowth and bacterial translocation in cirrhosis. *Hepatology* 2000; **31**: 858.
62 Pateron D, Beyne P, Laperche T *et al*. Elevated circulating cardiac troponin I in patients with cirrhosis. *Hepatology* 1999; **29**: 640.
63 Pauwels A, Mostefa-Kara N, Debenes B *et al*. Systemic antibiotic prophylaxis after gastrointestinal haemorrhage in cirrhotic patients with a high risk of infection. *Hepatology* 1996; **24**: 802.
64 Pauwels A, Pines E, Abboura M *et al*. Bacterial meningitis in cirrhosis: review of 16 cases. *J. Hepatol.* 1997; **27**: 830.
65 Piche T, Schneider SM, Tran A *et al*. Resting energy expenditure in chronic hepatitis C. *J. Hepatol.* 2000; **33**: 623.
66 Plauth M, Merli M, Kondrup J *et al*. ESPEN guidelines for nutrition in liver disease and transplantation. *Clin. Nutr.* 1997; **16**: 43.
67 Poonawala A, Nair S, Thuluvath PJ. Prevalence of obesity and diabetes in patients with cryptogenic cirrhosis: a case-control study. *Hepatology* 2000; **32**: 689.
68 Pozzi M, Carugo S, Boari G *et al*. Evidence of functional and structural cardiac abnormalities in cirrhotic patients with and without ascites. *Hepatology* 1997; **26**: 1131.
69 Richardson RA, Davidson HI, Hinds A *et al*. Influence of the metabolic sequelae of liver cirrhosis on nutritional intake. *Am. J. Clin. Nutr*. 1999; **69**: 331.
70 Rudolph KL, Chang S, Millard M *et al*. Inhibition of experimental liver cirrhosis in mice by telomerase gene delivery. *Science* 2000; **287**: 1253.
71 Schalm SW. The diagnosis of cirrhosis: clinical relevance and methodology. *J. Hepatol.* 1997; **27**: 1118.
72 Scheuer PJ, Lefkowitch JH. *Liver Biopsy Interpretation*, 2th edn. London: WB Saunders, 2000, p. 173.
73 Sheen I-S, Liaw Y-F. The prevalence and incidence of cholecystolithiasis in patients with chronic liver diseases: a prospective study. *Hepatology* 1989; **9**: 538.
74 Simpson KJ, Lukacs NW, Colletti L *et al*. Cytokines and the liver. *J. Hepatol.* 1997; **27**: 1120.
75 Siringo S, Burroughs AK, Bolondi L *et al*. Peptic ulcer and its course in cirrhosis: an endoscopic and clinical prospective study. *J. Hepatol.* 1995; **22**: 633.
76 Siringo S, Vaira D, Menegatti M *et al*. High prevalence of *Helicobacter pylori* in liver cirrhosis. Relationship with clinical and endoscopic features and the risk of peptic ulcer. *Dig. Dis. Sci.* 1997; **42**: 2024.

77 Sørensen HT, Friis S, Olsen JH *et al*. Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. *Hepatology* 1998; **28**: 921.
78 Summerskill WHJ, Molnar GD. Eye signs in hepatic cirrhosis. *N. Engl. J. Med*. 1962; **266**: 1244.
79 Trevisani F, Sica G, Mainquà P *et al*. Autonomic dysfunction and hyperdynamic circulation in cirrhosis with ascites. *Hepatology* 1999; **30**: 1387.
80 Urbain D, Muls V, Thys O *et al*. Aminopyrine breath test improves long-term prognostic evaluation in patients with alcoholic cirrhosis in Child classes A and B. *J. Hepatol*. 1995; **22**: 179.
81 Weber FL Jr, Bagby BS, Licate L *et al*. Effects of branched-chain amino acids on nitrogen metabolism in patients with cirrhosis. *Hepatology* 1990; **11**: 942.
82 Xiol X, Castellví JM, Guardiola J *et al*. Spontaneous bacterial empyaema in cirrhotic patients: a prospective study. *Hepatology* 1996; **23**: 719.
83 Yoshiji H, Kuriyama S, Miyamoto Y *et al*. Tissue inhibitor of metalloproteinase-1 promotes liver fibrosis development in a transgenic mouse model. *Hepatology* 2000; **32**: 1248.
84 Zein NN, Abdulkarim AS, Wiesner RH *et al*. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. *J. Hepatol.* 2000; **32**: 209.

Chapter 22
Alcohol and the Liver

The association of alcohol with cirrhosis was recognized by Matthew Baillie in 1793. Over the last 20 years alcohol consumption has correlated with deaths from cirrhosis. In the USA, cirrhosis is the fourth commonest cause of death in adult males. The prevalence of alcoholic liver disease depends largely on religious and other customs and on the relation between the cost of alcohol and earnings—the lower the cost of alcohol, the more lower socioeconomic groups are affected.

Worldwide, alcohol consumption is increasing. In France, however, the past 20 years has seen a decrease, perhaps due to government propaganda. In the USA, alcohol consumption, particularly of spirits, has fallen, perhaps due to changing lifestyles.

Risk factors for alcoholic liver diseases

Not all those who abuse alcohol develop liver damage; the incidence of cirrhosis among alcoholics at autopsy is about 10–15% (fig. 22.1) [68]. The explanation of the apparent predisposition of certain people to develop alcoholic cirrhosis is unknown.

Drinking patterns

The average intake of alcohol in a large group of male alcoholic cirrhotics was 160 g/day for 8 years [42]. Alcoholic hepatitis, a pre-cirrhotic lesion, was noted in 40% of those who drank less than 160 g/day. For most individuals the danger dose is greater than 80 g alcohol daily (table 22.1). Duration is important. Neither cirrhosis nor alcoholic hepatitis was seen in patients who consumed an average of 160 g of ethanol per day for less than 5 years, whereas 50% of 50 patients consuming high levels of alcohol for an average of 21 years developed cirrhosis.

The liver injury is unrelated to the type of beverage; it is related only to its alcohol content. The non-alcoholic constituents of the drink—congeners—are not particularly hepato-toxic.

Continued daily imbibing is more dangerous than intermittent consumption when the liver is given a chance to recover. For at least 2 days in the week a person should not drink alcohol.

Those who develop alcoholic liver damage are only mildly dependent on alcohol. They escape florid withdrawal symptoms, and are at greater risk of developing liver damage because they are able to maintain a high consumption over many years.

Table 22.1. Alcohol equivalents

Whisky	30 ml	10 g
Wine	100 ml	10 g
Beer	250 ml	10 g

?80 g/day safe.

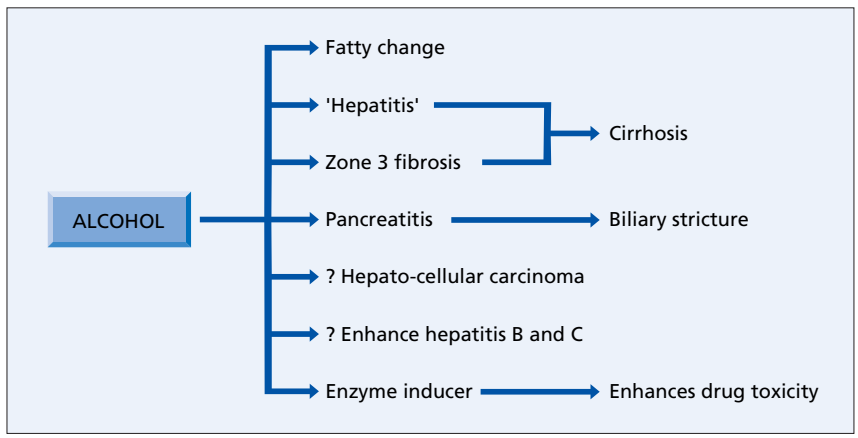


Fig. 22.1. The hepato-biliary effects of alcohol abuse; 80–90% of abusers have no liver disease.

Table 22.2. Alcoholic liver disease—males : females [56]

Females suspected	38%
Males suspected	77%
Continued to abuse alcohol	
males	71%
females	91%

Sex

Alcoholism is increasing among women, owing to a decline in the social stigma attached to drinking and to the ready availability of alcohol in supermarkets. Women are less likely to be suspected of alcohol abuse; they present at a later stage, are more susceptible to hepatic damage and are more likely to relapse after treatment (table 22.2) [56]. Women develop higher blood ethanol values following a standard dose, possibly because of a smaller mean apparent volume of distribution of alcohol [51]. Women are more likely to progress from alcoholic hepatitis to cirrhosis even if they abstain.

Genetics

Patterns of alcohol drinking are inherited. However, a specific genetic abnormality involved in susceptibility has not been identified [47]. Rates of alcohol elimination vary as much as three-fold among individuals.

Prevalence of alcoholism is greater among monozygotic than dizygotic twins, suggesting an inherited defect.

Different rates of alcohol elimination may be related to genetic polymorphism of enzyme systems [21]. Individuals with different alcohol dehydrogenase (ADH) isoenzymes have different alcohol elimination rates. Polymorphism of ADH2 and ADH3, which are more active forms, may be protective as faster acetaldehyde accumulation leads to lower tolerance to alcohol. However, if such persons do imbibe, more acetaldehyde is produced so increasing the risk of liver disease.

The microsomal, ethanol-inducible cytochrome P450-II-E1 (CYP 2E1) is the key in non-ADH oxidation of ethanol which produces acetaldehyde. However, there is little or no association between polymorphisms in the CYP 2E1 gene and the incidence of alcoholic liver disease [76].

Acetaldehyde is metabolized to acetate by aldehyde dehydrogenase (ALD). ALD H2, the main mitochondrial enzyme is responsible for the majority of aldehyde oxidation. Inactive ALD H2 is found in 50% of Japanese and Chinese and this explains the aldehyde flush reaction when they consume alcohol. This inhibits Orientals from taking alcohol and is a negative risk for the development of alcoholic liver disease [81].

Polymorphism in tumour necrosis factor (TNF) promoter is associated with susceptibility to alcoholic steato-hepatitis [32].

Polymorphism in genes encoding enzymes involved in fibrogenesis may prove important in determining individual susceptibility to the fibrotic effect of alcohol.

Susceptibility to liver damage from alcohol is probably caused by a cumulative interaction of a number of genes [47]. Alcoholism and alcohol related liver damage are polygenic disorders.

Nutrition

Body composition shows protein depletion in chronic, stable, alcoholic cirrhotics related to the severity of the liver disease [72]. The extent of the nutritional defect depends on the type of alcoholic, whether of low socio-economic status where protein-calorie malnutrition often precedes liver injury or in the socially adequate where diet is good and liver damage seems unrelated to nutrition [77]. Animals show species variation. The rat given alcohol develops liver damage only if the diet is deficient, whereas baboons develop cirrhosis with a good diet. In rhesus monkeys, alcoholic liver damage is prevented by increasing dietary protein and choline [75]. Certainly, patients with decompensated liver disease, given a third of their calories as alcohol together with a nutritious diet, improve steadily [74], whereas liver function does not improve with alcohol abstinence if dietary protein remains low [69]. Nutrition and hepatotoxicity may act synergistically.

Alcohol may increase minimum daily requirements of choline, folic acid and other nutrients. Nutritional deficiencies, particularly of protein, may promote the toxic effects of alcohol by depleting hepatic amino acids and enzymes.

Both alcohol and nutrition play a part in alcohol hepato-toxicity, alcohol being the more important. There may be a range of alcohol intake that is tolerated without liver damage under optimal dietary conditions. However, it is also likely that there is a threshold of alcohol toxicity beyond which no protection is afforded by dietary manipulation [67].

Metabolism of alcohol (figs 22.2, 22.3)

Alcohol cannot be stored and obligatory oxidation must take place, predominantly in the liver. The healthy individual cannot metabolize more than 160–180 g/day. Alcohol induces enzymes used in its catabolism, and the alcoholic, at least while the liver is relatively unaffected, may be able to metabolize more.

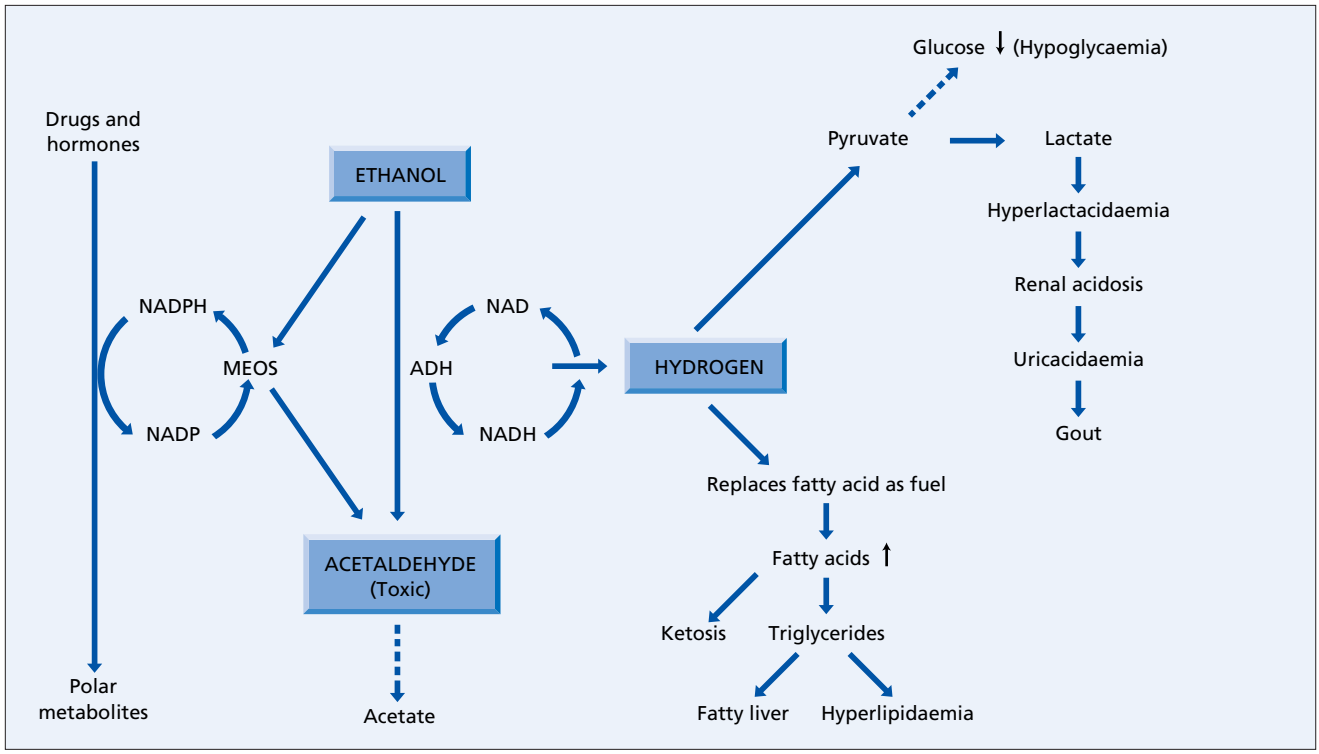


Fig. 22.2. Oxidation of alcohol in the hepatocyte. The production of acetaldehyde (toxic) is enhanced and conversion to acetate reduced. The hydrogen produced replaces fatty acid as a fuel so that fatty acids accumulate with consequent ketosis, triglyceridaemia, fatty liver and hyperlipidaemia. Unwanted hydrogen is used to convert pyruvate to lactate, which is produced in excess. Hyperlactacidaemia leads to renal acidosis, a rise in serum uric acid and gout. Collagen synthesis may be stimulated. Reduction of the pyruvate to glucose pathway results in hypoglycaemia. Stimulation of the MEOS drug-metabolizing system leads to drug and alcohol tolerance, and increased testosterone metabolism may be related to feminization and infertility. Broken lines indicate depressed pathways. ADH, alcohol dehydrogenase; MEOS, microsomal ethanol oxidizing system; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate. (From [44].)

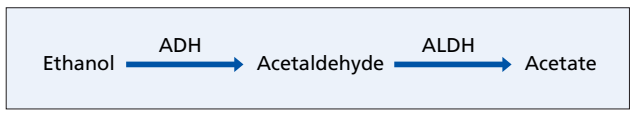


Fig. 22.3. Alcohol metabolism in the liver. ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase.

Table 22.3. The 'empty' (i.e. nutritionally valueless) calories supplied by alcohol

1 g alcohol = 7 calories
200 g (500 ml proof spirits) = approx. 1400 calories

One gram of alcohol gives 7 calories and alcoholics literally run on spirit. The empty calories provide only energy with no contribution to nutrition (table 22.3).

Between 80 and 85% ethanol oxidation is by initial conversion to acetaldehyde catabolized by ADH (fig. 22.3). This takes place in the cytosol. Acetaldehyde in mitochondria and cytosol may be injurious, causing membrane damage and cell necrosis. The acetaldehyde is converted to acetyl CoA with ALD acting as a co-enzyme (fig. 22.3). This can be further broken down to acetate, which may be oxidized to carbon dioxide and water, or converted by the citric acid cycle to other biochemically important compounds including fatty acids. NAD is a co-factor and hydrogen acceptor when alcohol is converted to acetaldehyde and further to acetyl CoA. The NADH generated shuttles into the mitochondria and changes the NADH:NAD ratio and the redox state of the liver. The hydrogen generated replaces fatty acid as a fuel and is followed by triglyceride accumulation and fatty liver. The redox state of the liver changes, protein synthesis is inhibited and lipid peroxidation increases [79].

Diminished hepatic ADH and ALD are secondary to zone 3 necrosis.

The activity of the citric acid cycle is reduced, and this may be responsible for decreased fatty acid oxidation.

Lipoprotein synthesis is increased by alcohol. The NADH may serve as the hydrogen carrier for the conversion of pyruvate to lactate, and blood lactate and uric acid levels rise after alcohol. Post-alcoholic hypoglycaemia and gout after alcohol ingestion may be explained by this mechanism. The conversion of alcohol to acetaldehyde also leads to inhibition of protein synthesis.

Between 10 and 15% of alcohol is metabolized by a P450 ethanol oxidizing system (MEOS). P450-II-E1 (CYP 2E1) is inducible by alcohol and by drugs such as paracetamol (acetaminophen) [44]. This accounts for the susceptibility of the alcoholic to drugs that are hepatotoxic on account of metabolites and which, when given in recognized therapeutic doses, can cause serious liver injury. Induction of P450-II-E1 increases oxygen consumption, acetaldehyde production and promotes lipid peroxidation. During microsomal peroxidation, potentially injurious reactive oxygen radicals (*free radicals*) are produced and may initiate lipid peroxidation [15]. The endogenous free radical scavengers such as glutathione are decreased. The lack of protection against free radicals may partly explain mitochondrial injury.

Mechanisms of liver injury [44]

Relation to alcohol and its metabolites

Rodents given alcohol develop only a fatty liver. However, they cannot match the quantities of alcohol consumed by humans, who may take 50% of total calories as alcohol. This level can be achieved in the baboon who, after 2–5 years of alcoholism, develops cirrhosis. Evidence for the direct hepato-toxic effect of alcohol, apart from nutritional changes, comes from human volunteers, both normal and alcoholic who, after 300–600 ml (10–20 oz) of 86% proof alcohol daily for 8–10 days, develop fatty change and electron microscopic abnormalities on liver biopsy.

Acetaldehyde

Acetaldehyde is generated by both ADH and the MEOS systems. Blood acetaldehyde levels in alcoholics increase after chronic alcohol consumption but only very small amounts leave the liver.

Acetaldehyde is held responsible for many of the features of acute alcoholic hepatitis (table 22.4). Acetaldehyde is extremely reactive and toxic; it binds to phospholipids, amino acid residues and sulphydryl groups. It affects the plasma membranes by depolymerizing proteins and producing altered surface antigens. Lipid peroxidation is favoured.

Acetaldehyde reacts with serotonin, dopamine and noradrenaline, yielding pharmacologically active compounds. It stimulates procollagen type I and fibronectin synthesis from hepatic stellate cells [14].

Table 22.4. The possible hepato-toxic effects of acetaldehyde

Increases lipid peroxidation
Binds plasma membranes
Interferes with mitochondrial electron-transport chain
Inhibits nuclear repair
Interferes with microtubule function
Forms adducts with proteins
Activates complement
Stimulates superoxide formation by neutrophils
Increases collagen synthesis

Changes in the intra-cellular redox potential

The marked increase in the NADH:NAD ratio in hepatocytes actively oxidizing alcohol produces profound metabolic consequences. Thus the redox ratio of lactate to pyruvate is markedly increased, leading to lactic acidosis. This acidosis, in conjunction with ketosis, impairs urate excretion and leads to gout. The altered redox potential has also been implicated in the pathogenesis of fatty liver, collagen formation, altered steroid metabolism and impaired gluconeogenesis.

Mitochondria

Alcohol has a profound effect on hepatic mitochondrial function and DNA [16].

Mitochondria show swelling and abnormal cristae, perhaps due to acetaldehyde. Functionally, fatty acid and acetaldehyde oxidation is decreased with a reduction in cytochrome oxidase activities, respiratory capacity and oxidative phosphorylation.

Liver cell water and protein retention

In rat liver slices, alcohol inhibits secretion of newly synthesized glycoprotein and albumin by the hepatocyte. This may be due to acetaldehyde binding to tubulin, so impairing the microtubules on which protein secretion from the cell depends [44]. In rats fed alcohol, fatty acid binding protein increases and this accounts for some of the total rise in cytosolic protein.

Water is retained in proportion to the protein and the resultant hepatocyte swelling is the major cause of hepatomegaly in alcoholics.

Hypermetabolic state

Chronic alcohol ingestion results in an increased consumption of oxygen largely due to increased re-

oxidation of NADH. The increased hepatic oxygen requirement results in a steeper oxygen gradient along the sinusoidal length so that cell necrosis is in zone 3 (centrizonal) (fig. 22.4). Necrosis in this area may be hypoxic. P450-II-E1 is found in greatest concentration in zone 3 where the redox changes are also most marked.

Increased liver fat

The fat can be of exogenous (dietary) origin, can come from adipose tissue being transported to the liver as free fatty acids, or come from lipids synthesized in the liver itself. The origin depends upon the dose of ethanol ingested and the lipid content of the diet. After an acute, isolated ingestion of a large dose of ethanol the fatty acids found in the liver originate from adipose tissue, whereas following chronic ingestion, there is increased synthesis and decreased degradation of fatty acids.

Immunological liver damage [40]

Impaired humoral immunity is shown by elevation of serum immunoglobulin levels and deposition of IgA along hepatic sinusoidal walls. Impaired cell-mediated immunity is shown by circulating lymphocytes which are directly cytotoxic to different cells. These are also present in advancing alcoholic hepatitis. Cytotoxic T-lymphocyte interaction may play a role in the genesis or perpetuation of alcoholic liver disease [18].

Protein adducts can serve as neoantigens to incite these humoral B-cell and cytotoxic T-cell lymphocyte responses. Antibodies can be shown against acetaldehyde protein adduct derived epitopes [40]. Antibodies also recognize hydroxyethyl radical–P450-II-E1 adducts. This suggests autoimmune mechanisms in alcoholic liver disease [19].

Fibrosis

In the alcoholic, cirrhosis can develop from fibrosis without an intervening acute alcoholic hepatitis. The mechanism is uncertain. Lactic acid increases fibrogenesis but seems non-specific and related to any type of severe liver disease. Fibrosis is due to transformation of stellate cells to fibroblasts and myofibroblasts (fig. 22.5) (Chapter 21). Type III procollagen is found in the perisinusoidal collagen (fig. 22.6).

Although cell necrosis is the major stimulus to collagen formation, there are other possibilities. Zone 3 hypoxia might be the stimulus. Increased pressure due to hepatocyte enlargement is another possible fibrogenetic stimulus. Degradation products from lipid peroxi-

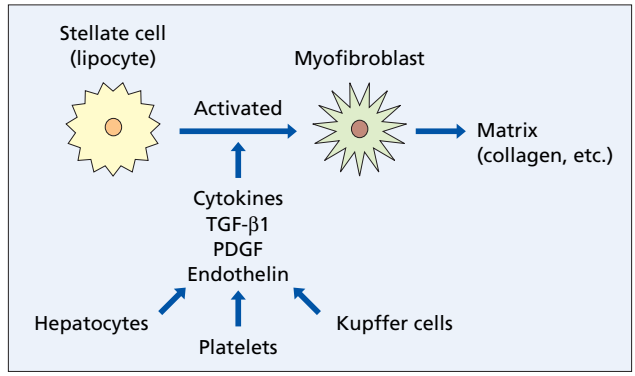


Fig. 22.5. The activation of stellate cells to become myofibroblasts and to increase matrix.

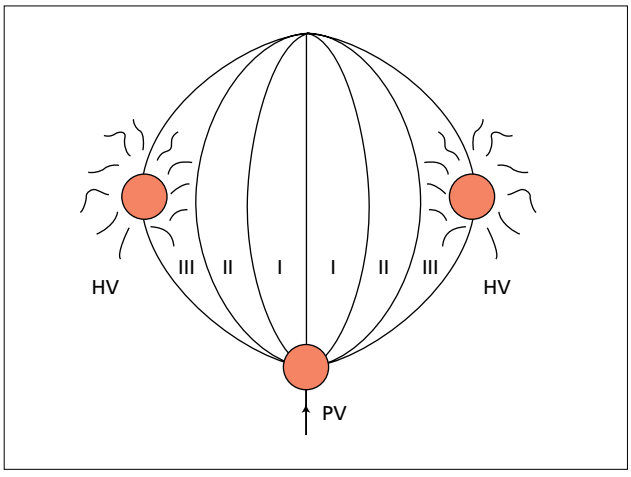


Fig. 22.4. Zone 3 collagenosis. HV, hepatic venule; PV, portal venule.

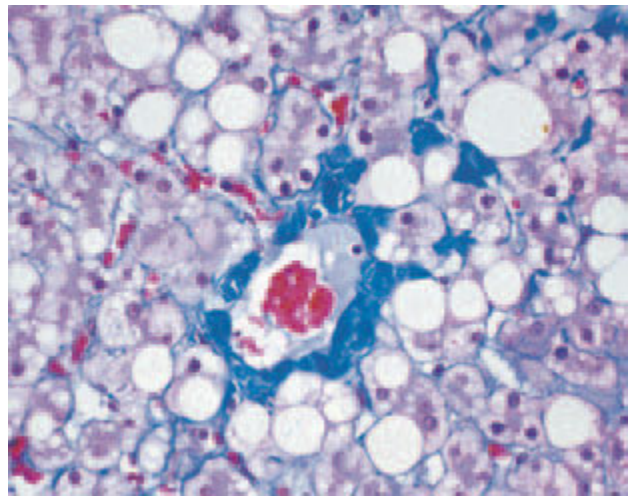


Fig. 22.6. Peri-venular (zone 3) and phlebosclerosis fibrosis with adjacent fatty change. (Chromophobe aniline blue, ×100.)

dation motivate stellate cells to produce collagen. Cytokines are also important [2].

Cytokines

A complex relationship exists between endotoxins, stellate cell activation and release of cytokines and chemokines. Endotoxins are increased in the blood of alcoholics [33]. This is related to increased intestinal bacterial flora, increased gut permeability and reduced endotoxin scavenging by the reticulo-endothelial system (fig. 22.7). The endotoxin releases a battery of cytokines [33]. Cytokines IL1, IL2 and TNF-α are released from non-parenchymal cells. In alcoholic hepatitis, TNF-α produced by monocytes is increased. IL8, the neutrophilic chemotactic factor, might be related to the neutrophilia and hepatic polymorph infiltration. It is also possible that the stimulus for cytokine production comes from alcohol-induced or alcohol-injured hepatocytes.

The biological effects of certain cytokines resemble the clinical manifestations of acute alcoholic liver disease (table 22.5). Cytokines stimulate fibroblast production. TGF-β activates collagen production from stellate cells [52]. TNF-α can depress P450 drug metabolism, induce cell surface expression of HLA antigens and cause hepato-toxicity.

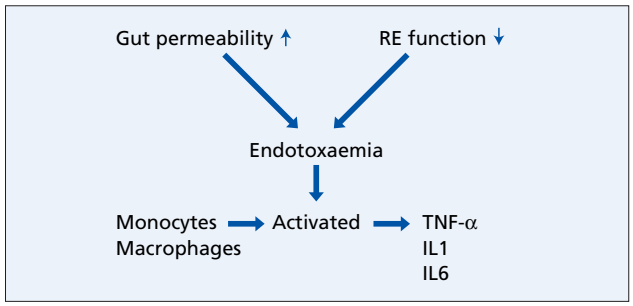


Fig. 22.7. The relation of gut permeability and reticulo-endothelial (RE) function to endotoxaemia and cytokine production.

Morphological changes

The changes are usually classified into fatty liver, alcoholic hepatitis and cirrhosis.

Fatty liver (steatosis) (figs 22.8, 22.9)

The fat accumulates in zones 3 and 2. In the more severely affected, the fatty change is diffuse. The fat may be in macrovesicular (large droplet) form. Less often it is in microvesicular (small droplet) form.

Table 22.5. The biological effects of cytokine-inducers of the acute phase response compared with the changes seen in acute alcoholic liver disease (ALD)

Change	ALD	Cytokines
Fever	+	+
Anorexia	+	+
Muscle wasting	+	+
Hypermetabolism	+	+
Neutrophilia	+	+
Decreased albumin	+	+
Collagen disposition	+	+
Increased triglycerides	+	+
Decreased bile flow	+	+
Shock	+	+

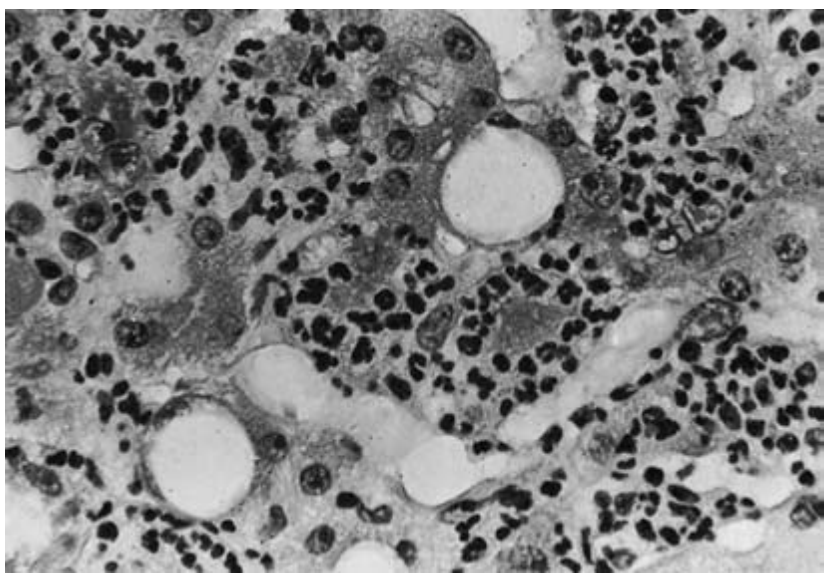


Fig. 22.8. Acute alcoholic hepatitis. Liver cells undergoing necrosis and containing clumps of Mallory's hyaline are surrounded by cuffs of polymorphonuclear cells. There is fatty change. (H & E,×120.)

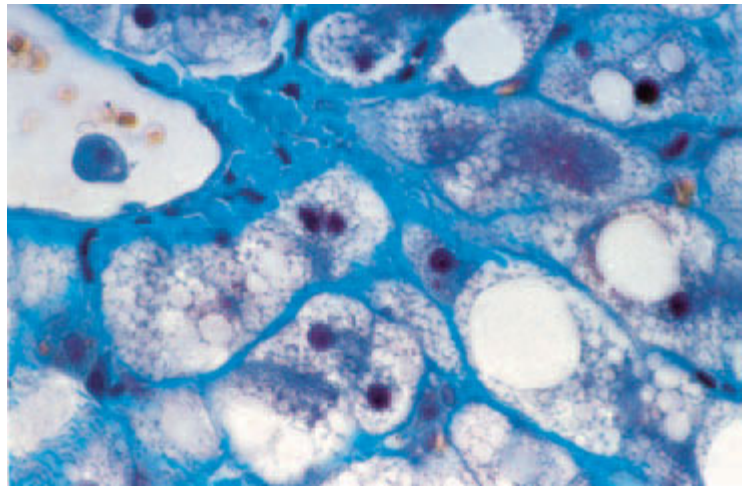


Fig. 22.9. Acute alcoholic hepatitis. Hepatocytes are ballooned and contain micro- and macrovesicular fat and clumps of purplish-red Mallory's alcoholic hyaline. (Chromophobe aniline blue, ×100.)

Large fat droplets appear in hepatocytes within 3–7 days of excess alcohol ingestion. Microvesicular fat represents mitochondrial damage and more active lipid synthesis by the hepatocyte. Hepatic mitochondrial DNA deletion is associated [27].

The fatty change can be quantified as follows:

+ less than 25% of liver cells contain fat
++ 25–50% of liver cells contain fat
+++ 50–75% of liver cells contain fat
++++ more than 75% of liver cells contain fat.

Alcoholic hepatitis

The full picture of a florid, acute alcoholic hepatitis is relatively rare. There are all gradations of severity. The hepatitis may be separate or combined with an established cirrhosis.

Balloon degeneration. Hepatocytes are swollen with granular cytoplasm often dispersed into fine strands. The nucleus is small and hyperchromatic. Steatosis, is usually macrovesicular, but with some microvesicular change. The ballooning is due to retention of water and to failure of the microtubular excretion of protein from the hepatocyte.

Acidophilic bodies represent apoptosis.

Mallory bodies are seen by haematoxylin and eosin as purplish-red intra-cytoplasmic inclusions [37, 38]. They may be more obvious with Masson's trichrome or chromophobe aniline blue stains (fig. 22.9). They consist of clumped organelles—largely intermediate filaments. They target the hepatocyte for destruction. The Mallory-containing cell is surrounded by a satellite of polymorphs (fig. 22.8).

Giant mitochondria form globular intra-cytoplasmic inclusions seen by light microscopy using a Masson trichrome stain.

Sclerosing hyaline necrosis. Collagen deposition is maximal in zone 3. The fibres are peri-sinusoidal and enclose normal or ballooned hepatocytes. The pericellular fibrosis is like lattice or chicken wire and has been termed 'creeping collagenosis' (fig. 22.10) [23].

Collagenization of the space of Disse is shown by electron microscopy (fig. 22.11). The number and porosity of the sinusoidal lining is reduced [35]. These changes interfere with the exchange of substances between plasma and the hepatocyte cell membrane and contribute to portal hypertension [29]. Lesions in terminal and sublobular veins include lymphocytic phlebitis, gradual obliteration and veno-occlusion [30].

Portal zone changes are inconspicuous and mild chronic inflammation is seen only in the advanced case. Marked zone 1 fibrosis suggests a complicating chronic pancreatitis (fig. 22.12) [58].

Cholestasis in bile canaliculi is a feature of all types of alcoholic liver disease. It is strongly associated with decreased survival [60].

The *histological patterns* form a spectrum from minimal alcoholic hepatitis to an advanced, probably irreversible, picture, where necrosis is more extensive and scars form. Alcoholic hepatitis is a precursor of cirrhosis.

Hyperplastic nodules develop in those who reduce their alcohol consumption [28].

Cirrhosis

Classically, cirrhosis of the alcoholic is micronodular (fig. 22.13). No normal zonal architecture can be identified, and zone 3 venules are difficult to find. The formation of nodules is often slow because of a presumed inhibitory effect of alcohol on hepatic regeneration. The amount of fat is variable and acute alcoholic hepatitis may or may not coexist. With continuing necrosis and replacement

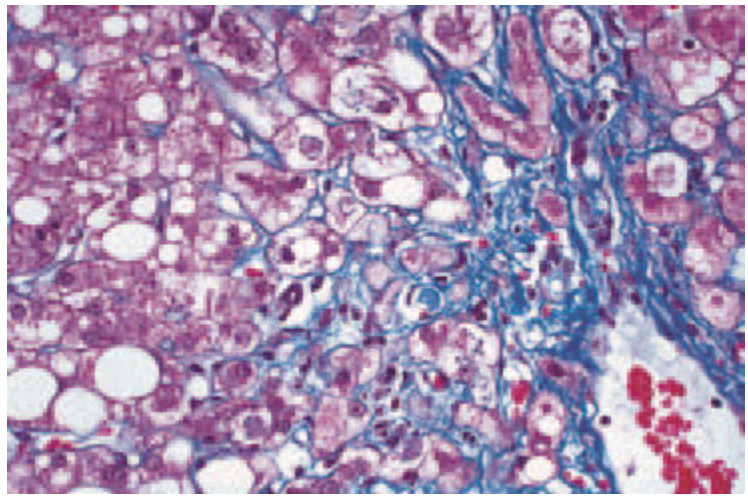


Fig. 22.10. Advanced zone 3 collagenosis with fatty change. A thickened hepatic vein can be seen bottom right. (Chromophobe aniline blue, ×100.)

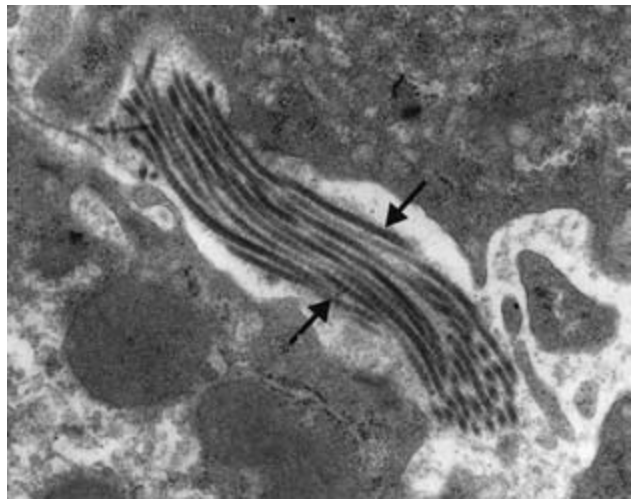


Fig. 22.11. Electron micrograph of liver in a patient with alcoholic liver disease. Note the deposition of collagen fibrils in Disse's space (arrowed). This could interfere with oxygen and metabolite exchange between blood and hepatocytes.

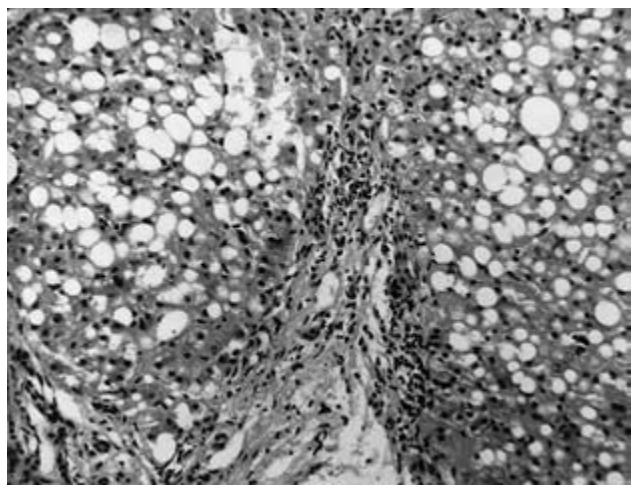


Fig. 22.13. Cirrhosis of the alcoholic. Fibrous bands divide the liver into small regular nodules. Fatty change is conspicuous. (H & E, ×120.)

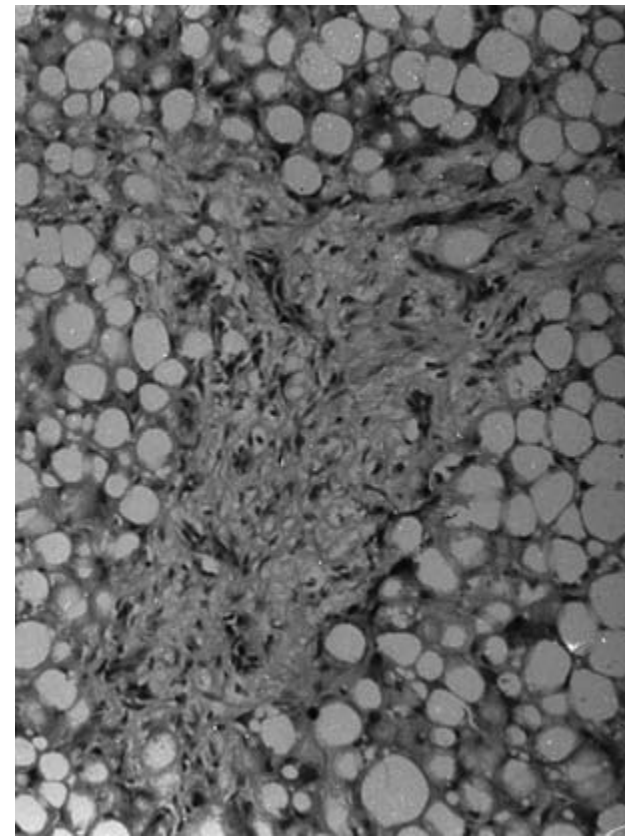


Fig. 22.12. Portal zone (zone 1) with marked fibrosis and fatty change in the hepatocytes. This patient suffered from chronic alcoholic pancreatitis with partial biliary obstruction. (H & E, ×120.)

Table 22.6. Alcoholism—the CAGE questionaire

C	Have you felt the need to cut down?
A	*A*nnoyed at the suggestion of a drinking problem
G	*G*uilty of excess drinking
E	Drink (eye opener) in the morning

fibrosis, the cirrhosis may progress from a micro- to a macronodular pattern, but this is usually accompanied by a reduction in steatosis. When this end-stage picture is reached, an alcoholic aetiology is difficult to confirm on histological grounds.

Cirrhosis may follow peri-cellular fibrosis without apparent hepatic necrosis and inflammation. Zone 3 myofibroblastic proliferation and collagen deposition may be the first lesions in the sequence of events leading to alcoholic cirrhosis.

Increased hepatic iron is found in approximately one-third of alcohol subjects [24]. This is partly due to increased intestinal absorption and to the iron content of beverages, especially wine. Free radical mediated toxicity contributes.

Early recognition

This depends on a high index of suspicion. If alcoholism is suspected, the CAGE questionnaire should be used (table 22.6). One point is scored for each positive response. Scores of 2 or more suggest alcohol-related problems. A patient may present with non-specific digestive symptoms such as anorexia, morning nausea with dry retching, diarrhoea, vague right upper abdominal pain and tenderness or pyrexia.

The patient may seek medical advice because of the effects of alcoholism such as social disruption, poor work performance, accidents, violent behaviour, fits, tremulousness or depression.

The diagnosis may be made when hepatomegaly, a raised serum transaminase or γ-glutamyl transpeptidase (γ-GT) level or macrocytosis are discovered at a routine examination, for instance at a life insurance check-up or during investigation of another condition.

Physical signs may be non-contributory, although tender hepatomegaly, prominent vascular spiders and associated features of alcoholism may be helpful. The clinical features do not reflect the hepatic histology and biochemical tests of liver function may be normal.

Investigation

Biochemical tests [54]

Serum transaminase levels rarely exceed 300 iu/l. AST (SGOT), which is derived from alcoholic damage to mitochondria or smooth muscle, is more increased than the ALT (SGPT) which is confined to the liver. In alcoholic liver disease, the AST : ALT ratio usually exceeds 2. This is partially explained by the depletion in alcoholics of pyridoxal 5-phosphate, the biologically active form of vitamin B_6 which is necessary for the activity of both enzymes and is depleted in alcoholics.

The serum γ-GT is a widely used screening test for alcohol abuse. The rise results mainly from enzyme induction, although hepato-cellular damage and cholestasis may contribute. There are many false positives due to other factors, such as drugs, other diseases and the patient having a value at the upper limit of the normal range.

Serum alkaline phosphatase may be markedly increased (greater than four times normal) especially in those with severe cholestasis and alcoholic hepatitis. Serum IgA values may be very high.

Blood and urinary alcohol levels can be used in the clinic to refute the individual who has a high blood alcohol level but denies imbibing.

Non-specific serum changes in acute and chronic alcoholism include elevations in uric acid, lactate and triglyceride, and reductions in glucose and magnesium. Hypophosphataemia is related to a renal tubular defect, independent of liver function impairment [3]. Low serum tri-iodothyronine (T_3) levels presumably reflect decreased hepatic conversion of thyroxine to T_3. Levels correlate inversely with the severity of alcoholic liver disease.

Type III collagen can be estimated by the serum procollagen type III peptides. Serum type IV collagen and laminin estimate components of basement membranes. Results of these three tests correlate with disease severity, degree of alcoholic hepatitis and alcohol intake [59].

Other serum tests are markers of alcohol abuse rather than alcoholic liver damage. They include serum glutamate dehydrogenase, the mitochondrial isoenzyme of aspartate transaminase. Serum carbohydrate-deficient (de-sialylated) transferrin levels may be a useful marker of excessive alcohol intake irrespective of liver disease but this test is not generally available [6].

Even sensitive biochemical methods may fail to reveal alcoholic liver damage and liver biopsy is necessary in cases of doubt.

Haematological changes

Macrocytosis (MCV) greater than 95 fl is presumably due to a direct effect of alcohol on bone marrow. Deficiencies of folate and vitamin B_{12} contribute in the malnourished. The combination of a raised MCV and serum γ-GT will identify 90% of alcohol-dependent patients.

Liver biopsy

This confirms liver disease and identifies alcohol abuse as the likely cause (table 22.7). The dangers of the liver damage can be emphasized more forcibly to the patient.

Table 22.7. Liver biopsy in alcoholic patients

Diagnosis: exclude
chronic viral hepatitis (hepatitis C virus)
genetic haemochromatosis
Prognosis
fatty change
alcoholic hepatitis
cirrhosis
Enforce abstinence

Liver biopsy is important prognostically. Fatty change alone is not nearly so serious as peri-venular sclerosis, which is a precursor of cirrhosis [80]. An established cirrhosis can be confirmed.

Non-alcoholic steato-hepatitis (*NASH*) may be due to various causes. In contrast to the alcoholic, the lesion is largely peri-portal (Chapter 25).

Portal hypertension

Splenomegaly is not prominent. Portal hypertension and gastrointestinal bleeding, however, are frequent at all stages. Bleeding is not only from oesophageal varices but from duodenal ulcers, gastritis and Mallory–Weiss lower oesophageal tears following repeated vomiting.

The portal hypertension may be related to cirrhosis. Fatty change and zone 3 collagenosis (peri-venular sclerosis) lead to a pre-sinusoidal portal hypertension [30]. Collagenization of the space of Disse raises portal pressure. Enlargement of hepatocytes probably plays little part.

Scanning

With severe alcoholic hepatitis or cirrhosis, isotopes are hardly taken up by the liver because the blood shunts past the reticulo-endothelial cells.

Ultrasound will not detect minimal change, fat or fibrosis. However, in more advanced disease, the liver is diffusely abnormal and the changes correlate with those seen on liver biopsy.

CT and MRI scanning are very useful in demonstrating fatty liver (see fig. 22.16), irregular liver surface, splenomegaly, portal collateral circulation, ascites and pancreatitis. It may show alcoholic pseudo-tumour (fig. 22.14).

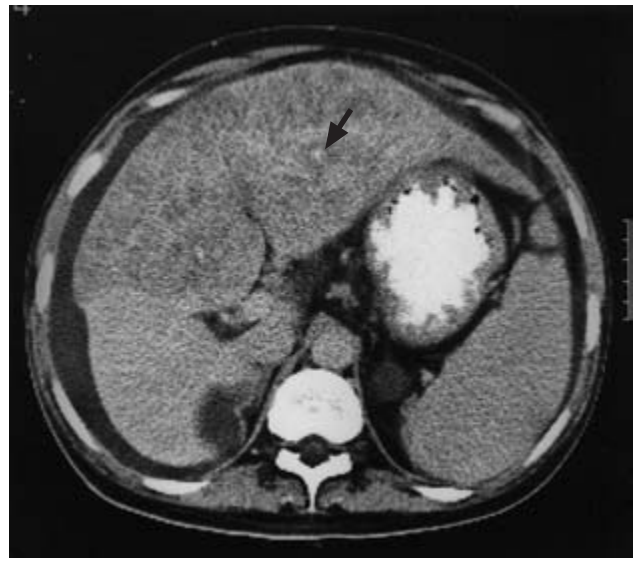


Fig. 22.14. Alcoholic pseudo-tumour. A mass was felt in the upper abdomen and a liver tumour was suspected. This CT scan (enhanced oral contrast) shows features suggestive of hepato-cellular carcinoma (arrowed). Directed needle biopsy showed only acute alcoholic hepatitis. This is a rare type of alcoholic hepatitis, affecting particularly one part of the liver.

Clinical syndromes

Fatty liver

The patients are usually asymptomatic, the diagnosis being made when an enlarged, smooth, firm liver is discovered. Liver function tests may be normal or the transaminases and alkaline phosphatase slightly increased. If the alcoholic fatty liver is sufficiently severe to merit admission to hospital the patient has usually been drinking heavily for some time and is anorexic. There may be nausea and vomiting with peri-umbilical, epigastric or right upper quadrant pain. Clinically, the fatty liver patient cannot be separated from one with mild alcoholic hepatitis. Needle liver biopsy is essential to diagnose alcoholic hepatitis.

Acute alcoholic hepatitis

In the very mildest case, the diagnosis may be made only by a liver biopsy in an asymptomatic patient who is misusing alcohol and has shown abnormal serum enzyme tests and macrocytosis.

Patients in the next category complain only of fatigue, anorexia and weight loss. There is tender hepatomegaly and usually pyrexia. The patient may be obese, but some features of malnutrition are present in 90% of patients.

In the more severe case, the patient has usually been drinking particularly heavily and not eating. The severe hepatic decompensation may be precipitated by vomiting, diarrhoea, an intercurrent infection or prolonged anorexia.

Intake of quite modest doses of paracetamol may precipitate the alcoholic into severe hepatitis (fig. 22.15). Transaminase levels are enormous [89].

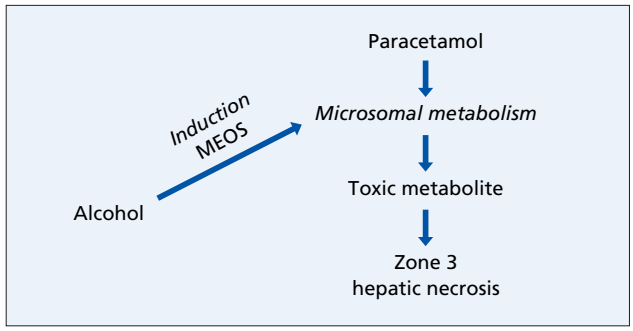


Fig. 22.15. Alcohol, by inducing microsomal metabolism, enhances the effects of toxic metabolites of drugs such as paracetamol (acetaminophen) on the liver.

Severe alcoholic hepatitis is marked by pyrexia, anorexia, jaundice and repeated vomiting. The patient may experience pain over a very enlarged tender liver. In about half, an arterial murmur may be heard over the liver. Florid vascular spiders are usual. There may be signs of liver failure such as ascites, encephalopathy and a bleeding diathesis. The blood pressure is usually low with a hyperdynamic circulation. Signs of vitamin deficiencies, such as beri beri or scurvy, are usual in the malnourished.

Diarrhoea with steatorrhoea can be related to decreased biliary excretion of bile salts, to pancreatic insufficiency and to a direct, toxic effect of alcohol on the intestinal mucosa.

Patients with acute fatty liver may die suddenly in shock, attributable to pulmonary fat emboli. Sudden deaths have also been reported in hypoglycaemia.

Gastrointestinal haemorrhage is frequently from a local gastric or duodenal lesion, rather than related to portal hypertension.

Acute alcoholic hepatitis may be confused with acute viral hepatitis. Helpful diagnostic points are the history, the florid vascular spiders, the very large liver and the leucocytosis.

Laboratory tests

Serum transaminases are increased, but rarely to greater than 300 iu/l. Very high values suggest complicating ingestion of paracetamol (fig. 22.15). The AST : ALT ratio exceeds 2. Serum alkaline phosphatase is usually increased.

The severity is best correlated with the serum bilirubin level and prothrombin time after vitamin K administration [49]. Serum IgA is markedly increased with IgG and IgM raised to a much lesser extent, and serum IgG falls with improvement. The serum albumin level is decreased, increasing as the patient improves. Serum cholesterol levels are usually increased.

The serum potassium value is low, largely due to the low dietary protein intake, diarrhoea and secondary hyperaldosteronism if fluid retention is present. Albumin-bound serum zinc is decreased, and this is related to a low liver zinc concentration, not found in patients with non-alcoholic liver disease. The blood urea and creatinine values increase and these reflect severity. They predict the development of the hepato-renal syndrome.

A polymorph leucocytosis of about $15–20\times10^9$/l is in proportion to severity.

Platelet function is depressed even in the absence of thrombocytopenia or of alcohol in the blood.

Hepatic cirrhosis

Established cirrhosis can present without a stage of acute alcoholic hepatitis having been recognized clinically or histologically, and the picture can resemble any end-stage liver disease. Points suggesting an alcoholic aetiology include the history of alcohol abuse (which may be forgotten), the hepatomegaly and the associated features of alcoholism. Splenomegaly is a late feature.

Liver biopsy findings supporting an alcoholic aetiology include a micronodular cirrhosis, peri-venular sclerosis and paucity of hepatic veins. It may be impossible on histological grounds to determine an alcoholic cause.

Cholestatic syndromes

Occasionally, the patient presents with deep jaundice, hepatomegaly and an increase in serum alkaline phosphatase, transaminases, triglycerides and cholesterol [84]. Functional renal failure is usual. This is usually the first episode of decompensation.

Liver biopsy shows massive accumulation of microvesicular fat (see fig. 22.6) with zone 3 cholestasis. Inflammation is inconspicuous and there is little or no hyaline [57]. Electron microscopy shows extensive disorganization of the organelles in affected hepatocytes. The condition has been termed *alcoholic foamy degeneration* [84]. Prognosis is very variable and foamy degeneration can be found in the asymptomatic.

Cholestasis may also be due to compression of the intra-pancreatic portion of the common bile duct by chronic pancreatitis (fig. 22.16). ERCP confirms the diagnosis (fig. 22.17).

Relationship to hepatitis B and C

Markers of past or current hepatitis B or C are commoner in patients with alcoholic disease than in the general population. It may be difficult to distinguish the viral from the alcoholic aetiology. The identification of risk factors is helpful. The effect of abstinence in the alcoholic

is a fall in transaminases but in the viral patient these continue their fluctuating course. Liver biopsy appearances may be helpful although there may be considerable difficulty in interpretation. Serological HBsAg may be absent and serum hepatitis B virus DNA testing may be necessary to diagnose hepatitis B infection [88]. Positive second-generation ELISA tests usually correlate with a positive hepatitis C virus RNA and allow diagno-

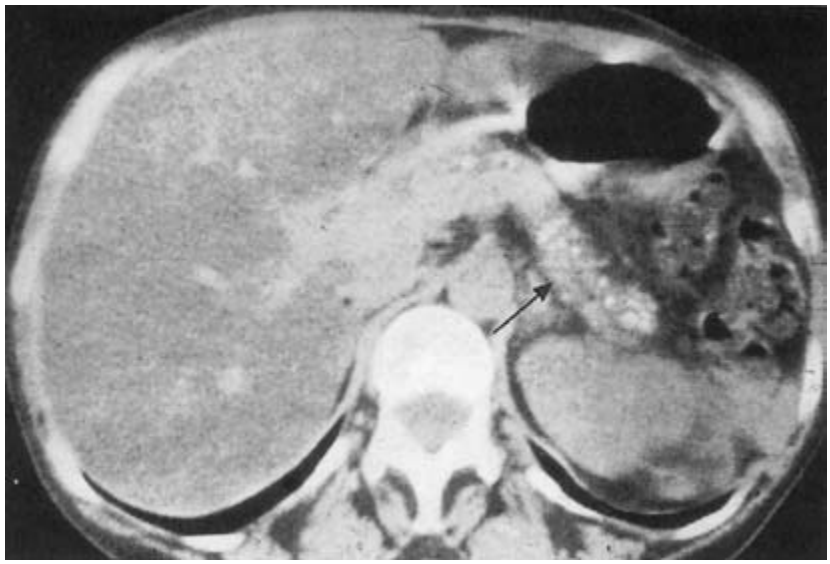


Fig. 22.16. CT scan showing an enlarged fatty liver with a chronic calcific pancreatitis (arrowed).

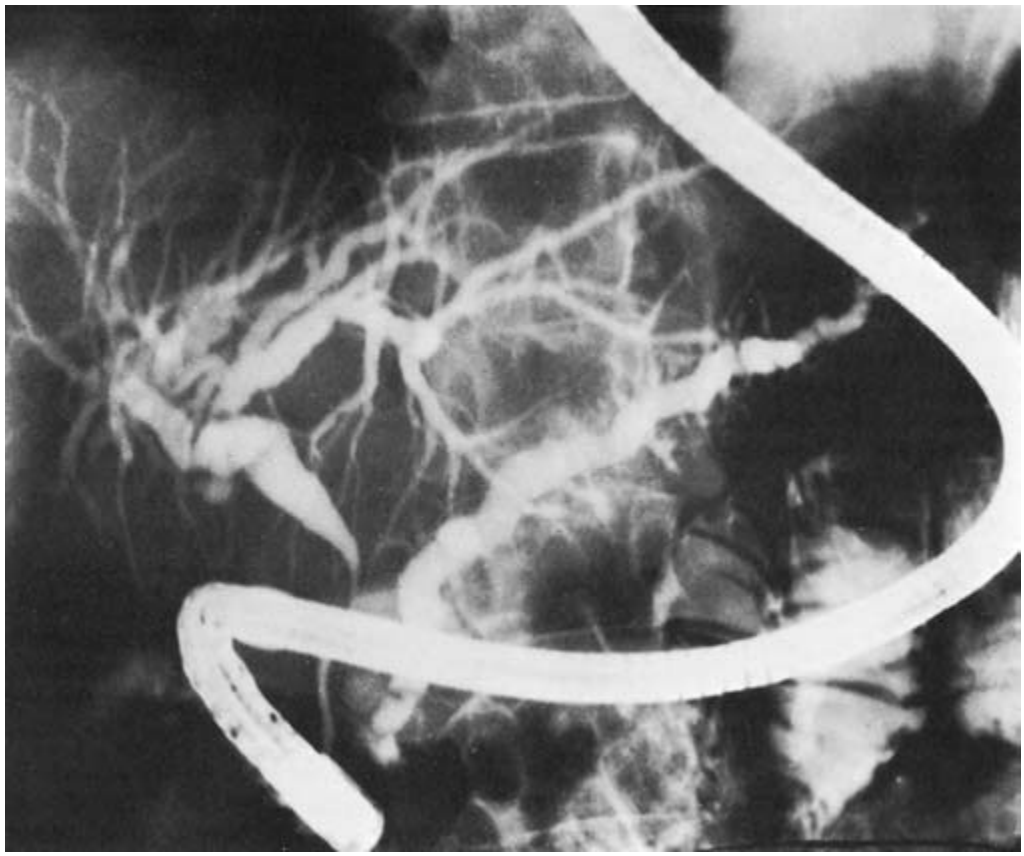


Fig. 22.17. ERCP in an alcoholic patient with chronic pancreatitis and cholestasis. It shows dilatation and irregularity of the pancreatic duct and smooth constriction of the common bile duct as it passes behind the inflamed pancreas.

sis of complicating hepatitis C disease [25]. Alcohol aggravates liver damage due to hepatitis C virus [25]. Viraemia increases and the natural history is adversely affected [20, 31]. The relative risk of developing cirrhosis is increased.

Antiviral therapy should not be given to those who continue to drink. Hepatitis C virus quasi-species complexity in alcoholic patients may help explain poor interferon responsiveness [78].

Hepato-cellular cancer

This may develop particularly after abstinence when nodular regeneration increases. The presence of hepatitis C virus or hepatitis B virus is a major risk factor to the development of hepato-cellular cancer [22, 87].

Associated features

Bilaterally enlarged parotids may be analogous to those seen with other types of malnutrition. Gynaecomastia often appears after treatment and is a frequent complication of spironolactone therapy. The testes atrophy and sexual performance in men declines. Muscle mass wastes.

Dupuytren's contracture of the palmar fascia is related to the alcoholism and not to the cirrhosis [11].

Loss of memory and concentration, insomnia, irritability, hallucinations, convulsions, 'rum-fits' and tremor may be the signs of alcoholism. These must be distinguished from early hepatic encephalopathy.

Hepato-renal syndrome seems particularly common in alcoholics.

Serum IgA is increased and this is probably related to local stimulation of the secretory immune system [85].

Renal glomerular abnormalities, in particular mesangial expansion are related to immune complex deposition [7]. These contain IgA, Mallory body antigen and complement.

Impaired renal acidification may be a sign of liver cell failure [66].

Prognosis

The outlook in alcoholics is much better than for other forms of cirrhosis. It depends on the ability to abstain which in turn is related to family support, financial resources and socioeconomic state. Working-class, 'skid-row' alcoholics have a life expectancy of 33 months, compared with patients with decompensated cirrhosis from a high socioeconomic class who have a 5-year survival of 50% [70]. In this study, if they persisted in alcoholism, this fell to 40%, whereas if they abstained, it was 60%. Very similar figures come from the UK (fig. 22.18) [12].

Women with alcoholic cirrhosis survive a shorter time than men (fig. 22.19). Liver biopsy is the best indicator of prognosis. Zone 3 fibrosis, peri-venular sclerosis and alcoholic hepatitis are very unfavourable [86]. At present, these lesions can only be detected by liver biopsy.

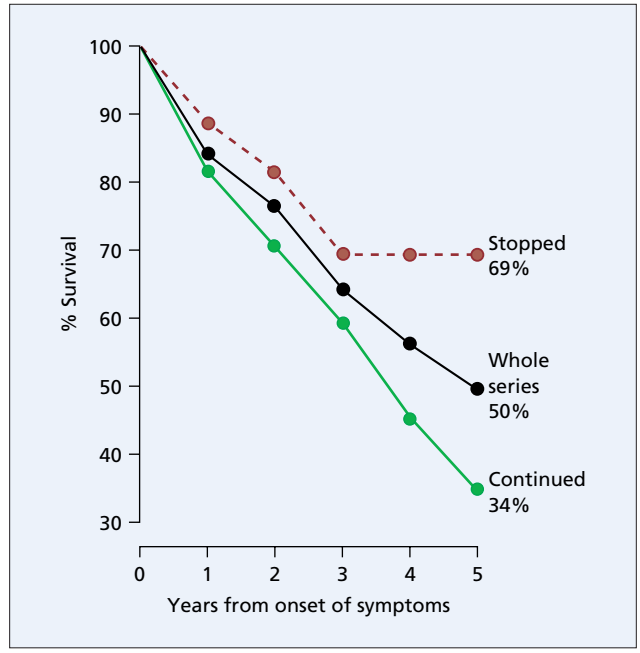


Fig. 22.18. The probability of survival of patients with established alcoholic liver disease: 50% survived 5 years; 69% of those who abstained from alcohol were alive at 5 years, but only 34% of those who continued to imbibe [12].

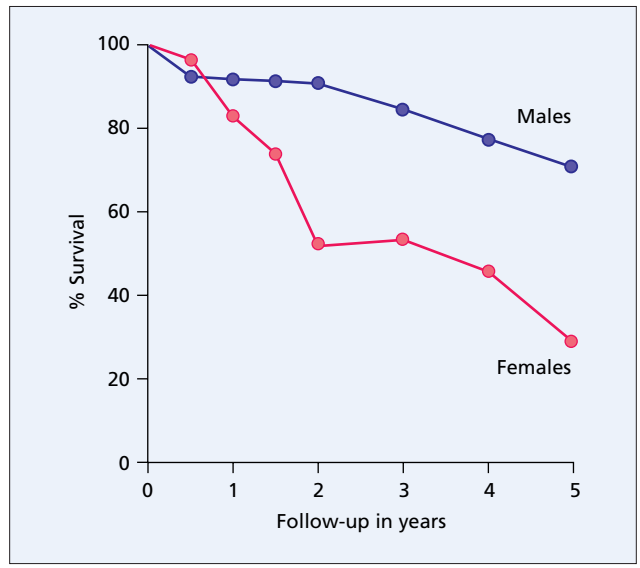


Fig. 22.19. The percentage survival of males and females with alcoholic cirrhosis.

Histological cholestasis is a bad prognostic indicator in alcoholic hepatitis [60].

In one study, 50% of patients with alcoholic hepatitis developed cirrhosis after 10–13 years [80]. In another study 23% of patients without cirrhosis developed cirrhosis after an average of 8.1 years [50].

'Pure' fatty liver can be serious. In a study of 86 patients followed for 10.5 years, nine developed cirrhosis and another seven developed fibrosis. Micro- and macrovesicular fat, giant mitochondria and continued alcoholism predicted these serious developments [83].

Features with independent but bad prognostic significance are encephalopathy, low serum albumin, increased prothrombin time, low haemoglobin level and large oesophageal varices [29]. Patients with pre-coma, persistent jaundice and azotaemia are very liable to develop the hepato-renal syndrome.

The patient with decompensated disease improves slowly. Overt jaundice and ascites after 3 months carry a grave prognosis. In the very late, irreversible stage, abstinence cannot be expected to affect the prognosis. The damage has been done and there is no turning back. The highest mortality for patients with either cirrhosis or alcoholic hepatitis or both is in the first year of follow-up [62].

Patients with acute alcoholic hepatitis often deteriorate during the first few weeks in hospital. It may take 1–6 months for resolution, and 20–50% die. Those with a markedly prolonged prothrombin time, unresponsive to intramuscular vitamin K, and with a serum bilirubin level greater than 20 mg, have a particularly bad outlook [49]. Alcoholic hepatitis is slow to resolve even in those who abstain.

In a multi-centre Veterans Hospital study, predictors of survival were age, grams of alcohol consumed, AST: ALT ratio and the histological and clinical severity of disease [17]. Those with poor nutrition, particularly if they had been starving, were liable to die [53].

Prothrombin time and bilirubin can be used to determine a *discriminant function* to estimate prognosis in alcoholic hepatitis (fig. 22.20) [13].

Computer neural networks which can include prothrombin time, bilirubin and encephalopathy have a high prognostic accuracy for mortality in severe alcoholic liver disease [41].

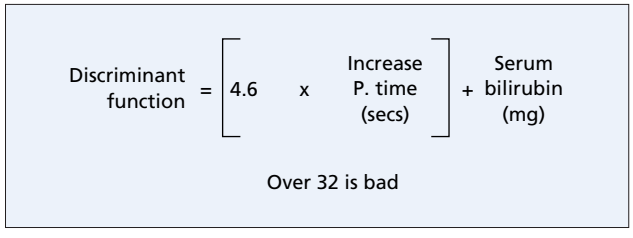


Fig. 22.20. Discriminant function for prognosis in alcoholic hepatitis [13]. P, prothrombin. Serium bilirubin in µmol/l is divided by 17.1 to convert to mg/dl.

Treatment

The most important measure is to ensure total and immediate abstinence from alcohol. Patients with severe physical ailments are more likely to abstain than those who present with psychological problems. In a long-term follow-up of men attending a liver clinic, severe medical illness was critical in the decision to stop drinking [67]. Continued medical care is also essential. Follow-up of patients with alcoholic liver disease treated at the Royal Free Hospital between 1975 and 1990 showed 50% remained abstinent, 25% took alcohol but were not abusing it and 25% continued alcohol abuse regardless of therapy. The less severely affected can receive *'brief interventional counselling'* from a doctor, nurse or similar person. This results in a 38% treatment benefit albeit often temporary [10]. The more severely affected will need psychiatric referral.

The development of a withdrawal syndrome (*delirium tremens*) should be anticipated by the administration of chlordiazepoxide.

Striking improvement following abstinence and nutritional support is virtually diagnostic of previous alcoholism.

During 'drying out' or recovery from hepatic decompensation, dietary protein should increase to 1 g/kg body weight, as soon as possible. Supplements of potassium chloride, together with magnesium and zinc, are given. Vitamins, especially the B complex, C and K are given in large doses, if necessary intravenously.

Alcoholics should be advised to abstain completely. Nutritional support is essential with 1.2–1.5 g protein/kg body weight [48, 61]. Intake should increase with intercurrent illness. Modest vitamin supplements are advised [77].

Acute alcoholic hepatitis

Ascites is treated cautiously as the hepato-renal syndrome is a likely development (table 22.8).

Table 22.8. Treatment of acute alcoholic hepatitis

Stop alcohol
Investigate precipitant (infections, bleeding, etc.)
Anticipate acute alcohol withdrawal
Intramuscular multivitamins
Treat ascites and encephalopathy
Potassium and zinc supplements
Maintain nitrogen intake—oral or enteral
Consider corticosteroids in severe disease with encephalopathy, without gastrointestinal bleeding

Corticosteroids reduce cytokine production and acetaldehyde adduct formation. Results have been extremely conflicting. Seven clinical trials in mild or moderately ill patients showed no effect on clinical recovery, biochemical tests or rate of histological progression. However, more favourable results were reported from a randomized, multi-centre trial [13]. Patients were included with either spontaneous hepatic encephalopathy or a discriminant function value exceeding 32 (see fig. 22.20). Methyl-prednisolone (30 mg daily) or placebo was given within 7 days of admission and continued for 28 days when it was tapered over 2 weeks and discontinued. The mortality rate was 35% of 31 patients receiving placebo, compared with 6% of 35 patients given prednisolone ($P = 0.006$). Prednisolone seemed particularly valuable in those with encephalopathy. The fall in serum bilirubin and prothrombin time was greater in the treated group.

A randomized trial [73] and meta-analysis of all trials [36] confirmed initial survival benefit. These positive results are difficult to reconcile with previous negative ones. The numbers may have been too small in the earlier trials and a type 1 error is possible, the control and treated patients not being comparable. The patients may have been less sick, and at risk of death in the later trials. It is now recommended that corticosteroids should be given to those with encephalopathy, but without bleeding, systemic infections or renal failure. Discriminant function values should exceed 32. Only about 25% of hospitalized patients will fulfil all the above criteria. The mortality remains 44% even in those receiving corticosteroids.

Testosterone is of little benefit.

Oxandrolone (an anabolic steroid) is useful in those with moderate disease, but has no effect in those with severe malnutrition and inadequate calorie intake [53].

Protein malnutrition must be corrected. Nutrition is particularly important during the first few days. Most patients can take adequate, natural protein by mouth. An improvement may follow the use of casein-based naso-duodenal tube feeding supplements (1.5 g protein/kg body weight/day) [39]. Oral or intravenous amino acid supplementation should be reserved for the very few jaundiced and severely malnourished patients [48].

Colchicine has failed to improve short-time survival in patients with alcoholic hepatitis [1].

Propylthiouracil. Alcohol induces a hypermetabolic state which potentiates zone 3 anoxic liver injury. This is reduced by propylthiouracil in experimental animals. A long-term beneficial effect has been shown in patients with alcoholic cirrhosis who continue to drink, but at lower levels [63]. This therapy has never gained general acceptance.

S-adenosyl-methionine (*SAME*) in less advanced disease and phosphatidyl choline [43] have shown benefit in animal disease but cannot be recommended for clinical use at the present time.

Cirrhosis

Cirrhosis is irreversible and therapy has to be directed at the complications. These include portal hypertension, encephalopathy and ascites. Drug metabolism is impaired and particular care must be taken, especially with sedatives. Diazepam seems to be the safest.

Oral supplementation with a purified soya bean, polyunsaturated, lecithin extract containing 94–98% phosphatidyl choline prevents the development of septal fibrosis and cirrhosis in baboons fed alcohol long term [43]. The mechanism is unknown, but is possibly by stimulating lipocyte collagenase.

Porta-caval shunting, including TIPS, is associated with a reduction of bleeding from varices but a 30% incidence of hepatic encephalopathy and only a marginal increase in survival. Results with the selective splenorenal shunt are less good in alcoholic than in non-alcoholic patients. In general, alcoholics are not good candidates for any surgical procedure, especially if they continue to imbibe.

Hepatic transplantation

Alcoholic liver disease now accounts for 20% of all indications for liver transplant in the USA [5]. Early results are similar to those for other forms of cirrhosis. Initial graft and patient survival is similar to that found in other transplant recipients. The 5-year survival is increased, the benefit being greatest in those with severe disease [71]. After the first 2 years, survival curves decline more rapidly in the alcoholic compared with the non-alcoholic recipient [82]. This could be related to a greater reluctance to re-transplant alcoholics. After the operation, quality of life and return to work are similar.

The selection for transplant is difficult (table 22.9). The cirrhosis is self-inflicted. The patient may return to alcoholism and compliance with immunosuppression may be poor. Should alcoholics compete with other patients when donor livers are in short supply [8]? Those selected should have a stable psychiatric and socioeconomic

Table 22.9. Selection of patients with alcoholic liver disease for liver transplantation

Abstinent for 6 months
Child's grade C
Socioeconomically stable
Job to return to after operation
No extra-hepatic organ alcoholic damage

Table 22.10. Liver biopsy follow-up 177–711 days post-transplant of 330 patients having a liver transplant for alcoholic liver disease; 23 definitely resumed alcohol abuse [4]

Definitely resumed alcohol	23
alcoholic hepatitis	22
cirrhosis	4

background and a job to return to after the transplant. Alcohol counselling before and after the operation should include family participation. Alcohol-related disease such as pancreatitis, cardiomyopathy or cerebral atrophy should be assessed.

Six months' abstinence from alcohol is usually demanded and is the most important predictor of post-transfusion recidivism [64]. Nevertheless, the 6 months may be adjusted on an individual basis and is not always predictive of relapse [26].

A conference held at the National Institutes of Health in 1996 concluded that a third to a half of transplant recipients would return to some form of drinking, but this was minimal for most patients [34]. However, 10–20% would drink excessively within the first 5 years, although this rarely led to significant liver disease. Recidivism increases with time [9, 45]. Relapse which is not serious or which does not effect compliance with the immuno-suppresive regime justifies transplant [65]. Patients returning to serious alcohol abuse can develop liver biopsy evidence of alcoholic hepatitis and cirrhosis within 6 months to 2 years (table 22.10) [4].

More long-term (5–10 years) studies post-transplant are needed with better methods of documenting relapse to alcohol use and the factors which lead to this relapse [34].

Selection is all important [46]. Patients rejected because they are too well need continued surveillance as their condition can deteriorate. Those omitted because they are too sick or psychiatrically unsuitable, have a significantly lower survival than those transplanted.

Hepatic transplantation for alcoholic hepatitis is even more difficult to justify than for end-stage alcoholic cirrhosis in a patient with a proven record of compliance. It should not be performed until we have reliable techniques to predict relapse. Well-designed controlled trials must be performed [55].

References

1 Akriviadis EA, Steindel H, Pinto PC *et al*. Failure of colchicine to improve short-term survival in patients with alcoholic hepatitis. *Gastroenterology* 1990; **99**: 811.

2 Alcolado R, Arthur MJP, Iredale JP. Pathogenesis of liver fibrosis. *Clin. Sci.* 1997; **92**: 103.

3 Angeli P, Gatta A, Caregaro L *et al*. Hypophosphatemia and renal tubular dysfunction in alcoholics: are they related to liver function impairment? *Gastroenterology* 1991; **100**: 502.

4 Baddour N, Demetris AJ, Shah G *et al*. The prevalence, rate of onset and spectrum of histological liver disease in alcohol abusing liver allograft recipients. *Gastroenterology* 1992; **102**: A777.

5 Belle SH, Beringer KC, Detre KM. Liver transplantation for alcoholic liver disease in the United States: 1988 to 1995. *Liver Transpl. Surg*. 1997; **3**: 212.

6 Bell H, Tallaksen C, Sjaheim T *et al*. Serum carbohydrate-deficient transferrin as a marker of alcohol consumption in patients with chronic liver disease. *Alcohol Clin. Exp. Res.* 1993; **17**: 246.

7 Bene MC, De Korwin JD, De Ligny BH *et al*. IgA nephropathy and alcoholic liver disease. A prospective necropsy study. *Am. J. Clin. Path.* 1988; **89**: 769.

8 Benjamin M. Transplantation for alcoholic liver disease: the ethical issues. *Liver Transpl. Surg*. 1997; **3**: 337.

9 Berlakovich GA, Steininger R, Herbst F *et al*. Efficacy of liver transplantation for alcoholic cirrhosis with respect to recidivism and compliance. *Transplantation* 1994; **58**: 560.

10 Bien TH, Miller WR, Tonigan JS. Brief interventions for alcohol problems: a review. *Addiction* 1993; **88**: 315.

11 Bradlow A, Mowat AG. Dupuytren's contracture and alcohol. *Ann. Rheum. Dis.* 1986; **45**: 304.

12 Brunt PW, Kew MC, Scheuer PJ *et al*. Studies in alcoholic liver disease in Britain. I. Clinical and pathological patterns related to natural history. *Gut* 1974; **15**: 52.

13 Carithers RL, Herlong HF, Diehl AM *et al*. Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicentre trial. *Ann. Intern. Med.* 1989; **110**: 685.

14 Casini A, Cunningham M, Rojkind M *et al*. Acetaldehyde increases procollagen type I and fibronectin gene transcription in cultured rat fat-storing cells through a protein synthesis-dependent mechanism. *Hepatology* 1991; **13**: 758.

15 Castillo T, Koop DR, Karmimura S *et al*. Role of cytochrome P-450 2E1 in ethanol-carbon tetrachloride and iron-dependent microsomal lipid peroxidation. *Hepatology* 1992; **16**: 992.

16 Cederbaum AI. Effects of alcohol on hepatic mitochondrial function and DNA. *Gastroenterology* 1999; **117**: 265.

17 Chedid A, Mendenhall CL, Gartside P *et al*. Prognostic factors in alcoholic liver disease. *Am. J. Gastroenterol.* 1991; **86**: 210.

18 Chedid A, Mendenhall CL, Moritz TE *et al*. Cell-mediated hepatic injury in alcoholic liver disease. *Gastroenterology* 1993; **105**: 254.

19 Clot P, Albano E, Eliasson E *et al*. Cytochrome P4502E1 hydroxyethyl radical adducts as the major antigen in autoantibody formation among alcoholics. *Gastroenterology* 1996; **111**: 206.

20 Cromir SL, Jenkins PJ, Bowen DS *et al*. Chronic hepatitis C: effect of alcohol on hepatitic activity and viral titre. *J. Hepatol.* 1996; **25**: 821.

21 Day CP, Bassendine MF. Genetic predisposition to alcoholic liver disease. *Gut* 1992; **33**: 1444.

22 Donato F, Tagger A, Chiesa R *et al*. Hepatitis B and C virus infection, alcohol drinking, and hepatocellular carcinoma: a case–control study in Italy. *Hepatology* 1997; **26**: 579.

23 Edmondson HA, Peters RL, Reynolds TB *et al*. Sclerosing hyaline necrosis of the liver in the chronic alcoholic. A

recognizable clinical syndrome. *Ann. Intern. Med.* 1963; **59**: 646.
24 Fletcher LM, Halliday JW, Powell LW. Interrelationships of alcohol and iron in liver disease with particular reference to the iron-binding proteins, ferritin and transferrin. *J. Gastroenterol. Hepatol.* 1999; **14**: 202.
25 Fong T-L, Kanel GC, Conrad A *et al*. Clinical significance of concomitant hepatitis C infection in patients with alcoholic liver disease. *Hepatology* 1994; **19**: 554.
26 Foster PF, Fabrega F, Karademir S *et al*. Prediction of abstinence from ethanol in alcoholic recipients following liver transplantation. *Hepatology* 1997; **25**: 1469.
27 Fromerty B, Grimbert S, Yensouri A *et al*. Hepatic mitochondrial DNA detection in alcoholics: association with microvesicular steatosis. *Gastroenterology* 1995; **108**: 193.
28 Gluud C, Christoffersen P, Eriksen J *et al*. Influence of ethanol on development of hyperplastic nodules in alcoholic men with micronodular cirrhosis. *Gastroenterology* 1987; **93**: 256.
29 Gluud C, Henriksen JH, Nielsen G. Prognostic indicators in alcoholic cirrhotic men. *Hepatology* 1988; **8**: 222.
30 Goodman ZD, Ishak KG. Occlusive venous lesions in alcoholic liver disease. *Gastroenterology* 1982; **83**: 786.
31 Grellier LFL, Dusheiko GM. The role of hepatitis C virus in alcoholic liver disease. *Alcohol* 1997; **32**: 103.
32 Grove J, Daly AK, Bassendine MF *et al*. Association of a tumour necrosis factor promoter polymorphism with susceptibility to alcoholic steatohepatitis. *Hepatology* 1997; **26**: 143.
33 Hoek JB. Endotoxin and alcoholic liver disease: tolerance and susceptibility. *Hepatology* 1999; **29**: 1602.
34 Hoofnagle JH, Kresina T, Fuller RK *et al*. Liver transplantation for alcoholic liver disease: executive statement and recommendations. Summary of a National Institutes of Health Workshop held December 6–7, 1996, Bethesda, Maryland. *Liver Transpl. Surg.* 1997; **3**: 347.
35 Horn T, Christoffersen P, Henriksen JH. Alcoholic liver injury: defenestration in noncirrhotic livers—a scanning electron microscopic study. *Hepatology* 1987; **7**: 77.
36 Imperiale TF, McCullough AJ. Do corticosteroids reduce mortality from alcoholic hepatitis? A meta-analysis of the randomized trials. *Ann. Intern. Med.* 1990; **113**: 299.
37 Jensen K, Gluud C. The Mallory body: morphological, clinical and experimental studies (part 1 of a literature survey). *Hepatology* 1994; **20**: 1061.
38 Jensen K, Gluud C. The Mallory body: theories on development and pathological significance (part 2 of a literature survey). *Hepatology* 1994; **20**: 1330.
39 Kearns PJ, Young H, Garcia G *et al*. Accelerated improvement of alcoholic liver disease with enteral nutrition. *Gastroenterology* 1992; **102**: 200.
40 Klassen LW, Tuma D, Sorrell MF. Immune mechanisms of alcohol-induced liver disease. *Hepatology* 1995; **22**: 355.
41 Lapuerta P, Rajan S, Bonacini M. Neural networks as predictors of outcomes in alcoholic patients with severe liver disease. *Hepatology* 1997; **25**: 302.
42 Lelbach WK. Cirrhosis in the alcoholic and the relation to the volume of alcohol abuse. *Ann. NY Acad. Sci.* 1975; **252**: 85.
43 Lieber CS. Alcohol and the liver: 1994 update. *Gastroenterology* 1994; **106**: 1085.
44 Lieber CS. Medical disorders of alcoholism. *N. Engl. J. Med.* 1995; **333**: 1058.
45 Lucey MR, Carr K, Beresford TP *et al*. Alcohol use after liver transplantation in alcoholics: a clinical cohort follow-up study. *Hepatology* 1997; **25**: 1223.
46 Lucey MR, Merion RM, Henley KS *et al*. Selection for and outcome of liver transplantation in alcoholic liver disease. *Gastroenterology* 1992; **102**: 1736.
47 Lumeng L, Crabb DW. Genetic aspects and risk factors in alcoholism and alcoholic liver disease. *Gastroenterology* 1994; **107**: 572.
48 McCullough AJ, O'Connor JF. Alcoholic liver disease: proposed recommendations for the American College of Gastroenterology. *Am. J. Gastroenterol.* 1998; **93**: 2022.
49 Maddrey WC, Boitnott JK, Bedine MS *et al*. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology* 1978; **75**: 193.
50 Marbet UA, Bianchi L, Meury U *et al*. Long-term histological evaluation of the natural history and prognostic factors of alcoholic liver disease. *J. Hepatol.* 1987; **4**: 364.
51 Marshall AW, Kingstone D, Boss M *et al*. Ethanol elimination in males and females: relationship to menstrual cycle and body composition. *Hepatology* 1983; **3**: 701.
52 Matsuoka M, Tsukamoto H. Stimulation of hepatic lipocyte collagen production by Kupffer cell-derived transforming growth factor β: implication for a pathogenetic role in alcoholic liver fibrogenesis. *Hepatology* 1990; **11**: 599.
53 Mendenhall CL, Moritz TE, Roselle GA *et al*. A study of oral nutritional support with oxandrolone in malnourished patients with alcoholic liver hepatitis: results of a Department of Veterans Affairs Cooperative Study. *Hepatology* 1993; **17**: 564.
54 Mihas AA, Tavassoli M. Laboratory markers of ethanol intake and abuse: a critical appraisal. *Am. J. Med. Sci.* 1992; **303**: 415.
55 Miller C, Kamean J, Berk PD. Liver transplantation for alcoholic hepatitis? An unanswered question. *Alcohol Clin. Exp. Res.* 1994; **18**: 224.
56 Morgan MY, Sherlock S. Sex-related differences among 100 patients with alcoholic liver disease. *Br. Med. J.* 1977; **i**: 939.
57 Morgan MY, Sherlock S, Scheuer PJ. Acute cholestasis, hepatic failure and fatty liver in the alcoholic. *Scand. J. Gastroenterol.* 1978; **13**: 299.
58 Morgan MY, Sherlock S, Scheuer PJ. Portal fibrosis in the livers of alcoholic patients. *Gut* 1978; **19**: 1015.
59 Niemela O, Risteli J, Blake JE *et al*. Markers of fibrogenesis and basement membrane formation in alcoholic liver disease. Relation to severity, presence of hepatitis, and alcohol intake. *Gastroenterology* 1990; **98**: 1612.
60 Nissenbaum M, Chedid A, Mendenhall C *et al*. Prognostic significance of cholestatic alcoholic hepatitis. *Dig. Dis. Sci.* 1990; **35**: 891.
61 Nompleggi DJ, Bonkovsky HL. Nutritional supplementation in chronic liver disease: an analytical review. *Hepatology* 1994; **19**: 518.
62 Orrego H, Blake JE, Blendis LM *et al*. Prognosis of alcoholic cirrhosis in the presence and absence of alcoholic hepatitis. *Gastroenterology* 1987; **92**: 208.
63 Orrego H, Blake JE, Blendis LM *et al*. Long-term treatment of alcoholic liver disease with propylthiouracil. Part 2: Influence of drop-out rates and of continued alcohol consumption in a clinical trial. *J. Hepatol.* 1994; **20**: 343.
64 Osorio RW, Ascher NL, Avery M *et al*. Predicting recidivism after orthotopic liver transplantation for alcoholic liver disease. *Hepatology* 1994; **20**: 105.

65 Pageaux G-P, Michel J, Coste V *et al*. Alcoholic cirrhosis is a good indication for liver transplantation, even for cases of recidivism. *Gut* 1999; **45**: 421.
66 Pare P, Reynolds TB. Impaired renal acidification in alcoholic liver disease. *Arch. Intern. Med.* 1984; **144**: 941.
67 Patek AJ Jr, Hermos JA. Recovery from alcoholism in cirrhotic patients: a study of 45 cases. *Am. J. Med.* 1981; **70**: 782.
68 Pequignot G, Cyrulnik F. Chronic disease due to overconsumption of alcoholic drinks (excepting neuropsychiatric pathology). In *International Encyclopaedia of Pharmacology and Therapeutics*, vol. II. Pergamon Press, Oxford, 1970, pp. 375–412.
69 Phillips GB, Gabuzda GJ Jr, Davidson CS. Comparative effects of a purified and an adequate diet on the course of fatty cirrhosis in the alcoholic. *J. Clin. Invest.* 1952; **31**: 351.
70 Powell WJ Jr, Klatskin G. Duration of survival in patients with Laennec's cirrhosis. *Am. J. Med.* 1968; **44**: 406.
71 Poynard T, Naveau S, Doffoel M *et al*. Evaluation of efficacy of liver transplantation in alcoholic cirrhosis using matched and simulated controls: 5-year survival. *J. Hepatol.* 1999; **30**: 1130.
72 Prijatmoko D, Strauss PJG, Lambert JR *et al*. Early detection of protein depletion in alcoholic cirrhosis: role of body composition analysis. *Gastroenterology* 1993; **105**: 1839.
73 Ramond M, Poynard T, Rueff B *et al*. A randomized trial of prednisolone in patients with severe alcoholic hepatitis. *N. Engl. J. Med.* 1992; **326**: 507.
74 Reynolds TB, Redeker AG, Kuzma OT. Role of alcohol in pathogenesis of alcoholic cirrhosis. In McIntyre N & Sherlock S, eds. *Therapeutic Agents and the Liver*. Blackwell Scientific Publications, Oxford, 1965, p. 131.
75 Rogers AE, Fox JG, Whitney K *et al*. Acute and chronic effects of ethanol in nonhuman primates. In Hayes KC, ed. *Primates in Nutritional Research*. Academic Press, New York, 1979, p. 249.
76 Savolainen VT, Pajarinen J, Perola M *et al*. Polymorphism in the cytochrome P450 2E1 gene and the risk of alcoholic liver disease. *J. Hepatol.* 1997; **26**: 55.
77 Sherlock S. Alcoholic liver disease. *Lancet* 1995; **345**: 227.
78 Sherman KE, Rouster SD, Mendenhall C *et al*. Hepatitis cRNA quasispecies complexity in patients with alcoholic liver disease. *Hepatology* 1999; **30**: 265.
79 Situnayake RD, Crump BJ, Thurnham DI *et al*. Lipid peroxidation and hepatic antioxidants in alcoholic liver disease. *Gut* 1990; **31**: 1311.
80 Sorensen TIA, Orholm M, Bentsen KD *et al*. Prospective evaluation of alcohol abuse and alcoholic liver injury in men as predictors of development of cirrhosis. *Lancet* 1984; **ii**: 241.
81 Tanaka F, Shiratori Y, Yokosuka O *et al*. High incidence of ADH2*1/ALDH2*1 genes among Japanese alcohol dependents and patients with alcoholic liver disease. *Hepatology* 1996; **23**: 234.
82 Tang H, Boulton R, Gunson B *et al*. Patterns of alcohol consumption after liver transplantation. *Gut* 1998; **43**: 140.
83 Teli MR, Day CP, Burd AD *et al*. Determinants of progression to cirrhosis or fibrosis in pure alcoholic fatty liver. *Lancet* 1995; **346**: 987.
84 Uchida T, Kao H, Quispe-Sjogren M *et al*. Alcoholic foamy degeneration—a pattern of acute alcoholic injury of the liver. *Gastroenterology* 1983; **84**: 683.
85 Van de Weil A, Delacroix DL, van Hattum J *et al*. Characteristics of serum IgA and liver IgA deposits in alcoholic liver disease. *Hepatology* 1987; **7**: 95.
86 Worner TM, Lieber CS. Perivenular fibrosis as precursor lesion of cirrhosis. *JAMA* 1985; **253**: 627.
87 Yamauchi M, Nakahara M, Maezawa Y *et al*. Prevalence of hepatocellular carcinoma in patients with alcoholic cirrhosis and prior exposure to hepatitis C. *Am. J. Gastroenterol.* 1993; **88**: 39.
88 Zignego AL, Forschi M, Laffi G *et al*. 'Inapparent' hepatitis B virus infection and hepatitis C virus replication in alcoholic subjects with and without liver disease. *Hepatology* 1994; **19**: 577.
89 Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. *Hepatology* 1995; **22**: 767.

Chapter 23
Iron Overload States

The causes of iron overload can be broadly separated into those with a clear genetic mechanism, those associated with another pathology, and a small group of intermediate conditions where there appears to be an interplay between genetic and acquired mechanisms (table 23.1). There has been an explosion of information on classical genetic haemochromatosis (previously termed idiopathic or primary) now known to be due to a mutation in the *HFE* gene. These data have added much to the understanding of iron absorption from the intestine, to the identification of patients and family screening, and to the recognition of atypical patients. Inherited non-*HFE*-related iron overload is much less common than *HFE*-related genetic haemochromatosis.

Iron overload as a result of liver or haematological disease is not uncommon and genotyping for *HFE* mutations now allows these to be clearly separated from genetic haemochromatosis.

Normal iron metabolism [6, 9]

Absorption

The normal daily diet contains about 10–20 mg of iron (90% free; 10% bound in haem). Of this 1–1.5 mg is absorbed. This amount depends on body stores; more being absorbed as the need increases. The absorption process, sited in the duodenum and upper small intestine, is active and capable of transporting iron against a gradient.

The mechanism of absorption (fig. 23.1), although not fully understood, has gained much from the discovery of: (a) the *HFE* gene [36]; (b) the divalent metal transporter-1 (DMT-1) [39, 48]; (c) the intra-cellular mechanisms for controlling the expression of transport and storage proteins, in particular iron regulatory proteins (IRPs), which interact with iron responsive elements (IREs) [9]; and (d) the basolateral iron transporter (called IREG-1 or ferroportin) [30, 60].

In the intestinal lumen, ferric iron is reduced to ferrous iron by ferrireductase or ascorbic acid following which the iron is transported by DMT-1 into the enterocytes of the villus. Expression of DMT-1 within these cells is regulated by the level of intra-cellular iron through an interaction between IRP-1 and the IRE of DMT-1. The iron concentration within enterocytes is therefore important in determining the amount of iron absorbed from the intestinal lumen. Current data have raised the possibility that the interaction between the HFE protein and transferrin receptors (TfR) on the basolateral surface of crypt cells plays a role in determining the intra-cellular iron level of enterocytes [9].

Regulation

After the discovery of the *HFE* gene [36], immunohistochemical studies showed particular localization of

Table 23.1. Iron overload states

Inherited	
HFE mutation related	Genetic haemochromatosis
Non-*HFE* related	Juvenile haemochromatosis Autosomal dominant haemochromatosis 'Italian variant' Acaeruloplasminaemia Atransferrinaemia
Acquired	
Haematological disorders	Iron-loading anaemias thalassemia major sideroblastic anaemia chronic haemolytic anaemia Parenteral iron overload
Chronic liver disease	End-stage cirrhosis Hepatitis C Alcoholic liver disease Non-alcoholic steato-hepatitis Porta-caval shunt
Dysmetabolic syndrome	
Dietary iron overload	
Inherited/acquired?	
African iron overload	
Neonatal haemochromatosis	
Associations	
Porphyria cutanea tarda	

the protein to the crypt cells of the upper small intestine [69]. Further studies showed that the HFE protein is expressed on the surface of cells [89] and that it interacts with the TfR, reducing the affinity of the TfR for transferrin [37]. The transferrin/TfR interaction is the major mechanism for uptake of iron into many cells. The expression of TfR is inversely related to intra-cellular iron levels.

The association of HFE with TfR may therefore be important for the normal entry of iron into the crypt cell of the villus and hence the regulation of iron absorption. Binding of HFE to TfR may reduce the affinity of TfR for transferrin, allowing the release of iron into the cell from the endosomal compartment. The model that follows this assumption proposes that in iron deficiency crypt cell iron levels are low and villous cell DMT-1 is upregulated leading to iron absorption, while in iron replete or overloaded states the opposite occurs. This control mechanism would be disrupted in genetic haemochromatosis (see below).

Less is known of the regulation of iron absorption in relationship to haemopoiesis and reticulo-endothelial cell iron. A link is possible since macrophage iron handling has been found to be abnormal in genetic haemochromatosis. Transfection of normal *HFE* into these cells corrects transferrin–iron uptake and retention [65]. Thus whether the HFE-related control of iron absorption resides primarily in the intestinal crypt cell, or secondarily through a change in reticulo-endothelial cell iron metabolism, is unclear. Hepcidin may effect iron absorption [40]. Knock-out mice develop iron overload, but the mechanism is not known.

Basolateral transfer

After transport of iron from the intestinal lumen into the mucosal cell of the villus, the iron enters a cytosolic pool. Some passes to be stored in ferritin, and is then either mobilized as necessary, or is lost with exfoliation of mucosal cells. At the basolateral membrane, IREG-1 (also called ferroportin-1) [30, 60] transports iron from the cell to the circulation. Hephaestin, a ferroxidase, appears to promote the transfer of iron from IREG-1 to transferrin [88].

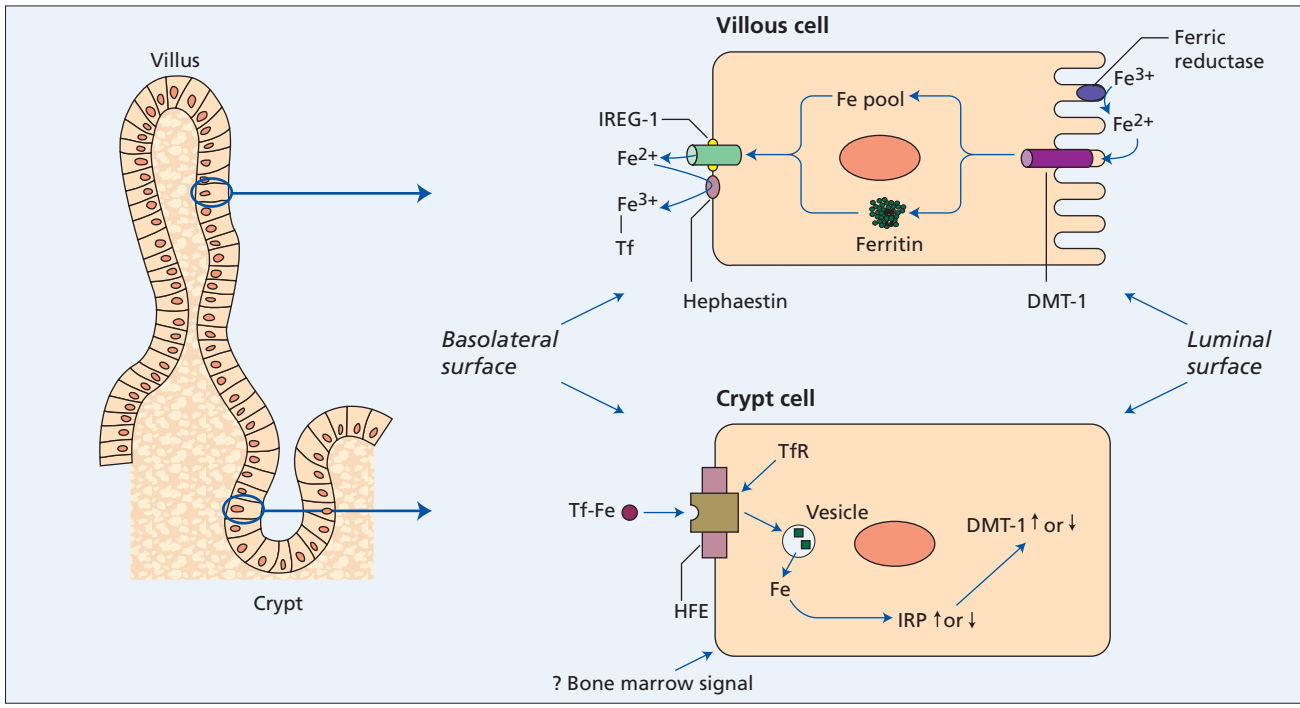


Fig. 23.1. Hypothetical model of regulation of iron absorption. Ferrous iron is transported from the gut lumen into the villous cell by the divalent metal transporter, DMT-1. Iron enters the cellular pool or is stored in ferritin. IREG-1 (ferroportin) transports iron out of the cell across the basolateral surface. Hephaestin converts ferrous to ferric iron which is bound to transferrin (Tf).

Activity of DMT-1 is regulated by intra-cellular iron level. This depends upon entry of iron into the crypt cell. It has been suggested that binding of transferrin receptor (TfR) to HFE protein at the basolateral surface of the crypt cell determines the entry of iron.

In iron deficiency little enters the crypt cell, DMT-1 is upregulated and more iron absorbed. When body stores are normal, DMT-1 is downregulated and iron absorption is reduced. In HFE-related haemochromatosis, it is hypothesized that the C282Y mutation disrupts association between HFE and transferrin receptor, iron does not enter the crypt cell, and DMT-1 is not downregulated as would normally occur with iron overload. Iron absorption continues.

Distribution to tissues

Transferrin (mol. wt 77 000 Da) is a glycoprotein largely synthesized in the liver. It can bind two ferric iron molecules, and is responsible for the 'total iron-binding capacity' of serum of 250–370 μg/dl. This is normally about one-third saturated with iron. Physiological entry of iron into reticulocytes and hepatocytes depends upon transferrin receptors (TfRs) at the cell surface which preferentially bind transferrin-carrying iron. The role of HFE in these tissues is not clear. Receptor/iron complex is internalized and the iron released. This process is saturable. TfRs are downregulated as the cell becomes replete with iron. When serum transferrin is fully saturated, as in overt haemochromatosis, iron circulates in 'non-transferrin-bound' forms, associated with low molecular weight chelators. Iron in this form readily enters cells by a non-saturable process. A stimulator of iron transport (SFT) may also be important for iron uptake when there is iron overload and downregulation of cell surface TfRs [98].

Storage

Iron is stored in cells as ferritin (mol. wt 480 000 Da), the combination of the protein apoferritin (H and L subunits) and iron, which appears under electron microscopy as particles 50 Å in diameter lying free in the cytoplasm. Up to 4500 atoms of iron can be stored within a single ferritin molecule. High concentrations of iron stimulate apoferritin synthesis.

Aggregates of degraded ferritin molecules make up haemosiderin which stains as blue granules with ferrocyanide. Approximately one-third of iron is stored in this form, increasing in iron storage disorders.

Lipofuscin, or wear and tear pigment, accumulates in association with iron overload. It is yellow–brown in colour and does not contain iron.

Iron contained in depots as ferritin or haemosiderin is available for mobilization and haemoglobin formation should the demand arise.

The normal total body content of iron is about 4 g, of which 3 g are present in haemoglobin, myoglobin, catalase and other respiratory pigments or enzymes. Storage iron comprises 0.5 g; of this 0.3 g is in the liver but is not revealed by the usual histological stains for iron. The liver is the predominant site for storage of iron absorbed from the gut. When its capacity is exceeded, iron is deposited in other parenchymal tissues, including the acinar cells of the pancreas, and the cells of the anterior pituitary gland. The reticulo-endothelial system plays only a limited part in iron storage unless the iron is given intravenously, when it becomes the preferential site for deposition. Iron from erythrocyte breakdown is concentrated in the spleen.

Iron overload and liver damage

Fibrosis and hepato-cellular damage are directly related to the iron content of the liver cell [54]. The pattern of damage is similar irrespective of whether the overload is due to genetic haemochromatosis or to multiple transfusions. The severity of fibrosis is maximal in peri-portal areas where iron is particularly deposited.

When iron deposition is low it is stored as ferritin. As the load increases more is present as haemosiderin.

Removal of iron by venesection or chelation leads to clinical and biochemical improvement with reduction or prevention of hepatic fibrosis [13].

There are several processes by which iron can damage the liver. There is enhanced oxidative stress in patients with iron overload and this is associated with increased TGF-β1 expression [53]. Oxidative stress causes lipid peroxidation of membranes of organelles leading to functional defects of lysosomes, mitochondria and microsomes. Mitochondrial cytochrome C oxidase activity is reduced [8]. There is lysosomal membrane fragility and release of hydrolytic enzymes into the cytosol.

Hepatic stellate cells (lipocytes) are activated in genetic haemochromatosis and activation is reversed by iron removal [76]. Stellate cell activation appears related to the release of cytokines and other substances from neighbouring cells rather than oxidant stress within stellate cells [64]. Anti-oxidant treatment protects against hepatic fibrosis in an animal model of iron overload [71]. Although excess iron increases hepatic collagen type I mRNA expression [70], altered matrix degradation also plays a part in the hepatic fibrogenesis due to iron overload (Chapter 21). There are increased levels of tissue inhibitor of metalloproteinase 1 (TIMP-1) and reduced matrix metalloproteinase (MMP) levels [45]. Serum type IV collagen correlates with the degree of hepatic fibrosis due to iron overload [46].

Genetic haemochromatosis

In 1865, Trousseau described the clinical syndrome of skin pigmentation, cirrhosis and diabetes now recognized as characteristic of late stage genetic haemochromatosis. This is an autosomal recessive metabolic disorder in which there is increased iron absorption over many years. The tissues contain enormous quantities of iron, of the order of 20–60 g. If 5 mg of dietary iron were retained by the tissues daily it would take about 28 years for 50 g to accumulate.

Molecular genetics

Sheldon [81] in his classical monograph described idiopathic haemochromatosis as an inborn error of metabolism. The discovery of genetic linkage of

haemochromatosis to the HLA serotype allowed the inheritance to be defined as autosomal recessive, and placed the gene on chromosome 6.

In 1996 a positional cloning approach was successful in identifying the *HFE* gene approximately 6 megabases telomeric to the HLA-A locus on chromosome 6 [36]. Eighty-five per cent of chromosomes from haemochromatosis patients contained a single mutation (C282Y, also designated Cys282Tyr) in the *HFE* gene compared with 3% of control chromosomes. In most populations of northern European origin over 90% of haemochromatosis patients have been found to be homozygous for this mutation [9]. In southern European populations the frequency of C282Y homozygosity is lower (65%) [72]. The high frequency of this mutation in genetic haemochromatosis points to individuals being descended from a single family or community (probably Celtic) in which the mutation initially occurred. The C282Y mutation is not found on African, Asian or Australasian chromosomes [62].

A second mutation described at the time of the discovery of the *HFE* gene (H63D; also known as His63Asp) is common in the normal population. Its role in iron metabolism is unclear (see below).

The frequency of C282Y homozygosity found in population screening studies is 1 in 200–300 [1, 19, 59, 68]. This frequency, however, does not correspond to the frequency of clinical haemochromatosis recognized [94, 95]. The explanation is not clear. Studies suggest that between 20 and 80% of patients homozygous for C282Y show evidence of increased iron stores (phenotypic penetrance) but studies of disease penetrance are awaited.

Individuals heterozygous for the C282Y mutation have not been found to be at risk of significant iron overload. However, individuals have been reported with iron overload in the range previously considered to represent true genetic haemochromatosis who are heterozygous for C282Y. The explanation is unclear. Environmental factors such as alcohol may play a role or there may be additional rare mutations in the HFE gene [24, 90].

The contribution of the H63D mutation to iron overload is unclear and the effect, if any, appears to have a low penetrance. Focus has mainly been on compound heterozygotes (C282Y/H63D) where it has been estimated that approximately 1.5% will develop significant iron overload [9, 58].

Biology and function of HFE *protein*

The hypothetical model protein based on homology with MHC molecules shows three α-domains, one of which binds to β_2-microglobulin (fig. 23.2). The C282Y mutation disrupts the disulphide bridge in the α_3-domain preventing association with β_2-microglobulin and the cell surface expression of HFE in cell culture [89]. The normal HFE protein complexes with the TfR [11] lowering the affinity of TfR for transferrin [37]. HFE/TfR binding is tight at the pH at the cell surface but not at pH6, suggesting that HFE may dissociate from TfR in acidified endosomes [56].

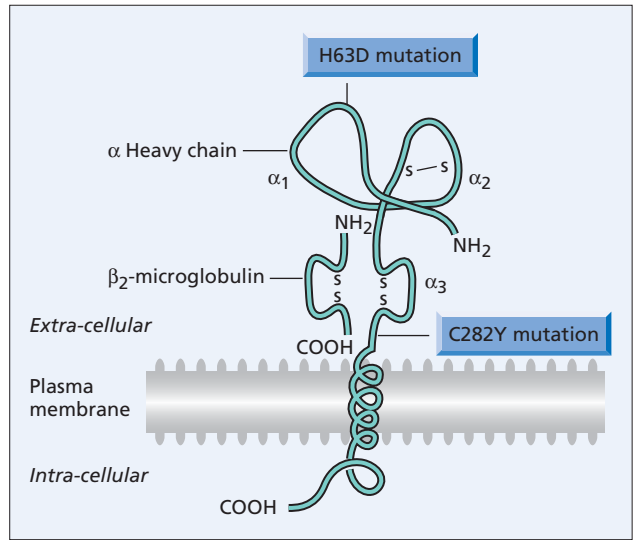


Fig. 23.2. Hypothetical model of the *HFE* protein based on homology with MHC molecules. The extra-cellular component has three α-domains, one of which binds to β_2-microglobulin, a membrane spanning region and a short cytoplasmic tail. The C282Y mutation disrupts the disulphide bond in the α_3-domain through the substitution of tyrosine for cysteine. The H63D mutation is in the α_1-domains. (Modified from [36] with permission.)

Genetic haemochromatosis occurs because of excess iron absorption despite replete or increased body iron stores. The C282Y mutation disrupts the normal biological activity of HFE protein. The mechanism by which this interferes with normal regulation of iron absorption remains hypothetical (fig. 23.1). It may reduce crypt cell iron levels, and thus DMT-1 expression [9].

The previous finding of a failure to downregulate duodenal TfRs [57] and recent data showing increased expression of DMT-1 in the duodenum in patients with genetic haemochromatosis [99] is consistent with this hypothesis.

Heterozygotes

The frequency of heterozygosity for the C282Y mutation in populations of northern European origin is approximately 10%. Although heterozygotes have mean serum iron and transferrin saturation values higher than normal subjects, significant iron overload is extremely rare [18]. However, since these individuals may have

slight increases in intra-cellular iron it has been questioned whether this would enhance damage from other diseases. Hepatic fibrosis/cirrhosis due to hepatitis C or alcohol, however has not been found to be worsened by heterozygosity for C282Y [47, 91]. An increased risk of cardiovascular disease has been reported [78, 85], but this finding awaits further study.

Pathology

A fibrous tissue reaction is found wherever the iron is deposited.

The *liver* in the early stages may show only portal zone fibrosis with deposition of iron in the peri-portal liver cells and, to a lesser extent, in the Kupffer cells. Fibrous septa then surround groups of lobules and irregularly shaped nodules (*holly leaf* appearance). There is partial preservation of the architecture, although ultimately a macronodular cirrhosis develops (fig. 23.3). Fatty change is unusual and the glycogen content of the liver cells is normal.

Cirrhotic patients with iron-free foci have a higher risk of developing hepato-cellular carcinoma [27].

The *pancreas* shows fibrosis and parenchymal degeneration with iron deposition in acinar cells, macrophages, islets of Langerhans and fibrous tissue.

Heart muscle is heavily involved, muscle fibres being replaced by a mass of iron pigment within the sheath. Degeneration of the fibres is rare.

Spleen, bone marrow and duodenal epithelium do not show the iron overload seen elsewhere. *Brain* and *nervous tissue* are also usually free of iron.

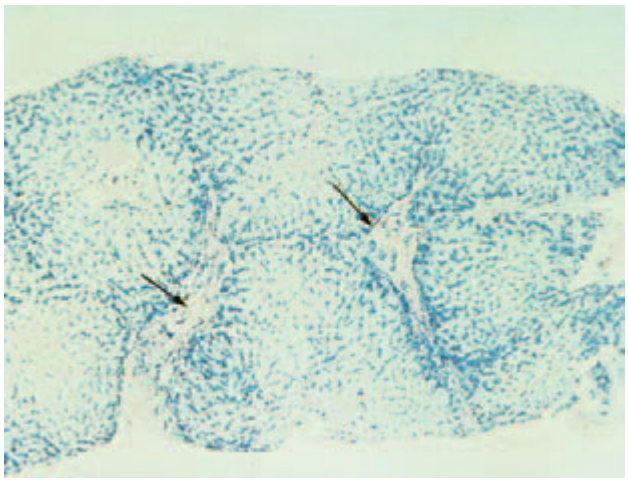


Fig. 23.3. The liver in genetic haemochromatosis. Cirrhosis is seen and hepatocytes are filled with blue-staining iron pigment. Fibrous tissue is also infiltrated with iron. The arrows indicate portal tracts. (Perls' strain, ×13.)

Epidermal atrophy may reduce the *skin* to a flattened sheet. Hair follicles and sebaceous glands are inconspicuous. Characteristically the melanin content of the basal layer is increased. Iron is usually absent from the epidermis but can often be seen deeper, especially in the basal layer.

Endocrine glands, including adrenal cortex, anterior lobe of pituitary, and thyroid show varying amounts of iron and fibrosis.

The testes are small and soft with atrophy of the germinal epithelium without iron overload. There is interstitial fibrosis and iron is found in the walls of capillaries.

Relation to alcoholism

In an experimental model of alcoholic liver disease, the addition of iron to the diet results in cirrhosis [84]. In patients, the combination of haemochromatosis and excess alcohol intake results in more advanced liver disease [2]. Hepatic iron deposition is recognized in alcoholic liver disease (as well as other end-stage liver disease) and may be due to increased intestinal iron absorption in chronic alcohol abusers [23, 31]. Increased hepatic iron is associated with worse liver pathology [43] but does not seem related to the C282Y mutation in HFE [47].

Clinical features

The classical picture is of a lethargic, middle-aged man with pigmentation, hepatomegaly, diminished sexual activity, loss of body hair and arthralgia; diabetes is common.

Diagnosis depends on a high degree of suspicion and should be considered in any patient with symptomless hepatomegaly and virtually normal biochemical tests of liver function. In view of the homozygote frequency found in the community, the condition must be considerably more frequent than is recognized. There is a mean delay of 5–8 years between presentation and diagnosis [4].

Overt haemochromatosis is 10 times more frequent in males than females [81]. Women are spared by iron loss with menstruation and pregnancy. Female patients with haemochromatosis usually, but not always, have absent or scanty menstruation, have had a hysterectomy or are many years post-menopausal.

Haemochromatosis is rarely diagnosed before the age of 20, and the peak incidence is between 40 and 60 years.

The grey-slaty pigmentation is maximal in the axillae, groins, genitalia, old scars and exposed parts. It can occur in the mouth. The colour, due to increased melanin in the basal layer, appears through the atrophied, superficial epidermis. The skin is shiny, thin and dry.

Hepatic changes

The liver is enlarged and firm. Abdominal pain, usually a dull ache with hepatic tenderness, is noted in 56% of cases [67]. The pain may be so severe that an acute abdominal emergency is simulated.

Signs of hepato-cellular failure are usually absent and ascites rare. The spleen is palpable but rarely large. Bleeding from oesophageal varices is unusual.

Primary liver cancer develops in 15–30% of cirrhotic patients [28, 67]. It may be the mode of presentation, particularly in the elderly. It should be suspected if the patient shows clinical deterioration with rapid liver enlargement, abdominal pain and ascites. Serum α-fetoprotein may be increased.

Endocrine changes

At diagnosis about 70% of cirrhotic patients, but only 17% of non-cirrhotics, have clinical diabetes [67]. This may be complicated by nephropathy, neuropathy, peripheral vascular disease and proliferative retinopathy. The diabetes may be easy to control or may be resistant to large doses of insulin. It could be related to a family history of diabetes, to cirrhosis of the liver which impairs glucose tolerance, or to direct damage to the pancreas by iron deposition.

Loss of libido or potency occurs in approximately 35% of patients and amenorrhoea in 15% of women [67]. Hypogonadism may be due to hypothalamic, pituitary or gonadal dysfunction or a combination of all three [86].

Pituitary function is impaired to a variable extent in about two-thirds of patients. This is related to iron deposition in the anterior pituitary. Gonadotrophin-producing cells are selectively affected. Hypogonadotrophic testicular failure is shown by impotence, loss of libido, testicular atrophy, skin atrophy and loss of secondary sexual hair. Plasma testosterone levels are subnormal. Testosterone levels increase following administration of gonadotrophins suggesting that the testes are capable of responding.

Osteoporosis is seen particularly when hypogonadism is present [29].

Pan-hypopituitarism with hypothyroidism and adrenal cortico-deficiency are rarer.

Cardiac changes

Changes on ECG are reported in 35% of patients presenting with haemochromatosis [67]. Echocardiographic abnormalities are also seen, are related to the degree of iron overload and improve with venesection [22]. Presentation with heart failure, particularly in younger subjects, is seen but is unusual. The picture is of progressive right-sided heart failure sometimes with sudden death. The 'iron heart' is a weak one. Dysrhythmias are also seen.

Cardiac complications are presumably related to iron deposits in the myocardium and conducting system.

Arthropathy

In about two-thirds of patients a specific arthropathy starts in the metacarpophalangeal joints (fig. 23.4). Wrists and hips may also be affected [33]. It may be a presenting feature. Radiologically there is a hypertrophic osteoarthritis [7]. Chondrocalcinosis is seen in the menisci and articular cartilage (fig. 23.5). It is related to an acute crystal synovitis with calcium pyrophosphate.

Arthralgia is often the most difficult long-term clinical problem as it is resistant to conventional anti-inflammatory agents. It is present in 45% of patients at diagnosis. After depletion of body iron, 30% improve but in 20% symptoms worsen [67].

Special investigations

Biochemical liver tests show surprisingly little disturbance. Later the changes are those of cirrhosis.

The *serum iron* is raised to about 220 μg/dl compared with the normal of about 125 μg/dl. The *serum transferrin* is about 90% saturated compared with 30% in the normal.

Serum ferritin

Ferritin is the major cellular iron storage protein. The form present in normal serum contains little iron. Its function there is uncertain. The serum concentration is proportional to body iron stores (fig. 23.6). It is of value in assessing body iron stores [74, 75], but can be unreliable in early diagnosis at the pre-cirrhotic stage, and in patients with hepatic inflammation and a raised transaminase. A normal value does not exclude iron storage disease [74]. It is useful in following treatment.

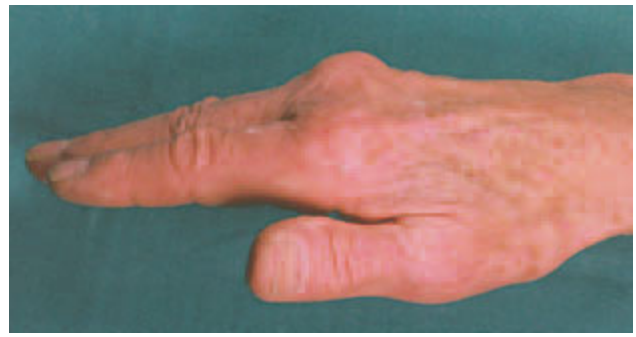


Fig. 23.4. Classical arthropathy of 1st and 2nd metacarpophalangeal joints in the hand.

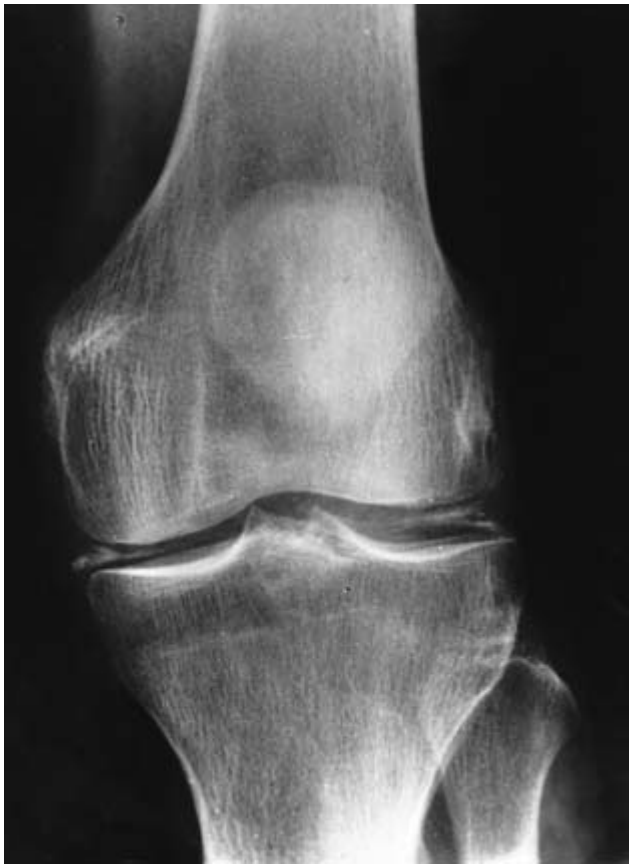


Fig. 23.5. Genetic haemochromatosis. Radiograph of the knee joint shows chondrocalcinosis in menisci and articular cartilage. (Courtesy of M. Barry.)

With severe hepato-cellular necrosis, serum ferritin levels increase as it is released from liver cells [74]. High serum ferritin levels are also seen with inflammatory conditions, such as hepatitis, fatty liver and some cancers.

Needle liver biopsy

Since the introduction of mutation analysis for the *HFE* gene, the indication for needle liver biopsy has changed [32, 83]. Previously hepatic histology and iron quantification was important for diagnosis, giving an indication of the severity and pattern of iron deposition. Measurement of liver iron was important for calculation of the liver iron index (the liver iron concentration divided by the age of the patient), which was of diagnostic value in genetic haemochromatosis. Since mutation analysis confirms the *diagnosis* in the majority of cases, liver biopsy is only necessary in C282Y homozygotes to assess whether there is severe fibrosis or cirrhosis (see fig. 23.3), which determines the protocol for subsequent follow-up. Analysis of risk factors has shown that cirrhosis is unlikely in patients without hepatomegaly, with a normal alanine transaminase and a serum ferritin of less than 1000 µg/l [49]. The current recommendation is that in the absence of these features, liver biopsy is not necessary. If any of these features are present then liver biopsy is recommended since there is an approximate 50% chance of severe fibrosis or cirrhosis.

The liver section is stained with Perls' reagent. Visual scoring of the iron load (0–4+) depends upon the per-

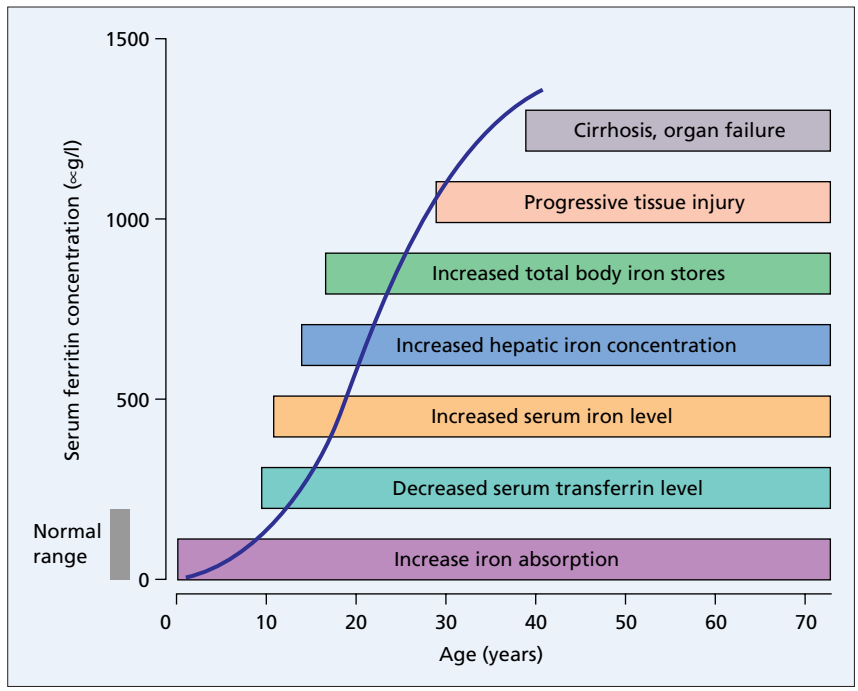


Fig. 23.6. Natural history of genetic haemochromatosis. Relationship between the serum ferritin and the progression of events leading to the clinical syndrome [74].

centage of parenchymal cells with positive staining (0–100%). Chemical measurement of iron should be made although it is recognized that the concentration varies between different samples from the same patient [87]. Iron can be measured on tissue extracted from the paraffin block if fresh tissue was not provided. If mutation analysis does not show homozygosity for C282Y then liver biopsy is usually necessary to show whether or not there is iron overload and also the pattern of iron deposition which may give an indication of the cause.

Liver biopsy is not necessary to follow de-ironing during treatment. Serum iron indices are sufficient.

Imaging

Using single-energy *CT scanning*, hepatic attenuation correlates with serum ferritin, but it is unable to detect hepatic iron overload less than five times the normal limit (40% of patients) [15].

The accuracy is greatly improved if dual-energy CT scanning is available.

MRI detects iron which is a naturally occurring paramagnetic contrast agent. In overload states, marked decreases in T2 relaxation time are shown (see fig. 5.20).

Although both CT and MRI detect heavy iron overload, they are not yet sufficiently precise to predict hepatic iron concentrations with accuracy.

Differential diagnosis

Differentiation between classical genetic haemochromatosis and other causes of iron overload has been simplified by the introduction of genotyping for the C282Y mutation in the *HFE* gene. The differential diagnosis is usually with other chronic liver diseases associated with iron accumulation, haematological disease (not related to transfusion overload) and, more rarely, inherited but non-HFE-related iron overload. Acaeruloplasminaemia is exceptionally rare. African iron overload and neonatal haemochromatosis are specific to particular groups.

Serum iron and transferrin saturation, as well as serum ferritin, are sometimes increased in cirrhosis due to causes other than genetic haemochromatosis. These include alcohol and hepatitis C. The clinical picture may confuse, since the association of diabetes mellitus and cirrhosis is not uncommon, and patients with cirrhosis may become impotent, hairless and develop skin pigmentation. Hepato-cellular failure, however, is unusual in haemochromatosis. The degree of iron overload with end-stage liver disease and juvenile haemochromatosis can be within the range of that seen in *HFE*-related haemochromatosis. Both are unrelated to mutations in *HFE*. A family history and clinical picture should make differentiation straightforward.

Prognosis

Much depends upon the amount and duration of iron overload. Early diagnosis and treatment is central to improving prognosis. Those treated in the pre-cirrhotic stage and before diabetes mellitus has developed, and who subsequently have normal iron levels maintained by phlebotomy, have a normal life expectancy [67]. This is important for patients applying for life insurance [73].

Cardiac failure worsens the outlook and such patients rarely survive longer than 1 year without treatment. Hepatic failure or bleeding oesophageal varices are rare terminal features.

The outlook is better than for cirrhosis in alcoholics who stop drinking. However, the patient with haemochromatosis who also abuses alcohol does worse than the abstinent patient.

The risk of developing hepato-cellular carcinoma in haemochromatotic patients with cirrhosis is increased about 200 times [67] and is not reduced by de-ironing [13]. A minority (approx. 15%) of hepato-cellular carcinomas develop in non-cirrhotic haemochromatotic liver [28]—as is found for hepato-cellular carcinoma related to other aetiologies.

Treatment [32, 83]

Iron can be removed by venesection and can be mobilized from tissue stores at rates as high as 130 mg/day [25]. Blood regeneration is extraordinarily rapid, haemoglobin production increasing to six or seven times normal. Large quantities of blood must be removed, for 500 ml removes only 250 mg of iron, whereas the tissues contain up to 200 times this amount. Depending on the initial iron stores, the amount necessary to reduce them to normal varies from 7 to 45 g. Venesections of 500 ml are carried out weekly, or even twice weekly in particularly co-operative patients, and are continued until serum iron, transferrin saturation and ferritin levels fall into the low normal range. Comparison of a venesection-treated with an untreated group showed a survival of 8.2 years compared with 4.9 years and a 5-year mortality of 11% compared with 67% [92]. Venesection treatment results in increased well-being and gain in weight. Pigmentation and hepato-splenomegaly decrease. Liver function tests improve. Control of diabetes improves in some patients [13, 67]. The arthropathy is usually unaffected. Hypogonadism may lessen in men aged less than 40 years at diagnosis [26]. Cardiac function improves depending upon the severity of cardiac damage before venesection.

Hepatic fibrosis can improve following venesection [67], but hepatic cirrhosis is generally regarded to be irreversible.

After de-ironing, venesection of 500 ml of blood every 3–6 months should prevent iron re-accumulation. A low iron diet is difficult to achieve and most patients remain on a normal diet with intermittent venesection.

Gonadal atrophy may be treated by replacement therapy with an intramuscular, depot testosterone. Human chorionic gonadotrophin (HCG) injections will increase testicular volume and sperm counts.

Diabetes should be treated by diet and, if necessary, insulin. Resistant cases may be encountered.

Transplantation

The survival of patients with genetic haemochromatosis after liver transplant is less than for other recipients (53% vs. 81% survival at 25 months) [35]. The lower survival is related to cardiac complications and sepsis, emphasizing the need for early diagnosis and treatment.

Approximately one-third of patients undergoing liver transplantation unrelated to genetic haemochromatosis have hepatic iron deposition. Ten per cent have hepatic siderosis in the range of that seen in genetic haemochromatosis. *HFE* gene mutations are rare in this group. Patient survival after transplantation is significantly lower in those with hepatic iron overload [17]. Transplantation of the liver from a C282Y heterozygote is safe [5].

Whereas previous reports of the transplantation of a haemochromatotic liver into a normal recipient have not shown evidence of subsequent iron accumulation, this has been reported where the donor intestine as well as liver were derived from a C282Y homozygote [3].

Screening for early haemochromatosis in relatives

There are two ways of screening: biochemical tests for iron overload, and mutation analysis (genotyping). Ideally both are done since the results are complementary. If biochemical screening (transferrin saturation and serum ferritin) shows evidence for iron overload then genotyping for the C282Y mutation is done to show whether the individual is homozygous or heterozygous. If heterozygosity for C282Y is shown, H63D analysis is needed to detect the compound heterozygote (C282Y/H63D).

If the transferrin saturation and ferritin levels are very high, then it is likely that the individual is homozygous for C282Y.

If there is only a mild elevation of transferrin saturation and ferritin, not unusual in the younger patient, it is not possible clinically to differentiate the C282Y homozygote from a heterozygote.

If genotyping is done as the first screening step or in the individual with normal iron studies, patients need to give consent. If they are found to be homozygous for C282Y there may be insurance or mortgage issues despite the absence of iron overload. There is a concern that the insurance companies may increase premiums for C282Y homozygotes despite the fact that subsequent monitoring will prevent iron overload and disease.

It is not possible at present to advise a C282Y homozygote who has no evidence of iron overload of the risk of developing iron overload (phenotypic penetrance) or disease (disease penetrance). Studies have shown that there is phenotypic penetrance in 20–80% of homozygotes. There is no information on disease penetrance although it is recognized that there is a discrepancy between the frequency of homozygosity for C282Y in populations of northern European descent (1 in 200–300) and the frequency of clinically overt genetic haemochromatosis.

Children of a patient with genetic haemochromatosis should also be screened because of the 1 in 10 chance in northern European populations of the spouse being a carrier for the C282Y mutation. This would give a 1 in 20 chance of the child being affected. Screening (as for siblings given above) could be done but for young children below the age of consent this is not practical. An alternative approach is to perform mutation analysis in the spouse (C282Y and H63D). This would then give an indication of the possible genotypes in children and the need for later screening.

It is usually recommended that parents are also screened because of the possibility of unrecognized genetic haemochromatosis.

Population screening [32]

Genetic haemochromatosis is a preventable condition and with early diagnosis and de-ironing life expectancy is normal. This is a powerful argument for population screening of appropriate groups. Transferrin saturation for initial screening followed by DNA testing is a cost-effective strategy [10]. Automated measurement of the unbound iron binding capacity (UIBC) is as effective and less expensive [51]. Population screening has not been adopted by public health bodies because of the lack of information on the disease penetrance of genetic haemochromatosis [1].

Other iron storage diseases

Non-*HFE*-related inherited iron overload

Not all patients with haemochromatosis have mutations in the *HFE* gene. The most well-defined group is *juvenile haemochromatosis* [20]. Patients present at an earlier age (second to fourth decade) with iron overload and cardiac and endocrine problems in particular. The male to female ratio is equal. The condition is not linked to chromosome 6 and the disease locus has been mapped

to chromosome 1 [79]. Treatment is by venesection although in patients with severe cardiac disease chelation therapy with desferrioxamine has also been used.

There are other types of inherited haemochromatosis associated with mutations in proteins related to iron metabolism, including the TfR type 2 gene [21]. Autosomal dominant iron overload has been related to mutations in ferroportin [63, 66], and in the iron-response element of H ferritin [55].

Dysmetabolic syndrome

Iron overload may be associated with diabetes, obesity, hyperlipidemia and hypertension [61]. There is an elevated serum ferritin but normal transferrin saturation. The condition does not appear to be familial and although some patients have *HFE* mutations there is no clear relationship.

Erythropoietic siderosis

Siderosis is associated with extremely high rates of erythropoiesis. The hyperplastic bone marrow may in some way direct the intestinal mucosa to take in excessive quantities of iron. This continues even in the presence of large iron stores. The iron is deposited first in the macrophages of the reticulo-endothelial system and later in parenchymal cells of liver, pancreas and other organs.

Siderosis can therefore be expected in chronic haemolytic states, especially β-thalassaemia, sickle cell disease, congenital spherocytosis and hereditary dyserythropoietic anaemia. Iron overload may develop in mild sideroblastic anaemia without severe anaemia or transfusions. In individuals with haematological disease the degree of iron overload seems more related to the underlying disorder than *HFE* mutations [12, 16] although rarely, inherited haemotological disease may be associated with C282Y homozygosity [34].

The siderosis is enhanced by *blood transfusions* as the iron given with the blood cannot be lost from the body. More than 100 units must have been transfused before siderosis is clinically recognizable. Misdirected iron therapy enhances the siderosis.

The siderosis is recognized clinically by increasing skin pigmentation and by hepatomegaly. Children fail to grow and to develop secondary sexual characteristics. Liver failure and frank portal hypertension are rare. The fasting blood glucose is raised, but clinical diabetes is excessively rare.

Although the amount of iron deposited in the heart is relatively small, myocardial damage is a major factor determining prognosis, especially in younger children. In children, symptoms arise when body iron reaches 20 g (100 units blood transfused); death from heart failure is likely when 60 g is reached.

Treatment is difficult. Splenectomy may reduce transfusion needs. A well-balanced, low-iron diet is virtually impossible. Twelve-hour overnight subcutaneous infusion of 2–4 g desferrioxamine given with a small syringe pump into the anterior abdominal wall is effective [52]. Such measures can only be made available to a very few children with haemoglobinopathies: the cost is prohibitive. Oral iron chelators remain at an experimental stage.

Late stage cirrhosis

Approximately 10% of explanted livers from patients having a transplant have a level of hepatic iron within the range for genetic haemochromatosis. In most cases this is not related to *HFE* mutations. Cryptogenic and alcoholic cirrhosis predominate [17].

The mechanisms of iron deposition are not fully understood. Increased iron absorption is found in cirrhotic patients irrespective of aetiology [93]. Cirrhotic patients with a large portal-systemic collateral circulation may absorb more. Interestingly, iron may accumulate rapidly in the liver of patients with surgical or spontaneous portal-systemic shunts [93], but in general the siderosis is slight and clinically insignificant.

Contributing factors to excess iron include alcoholic beverages with a high iron content, iron medications and haemolysis.

In the patient with alcoholic cirrhosis, hepatic histology shows the features of alcoholism as well as iron deposition. Iron deficiency follows limited venesection therapy suggesting that body iron stores are only moderately increased.

Chronic viral hepatitis

Nearly half of patients with chronic viral hepatitis (B and C) have an abnormal transferrin saturation and/or serum ferritin. *HFE* mutation analysis will identify those with genetic haemochromatosis. A high liver iron reduces the response rate to α-interferon in chronic hepatitis C. Removal of iron by venesection increases the end-of-treatment virological and histological response to short-term interferon therapy, but there is no significant benefit to the sustained response [41].

Non-alcoholic fatty liver disease

Serum iron indices are abnormal in around 50% of patients. In some populations increased hepatic iron is related to the C282Y mutation of *HFE*, and the presence of this mutation and increased hepatic iron correlates with the degree of hepatic fibrosis [14, 44]. This has not, however, been found in all populations [97].

Neonatal haemochromatosis

This very rare and fatal disorder is characterized by liver failure which starts *in utero*, together with hepatic and extra-hepatic parenchymal iron overload which spares the reticulo-endothelial system. Whether it represents a primary iron storage disorder, or the effect of liver disease of another cause superimposed on a liver already physiologically replete with iron, is not certain [82]. Liver transplantation, if successful, is curative.

Iron overload in children has been associated rarely with growth retardation, lactic acidosis and amino-aciduria [38].

African iron overload (Bantu siderosis)

This condition is seen in South African black people whose diet consists of porridge fermented in iron pots at an acid pH. Absorption is facilitated by the acid diet and by malnutrition. Traditional beer brewed in steel drums continues to cause iron overload in rural sub-Saharan Africa. Hepatic iron was considerably elevated (greater than 180 μg/g) in 5% of a study population [42]. The condition is not associated with mutations in *HFE*, but studies suggest that genetic as well as environmental factors affect the degree of iron overload.

Porphyria cutanea tarda (Chapter 25)

Increased iron, one of the triggers for clinical expression, is associated with a high frequency of homozygosity and heterozygosity for the C282Y mutation of *HFE* [77] but not in all populations [80]. Patients with evidence of iron overload are treated by venesection to remove the stimulus for attacks of photosensitivity.

Haemodialysis

Massive overload in liver and spleen reflect transfusion and haemolysis.

Acaeruloplasminaemia

In this very rare syndrome, acaeruloplasminaemia, due to a mutation in the caeruloplasmin gene, is associated with excessive iron deposition mainly in the brain, liver and pancreas. Patients show extra-pyramidal disorders, cerebellar ataxia and diabetes mellitus [96].

Transferrin deficiency

Absence of this binding protein has been found in a child with iron overload [50]. The haematological picture was of severe iron deficiency although the tissues were loaded with iron. The parents were heterozygotes and the patient a homozygote.

References

1 Adams PC. Population screening for haemochromatosis. *Gut* 2000; **46**: 301.
2 Adams PC, Agnew S. Alcoholism in hereditary haemochromatosis revisited: prevalence and clinical consequences among homozygous siblings. *Hepatology* 1996; **23**: 723.
3 Adams PC, Jeffrey G, Alanen K *et al*. Transplantation of haemochromatosis liver and intestine into a normal recipient. *Gut* 1999; **45**: 783.
4 Adams PC, Kertesz AE, Valberg LS. Clinical presentation of haemochromatosis: a changing scene. *Am. J. Med.* 1991; **90**: 445.
5 Alanen KW, Chakrabarti S, Rawlins JJ *et al*. Prevalence of the C282Y mutation of the haemochromatosis gene in liver transplant recipients and donors. *Hepatology* 1999; **30**: 665.
6 Andrews NC. Disorders of iron metabolism. *N. Engl. J. Med.* 1999; **341**: 1986.
7 Axford JS. Rheumatic manifestations of haemochromatosis. *Baillières Clin. Rheumatol.* 1991; **5**: 351.
8 Bacon B, O'Neill R, Britton R. Hepatic mitochondrial energy production in rats with chronic iron overload. *Gastroenterology* 1993; **105**: 1134.
9 Bacon BR, Powell LW, Adams PC *et al*. Molecular medicine and haemochromatosis: at the crossroads. *Gastroenterology* 1999; **116**: 193.
10 Bassett ML, Leggett BA, Halliday JW *et al*. Analysis of the cost of population screening for haemochromatosis using biochemical and genetic markers. *J. Hepatol.* 1997; **27**: 517.
11 Bennett MJ, Lebrón JA, Bjorkman PJ. Crystal structure of the hereditary haemochromatosis protein HFE complexed with transferrin receptor. *Nature* 2000; **403**: 46.
12 Beris P, Samii K, Darbellay R *et al*. Iron overload in patients with sideroblastic anaemia is not related to the presence of the haemochromatosis Cys282Tyr and His63Asp mutations. *Br. J. Haematol.* 1999; **104**: 97.
13 Bomford A, Williams R. Long-term results of venesection therapy in idiopathic haemochromatosis. *Q. J. Med.* 1976; **45**: 611.
14 Bonkovsky HL, Jawaid Q, Tortorelli K *et al*. Non-alcoholic steatohepatitis and iron: increased prevalence of mutations of the HFE gene in nonalcoholic steatohepatitis. *J. Hepatol.* 1999; **31**: 421.
15 Bonkovsky HL, Slaker DP, Bills EB *et al*. Usefulness and limitations of laboratory and hepatic imaging studies in iron-storage disease. *Gastroenterology* 1990; **99**: 1079.
16 Borgna Pignatti C, Solinas A, Bombieri C *et al*. The haemochromatosis mutations do not modify the clinical picture of thalassaemia major in patients regularly transfused and chelated. *Br. J. Haematol.* 1998; **103**: 813.
17 Brandhagen DJ, Alvarez W, Therneau TM *et al*. Iron overload in cirrhosis—HFE genotypes and outcome after liver transplantation. *Hepatology* 2000; **31**: 456.
18 Bulaj ZJ, Griffen LM, Jorde LB *et al*. Clinical and biochemical abnormalities in people heterozygous for haemochromatosis. *N. Engl. J. Med.* 1996; **335**: 1799.
19 Burt MJ, George PM, Upton J *et al*. The significance of haemochromatosis gene mutations in the general population: implications for screening. *Gut* 1998; **43**: 830.
20 Camaschella C. Juvenile haemochromatosis. *Baillières Clin. Gastroenterol.* 1998; **12**: 227.
21 Camaschella C, Roetto A, Calli A *et al*. The gene *TRF2* is

mutated in a new type of haemochromatosis mapping to 7q22. *Nature Genet*. 2000; **25**: 14.
22 Cecchetti G, Binda A, Piperno A *et al*. Cardiac alterations in 36 consecutive patients with idiopathic haemochromatosis: polygraphic and echocardiographic evaluation. *Eur. Heart J.* 1991; **12**: 223.
23 Cotler SJ, Bronner MP, Press RD *et al*. End-stage liver disease without haemochromatosis associated with elevated hepatic iron index. *J. Hepatol.* 1998; **29**: 257.
24 Crawford DHG, Jazwinska EC, Cullen LM *et al*. Expression of HLA-linked haemochromatosis in subjects homozygous or heterozygous for the C282Y mutation. *Gastroenterology* 1998; **114**: 1003.
25 Crosby WH. Treatment of haemochromatosis by energetic phlebotomy. One patient's response to the letting of 55 l of blood in 11 months. *Br. J. Haematol.* 1958; **4**: 82.
26 Cundy T, Butler J, Bomford A *et al*. Reversibility of hypogonadotrophic hypogonadism associated with genetic haemochromatosis. *Clin. Endocrinol.* 1993; **38**: 617.
27 Deugnier Y, Charalambous P, Quilleuc D *et al*. Preneoplastic significance of hepatic iron-free foci in genetic haemochromatosis: a study of 185 patients. *Hepatology* 1993; **18**: 1363.
28 Deugnier Y, Guyader D, Crantock L *et al*. Primary liver cancer in genetic haemochromatosis: a clinical, pathological, and pathogenetic study of 54 cases. *Gastroenterology* 1993; **104**: 228.
29 Diamond T, Stiel D, Posen S *et al*. Osteoporosis in haemochromatosis: iron excess, gonadal deficiency, or other factors? *Ann. Intern. Med.* 1989; **110**: 430.
30 Donovan A, Brownlie A, Zhou Y *et al*. Positional cloning of zebrafish ferroportin 1 identifies a conserved vertebrate iron exporter. *Nature* 2000; **403**: 776.
31 Duane P, Raja KB, Simpson RJ *et al*. Intestinal iron absorption in chronic alcoholics. *Alcohol* 1992; **27**: 539.
32 EASL International Consensus Conference. Genetic haemochromatosis. *J. Hepatol.* 2000; **33**: 485.
33 Faraawi R, Harth M, Kertesz A *et al*. Arthritis in haemochromatosis. *J. Rheumatol*. 1993; **20**: 448.
34 Fargion S, Valenti L, Fracanzani AL *et al*. Hereditary hemochromatosis in a patient with congenital dyserythropoietic anaemia. *Blood* 2000; **96**: 3653.
35 Farrell FJ, Nguyen M, Woodley S *et al*. Outcome of liver transplantation in patients with haemochromatosis. *Hepatology* 1994; **20**: 404.
36 Feder JN, Gnirke A, Thomas W *et al*. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nature Genet*. 1996; **13**: 399.
37 Feder JN, Penny DM, Irrinki A *et al*. The haemochromatosis gene product complexes with the transferrin receptor and lowers its affinity for ligand binding. *Proc. Natl. Acad. Sci. USA* 1998; **95**: 1472.
38 Fellman V, Rapola J, Pihko H *et al*. Iron-overload disease in infants involving fetal growth retardation, lactic acidosis, liver haemosiderosis, and aminoaciduria. *Lancet* 1998; **351**: 490.
39 Fleming MD, Trenor CC, Su MA *et al*. Microcytic anaemia mice have a mutation in Nramp2, a candidate iron transporter gene. *Nature Genet.* 1997; **16**: 383.
40 Fleming RE, Sly WS. Hepcidin: a putative iron-regulatory hormone relevant to hereditary hemochromatosis and the anemia of chronic disease. *Proc. Natl. Acad. Sci. USA*. 2001; **98**: 8160.
41 Fontana RJ, Israel J, LeClair P *et al*. Iron reduction before and during interferon therapy of chronic hepatitis C: results of a multicentre, randomized, controlled trial. *Hepatology* 2000; **31**: 730.
42 Gangaidzo IT, Moyo VM, Saungweme T *et al*. Iron overload in urban Africans in the 1990s. *Gut* 1999; **45**: 278.
43 Ganne-Carrié N, Christidis C, Chastang C *et al*. Liver iron is predictive of death in alcoholic cirrhosis: a multivariate study of 229 consecutive patients with alcoholic and/or hepatitis C virus cirrhosis: a prospective follow up study. *Gut* 2000; **46**: 277.
44 George DK, Goldwurm S, Macdonald GA *et al*. Increased hepatic iron concentration in nonalcoholic steatohepatitis is associated with increased fibrosis. *Gastroenterology* 1998; **114**: 311.
45 George DK, Ramm GA, Powell LW *et al*. Evidence for altered hepatic matrix degradation in genetic haemochromatosis. *Gut* 1998; **42**: 715.
46 George DK, Ramm GA, Walker NI *et al*. Elevated serum type IV collagen: a sensitive indicator for the presence of cirrhosis in haemochromatosis. *J. Hepatol.* 1999; **31**: 47.
47 Gordon HM, Wallace DF, Walker AP *et al*. The role of HFE mutation in determining predisposition to alcohol-related cirrhosis in a Celtic population. *Hepatology* 1998; **28**: 199A.
48 Gunshin H, Mackenzie B, Berger UV *et al*. Cloning and characterization of a mammalian proton-coupled metal-ion transporter. *Nature* 1997; **388**: 482.
49 Guyader D, Jacquelinet C, Moirand R *et al*. Noninvasive prediction of fibrosis in C282Y homozygous haemochromatosis. *Gastroenterology* 1998; **115**: 929.
50 Heilmeyer L, Keller W, Vivell O *et al*. Congenital transferrin deficiency in a seven-year-old girl. *Germ. Med. Mth.* 1961; **6**: 385.
51 Hickman PE, Hourigan LF, Powell LW *et al*. Automated measurement of unsaturated iron binding capacity is an effective screening strategy for C282Y homozygous haemochromatosis. *Gut* 2000; **46**: 405.
52 Hoffbrand AV, Gorman A, Laulicht M *et al*. Improvement in iron status and liver function in patients with transfusional iron overload with long-term subcutaneous desferrioxamine. *Lancet* 1979; **i**: 947.
53 Houglum K, Ramm GA, Crawford DHG *et al*. Excess iron induces hepatic oxidative stress and transforming growth factor β1 in genetic haemochromatosis. *Hepatology* 1997; **26**: 605.
54 Iancu TC, Deugnier Y, Halliday JW *et al*. Ultrastructural sequences during liver iron overload in genetic haemochromatosis. *J. Hepatol.* 1997; **27**: 628.
55 Kato J, Fujikawa K, Kanda M *et al*. A mutation, in the iron-responsive element of H ferritin mRNA, causing autosomal dominant iron overload. *Am. J. Hum. Genet.* 2001; **69**: 191.
56 Lebrón JA, Bjorkman, PJ. The transferrin receptor binding site on HFE, the class I MHC-related protein mutated in hereditary haemochromatosis. *J. Mol. Biol.* 1999; **294**: 1109.
57 Lombard M, Bomford A, Polson RJ *et al*. Differential expression of transferrin receptor in duodenal mucosa in iron overload. *Gastroenterology* 1990; **98**: 976.
58 Martinez PA, Biron C, Blanc F *et al*. Compound heterozygotes for haemochromatosis gene mutations: may they help to understand the pathophysiology of the disease? *Blood Cell. Mol. Dis.* 1997; **23**: 269.
59 McDonnell SM, Hover A, Gloe D *et al*. Population-based screening for haemochromatosis using phenotypic and

DNA testing among employees of health maintenance organizations in Springfield, Missouri. *Am. J. Med.* 1999; **107**: 30.

60 McKie AT, Marciani P, Rolfs A *et al*. A novel duodenal iron-regulated transporter, IREG1, implicated in the basolateral transfer of iron to the circulation. *Mol. Cell.* 2000; **5**: 299.

61 Mendler MH, Turlin B, Moirand R *et al*. Insulin resistance-associated hepatic iron overload. *Gastroenterology* 1999; **117**: 1155.

62 Merryweather-Clarke AT, Pointon JJ, Shearman JD *et al*. Global prevalence of putative haemochromatosis mutations. *J. Med. Genet.* 1997; **34**: 275.

63 Montosi G, Donovan A, Totaro A *et al*. Autosomal-dominant hemochromatosis is associated with a mutation in the ferroportin (SLC11A3) gene. *J. Clin. Invest.* 2001; **108**: 619.

64 Montosi G, Garuti C, Martinelli S *et al*. Hepatic stellate cells are not subjected to oxidant stress during iron-induced fibrogenesis in rodents. *Hepatology* 1998; **27**: 1611.

65 Montosi G, Paglia P, Garuti C *et al*. Wild type HFE protein normalizes transferrin iron accumutation in macrophages from subjects with hereditary hemochromatosis. *Blood* 2000; **96**: 1125.

66 Njajou OT, Vaessen N, Joosse M *et al*. A mutation in *SLC11A3* is associated with autosomal dominant hemochromatosis. *Nature Genet.* 2001; **28**: 213.

67 Niederau C, Fischer R, Purschel A *et al*. Long-term survival in patients with hereditary haemochromatosis. *Gastroenterology* 1996; **110**: 1107.

68 Olynyk JK, Cullen DJ, Aquilia S *et al*. A population-based study of the clinical expression of the haemochromatosis gene. *N. Engl. J. Med.* 1999; **341**: 718.

69 Parkkila S, Waheed A, Britton RS *et al*. Immunohistochemistry of HLA-H, the protein defective in patients with hereditary haemochromatosis, reveals unique pattern of expression in gastrointestinal tract. *Proc. Natl. Acad. Sci. USA* 1997; **94**: 2534.

70 Pietrangelo A, Gualdi R, Casalgrandi G *et al*. Enhanced hepatic collagen type I mRNA expression in fat-storing cells in a rodent model of haemochromatosis. *Hepatology* 1994; **19**: 714.

71 Pietrangelo A, Gualdi R, Casalgrandi G *et al*. Molecular and cellular aspects of iron-induced hepatic cirrhosis in rodents. *J. Clin. Invest.* 1995; **95**: 1823.

72 Piperno A, Sampietro M, Pietrangelo A *et al*. Heterogeneity of haemochromatosis in Italy. *Gastroenterology* 1998; **114**: 996.

73 Powell LW. Hemochromatosis: the impact of early diagnosis and therapy. *Gastroenterology* 1996; **110**: 1304.

74 Powell LW, Halliday JW, Cowlishaw JL. Relationship between serum ferritin and total body iron stores in idiopathic haemochromatosis. *Gut* 1978; **19**: 538.

75 Prieto J, Barry M, Sherlock S. Serum-ferritin in patients with iron overload and with acute and chronic liver diseases. *Gastroenterology* 1975; **68**: 525.

76 Ramm GA, Crawford DHG, Powell LW *et al*. Hepatic stellate cell activation in genetic haemochromatosis. *J. Hepatol.* 1997; **26**: 584.

77 Roberts AG, Whatley SD, Morgan RR *et al*. Increased frequency of the haemochromatosis Cys282Tyr mutation in sporadic porphyria cutanea tarda. *Lancet* 1997; **349**: 321.

78 Roest M, van der Schouw YT, de Valk B *et al*. Heterozygosity for a hereditary haemochromatosis gene is associated with cardiovascular death in women. *Circulation* 1999; **100**: 1268.

79 Roetto A, Totaro A, Cazzola M *et al*. Juvenile haemochromatosis locus maps to chromosone 1q. *Am. J. Hum. Genet.* 1999; **64**: 1388.

80 Sampietro M, Piperno A, Lupica L *et al*. High prevalence of the His63Asp HFE mutation in Italian patients with porphyria cutanea tarda. *Hepatology* 1998; **27**: 181.

81 Sheldon JH. *Haemochromatosis*. Oxford University Press, Oxford, 1935.

82 Sigurdsson L, Reyes J, Kocoshis SA *et al*. Neonatal haemochromatosis: outcome of pharmacologic and surgical therapies. *J. Pediatr. Gastroenterol. Nutr.* 1998; **26**: 85.

83 Tavill AS. AASLD Practice Guidelines. Diagnosis and management of hemochromatosis. *Hepatology* 2001; **33**: 1321.

84 Tsukamoto H, Horne W, Kamimura S *et al*. Experimental liver cirrhosis induced by alcohol and iron. *J. Clin. Invest.* 1995; **96**: 620.

85 Tuomainen P, Kontula K, Nyssnen K *et al*. Increased risk of acute myocardial infarction in carriers of the haemochromatosis gene Cys282Tyr mutation: a prospective cohort study in men in Eastern Finland. *Circulation* 1999; **100**: 1274.

86 Tweed MJ, Roland JM. Haemochromatosis as an endocrine cause of subfertility. *Br. Med. J.* 1998; **316**: 915.

87 Villeneuve J-P, Bilodeau M, Lepage R *et al*. Variability in hepatic iron concentration measurement from needle-biopsy specimens. *J. Hepatol.* 1996; **25**: 172.

88 Vulpe CD, Kuo YM, Murphy TL *et al*. Hephaestin, a ceruloplasmin homologue implicated in intestinal iron transport, is defective in the *sla* mouse. *Nature Genet.* 1999; **21**: 195.

89 Waheed A, Parkkila S, Zhou XY *et al*. Hereditary haemochromatosis: effects of C282Y and H63D mutations on association with β2-microglobulin, intracellular processing, and cell surface expression of the HFE protein in COS-7 cells. *Proc. Natl. Acad. Sci. USA* 1997; **94**: 12384.

90 Wallace DF, Dooley JS, Walker AP. A novel mutation of HFE explains the classical phenotype of genetic haemochromatosis in a C282Y heterozygote. *Gastroenterology* 1999; **116**: 1409.

91 Webster GJM, Saeb-Parsy K, Davies SE *et al*. The effect of heterozygosity for C282Y mutation on fibrosis and liver iron status in chronic hepatitis C. *Hepatology* 1998; **28**: 526A.

92 Williams R, Smith PM, Spicer EJF *et al*. Venesection therapy in idiopathic haemochromatosis. *Q. J. Med.* 1969; **38**: 1.

93 Williams R, Williams HS, Scheuer PJ *et al*. Iron absorption and siderosis in chronic liver disease. *Q. J. Med.* 1967; **36**: 151.

94 Willis G, Wimperis JZ, Lonsdale R *et al*. Incidence of liver disease in people with HFE mutations. *Gut* 2000; **46**: 401.

95 Yang Q, McDonnell SM, Khoury MJ *et al*. Hemochromatosis-associated mortality in the United States from 1979 to 1992: an analysis of multiple-cause mortality data. *Ann. Intern. Med.* 1998; **129**: 946.

96 Yoshida K, Furihata K, Takeda S *et al*. A mutation in the ceruloplasmin gene is associated with systemic haemosiderosis in humans. *Nature Genet.* 1995; **9**: 267.

97 Younossi ZM, Gramlich T, Bacon BR *et al*. Hepatic iron and nonalcoholic fatty liver disease. *Hepatology* 1999; **30**: 847.

98 Yu J, Wessling-Resnick M. Influence of copper depletion on iron uptake mediated by SFT, a stimulator of iron transport. *J. Biol. Chem.* 1998; **273**: 6909.

99 Zoller H, Koch RO, Theurl I *et al*. Expression of the duodenal iron transporters divalent-metal transporter 1 and ferroportin 1 in iron deficiency and iron overload. *Gastroenterology* 2001; **120**: 1412.

Chapter 24
Wilson's Disease

This rare autosomal recessive disorder of copper metabolism is characterized by liver disease and neurological symptoms. It is caused by mutations in a gene encoding a copper-transporting P-type ATPase. In affected individuals there is accumulation of excess copper in the liver, deficient caeruloplasmin synthesis and a marked reduction in biliary copper excretion.

Increased amounts of copper deposited in the tissues are responsible for the hepatic and neurological changes, the greenish-brown pigmented rings in the periphery of the cornea (Kayser–Fleischer rings) and lesions in the kidneys and other organs. Tissue damage leads to cirrhosis of the liver, and bilateral softening and degeneration of the basal ganglia of the brain. Kinnier Wilson [50] was the first to define this condition in an article entitled 'Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver'.

The normal daily dietary intake of copper is 4 mg, of which 2 mg is absorbed and excreted in bile so that the patient is in balance. In Wilson's disease, only 0.2–0.4 mg can be excreted in bile with 1 mg in the urine so that a positive copper balance develops.

In the affected individual the serum copper level is almost invariably reduced (fig. 24.1). Caeruloplasmin, an α_2-globulin responsible for transfer of copper in the plasma, is reduced. Urinary copper excretion is increased.

Wilson's disease is found worldwide but occurs particularly in Jews of eastern European origin, Arabs, Italians, Japanese, Chinese, Indians and any community having a high intermarriage rate.

Molecular genetics: pathogenesis

The prevalence of this autosomal recessive condition is around 1 in 30 000 with a carrier frequency of approximately 1 in 90 [30]. The Wilson's disease gene is on the long arm of chromosome 13 and has been cloned and characterized. The gene product is a copper-transporting P-type ATPase which binds six copper atoms [5].

Although not all studies agree [14, 27], data suggest that under normal circumstances the Wilson's disease protein is predominantly located in the membrane of the trans-Golgi network into which it transports copper for

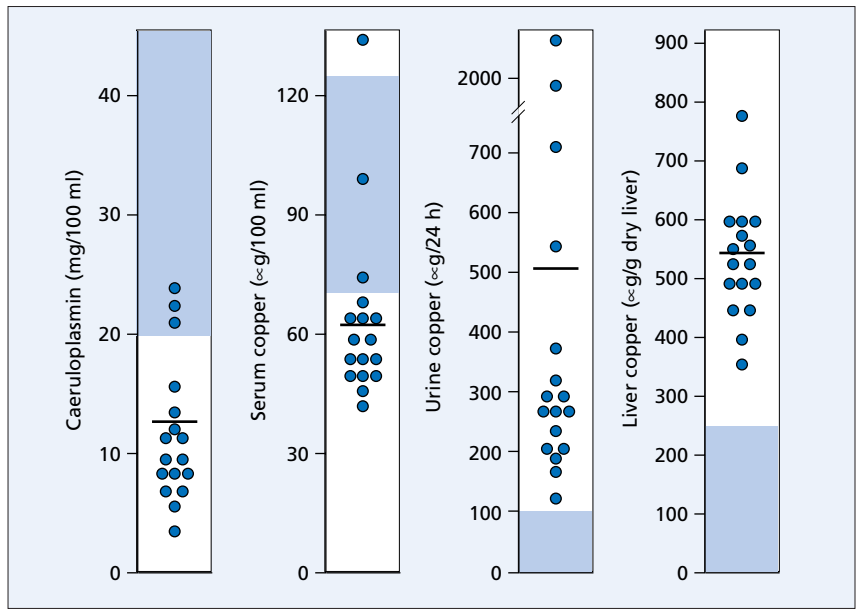


Fig. 24.1. Copper studies in 17 patients with Wilson's disease presenting as chronic hepatitis. Horizontal lines indicate mean values. Tinted areas represent the normal ranges for serum caeruloplasmin and serum copper, and delineate the levels above which urine copper (>100 µg/24 h) and liver copper concentration (>250 µg/g dry weight) are compatible with the diagnosis of Wilson's disease. Note that three patients had a normal serum caeruloplasmin level [34].

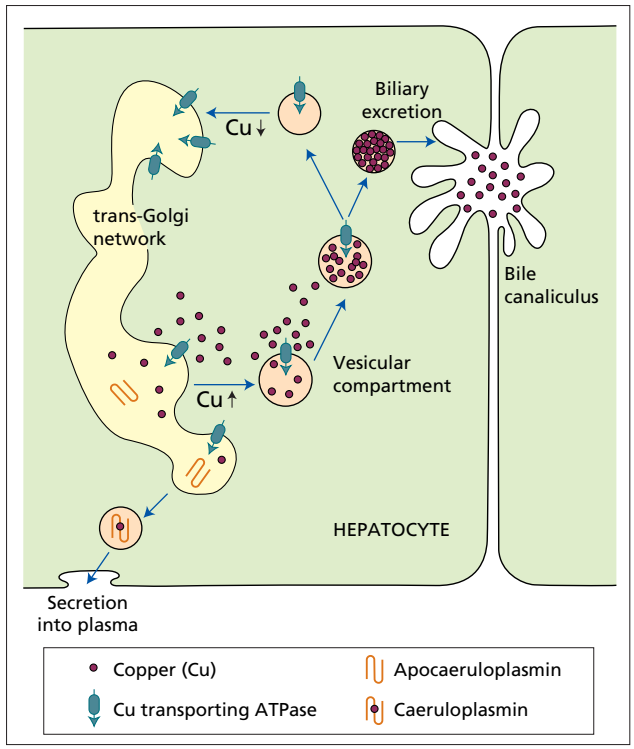


Fig. 24.2. Proposed function of Wilson's disease protein within hepatocytes. At a steady state of copper balance, the copper-transporting ATPase (Wilson's disease protein) is predominantly in the membrane of the trans-Golgi network providing copper both for incorporation into caeruloplasmin as well as sequestering copper for excretion. When intracellular copper concentrations rise, there is redistribution of the copper transporter to a vesicular compartment close to the bile canaliculus. This is thought to favour excretion of copper into bile. (From [27] with permission.)

incorporation into caeruloplasmin (fig. 24.2) [27, 28]. When cytoplasmic and then trans-Golgi copper concentrations rise, there is a change in distribution of the Wilson's disease protein to a vesicular compartment close to the biliary canalicular membrane [27]. Mutation of the Wilson's disease gene leads to defective transport of copper into the trans-Golgi and bile canaliculus. Biliary copper excretion falls, plasma caeruloplasmin and copper levels are low, and there is accumulation of copper in hepatocytes. Mitochondrial copper levels are particularly high [38].

More than 200 different mutations in Wilson's disease have been identified (www.medgen.med.ualberta.ca/database). Most are in the ATPase rather than the copper-binding region. The large number makes mutation analysis impractical as a diagnostic test although in areas with a predominance of one or two mutations it may be of value [20]. No clear relationship has been found between the different mutations and clinical disease although it has been suggested that homozygosity for the most common mutations in European populations (His1069Gln) may be associated with later onset disease [20]. The phenotypic variation even within families carrying the same mutation may be due to genetic variations in other factors involved in the sensing or trafficking functions of the Wilson's disease protein, or environmental factors affecting hepatocyte copper concentrations. The onset of symptoms is significantly delayed in patients with the ApoE epsilon 3/3 genotype [31].

Phenotype–genotype correlations are made difficult because most patients are compound heterozygotes for mutations, i.e. they have a different mutation on each chromosome. Haplotype analysis (analysis of the alleles of microsatellite markers in the area of the Wilson's disease gene on chromosome 13) was important in identifying the area of the gene on chromosome 13 before it was cloned. This technique remains valuable in determining the disease status of siblings of affected patients (homozygote, heterozygote or normal) when the mutations cannot be identified in the affected proband [15]. Such a distinction is important since heterozygote carriers do not develop clinical disease or need treatment.

The Long–Evans Cinnamon (LEC) rat is an animal model for Wilson's disease and has a deletion in the copper-transporting ATPase gene homologous to the Wilson's disease gene. There is marked hepatic copper accumulation in the first few months of life, a low serum caeruloplasmin and development of an acute, and later chronic, hepatitis [22]. D-penicillamine protects against these changes [44].

Reduced biliary excretion of copper in Wilson's disease and the animal model results in toxic levels of copper in the liver and other tissues. There is oxidant damage to mitochondria with lipid peroxidation, which can be reduced experimentally by vitamin E administration [37]. Mitochondril enzyme function in the liver of patients with fulminant Wilson's disease is significantly reduced compared with that in end-stage liver disease due to other conditions [51].

Normal neonates have greatly elevated hepatic copper concentrations and a reduced serum caeruloplasmin. In the neonatal guinea-pig, copper distribution and plasma binding protein soon revert to the adult form [39]. Whether this relates to the activity of the Wilson's disease gene is unknown.

Pathology

Liver

The liver shows all grades of change from peri-portal fibrosis through submassive necrosis to a coarse, macronodular cirrhosis.

Liver cells are ballooned, show multiple nuclei,

clumped glycogen and glycogen vacuolation of the nuclei (fig. 24.3). Fatty change is usual. Kupffer cells are large. In some patients a particularly florid picture is seen with Mallory's bodies, simulating acute alcoholic hepatitis. Alternatively the changes are those of a chronic hepatitis (fig. 24.4). Hepatic histology is not diagnostic, but in a young person with cirrhosis such a picture should always suggest Wilson's disease.

Rubeanic acid or rhodanine stains for copper may be unreliable as the metal is patchily distributed, being absent from regenerating nodules. The copper is usually peri-portal in distribution and associated with atypical lipofuscin deposits.

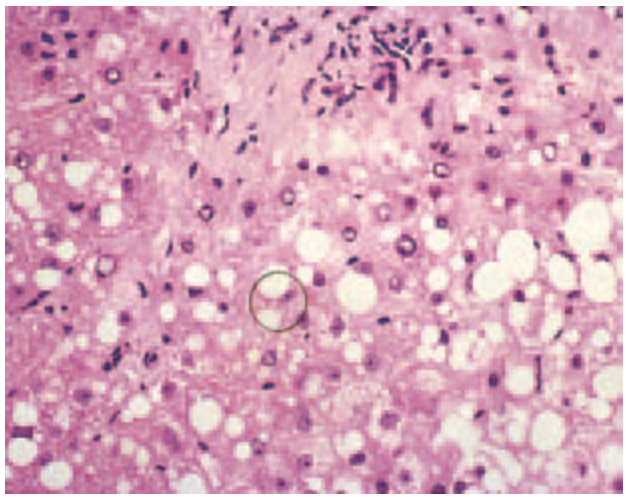


Fig. 24.3. Hepato-lenticular degeneration (Wilson's disease). Liver cells adjoining a fibrous tissue band show gross vacuolation of their nuclei (glycogenic degeneration) and fatty change. (H & E, ×65.)

Electron microscopy

Autophagic vacuoles are seen and mitochondria are large and abnormal even in asymptomatic patients. Fatty change can be related to the mitochondrial alterations. Collagen fibrils infiltrate between cells and light and dark liver cells are seen.

Other organs

The *kidney* shows fatty and hydropic change with copper deposition in the proximal convoluted tubules.

The *Kayser–Fleischer* ring is due to a copper-containing pigment deposited in Descemet's membrane at the periphery of the posterior surface of the cornea.

Clinical picture

The picture is a composite one due to general poisoning of the tissues with copper. The emphasis falls on different tissues at different ages (fig. 24.5). In children the liver is chiefly involved (*hepatic form*). Later neuropsychiatric changes become increasingly important (*neurological form*). Patients presenting after age 20 usually have neurological symptoms [43]. The two types may overlap. Most patients have developed symptoms or have been diagnosed between the ages of 5 and 30 [43]. There are, however, reports of a small number of patients diagnosed in their late 40s and 50s [13].

The *Kayser–Fleischer* ring (fig. 24.6) is a greenish-brown ring at the periphery of the cornea. The upper pole is first affected. Slit lamp examination by an expert is usually necessary to show it. It is usually present with neurological abnormalities. It may be absent in young people with an acute presentation [34]. A rather similar ring may

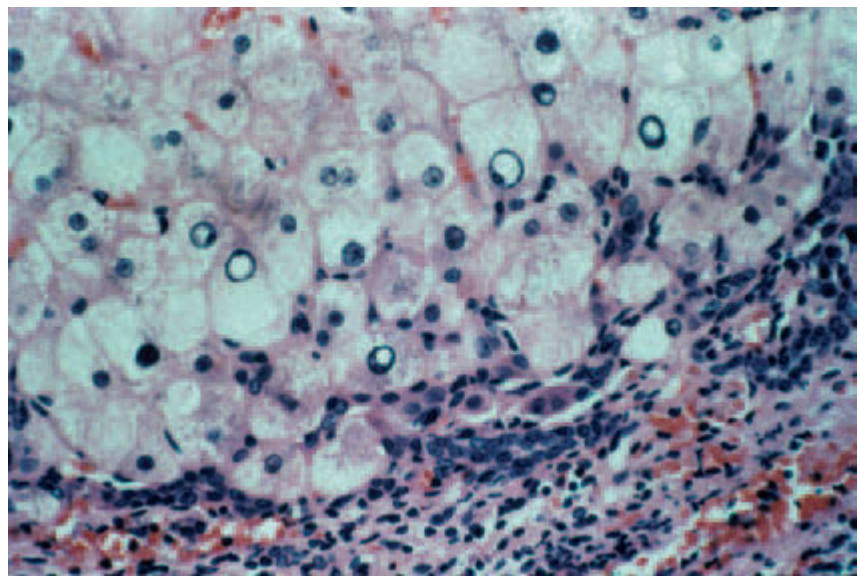


Fig. 24.4. Wilson's disease. In this example there is piecemeal necrosis and lymphocytic infiltration as in chronic hepatitis of other aetiologies. Note the hepato-cellular swelling due to finely divided fat, and vacuolization of nuclei. (H & E, ×350.)

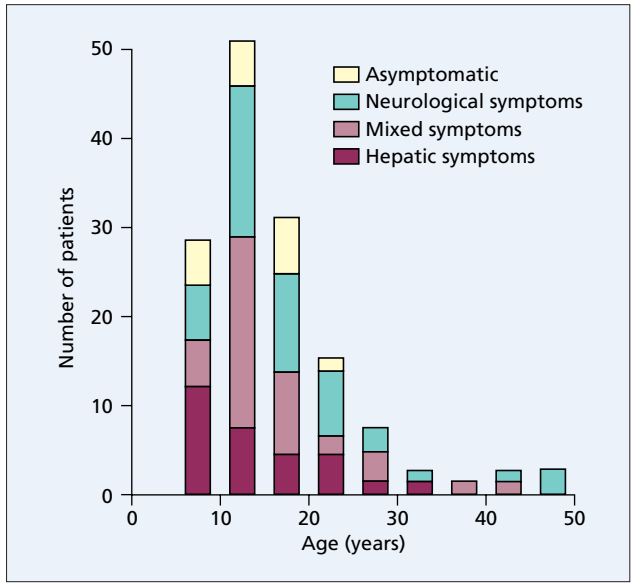


Fig. 24.5. Type of symptom complex at onset by age in 142 British and Chinese patients with Wilson's disease [43].

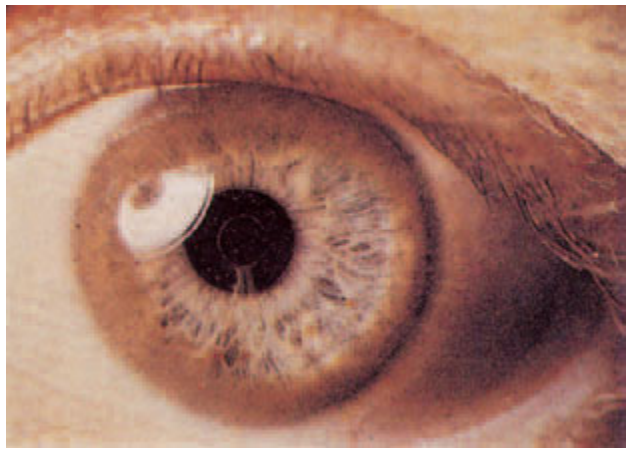


Fig. 24.6. Kayser–Fleischer ring. A brownish deposit is seen at the periphery of the cornea.

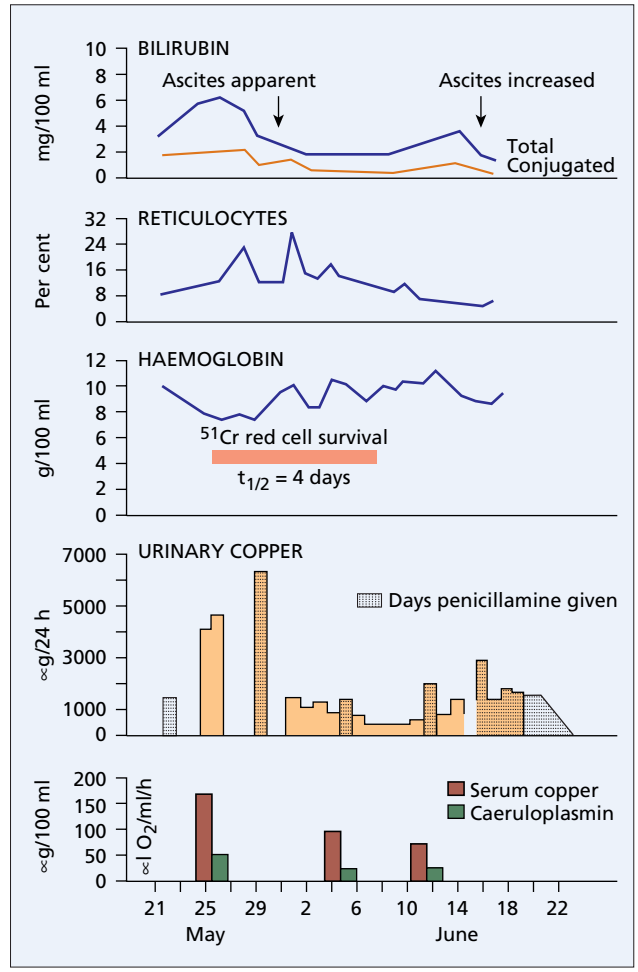


Fig. 24.7. Haemolytic crisis in Wilson's disease, marked by a rise in serum (mainly unconjugated) bilirubin and followed by reticulocytosis. The haemoglobin fell and red cell survival was reduced. Urinary copper was very high even without the administration of penicillamine. Serum copper was higher than that usually found in Wilson's disease. Ascites developed. The second episode of haemolysis, which was noted in June, was marked by a slight rise in serum bilirubin and a fall in haemoglobin [19].

rarely be found with prolonged cholestasis and cryptogenic cirrhosis [11].

Rarely the posterior layer of the capsule of the lens may show greyish-brown 'sunflower' cataracts, similar to those due to copper-containing foreign bodies.

Hepatic forms

Acute liver failure. This is characterized by progressive jaundice, ascites and hepatic and renal failure, usually in a child or young person. The liver cell necrosis is presumably related to accumulation of copper. Virtually all patients are already cirrhotic. Acute intravascular haemolysis may be due to destruction of erythrocytes by a sudden flux of copper from the necrotic hepatocytes (fig. 24.7) [19]. Haemolysis of similar type is reported in sheep with copper intoxication, and in humans in accidental copper poisoning.

Kayser–Fleischer rings may be absent. Urinary and serum copper levels are very high. Serum caeruloplasmin is usually low. However, it may be normal or raised as caeruloplasmin is an acute phase reactant, increased by underlying active liver disease. Serum transaminases and alkaline phosphatase levels are inappropriately low for fulminant viral hepatitis [35]. A low alkaline phosphatase : bilirubin ratio, although not diagnostic of fulminant Wilson's disease, is suggestive.

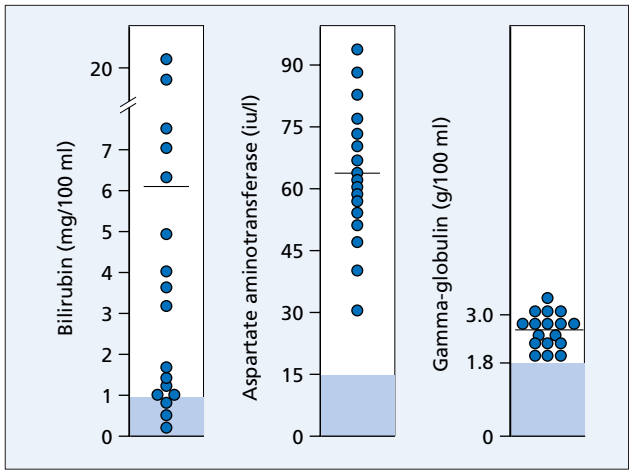


Fig. 24.8. Biochemical tests in 17 patients with Wilson's disease presenting as chronic hepatitis. Horizontal lines indicate mean values. Normal ranges are denoted by hatching (serum bilirubin 0.2–0.8 mg/dl; aspartate aminotransferase 4–15 iu/l; γ-globulin 0.7–1.8 g/dl) [34].

Chronic hepatitis. The condition presents at 10–30 years of age as a chronic hepatitis with jaundice, high transaminase values and hypergammaglobulinaemia (fig. 24.8) [34]. Neurological changes appear some 2–5 years later. The picture may resemble other forms of chronic hepatitis very closely. This emphasizes the need to screen all such patients for Wilson's disease.

Cirrhosis. The patient may present with insidiously developing cirrhosis. Clinical features include vascular spiders, splenomegaly, ascites and portal hypertension. The disease can exist without any neurological signs. In some patients the cirrhosis is well compensated. Hepatic biopsy with measurement of hepatic copper concentration may be necessary for diagnosis.

All young patients with chronic liver disease showing any mental peculiarity, any slurring of the speech, early ascites or haemolysis, and especially with a family history of cirrhosis should be screened for Wilson's disease.

Hepato-cellular carcinoma is very rare and copper may be protective [25].

Neuropsychiatric forms

These broadly form subgroups according to the predominant features, and in order of incidence are: parkinsonian, pseudosclerotic, dystonic (dyskinetic) and choreic [48]. The neurological presentation may be acute and rapidly progressive. Early changes include a flexion–extension tremor of the wrists, grimacing, difficulty in writing and slurred speech. The limbs show a fluctuating rigidity. The intellect is fairly well preserved although 61% of patients have some psychiatric disturbance usually presenting as a slow deterioration of the personality.

More usually the neurological changes are chronic. Onset is in early adult life with tremor, marked and of a wing-beating type, exaggerated by voluntary movement. Sensory loss and pyramidal tract signs are absent. The expression is vacant. Severely dystonic patients have a worse prognosis than other groups [49]. Of patients with neurological presentation, 20% may only have minimal changes or steatosis on liver biopsy [10].

The EEG shows generalized non-specific changes which may also be seen in asymptomatic siblings.

Renal changes

Aminoaciduria, glycosuria, phosphaturia, uricosuria and failure to excrete *p*-amino-hippurate (PAH) reflect renal tubular changes. These are presumably due to copper deposition in the proximal renal tubules.

Renal tubular acidosis is frequent and may be related to stone formation.

Other changes

Rarely, the lunulae of the nails are blue due to increased copper. Skeletal changes include demineralization, premature osteoarthritis, subarticular cysts and fragmentation of bone about the joints. Changes in the spine are common and due to calcium pyrophosphate dihydrate deposition [18]. Gallstones are related to haemolysis. Hypoparathyroidism is an association, possibly due to copper deposition. Cardiac disease, in particular dysrhythmias, has been reported.

Laboratory tests

Serum caeruloplasmin and copper levels are usually reduced [12, 13, 40]. A distinction must be made from acute or chronic hepatitis with reduced serum caeruloplasmin due to failure of synthesis. Malnutrition also reduces serum caeruloplasmin. The level may be raised by oestrogen administration, oral contraceptive drugs, biliary obstruction or pregnancy.

Twenty-four-hour urinary copper excretion is increased. Results may be difficult to evaluate unless strict precautions are taken. Wide-necked bottles with copper-free disposable polyethylene liners are recommended.

In those in whom liver biopsy is contraindicated and where the serum caeruloplasmin level is normal, incorporation of orally administered radio-copper into caeruloplasmin may be diagnostic [30].

Liver biopsy

The copper content must be measured although concentrations vary widely within a cirrhotic liver [9]. The biopsy can be extracted from the paraffin block for copper measurement [17]. The normal is less than 55 µg/g dry liver weight, and concentrations greater than 250 µg are usual in homozygous Wilson's disease (fig. 24.9) [36]. High values may even be found in those with normal hepatic histology. High values are also found in all forms of long-standing cholestasis (figs 24.1 and 24.9).

Scanning

Cranial CT scanning may show changes, including ventricular enlargement, before neurological changes appear. MRI is more sensitive. Dilatation of the third ventricle, focal lesions in the thalamus, putamen and pallidum are seen and bear a relationship to clinical subgroups [24].

Diagnostic difficulties

The combination of a reduced level of serum caeruloplasmin (<20 mg/dl) and the presence of Kayser–Fleischer rings establishes the diagnosis of Wilson's disease. However, in 20–35% of patients presenting with liver disease these characteristic features may not be present [13, 40]. Although there may be technical reasons to explain false negative tests [33], the need to pursue the diagnosis in patients where there is any clinical suspicion of Wilson's disease based on clinical, hepatic or neurological features must be emphasized. Other non-invasive tests may be of value. Urinary copper excretion should be measured. Various non-invasive tests have been used (urinary copper excretion after penicillamine challenge, radio-copper handling test) but these remain either unsubstantiated or difficult to obtain. Genotyping for a mutation known to be common in the local population could be helpful (e.g. the His1069Gln in central Europe). It is recognized that in the absence of typical clinical symptoms, no single laboratory test allows a certain diagnosis of Wilson's disease [33]. Liver biopsy with estimation of liver copper concentration remains the cornerstone for diagnosis, although sampling error may give a misleading result.

Detection of symptom-free homozygotes

All siblings of sufferers must be screened. A homozygote is suggested by such features as hepatomegaly, splenomegaly, vascular spiders and a slight rise in serum transaminase values. The Kayser–Fleischer rings may or may not be seen. Serum caeruloplasmin will usually be reduced to below 20 mg/100 ml. Liver biopsy with copper analysis is confirmatory.

Some difficulty may arise in distinguishing the homozygote from the heterozygote but the distinction is usually clear-cut. If the two mutations of the index case are known, these can be tested in the siblings. If mutations cannot be detected in the Wilson's disease gene, haplotype analysis comparing the affected patient with siblings should be done [15]. The homozygote must be treated, even if symptom-free. The heterozygote does not require treatment.

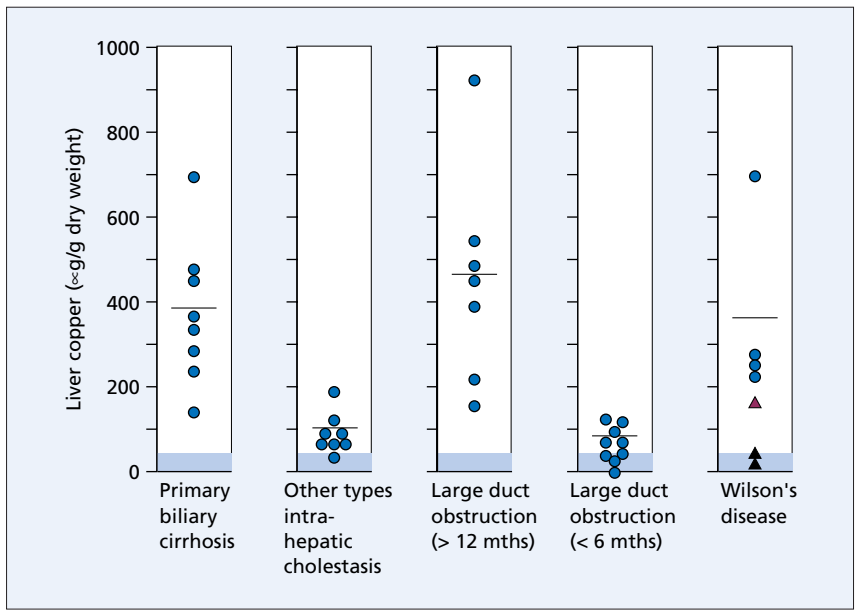


Fig. 24.9. Liver copper levels in patients with Wilson's disease and various types of cholestasis. Wilson's disease: ▲, heterozygote; ▲, siblings probably homozygous normal (these three patients not included in the calculation of the mean). Normal ranges are denoted by hatching [36].

Treatment (table 24.1)

Although there is debate surrounding the specifics of medical management [1, 46], there is general agreement on the broad principles. Liver transplantation is indicated for the fulminant form and in those with severe disease not responding to optimal medical management. For the patient with symptomatic hepatic or neurological disease chelation therapy is given. For maintenance therapy after successful initial treatment, options include a reduction in the dose of chelator, or the substitution or addition of zinc. Different centres have their own protocol, but formal comparisons are lacking.

The initial phase of therapy is aimed at clinical improvement or stabilization. The front-line agents are D-penicillamine or trientine. Ammonium tetrathiomolybdate is an investigational drug currently undergoing evaluation in the initial therapy of patients with neurological disease. D-penicillamine has been the mainstay of treatment since its therapeutic value was described by Walshe over 40 years ago. Despite its proven efficacy, debate on the use of this drug centres on its side-effects and the reported initial worsening of symptoms in a proportion of patients presenting with neurological disease. Trientine initially was used in patients intolerant of D-penicillamine in whom it is effective. Experience is less extensive for its use as first-line therapy for patients with hepatic and neurological disease. Since it has fewer reported side-effects than D-penicillamine, it is now being suggested as an alternative initial treatment.

Zinc salts produce negative copper balance by inducing intestinal cell metallothionein, which has a high affinity for copper and prevents absorption. They have a delayed onset of action.

An important facet of all treatments is the absolute need for compliance, which is often a problem in patients constrained to take lifelong regular medication despite feeling perfectly well.

Penicillamine chelates copper and increases urinary excretion to as much as 1000–3000 µg daily. Treatment is started with 1.5 g D-penicillamine hydrochloride daily by mouth in four divided doses taken before meals. Improvement is slow and at least 6 months of continuous therapy should be given at this dose. If there is no improvement, the dose may be increased to 2 g daily. Of patients with neurological disease, 25% may deteriorate before improvement is seen [49]. Improvement is marked by fading and disappearance of the Kayser–Fleischer rings. Speech is clearer, tremor and rigidity lessen. Hand-writing is a good test of progress. Liver function improves. Hepatic biopsy, which is not necessary clinically for follow-up, shows lessening of activity and reversion to an inactive cirrhosis. Failure to improve implies that irreparable tissue damage was present before treatment started or that there is a lack of compliance with treatment. Failure should not be admitted until 2 years of optimal therapy has been given. This is the usual period for adequate initial therapy.

Success during this initial period of therapy is judged by clinical improvement, a fall in serum free copper below 10 µg/dl (total serum copper minus caeruloplasmin-bound copper) and de-coppering indicated by a 24-h urine copper excretion falling to 500 µg or less. There is controversy concerning whether the liver copper level returns to normal [29]—a situation complicated further by the different copper levels found within the same liver [9]—but when it does, it takes many years of treatment. After the initial period of treatment, if there is the expected improvement, the dose of D-penicillamine should be reduced to 750–1000 mg/day [10]. Close follow-up is necessary to ensure continued improvement/stability, and to monitor the free serum copper concentration and urinary copper output and thus compliance. A fulminant course may follow non-compliance of penicillamine treatment in a previously well-controlled patient [29, 47].

Reactions to D-penicillamine occur in about 20% of patients with Wilson's disease [49]. These include sensitivity reactions within the first few weeks of treatment with fever and rash, leucopenia, thrombocytopenia and lymphadenopathy. These are usually resolved by stopping D-penicillamine and recommencing with slowly increasing doses of penicillamine in combination with

Table 24.1. Treatment of Wilson's disease

Treatment	Indications	Side-effects
Liver transplantation	Severe hepatic insufficiency/failure	Chapter 38
Chelators		
D-penicillamine	Initial therapy/maintenance	++
trientine	Initial therapy/maintenance	+/±
(tetrathiomolybdate)	(Under evaluation)	
Zinc acetate	Maintenance/pre-symptomatic?*	±

*Choice debatable, see text.

prednisolone. Prednisolone is gradually withdrawn after about 2 weeks. D-penicillamine may also cause proteinuria and a systemic lupus erythematosus (SLE)-like syndrome. Skin changes include elastosis perforans serpiginosa and cutis laxa (progeric wrinkling). The latter is dose-related, so that long-term treatment with doses over 1 g/day are not recommended [30]. In the event of serious or unremitting adverse effects of penicillamine, trientine should be substituted.

During the first 2 months of D-penicillamine treatment, white cell and platelet counts are done twice a week, then monthly up to 6 months and thereafter less frequently. Proteinuria should be checked on these occasions. Clinical pyridoxine deficiency is a theoretical possibility with penicillamine therapy but is exceedingly rare. When large doses have been given, pyridoxine supplements can be added.

Trientine (tetraethylene tetramine dihydrochloride) is another copper chelator which was initially introduced successfully to treat patients intolerant of D-penicillamine [29, 45]. It has a lower cupriuretic effect than D-penicillamine but is clinically effective [6] and reports indicate that it can be a satisfactory first line of treatment for Wilson's disease [10, 26]. Early toxicity includes bone marrow suppression and proteinuria, with autoimmune disorders (SLE, Goodpasture's syndrome) being potential later problems [2].

Elemental zinc (50 mg) as acetate three times a day between meals inhibits gastrointestinal absorption of copper through the induction of intestinal metallothionein [3]. There is a delay before a full therapeutic effect and therefore it is not recommended for initial treatment in symptomatic patients. It is being increasingly used for maintenance therapy after initial treatment with chelators. This area is not without debate since some authorities recommend maintenance therapy with reduced doses of the initial chelator (D-penicillamine and trientine) whereas others rely on zinc alone. The same debate exists for the treatment of the pre-symptomatic patient. Proponents of zinc therapy employ it after a period of chelation therapy [3]. Most long-term experience is in pre-symptomatic patients or those with neurological presentation. Experience with zinc alone for hepatic disease after a period of chelation therapy is limited [3]. Further data are awaited to support its role as maintenance monotherapy in patients with a hepatic presentation. As with other treatments, compliance is essential.

Dimercaptopropanol (British Anti-Lewisite, BAL) was the first available chelator therapy for Wilson's disease but is now only used as an adjunct in patients with neurological and/or psychiatric disease refractory to D-penicillamine or trientine alone.

Tetrathiomolybdate is an investigational agent which complexes with protein and copper. In the intestine it prevents the absorption of copper. Absorbed drug complexes copper with albumin in the blood preventing copper entering and damaging cells. In the initial treatment of patients with neurological disease, preliminary studies suggest no worsening of neurological symptoms as seen occasionally with D-penicillamine [2]. Further comparative studies are awaited.

Physiotherapy is of value in the re-education of the patient's gait, writing and movement generally.

A low-copper diet is of little value but high copper-containing foods, including liver and shellfish, should be avoided.

Pregnancy in women with Wilson's disease is safe. Treatment is continued with the patient's normal medication. Interruption of treatment carries a risk of haemolytic episodes, hepatic insufficiency and possible death. Continued treatment with D-penicillamine [41], trientine [41] and zinc [4] have been well tolerated by mothers. There does not appear to be increased risk to the infants born. A dose of 750–1000 mg of either D-penicillamine or trientine, in well-controlled patients, has been used during the first two trimesters of pregnancy with reduction to 500 mg/day during the last trimester [41].

Hepatic transplantation may be indicated for the fulminant form (which is usually fatal), the young cirrhotic in severe hepato-cellular failure who fails to improve after 2–3 months of penicillamine, or the patient who develops severe liver failure with haemolysis after unwisely stopping therapy. Survival at 1 year is 79% [32]. The metabolic defect is corrected [8]. Neurological features show improvement in 80% of patients [42].

Before transplant, renal failure and haemolytic anaemia may be treated by albumin dialysis [16]. Acute haemolysis due to Wilson's disease has also been successfully treated by exchange transfusion [21].

Prognosis

Untreated Wilson's disease is progressive and fatal. The great danger is that the patient remains undiagnosed and dies untreated.

In the acute neurological form the prognosis is poor, for cystic changes in the basal ganglia are irreversible. In the more chronic form the outlook depends on early diagnosis, preferably before symptoms have appeared. The final prognosis also depends on the response to 6 months of continuous penicillamine treatment. In one series [43], 16 asymptomatic patients were treated and remained alive and asymptomatic, and three-quarters of 24 symptomatic patients treated for longer than 2 years became asymptomatic. Dystonia carries a poor prognosis, being little affected by chelation therapy.

In chronic hepatitis, response to treatment can be poor, nine of 17 patients dying in one series before the era of liver transplantation [34]. Jaundice, ascites and a high

serum bilirubin, asparate transaminase and prothrombin time are ominous signs [23]. In children, a prolonged prothrombin time (INR > 1.5), total bilirubin greater than 100 µmol/l and a serum copper of greater than 12 µmol/l at diagnosis taken together predict a poor outcome and may be helpful in identifying patients where liver transplantation should be considered [7]. Liver transplantation is life saving in such patients.

Otherwise death is from liver failure, bleeding oesophageal varices or intercurrent infections in those bedridden from neurological disability.

Indian childhood cirrhosis

See Chapter 26.

Hereditary acaeruloplasminaemia

See Chapter 23.

References

1 Brewer GJ. Penicillamine should not be used as initial therapy in Wilson's disease. *Mov. Disord*. 1999; **14**: 551.

2 Brewer, GJ. Recognition, diagnosis, and management of Wilson's disease. *Proc. Soc. Exp. Biol. Med*. 2000; **223**: 39.

3 Brewer GJ, Dick RD, Johnson V *et al*. Treatment of Wilson's disease with zinc: XV. Long-term follow-up studies. *J. Lab. Clin. Med*. 1998; **132**: 264.

4 Brewer GJ, Johnson VD, Dick RD *et al*. Treatment of Wilson's disease with zinc: XVII. Treatment during pregnancy. *Hepatology* 2000; **31**: 364.

5 Bull PC, Cox DW. Wilson disease and Menkes disease; new handles on heavy-metal transport. *Trends Genet*. 1994; **10**: 246.

6 Dahlman T, Hartvig P, Löholm M *et al*. Long-term treatment of Wilson's disease with triethylene tetramine dihydrochloride (trientine). *Q. J. Med*. 1995; **88**: 609.

7 Dhawan A, D'Silva P, Taylor RM *et al*. Wilson's disease in children: predictors of outcome. Thirty years experience at King's College Hospital. *J. Hepatol*. 2000; **32** (suppl. 2): 136.

8 Eghtesad B, Nezakatgoo N, Geraci LC *et al*. Liver transplantation for Wilson's disease: a single-centre experience. *Liver Transplant Surg*. 1999; **5**: 467.

9 Faa G, Nurchi V, Demelia L *et al*. Uneven hepatic copper distribution in Wilson's disease. *J. Hepatol*. 1995; **24**: 303.

10 Ferenci P. Wilson's disease. In Bacon BR, Di Bisceglie AM, eds. *Liver Disease: Diagnosis and Management*. Churchill Livingstone, Edinburgh, 2000, p. 150.

11 Frommer D, Morris J, Sherlock S *et al*. Kayser–Fleischer-like rings in patients without Wilson's disease. *Gastroenterology* 1977; **72**: 1331.

12 Gibbs K, Walshe JM. A study of the caeruloplasmin concentrations found in 75 patients with Wilson's disease, their kinships and various control groups. *Q. J. Med*. 1979; **48**: 447.

13 Gow PJ, Smallwood RA, Angus PW *et al*. Diagnosis of Wilson's disease: an experience over three decades. *Gut* 2000; **46**: 415.

14 Harada M, Sakisaka S, Terada K *et al*. Role of ATP7B in biliary copper excretion in a human hepatoma cell line and normal rat hepatocytes. *Gastroenterology* 2000; **118**: 921.

15 Houwen RHJ, Roberts EA, Thomas GR *et al*. DNA markers for the diagnosis of Wilson disease. *J. Hepatol*. 1993; **17**: 269.

16 Kreymann B, Seige M, Schweigart U *et al*. Albumin dialysis: effective removal of copper in a patient with fulminant Wilson disease and successful bridging to liver transplantation: a new possibility for the elimination of protein-bound toxins. *J. Hepatol*. 1999; **31**: 1080.

17 Ludwig J, Moyer TP, Rakela J. The liver biopsy diagnosis of Wilson's disease: methods in pathology. *Am. J. Clin. Pathol*. 1994; **102**: 443.

18 McClure J, Smith PS. Calcium pyrophosphate dihydrate deposition in the intervertebral discs in a case of Wilson's disease. *J. Clin. Pathol*. 1983; **36**: 764.

19 McIntyre N, Clink HM, Levi AJ *et al*. Hemolytic anaemia in Wilson's disease. *N. Engl. J. Med*. 1967; **276**: 439.

20 Maier-Dobersberger T, Ferenci P, Polli C *et al*. Detection of the His1069Gln mutation in Wilson disease by rapid polymerase chain reaction. *Ann. Intern. Med*. 1997; **127**: 21.

21 Matsumura A, Hiraishi H, Terano A *et al*. Plasma exchange for haemolytic crisis in Wilson disease. *Ann. Intern. Med*. 1999; **131**: 866.

22 Mori M, Hattori A, Sawaki M *et al*. The LEC rat: a model for human hepatitis, liver cancer and much more. *Am. J. Pathol*. 1994; **144**: 200.

23 Nazer H, Ede RJ, Mowat AP *et al*. Wilson's disease: clinical presentation and use of prognostic index. *Gut* 1986; **27**: 1377.

24 Oder W, Prayer L, Grimm G *et al*. Wilson's disease: evidence of subgroups derived from clinical findings and brain lesions. *Neurology* 1993; **43**: 120.

25 Polio J, Enriquez RE, Chow A *et al*. Hepatocellular carcinoma in Wilson's disease: case report and review of the literature. *J. Clin. Gastroenterol*. 1989; **11**: 240.

26 Santos-Silva EE, Sarles J, Buts JP *et al*. Successful medical treatment of severely decompensated Wilson disease. *J. Pediatr*. 1996; **128**: 285.

27 Schaefer M, Hopkins RG, Failla ML *et al*. Hepatocyte-specific localization and copper-dependent trafficking of the Wilson's disease protein in the liver. *Am. J. Physiol*. 1999; **276**: G639.

28 Schaefer M, Roelofsen H, Wolters H *et al*. Localization of the Wilson's disease protein in human liver. *Gastroenterology* 1999; **117**: 1380.

29 Scheinberg IH, Jaffe ME, Sternlieb I. The use of trientine in preventing the effects of interrupting penicillamine therapy in Wilson's disease. *N. Engl. J. Med*. 1987; **317**: 209.

30 Scheinberg IH, Sternlieb I. *Wilson's Disease*. WB Saunders, Philadelphia, 1984.

31 Schiefermeier M, Kollegger H, Madl C *et al*. The impact of apolipoprotein E genotypes on age at onset of symptoms and phenotypic expression in Wilson's disease. *Brain* 2000; **123**: 585.

32 Schilsky ML, Scheinberg IH, Sternlieb I. Liver transplantation for Wilson's disease: indications and outcome. *Hepatology* 1994; **19**: 583.

33 Schilsky ML, Sternlieb I. Overcoming obstacles to the diagnosis of Wilson's disease. *Gastroenterology* 1997; **113**: 350.

34 Scott J, Gollan JL, Samourian S *et al*. Wilson's disease, presenting as chronic active hepatitis. *Gastroenterology* 1978; **74**: 645.
35 Shaver WA, Bhartt H, Combes B. Low serum alkaline phosphatase activity in Wilson's disease. *Hepatology* 1986; **6**: 859.
36 Smallwood RA, Williams HA, Rosenoer VM *et al*. Liver-copper levels in liver disease. Studies using neutron activation analysis. *Lancet* 1968; **ii**: 1310.
37 Sokol RJ, McKim JM, Devereaux MW. α-Tocopherol ameliorates oxidant injury in isolated copper-overloaded rat hepatocytes. *Paediatr. Res*. 1996; **39**: 259.
38 Sokol RJ, Twedt D, McKim JM *et al*. Oxidant injury to hepatic mitochondria in patients with Wilson's disease and Bedlington terriers with copper toxicosis. *Gastroenterology* 1994; **107**: 1788.
39 Srai SKS, Burroughs AK, Wood B *et al*. The ontogeny of liver copper metabolism in the guinea pig: clues to the aetiology of Wilson's disease. *Hepatology* 1986; **6**: 427.
40 Steindl P, Ferenci P, Dienes HP *et al*. Wilson's disease in patients presenting with liver disease: a diagnostic challenge. *Gastroenterology* 1997; **113**: 212.
41 Sternlieb I. Wilson's disease and pregnancy. *Hepatology* 2000; **31**: 531.
42 Stracciari A, Tempestini A, Borghi A *et al*. Effect of liver transplantation on neurological manifestations in Wilson disease. *Arch. Neurol*. 2000; **57**: 384.
43 Strickland GT, Frommer D, Leu M-L *et al*. Wilson's disease in the United Kingdom and Taiwan. I. General characteristics of 142 cases and prognosis. II. A genetic analysis of 88 cases. *Q. J. Med*. 1973; **42**: 619.
44 Togashi Y, Li Y, Kang J-H *et al*. D-Penicillamine prevents the development of hepatitis in Long–Evans Cinnamon rats with abnormal copper metabolism. *Hepatology* 1992; **15**: 82.
45 Walshe JM. Treatment of Wilson's disease with trientine (triethylene tetramine) dihydrochloride. *Lancet* 1982; **ii**: 643.
46 Walshe JM. Penicillamine: the treatment of first choice for patients with Wilson's disease. *Mov. Disord*. 1999; **14**: 545.
47 Walshe JM, Dixon AK. Dangers of noncompliance in Wilson's disease. *Lancet* 1986; **i**: 845.
48 Walshe JM, Yealland M. Wilson's disease: the problem of delayed diagnosis. *J. Neurol. Neurosurg. Psych*. 1992; **55**: 692.
49 Walshe JM, Yealland M. Chelation treatment of neurological Wilson's disease. *Q. J. Med*. 1993; **86**; 197.
50 Wilson AK. Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. *Brain* 1912; **34**: 295.
51 Wu M, Cooper JM, Butler P *et al*. Oxidative phosphorylation defects in Wilson's disease liver. *Lancet* 2000; **356**: 469.

Chapter 25
Nutritional and Metabolic Liver Diseases

Malnutrition

Worldwide, protein malnutrition is extremely common. The clinical spectrum includes *kwashiorkor*, historically thought due to protein malnutrition, a view that has been challenged [17], and *marasmus* in which there is decreased energy intake relative to need, through starvation and/or medical illness. The liver suffers in common with other organs.

Kwashiorkor is classically associated with accumulation of fat in the liver (up to 50% of wet weight in severe cases), although the reason remains unclear (see below). It appears that fat can also occur with marasmus, although it is less frequent and less extensive than in kwashiorkor [13], perhaps because of the wide range of causes. Liver biopsies from malnourished children show a reduction in liver protein.

The liver is involved in wasting diseases, especially with chronic diarrhoea such as ulcerative colitis, and the hepatic changes in the alcoholic may be partly nutritional. Hepatic necrosis and fibrosis can be produced in experimental animals by certain diets, particularly those low in protein and essential amino acids [20]. Previous malnutrition may 'condition' the liver to toxic and infective agents, but this has not been proved. Oxidant injury rather than protein deficiency is being proposed as a possible cause of some of the changes in malnutrition [17].

Liver enzymes are usually normal in patients with *anorexia nervosa*. Histological findings have been described in individual patients only.

Fatty liver

This is defined as fat, largely triglyceride, exceeding 5% of the liver weight. It is caused by failure of normal hepatic fat metabolism either due to a defect within the hepatocyte or to delivery of excess fat, fatty acid or carbohydrate beyond the secretory capacity for lipid of the liver cell. Liver biopsy and imaging procedures, such as ultrasound and CT, are increasing the number of patients being identified with excess fat in the liver.

Theoretically fatty liver could accumulate through at least four mechanisms.

1 *Increased delivery of dietary fat or fatty acids to the liver.* Dietary fat is transported in the circulation mainly as chylomicrons (fig. 25.1). Lipolysis in adipose tissue liberates the fatty acids. These are incorporated into trigly-

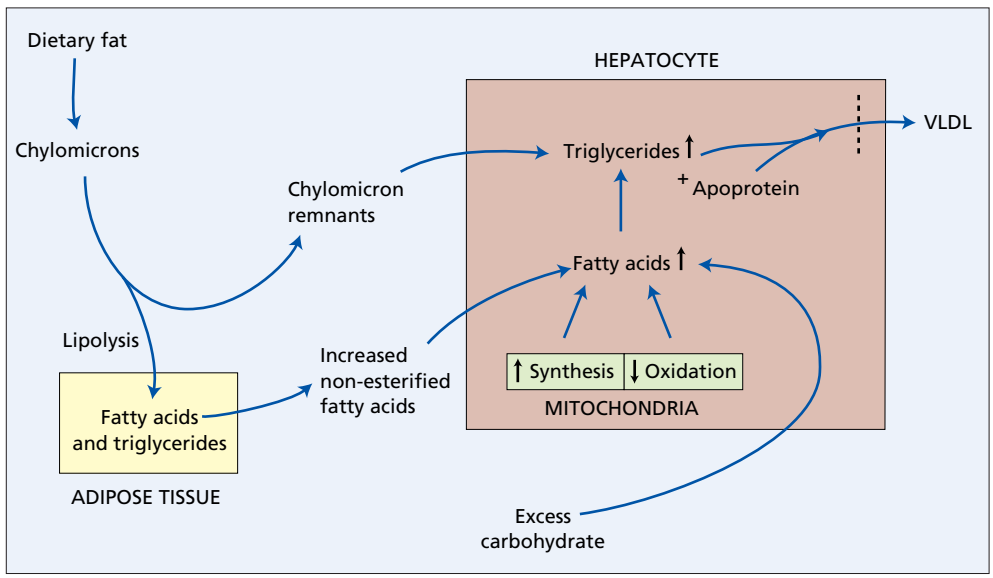


Fig. 25.1. Factors in fatty liver.

ceride within the adipocyte but some fatty acid may be released into the circulation and taken up by the liver. The chylomicron remnants also enter the liver.

2 *Increased mitochondrial synthesis of fatty acids or reduced oxidation*. Both augment triglyceride production.

3 *Impaired export of triglyceride out of the liver cell*. Export of triglycerides from the hepatocyte depends upon packaging with apoprotein, phospholipid and cholesterol to form very low density lipoprotein (VLDL). This process may be inhibited.

4 *Excess carbohydrate* delivered to the liver may be converted to fatty acids.

Diagnosis

Fatty liver may present as diffuse, smooth hepatomegaly in appropriate circumstances such as obesity, diabetes or alcoholism.

Ultrasound may show a bright echo pattern but can be normal [30]. Reflective echoes from fibrosis or cirrhosis are difficult to distinguish. CT can show a reduced attenuation. Portal and hepatic vein branches appear prominent in a scan unenhanced with contrast. The attenuation is less than that of the spleen or kidneys (fig. 25.2). CT scan is useful to follow the effects of therapy. MRI scanning may also detect fatty infiltration.

Liver biopsy is the best method of diagnosing fatty liver. Appropriate stains such as oil red O on frozen sections are essential to diagnose lesser degrees of fatty change. Liver biopsy appearances are not diagnostic of the cause of the fatty change.

In most instances, the fat is maximal in hepatocytes in zone 3 (central). A zone 1 (peri-portal) distribution is found in protein-calorie malnutrition, kwashiorkor, total parenteral nutrition, phosphorus poisoning, methotrexate injury and various other toxic states.

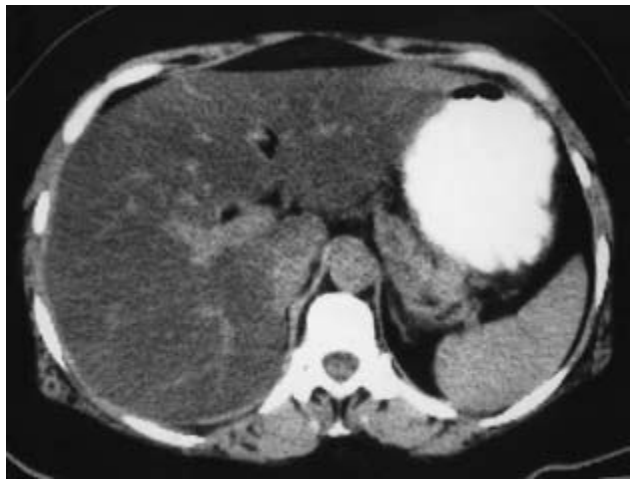


Fig. 25.2. CT scan of a fatty liver (unenhanced). The liver is enlarged, smooth and less dense than the spleen. The intrahepatic portal vein radicles are more prominent than normal.

Classification

Increased fat in the liver is divided into two morphological categories: macrovesicular and microvesicular (fig. 25.3). The two may be combined.

Macrovesicular (large droplet) fat

In haematoxylin and eosin stained liver sections, the hepatocytes contain punched out, empty vacuoles. The nucleus is displaced to the periphery of the cell (fig. 25.4).

Fat in the hepatocyte *per se* is not damaging. The serious association is with steatonecrosis (table 25.1). This is marked by zone 3 (Disse space) peri-cellular fibrosis (creeping collagenosis) often with hepatocyte

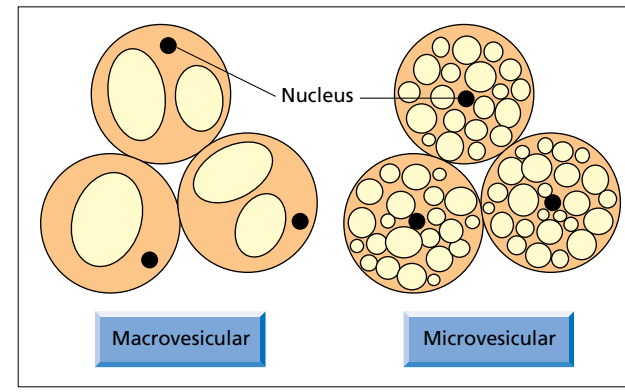


Fig. 25.3. Fatty liver may be classified into macrovesicular (large droplet) and microvesicular (small droplet) types.

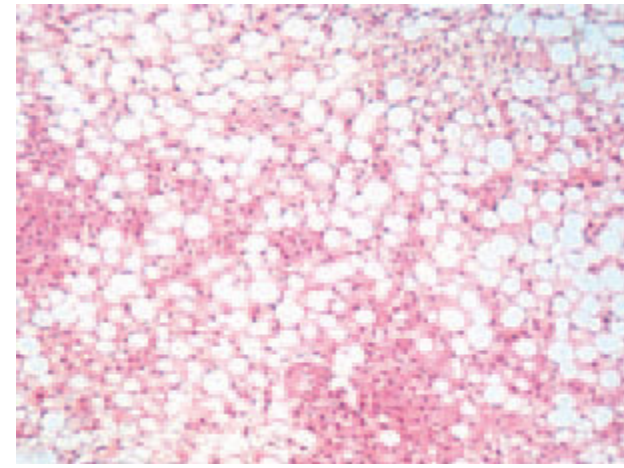


Fig. 25.4. Macrovesicular fat. The liver cells appear empty. (H & E, ×135.)

Table 25.1. The aetiology of large droplet macrovesicular fatty liver

Nutritional
Kwashiorkor
Gastrointestinal disease
Pancreatic disease
Obesity*
Intestinal bypass*
Prolonged parenteral nutrition*
Metabolic diseases
Type II diabetes mellitus*
Galactosaemia
Glycogenoses
Fructose intolerance
Wilson's disease
Tyrosinaemia
Hyperlipidaemias
Abetalipoproteinaemia
Weber–Christian disease
Acylcoenzyme A dehydrogenase deficiency
Drug-related
Alcohol*
Corticosteroids
Direct hepato-toxicity (Chapter 20)
High-dose oestrogens*
Amiodarone*
General
Fever
Systemic disease
Viral infections
Cryptogenic

*Steatonecrosis can develop.

swelling and deposits of Mallory's hyaline in hepatocytes which are surrounded by neutrophils. This lesion is due to some factor in addition to that which causes fatty liver. It is pre-cirrhotic and can be diagnosed only by liver biopsy.

Clinical features. Patients with macrovesicular steatosis is usually symptom free. They may complain of right upper quadrant heaviness and discomfort, worse on movement. Pain over the liver is usually related to rapid accumulation of fat associated with alcoholism or diabetes.

The liver is usually, but not always, smoothly enlarged.

Biochemical tests. These correlate poorly with hepatic histology. γ-Glutamyl transpeptidase is usually elevated. Serum transaminases and alkaline phosphatase show mild increases. Bilirubin and serum albumin are usually normal. Fatty liver is one of the commonest causes of a raised serum transaminase value detected in 'healthy' blood donors.

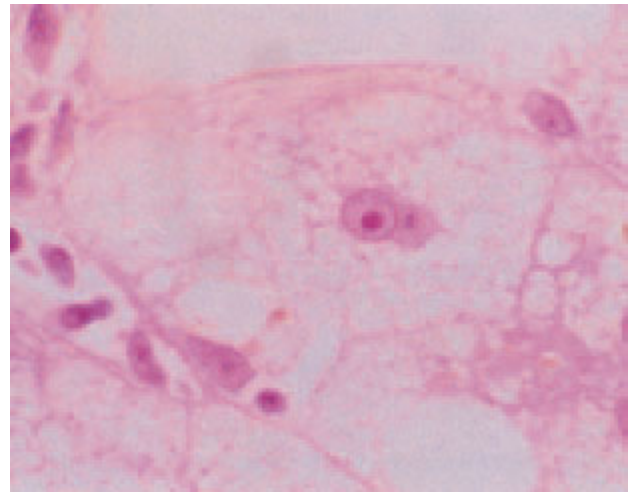


Fig. 25.5. Microvesicular fat. The hepatocyte has a foamy appearance. The nucleus is central with a dense nucleolus.

Cryptogenic macrovesicular fatty liver

When common causes, such as obesity, alcoholism, diabetes and hyperlipidaemia have been excluded a hard core remains with no obvious aetiology. Some may be pre-diabetic or give a family history of diabetes. Patients usually have no symptoms other than anxiety. Serum transaminases may be slightly increased. Liver biopsy is the only method to differentiate steatosis from non-alcoholic steato-hepatitis (NASH) (see below).

Microvesicular fat

Hepatic histology shows zone 3 microvesicular fat. Cell necrosis is variable and minor, although, occasionally, there may be massive zone 3 necrosis. Hepatocytes show central nuclei with prominent nucleoli (fig. 25.5). Inflammation is minimal, and centrizonal cholestasis is occasionally found. Frozen sections stained for fat are necessary for diagnosis in mild cases. Electron microscopy shows the mitochondria swollen, pleomorphic and varying in shape. The smooth endoplasmic reticulum is increased.

Microvesicular fat diseases can be related to a widespread hepatic metabolic disturbance, particularly involving mitochondria. Perhexiline inhibits both oxidative phosphorylation and the mitochondrial β-oxidation of fatty acids, and is associated with microvesicular steatosis [12]. Experimentally, administration of oestradiol and progesterone (to simulate changes in pregnancy) produce ultrastructural changes in mitochondria and decrease oxidation of fatty acids [18]. Disruption of mitochondrial DNA either due to an inborn error [6], a

sporadic deletion [14] or incorporation of a nucleoside analogue [26] may lead to steatosis, more of the microvesicular than macrovesicular pattern. There are mitochondrial abnormalities on electron microscopy. Fatty acid oxidation may be depressed. Increases in blood ammonia and low citrulline values can be related to reduction of mitochondrial Krebs' cycle enzymes. Hypoglycaemia is frequent.

Triglyceride accumulation reflects disordered lipoprotein secretion and assembly. Synthesis of the apoprotein of VLDL is depressed with interference with the exit of lipid from the liver.

This group has several members (table 25.2) [19, 36]. Although many show the same clinical pattern, the recognition of this pathology in a wider range of disorders has revealed a heterogeneity of features and outcome.

The onset is often marked by fatigue, nausea, vomiting with variable jaundice, impairment of consciousness, coma and fits (table 25.3). Renal failure and disseminated intravascular coagulation may be complications. The liver is not the only organ involved, and triglyceride accumulations may be found in the renal tubules and occasionally in myocardium, brain and pancreas. Liver failure is not the usual cause of death. Coma may be related to an increase in blood ammonia levels or to cerebral oedema.

The mode of initiation of these diseases is diverse and in most instances not fully understood. Viral, toxic and nutritional factors have been implicated.

Table 25.2. The microvesicular fat diseases

Acute fatty liver of pregnancy
Reye's syndrome
Vomiting disease of Jamaica
Drug toxicity
sodium valproate
tetracycline
salicylate
fialuridine (FIAU)
Congenital defects of urea cycle enzymes
Genetic defects of mitochondrial fatty acid oxidation
Wolman's disease
Cholesterol ester storage disease
Alcoholic foamy fat syndrome
Delta virus hepatitis in northern South America

Table 25.3. Features of the microvesicular fat diseases [36]

Vomiting
Variable jaundice
Coma
Disseminated intravascular coagulation
Renal failure
Raised blood ammonia values
Hypoglycaemia
Rise in serum fatty acids
Liver biopsy
microvesicular fat
necrosis and cellular infiltration not prominent
Electron microscopy
mitochondrial abnormalities

Focal fatty liver

This condition is recognized by ultrasound, when areas of increased echogenicity are seen [30]. The CT scan shows areas of low attenuation (figs 25.6, 25.7). Dual energy CT helps to differentiate focal fat from other low density lesions [33]. Needle biopsy under CT guidance confirms the diagnosis. The lesions are usually multiple and resolve with time. They may recur. Patients at risk

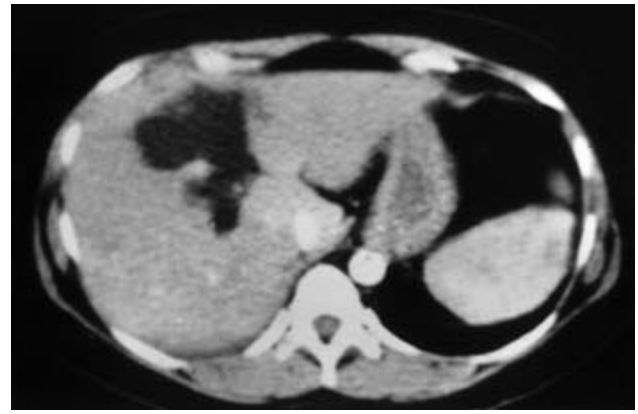


Fig. 25.6. Focal fatty liver. CT scan shows a low attenuation filling defect in the right lobe of the liver. This lesion disappeared spontaneously.

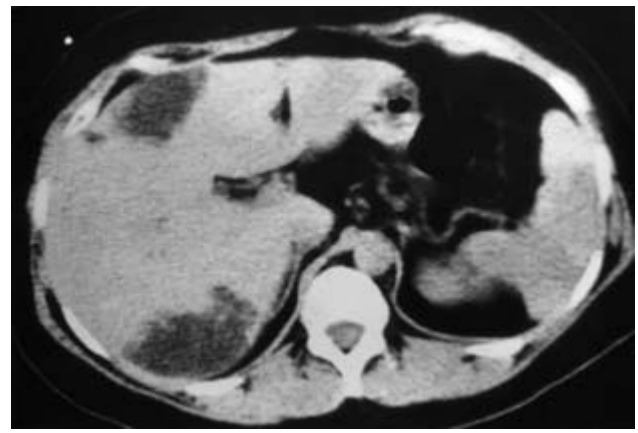


Fig. 25.7. The same patient as in fig. 25.6. A further CT scan performed 6 months later showed two further areas of focal filling defects anteriorly and posteriorly in the right lobe of the liver.

include diabetics, alcoholics, the obese, those on hyperalimentation and sufferers from Cushing's syndrome.

Kwashiorkor syndrome

Oedema is the characteristic of kwashiorkor, a severe form of protein-energy malnutrition, particularly seen in children. It has a worldwide distribution in underprivileged, overpopulated communities, especially tropical and subtropical. It is rare in Europe and indeed in the temperate areas of any continent.

The mechanism resulting in oedema is not clear. Potassium deficiency, dietary protein deficiency, hypoalbuminaemia and renal electrolyte loss have been suggested, and more recently increased oxidative stress and oxidative damage to cell membranes [17]. Concentrations of anti-oxidants including vitamin E, β-carotene and glutathione are reduced. In children with kwashiorkor there is an increased urinary excretion of oxidized amino acids (*o,o'*-dityrosine and orthotyrosine) suggesting the presence of oxidative stress [27]. Deficiency of sulphur amino acids, particularly methionine, may be important [35].

Pathology

The liver shows extensive zone 1 fatty change. Electron microscopy shows surprisingly mild changes. The fatty infiltration bears little relationship to clinical severity of kwashiorkor and causes little disturbance of liver function. There is no progressive fibrosis or cirrhosis [11]. During treatment, the fat is mobilized slowly [13].

The pathogenesis of the hepatic steatosis is not known. Suggested mechanisms include an imbalance in hepatic carbohydrate, protein and fat metabolism, endocrinological abnormalities, increased fat synthesis, redistribution from adipose tissue, reduced lipoprotein synthesis and peroxisomal dysfunction [13].

The acinar cells of the pancreas, salivary and lacrymal glands, and glands of the small intestine are atrophied. There is muscle wasting. The parotid glands may enlarge during recovery. Hepatic steatosis could be secondary to the pancreatic damage and analogous to the fatty liver following experimental pancreatectomy.

Clinical features

Children are most commonly affected 6–18 months after weaning when they are fed on an almost pure carbohydrate diet. Even before weaning, the milk of the undernourished mother may have been poor in protein, and this lack is emphasized by the demands of growth. Malaria and hookworm disease or an additional insult such as aflatoxin may contribute.

The acute breakdown is often initiated by a diminished food intake due to deprivation of mother love, the birth of another child or to an infection [42]. The child is extremely miserable with arrested growth, generalized oedema and cold extremities. The hair shows characteristic depigmentation, becoming pale, thin, straight and soft, losing its crisp black curliness. The characteristic dermatosis starts in the inguinal region and napkin area and spreads to sites of pressure and irritation. The dusky red patches have been likened to crazy paving. The skin desquamates and becomes pallid.

Appetite is decreased and diarrhoea is prominent, especially in the severe case, the stools showing undigested food. The liver may be enlarged or of normal size.

Severe protein malnutrition in *adults*, resembling kwashiorkor, can be related to ineffective utilization of dietary protein due to pancreatic exocrine deficiency or enteric bacterial colonization.

Laboratory findings include reduced haemoglobin and plasma protein concentrations. Pancreatic enzymes are diminished.

Analysis of liver biopsy material shows that enzymes subserving respiration and oxidative phosphorylation are well preserved.

Serum transaminase and plasma-free fatty acid levels are increased [25].

Non-alcoholic fatty liver disease

This includes a spectrum of hepatic changes from steatosis alone, to NASH which also encompasses the findings of steatonecrosis, Mallory bodies and fibrosis. There may be cirrhosis. Children as well as adults may be affected [4, 38]. Liver biopsy is necessary to differentiate between patients with steatosis alone and steatosis with other changes (inflammation, necrosis or fibrosis). Some patients with 'cryptogenic' cirrhosis have features suggestive of a fat-related pathology [9].

The development of fat, usually macrovesicular, within the hepatocyte is associated in particular with obesity and diabetes mellitus. Increased delivery of fatty acids from peripheral adipose tissue and impaired export of triglyceride from the hepatocyte are important. Most patients have the clinical characteristics of the insulin resistance syndrome including obesity (visceral fat), hypertension, glucose intolerance and typical dyslipidaemia. Insulin resistance plays a role not only in obese individuals, but also in lean non-diabetic patients with hepatic steatosis [28].

The progression of pure steatosis to steato-hepatitis, necrosis and fibrosis is thought to be related to oxidative stress with lipid peroxidation, and increased cytokine activity [21]. Thus it is has been suggested that progression of pure fatty change to the necroinflammatory fibrotic stage is a 'two-hit' process: fat deposition followed by factors (oxidative stress, cytokines) that

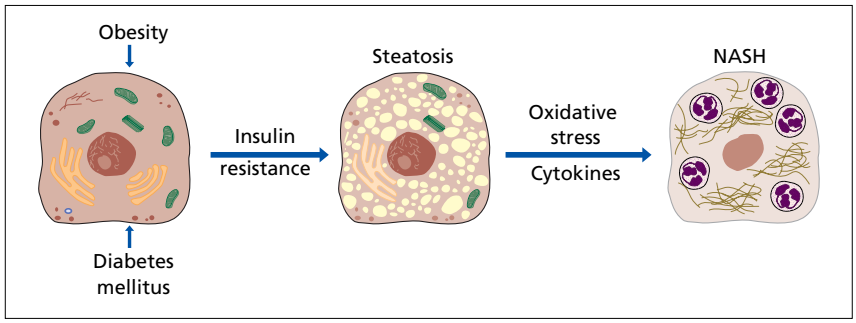


Fig. 25.8. The 'two-hit' model of non-alcoholic steato-hepatitis (NASH).

produce inflammation and cell damage (fig. 25.8). The two 'hits' interact, more severe steatosis being itself a risk factor for NASH. Oxidative stress may be due to peroxisomal fatty acid metabolism (when mitochondrial pathways are saturated), and cytochrome P450 CYP-2E1 enzyme induction [43] which produces oxyradicals. Increased hepatic iron and frequency of *HFE* gene mutations in NASH has been found in some but not all studies [7, 16, 45]. Obesity increases the sensitivity of the liver to endotoxin because of a defect in macrophage function [44].

This group of hepatic diseases is among the top three causes of liver disease in the USA (with alcohol and hepatitis C). It has been estimated that NASH is present in 20% of obese individuals. An autopsy study showed NASH in 18% of those > 40% above their ideal body weight, and 2.7% of those not overweight [41].

NASH is also seen after jejuno-ileal bypass and during parenteral nutrition, and may be caused by drugs including amiodarone and perhexiline [5] and tamoxifen [40].

Non-alcoholic hepatic steatosis

Most patients are overweight and/or have diabetes mellitus type 2, although hepatic steatosis is seen without this characteristic background. Early studies suggested that women were more likely to have steatosis, but more recent studies show men and women equally affected [21]. Presentation is with abnormal liver function tests, either in an individual within a risk group or by chance at a routine medical examination.

Patients are usually asymptomatic. There may be right upper quadrant discomfort or fatigue.

Examination usually shows an enlarged liver, which may be tender.

Liver enzyme tests are usually only mildly abnormal. There may be an isolated rise in ALT, AST, alkaline phosphatase or γ-glutamyl transferase, or a combination of these. When elevated, the ALT is greater than the AST, unlike the reversed ratio found in the alcoholic. Blood glucose, cholesterol and triglycerides are done and may be elevated. Serum ferritin is elevated in 50% of patients [3], both those with and without hepatic siderosis.

Investigations are done to exclude chronic hepatitis B and C, autoimmune liver disease, haemochromatosis, Wilson's disease and α_1-antitrypsin deficiency. A history of alcohol excess is pursued as far as possible to exclusion. If another cause cannot be found, non-alcoholic fatty liver is the likely cause.

Ultrasonography shows fatty liver [30], depending on the severity. CT and MRI also show fat but are second-line tests.

Treatment by gradual weight reduction (rapid weight loss can increase hepatic damage), optimal diabetic control and exercise is accompanied by improvement in fatty change and liver function tests [39]. Trials of drugs to increase insulin sensitivity have been proposed but are awaited.

The prognosis of fatty liver (without inflammation, necrosis or fibrosis) is excellent, with no progression in the vast majority [37].

Non-alcoholic steatonecrosis

For the patient groups at risk, presentation, clinical features, laboratory tests and imaging are similar to those for hepatic steatosis alone.

The differentiation between hepatic steatosis and NASH requires liver biopsy (fig. 25.9).

The features of NASH are macrovesicular fat, inflammation, lobular necrosis, peri-cellular fibrosis and Mallory bodies—all the features of alcohol-related steato-hepatitis. Standardized criteria for the diagnosis of NASH are not universal, making analysis of data from different studies a problem. Electron microscopy shows mitochondral abnormalities similar to those seen in alcoholic liver disease [10].

Studies show progression of steato-hepatitis/necrosis to fibrosis and cirrhosis in 30–60% of patients [3, 21, 32]. Clinical features associated with severe fibrosis (bridging fibrosis/cirrhosis) are older age, obesity, diabetes mellitus and an AST/ALT ratio greater than 1 [2]. Histological features associated with a greater risk of progression include intra-hepatic inflammation [15], and ballooning degeneration of hepatocytes and Mallory hyaline or fibrosis [29].

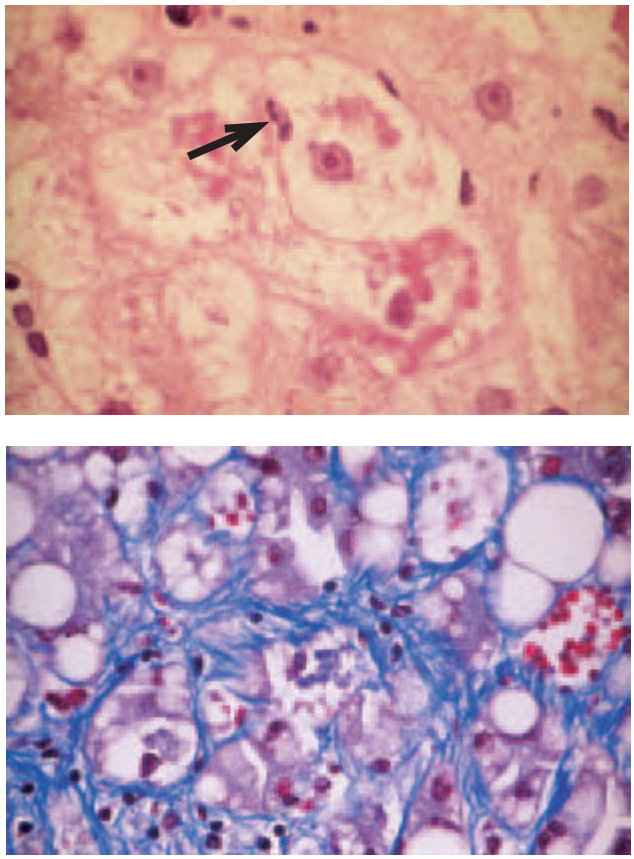


Fig. 25.9. Non-alcoholic steato-hepatitis. (a) A neutrophil (arrow) adjacent to a swollen hepatocyte containing microvesicular fat (H & E). (b) Trichrome stain shows blue staining fibrosis around swollen hepatocytes.

Treatment is by weight reduction and optimal control of blood glucose. Excessive rapid weight reduction may be damaging. Drug treatment remains experimental, but short-term limited trials of ursodeoxycholic acids [23], vitamin E [24] and betaine glucuronate [31] suggest benefit. Liver transplantation is occasionally required, but NASH has recurred [22].

Effects of jejuno-ileal bypass

The hepatic changes of obesity are enhanced. Hepatic lipid concentrations increase, and the morphological changes of NASH may be present. Progressive inflammation, fibrosis, zone 3 sclerosis and cirrhosis can develop. Liver disease including the development of cirrhosis is seen in 10% of patients at 15 years after operation [34]. The patient may die in hepatic failure. Reversal of the bypass may not be effective treatment although liver fat decreases.

The hepatic changes are probably related to rapid weight loss, protein-calorie malnutrition, bacterial overgrowth in the blind loop of intestine, malabsorption and other complex nutritional deficiencies. They can also follow gastric partitioning operations, and are found associated with small intestinal diverticulosis and coeliac disease.

Parenteral nutrition [1]

Cholestasis has developed in infants given long-term parenteral nutrition for neonatal intestinal obstruction. In adults, increases in serum transaminase, alkaline phosphatase and bilirubin values follow fat-free total parenteral nutrition for 2 weeks or longer. Liver biopsies show fatty change and mild peri-portal cholestasis. Abnormal biochemical tests also complicate enteral elemental diets in adults.

Hepatic steatosis occurs particularly with high glucose feeding and when the rate of infusion exceeds the hepatic oxidative capacity so that fat is synthesized. Similar effects follow intravenous fat emulsions. These changes do not develop if the infusion is balanced in terms of carbohydrate and fat. Choline deficiency may play a part and steatosis is reversed by choline supplementation [8].

Gallbladder biliary sludge and pigment gallstones may follow prolonged total parenteral nutrition, especially in infants. It is detected by ultrasound.

Vitamins

The fat-soluble vitamins A, D, E and K are not absorbed if biliary bile acid excretion is inadequate. Deficiencies therefore complicate cholestasis (Chapter 13).

Hypervitaminosis A leads to peri-sinusoidal fibrosis, central vein sclerosis and focal congestion with peri-sinusoidal lipid storage cells. Vitamin A fluorescence may be shown in frozen sections. Portal hypertension and ascites are consequences. Similar changes can complicate *retinoid* treatment for psoriasis or acne.

Vitamin E deficiency causes a neuromuscular syndrome in cholestatic children, but rarely in adults.

Alcoholics may show thiamine deficiency. Clinical evidence of this in non-alcoholic patients with liver disease is very rare. Folic acid may be reduced in alcoholics.

Low circulating levels of pyridoxal phosphate, the active form of vitamin B_6 compounds, in cirrhosis is probably due to increased degradation.

References

1 Angelico M, Della Guardia P. Review article. Hepatobiliary complications associated with total parenteral nutrition. *Aliment. Pharmacol. Ther.* 2000; **14**: 54.

2 Angulo P, Keach JC, Batts KP *et al.* Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology* 1999; **30**: 1356.

3 Bacon BR, Farahvash MJ, Janney CG *et al.* Non-alcoholic

steatohepatitis: an expanded clinical entity. *Gastroenterology* 1994; **107**: 1103.
4 Baldridge AD, Perez-Atayde AR, Graeme-Cook F *et al*. Idiopathic steatohepatitis in childhood: a multicentre retrospective study. *J. Pediatr*. 1995; **127**: 700.
5 Berson A, De Beco V, Letteron P *et al*. Steatohepatitis-inducing drugs cause mitochondrial dysfunction and lipid peroxidation in rat hepatocytes. *Gastroenterology* 1998; **114**: 764.
6 Bioulac-Sage P, Parrot-Roulaud F, Mazat JP *et al*. Fatal neonatal liver failure and mitochondrial cytopathy (oxidative phosphorylation deficiency): a light and electron microscopic study of the liver. *Hepatology* 1993; **18**: 839.
7 Bonkovsky HL, Jawaid Q, Tortorelli K *et al*. Non-alcoholic steatohepatitis and iron: increased prevalence of mutations of the HFE gene in nonalcoholic steatohepatitis. *J. Hepatol.* 1999; **31**: 421.
8 Buchman AL, Dubin MD, Moukarzel AA *et al*. Choline deficiency: a cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. *Hepatology* 1995; **22**: 1399.
9 Caldwell SH, Oelsner D, Iezzoni JC *et al*. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. *Hepatology* 1999; **29**: 664.
10 Caldwell SH, Swerdlow RH, Khan E *et al*. Mitochondrial abnormalities in nonalcoholic steatohepatitis. *J. Hepatol.* 1999; **31**: 430.
11 Cook GC, Hutt MSR. The liver after kwashiorkor. *Br. Med. J.* 1967; **iii**: 454.
12 Deschamps D, DeBeco V, Fisch C *et al*. Inhibition by perhexiline of oxidative phosphorylation and the β-oxidation of fatty acids: possible role in pseudoalcoholic liver lesions. *Hepatology* 1994; **19**: 948.
13 Doherty JF, Adam EJ, Griffin GE *et al*. Ultrasonographic assessment of the extent of hepatic steatosis in severe malnutrition. *Arch. Dis. Child.* 1992; **67**: 1348.
14 Fromenty B, Grimbert S, Mansouri A *et al*. Hepatic mitochondrial DNA deletion in alcoholics: association with microvesicular steatosis. *Gastroenterology* 1995; **108**: 193.
15 García-Monzón C, Martín-Pérez E, Lo Iacono O *et al*. Characterization of pathogenic and prognostic factors of nonalcoholic steatohepatitis associated with obesity. *J. Hepatol.* 2000; **33**: 716.
16 George DK, Goldwurm S, MacDonald GA *et al*. Increased hepatic iron concentration in nonalcoholic steatohepatitis is associated with increased fibrosis. *Gastroenterology* 1998; **114**: 311.
17 Golden MHN. Oedematous malnutrition. *Br. Med. Bull.* 1998; **54**: 433.
18 Grimbert S, Fisch C, Deschamps D *et al*. Effects of female sex hormones on mitochondria: possible role in acute fatty liver of pregnancy. *Am. J. Physiol.* 1995; **268**: G107.
19 Hautekeete ML, Degott C, Benhamou J-P. Microvesicular steatosis of the liver. *Acta Clin. Belgica* 1990; **45**: 311.
20 Himsworth HP, Glynn LE. Massive hepatic necrosis and diffuse hepatic fibrosis (acute yellow atrophy and portal cirrhosis): their production by means of diet. *Clin. Sci.* 1994; **5**: 93.
21 James O, Day C. Non-alcoholic steatohepatitis: another disease of affluence. *Lancet* 1999; **353**: 1634.
22 Kim WR, Poterucha JJ, Porayko MK *et al*. Recurrence of nonalcoholic steatohepatitis following liver transplantation. *Transplantation* 1996; **62**: 1802.
23 Laurin J, Lindor KD, Crippin JS *et al*. Ursodeoxycholic acid or clofibrate in the treatment of nonalcoholic-induced steatohepatitis: a pilot study. *Hepatology* 1996; **23**: 1464.
24 Lavine JE. Vitamin E treatment of nonalcoholic steatohepatitis in children: a pilot study. *J. Pediatr.* 2000; **136**: 734.
25 Lewis B, Hansen JDL, Wittman W *et al*. Plasma free fatty acids in kwashiorkor and the pathogenesis of the fatty liver. *Am. J. Clin. Nutr.* 1964; **15**: 161.
26 McKenzie R, Fried MW, Sallie R *et al*. Hepatic failure and lactic acidosis due to fialuridine (FIAU), an investigational nucleoside analogue for chronic hepatitis B. *N. Engl. J. Med.* 1995; **333**: 1099.
27 Manary MJ, Leeuwenburgh C, Heinecke JW. Increased oxidative stress in kwashiorkor. *J. Pediatr.* 2000; **137**: 421.
28 Marchesini G, Brizi M, Morselli-Labate AM *et al*. Association of nonalcoholic fatty liver disease with insulin resistance. *Am. J. Med.* 1999; **107**: 450.
29 Matteoni CA, Younossi ZM, Gramlich T *et al*. Nonalcoholic fatty liver disease; a spectrum of clinical and pathological severity. *Gastroenterology* 1999; **116**: 1413.
30 Mendler M-H, Bouillet P, Le Sidaner A *et al*. Dual-energy CT in the diagnosis and quantification of fatty liver: limited clinical value in comparison to ultrasound scan and single-energy CT, with special reference to iron overload. *J. Hepatol.* 1998; **28**:·785.
31 Miglio F, Rovati LC, Santoro A *et al*. Efficacy and safety of oral betaine glucuronate in nonalcoholic steatohepatitis. A double-blind, randomized, parallel-group, placebo-controlled prospective clinical study. *Arzneimittelforschung* 2000; **50**: 722.
32 Powell EE, Cooksley WGE, Hanson R *et al*. The natural history of nonalcoholic steatohepatitis: a follow-up study of 42 patients for up to 21 years. *Hepatology* 1990; **11**: 74.
33 Raptopoulos V, Karellas A, Bernstein J *et al*. Value of dual-energy CT in differentiating focal fatty infiltration of the liver from low-density masses. *Am. J. Roentgenol.* 1991; **157**: 721.
34 Requarth JA, Burchard KW, Colacchio TA *et al*. Long-term morbidity following jejunoileal bypass. The continuing potential need for surgical reversal. *Arch. Surg.* 1995; **130**: 318.
35 Roediger WEW. New views on the pathogenesis of kwashiorkor: methionine and other amino acids. *J. Pediatr. Gastroenterol. Nutr.* 1995; **21**: 130.
36 Sherlock S. Acute fatty liver of pregnancy and the microvesicular fat diseases. *Gut* 1983; **24**: 265.
37 Teli MR, James OFW, Burt AD *et al*. The natural history of nonalcoholic fatty liver: a follow-up study. *Hepatology* 1995; **22**: 1714.
38 Tominaga K, Kurata JH, Chen YK *et al*. Prevalence of fatty liver in Japanese children and relationship to obesity. An epidemiological ultrasonographic study. *Dig. Dis. Sci.* 1995; **40**: 2002.
39 Ueno T, Sugawara H, Sujaku K *et al*. Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. *J. Hepatol.* 1997; **27**: 103.
40 Van Hoof M, Rahier J, Horsmans Y. Tamoxifen-induced steatohepatitis. *Ann. Intern. Med.* 1996; **124**: 855.
41 Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology* 1990; **12**: 1106.
42 Waterlow JC. Kwashiorkor revisited: the pathogenesis of oedema in kwashiorkor and its significance. *Trans. R. Soc. Trop. Med. Hyg.* 1984; **78**: 436.

43 Weltman MD, Farrell GC, Hall P *et al*. Hepatic cytochrome P450 2E1 is increased in patients with nonalcoholic steatohepatitis. *Hepatology* 1998; **27**: 128.
44 Yang SQ, Lin HZ, Lane MD *et al*. Obesity increases sensitivity to endotoxin liver injury; implications for the pathogenesis of steatohepatitis. *Proc. Natl. Acad. Sci. USA* 1997; **94**: 2557.
45 Younossi ZM, Gramlich T, Bacon BR *et al*. Hepatic iron and nonalcoholic fatty liver disease. *Hepatology* 1999; **30**: 847.

Carbohydrate metabolism in liver disease

Hypoglycaemia

This is usually due to reduction in hepatic glucose release. The hepatectomized dog rapidly develops hypoglycaemia [1] and this is seen in acute liver failure (Chapter 8). When it may be intractable. Hypoglycaemia is rare in chronic liver disease, even terminally. Very rarely it is found in cirrhotic patients after a porta-caval anastomosis. Reactive hypoglycaemia, 1.5–2 h after glucose, has been seen in two patients with chronic hepatitis; blood insulin levels were high. Alcohol can also induce hypoglycaemia, especially in cirrhotic patients.

Hypoglycaemia may complicate Reye's syndrome in children and primary hepato-cellular carcinoma.

Hyperglycaemia

See p. 432 (glucose intolerance in cirrhosis).

Reference

1 Mann FC, Magath TB. Studies on the physiology of the liver. II. The effect of the removal of the liver on the blood sugar level. *Arch. Intern. Med.* 1922; **30**: 73.

The liver in diabetes mellitus

Insulin and the liver

The liver is the principal organ for the degradation of insulin. Peripheral tissues take up insulin to a lesser extent and also remove glucagon. Hyperinsulinaemia is a characteristic association of cirrhosis and is due to peripheral insulin resistance, with reduced degradation and clearance, rather than impaired hepato-cellular function or portal-systemic shunting [1, 8].

In diabetes, glucose-6-phosphatase increases in the liver, facilitating glucose release into the blood. The opposing enzymes which phosphorylate glucose are hexokinase, which is unaffected by insulin, and glucokinase, which decreases in diabetes. As a result, the liver continues to produce glucose even with severe hyperglycaemia. Under these circumstances the normal liver would shut off and deposit glycogen. Fructose-1,6-phosphate activity is also increased in diabetes. Gluconeogenesis is thus favoured.

Substances released from the pancreas into the portal blood are known to increase hepatic regeneration (*hepatotrophic substances*). Insulin is the main hepatotrophic substance although glucagon may also be important. Blood glucagon is increased in liver disease, probably due to pancreatic over-secretion.

Hepatic histology

Needle biopsy shows normal or increased amounts of glycogen in the livers of severe untreated diabetes. Even higher values follow the administration of insulin, provided hypoglycaemia is prevented.

Histologically the zonal structure is normal. In sections stained with haematoxylin and eosin, the glycogen-filled cells appear pale and fluffy. Zone 1 cells always contain less glycogen than zone 3 and this is accentuated by glycogenolysis. In type 1 diabetes, the liver cells appear bloated and oedematous: glycogen is maintained or even increased.

Glycogenic infiltration of the liver cell nuclei (fig. 25.10) is shown as vacuolization, the nature of which is confirmed by glycogen stains. It is not specific but is found in about two-thirds of diabetics.

Fatty change, randomly distributed but mainly in zone 2 and 3, and with a macrovesicular pattern (fig. 25.4), is common in the obese type 2 diabetic. The mechanism is the increased delivery of fatty acids to the liver where they are incorporated into triglyceride which is retained in the hepatocyte (fig. 25.1). The fatty acids are derived from increased lipolysis in adipose tissue secondary to insulin resistance and impaired insulin secretion.

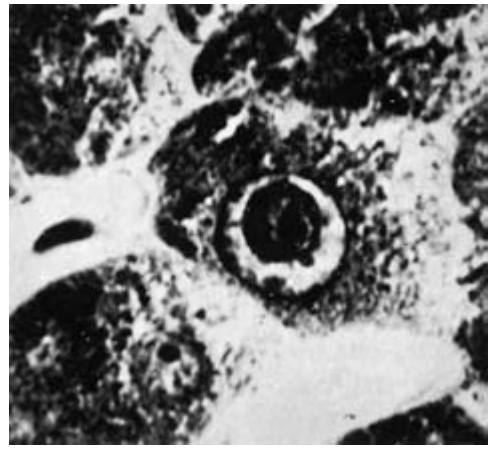


Fig. 25.10. Glycogen infiltration of a hepatic nucleus. Cells contain much glycogen. (Best's carmine for glycogen, ×1150.)

Non-alcoholic steato-hepatitis (NASH) is less frequent than pure fatty change but may lead to fibrosis and cirrhosis.

At autospy cirrhosis is seen twice as commonly in 'diabetics' as in the general population, but this excess incidence may be flawed because the hyperglycaemia recorded in life might be secondary to unrecognized cirrhosis.

Clinical features

Type 1 diabetes

There are usually no clinical features referable to the liver. Occasionally, however, the liver is greatly enlarged, firm and with a smooth, tender edge. Some of the nausea, abdominal pain and vomiting of diabetic ketosis may be due to hepatomegaly. Hepatic enlargement is found particularly in young people and children with severe, uncontrolled diabetes. Hepatomegaly is present in around 10% of well-controlled diabetics, in 60% of uncontrolled diabetics and in 10% of patients in ketosis. The liver returns to a normal size when the diabetes is brought under complete control. The enlargement is due to increased glycogen. Insulin therapy in the presence of a very high blood sugar level augments still further the glycogen content of the liver and, in the initial stages of treatment, hepatomegaly may increase.

Type 2 diabetes

The liver may be enlarged with a firm, smooth, non-tender edge. Enlargement is due to increased deposition of hepatic fat largely related to the obesity.

Diabetes in childhood

The liver may be enlarged and this enlargement has been attributed both to fatty infiltration and to increased amounts of glycogen. Aspiration biopsy studies show that the fatty change is slight but that the liver does contain an excess of glycogen. The hepatic changes are similar to those already described in the type 1, insulin-sensitive diabetic.

Liver function tests

In well-controlled diabetics, routine tests are usually normal and any change is due to a cause other than diabetes. Acidosis may produce mild changes including hyperglobulinaemia and a slightly raised serum bilirubin level. These return to normal with diabetic control.

Eighty per cent of diabetics with a fatty liver have abnormal results for one or more serum biochemical test such as transaminases, alkaline phosphatase and γ-glutamyl-transpeptidase.

Hepatomegaly, whether due to increased amounts of glycogen in type 1 diabetes, or to fatty change in type 2, does not correlate with the results of the liver function tests.

Hepato-biliary disease and diabetes

Any real increase of cirrhosis in diabetics seems unlikely. In most instances, the cirrhosis is diagnosed first before impaired glucose tolerance is recognized.

Advanced genetic haemochromatosis causes diabetes mellitus. Diabetes is also associated with chronic hepatitis C virus infection [5], and may occur in patients with autoimmune chronic hepatitis, probably due to the shared immunogenetic predisposition (HLA-B8 and -DR3).

Gallstones are frequent in non-insulin-dependent diabetics. This is probably more related to the biliary changes of obesity than a direct effect of diabetes. The same applies to the finding of a reduced gallbladder contractility in these patients.

Elective surgery for gallbladder disease is not dangerous but emergency biliary surgery in diabetics is associated with an increased mortality and a high risk of wound infections.

Sulphonylurea therapy can be complicated by cholestatic or granulomatous liver disease.

Glucose intolerance of cirrhosis

About 80% of patients with cirrhosis are glucose intolerant, with hyperglycaemia after an oral glucose load (fig. 25.11) [6]. Around 25% become frankly diabetic. The underlying mechanism is complex and not fully understood [2]. There is peripheral insulin resistance [11] and reduced insulin clearance in most cirrhotics. Adipocytes show defects in insulin sensitivity [11]. The first-pass hepatic extraction of insulin is reduced compared with controls [4]. Most patients compensate for the peripheral insulin resistance with increased pancreatic insulin secretion. The result is high circulating insulin levels, a normal fasting blood glucose and minimal glucose intolerance.

In some patients there is a blunted or subnormal pancreatic secretion of insulin after oral glucose, shown by the delayed appearance of C-peptide (fig. 25.11) [4]. This leads to delayed peripheral utilization of glucose. The fasting glucose remains normal.

With more severe hyposecretion of insulin [3], there is also continued hepatic glucose production due to lack of inhibition by insulin [10]. The net result of these changes is fasting hyperglycaemia and marked hyperglycaemia after oral glucose. The patient is diabetic.

The glucose intolerance of cirrhotic patients can be distinguished from genuine diabetes mellitus as the

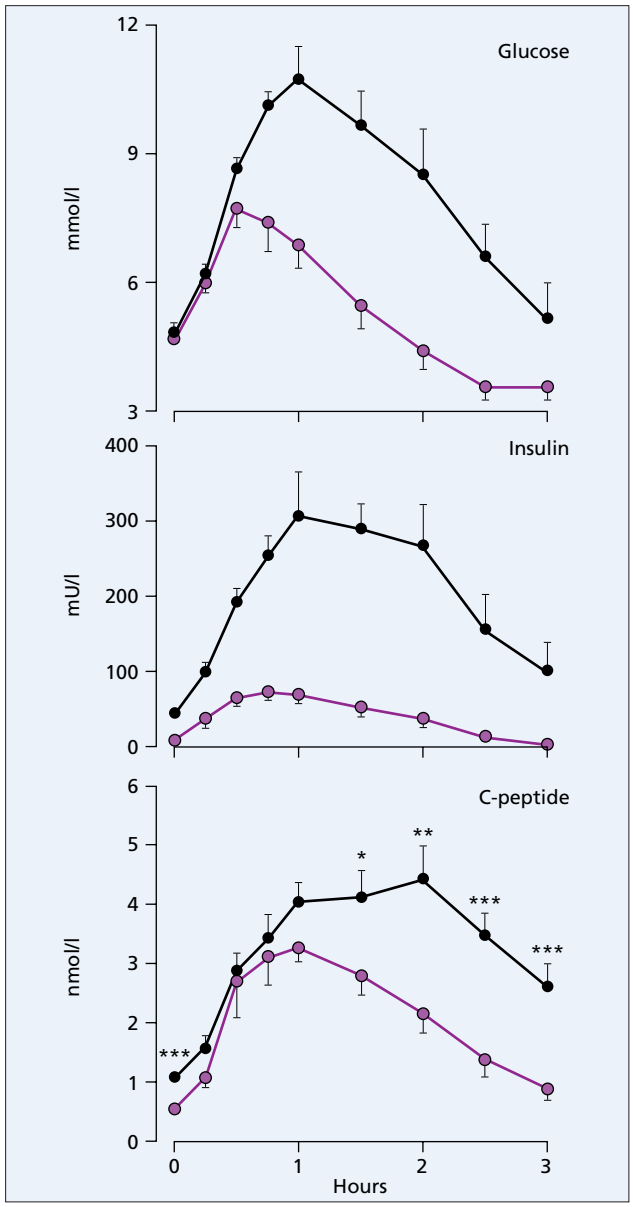


Fig. 25.11. Blood glucose, serum insulin and C-peptide responses to 75 g of oral glucose in cirrhotics ($n = 10$) (●) and normal controls ($n = 9$) (●). Note the normal fasting glucose followed by hyperglycaemia in the cirrhotics, despite greater insulin levels. The C-peptide response is blunted and only becomes significantly greater than controls at 90 min (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$) [4].

fasting blood glucose is usually normal. Clinical features of diabetes are not seen.

If the hyperinsulinaemia is reduced in cirrhotics for 96 h by the infusion of the somatostatin analogue octroetide, insulin-mediated glucose uptake returns to normal. This suggests that chronic hyperinsulinaemia in cirrhosis causes insulin resistance [9].

Liver transplantation reverses glucose intolerance and insulin resistance in cirrhotics. Both hepatic glucose uptake and peripheral glucose metabolism improve [7].

Diagnosis of cirrhosis in the presence of diabetes is usually easy from the clinical features. If necessary liver biopsy is diagnostic.

High carbohydrate feeding may be necessary in the management of cirrhosis, especially if there is encephalopathy. This always takes precedence over any impairment of glucose tolerance whether from genuine diabetes or secondary to the liver disease.

Treatment of diabetes in cirrhotic patients

There are few data on the treatment of diabetes in patients with cirrhosis [2]. Decisions depend upon the degree of hyperglycaemia and the severity and prognosis of the liver disease. Diet is appropriate for mild hyperglycaemia. Sulphonylureas can be used if diet is unsuccessful or the blood glucose is higher, but because these agents are metabolized by the liver, the shorter acting agents such as tolbutamide are preferred to reduce the risk of hypoglycaemia [2]. Because of the risk of lactic acidosis, biguanides such as metformin should be avoided. Insulin may be necessary but, as with other diabetics, regular self-monitoring of blood glucose is necessary. Short-acting insulin before meals, and intermediate-acting insulin in the evening, may be used. Strict guidelines do not exist and good control in this group of patients is often difficult and unsatisfactory. Steroid administration, necessary for example in autoimmune chronic liver disease, further complicates diabetic control.

References

1 Blendis L, Brill S, Oren R. Hepatogenous diabetes: reduced insulin sensitivity and increased awareness. *Gastroenterology* 2000; **119**: 1800.
2 Kruszynska YT. Glucose control in liver disease. *Curr. Med. Lit. Gastroenterol.* 1992; **11**: 9.
3 Kruszynska YT, Goulas S, Wollen N *et al*. Insulin secretory capacity and the regulation of glucagon secretion in diabetic and nondiabetic alcoholic cirrhotic patients. *J. Hepatol.* 1998; **28**: 280–91.
4 Kruszynska YT, Home PD, McIntyre N. Relationship between insulin sensitivity, insulin secretion and glucose tolerance in cirrhosis. *Hepatology* 1991; **14**: 103.
5 Mason AL, Lau JYN, Hoang N *et al*. Association of diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 1999; **29**: 328.
6 Megyesi C, Samols E, Marks V. Glucose tolerance and diabetes in chronic liver disease. *Lancet* 1967; **ii**: 1051.
7 Merli M, Leonetti F, Riggio O *et al*. Glucose intolerance and insulin resistance in cirrhosis are normalized after liver transplantation. *Hepatology* 1999; **30**: 649.
8 Perseghin G, Mazzafero V, Sereni LP *et al*. Contribution of reduced insulin sensitivity and secretion to the pathogenesis of hepatogenous diabetes: effect of liver transplantation. *Hepatology* 2000; **31**: 694.

9 Petrides AS, Stanley T, Matthews DE *et al*. Insulin resistance in cirrhosis: prolonged reduction of hyperinsulinemia normalizes insulin sensitivity. *Hepatology* 1998; **28**: 141.
10 Petrides AS, Vogt C, Schulze-Berge D *et al*. The pathogenesis of glucose intolerance and diabetes mellitus in cirrhosis. *Hepatology* 1994; **19**: 616.
11 Taylor R, Heine RJ, Collins J *et al*. Insulin action in cirrhosis. *Hepatology* 1985; **5**: 64.

Glycogen storage diseases [3, 14]

These are diseases with excessive and/or abnormal glycogen in the tissues. The frequency is approximately 1 in 25000 live births. Various types have different enzymatic (fig. 25.12) or structural defects. Most affect the liver (table 25.4). In the hepatic forms diagnosis is usually in infancy or early childhood with hypoglycaemia, massive hepatomegaly, poor physical growth, a tendency to increased fat deposition particularly in the cheeks, and biochemical abnormalities. Type V (muscle phosphorylase) and VII (phosphofructokinase) involve only muscle, or muscle and erythrocyte, respectively.

For those involving the liver, needle biopsy specimens should be examined histologically, quantitative glyco-

Table 25.4. The hepatic glycogen storage diseases

Type	Enzyme defect	Tissues involved
0	Glycogen synthetase	Liver
I	Glucose-6-phosphatase	Liver, kidney, intestines
II	Lysosomal α-1,4-glucosidase (acid maltase)	Generalized
III	Amylo-1,6-glucosidase (debranching enzyme)	Liver, muscle, WBC
IV	Amylo-1,4,1,6-transglucosidase (branching enzyme)	Generalized
VI	Liver phosphorylase	Liver, WBC
VIII	Phosphorylase activation	Liver
IXa, IXb	Phosphorylase kinase	Liver, WBC, RBC

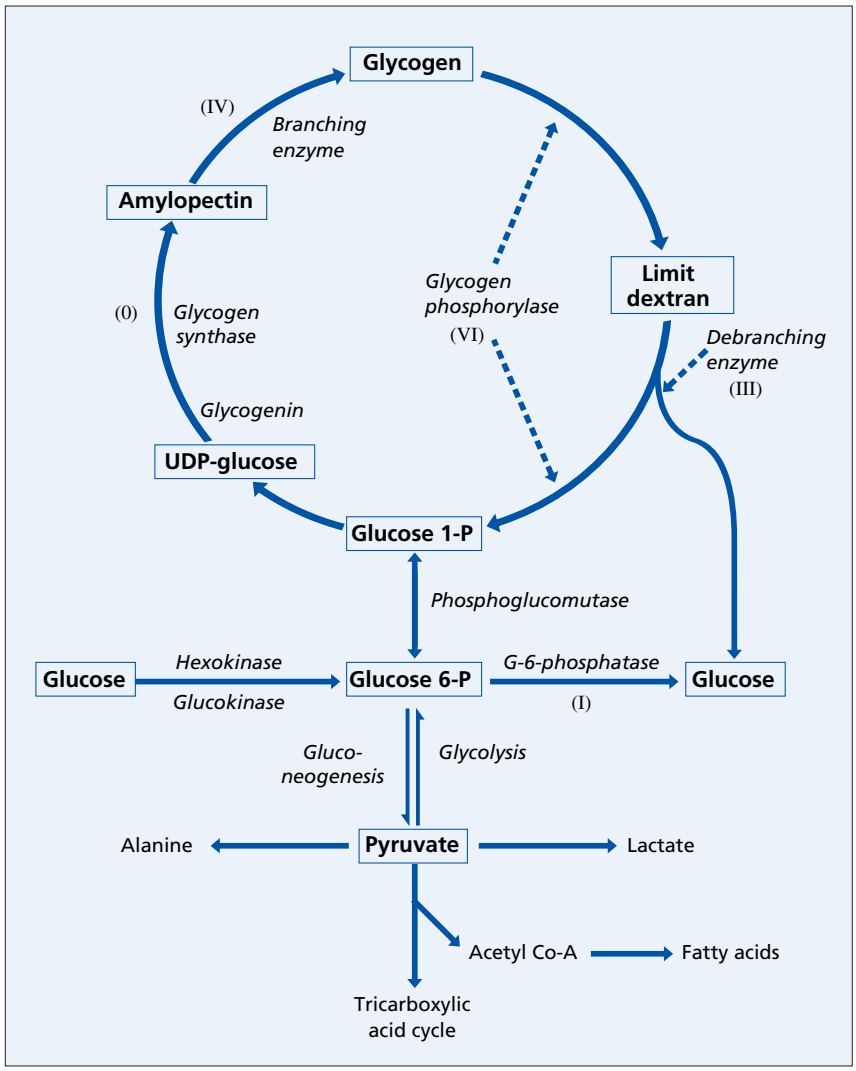


Fig. 25.12. Metabolic pathways in glycogen metabolism. Roman numerals indicate the defect in glycogen storage diseases (Modified from [14].)

gen analysis is helpful and a portion should be sent, appropriately preserved, to a centre where *in vitro* study of the enzymes present and of glycogen structure can be made (table 25.4). The diagnosis cannot be made on hepatic histology alone. All forms seem to be inherited, usually as an autosomal recessive, except type VI which is sex-linked. The types vary greatly in their severity and in their clinical picture. The critical abnormality is usually insufficient glucose production by the liver (fig. 25.12), which results in hypoglycaemia when the blood glucose level is not supported by an inflow of glucose from the intestinal tract. The other abnormalities follow from this defect and from the metabolic reactions to hypoglycaemia.

Type I (von Gierke's disease)

This type involves liver and kidney but not muscle and heart. The inheritance is autosomal recessive. Siblings may be involved, but transmission through successive generations has not been shown.

Type Ia is due to deficiency in the liver of glucose-6-phosphatase. In *type Ib*, the defect is in the translocase for glucose-6-phosphatase at the membrane of the endoplasmic reticulum. The clinical features of Ia and Ib are generally similar. Type Ib may affect adults.

Type Ic is due to a defect in hepatic microsomal phosphate/pyrophosphate translocase T_2.

Hepatic changes

The liver is enlarged, smooth and brown. The liver cells and their nuclei are laden with glycogen, but this is not diagnostic. In formol-fixed material, glycogen is washed out leaving an appearance of clear, plant-like cells. Excess fat is usually present. Peri-cellular zone 3 fibrosis and Mallory bodies have been described in type Ia glycogenesis [6]. The glycogen is usually stable, persisting many days post-mortem and despite severe ketosis or prolonged anaesthesia. Cirrhosis does not develop. Hepato-cellular adenomas and, rarely, carcinomas are late developments [2].

Clinical features

In early infancy the symptoms include irritability, pallor, cyanosis, feeding difficulties and seizures usually associated with hypoglycaemia. Episodes of diarrhoea and vomiting are frequent.

Presentation is as massive hepatomegaly at about 2 years old. The spleen is not enlarged—a point of distinction from the lipoidoses, the cirrhoses and congenital hepatic fibrosis.

The child is short and fat with particularly fat cheeks. Mental development is usually normal.

Hypoglycaemic episodes and fasting ketosis are usual.

Excessive bleeding is due to abnormal platelet function. In type Ib, infectious complications are due to neutropenia and neutrophil dysfunction related to abnormal glucose-6-phosphatase transport.

Untreated patients have a doll-like facies and hypotonia with delayed motor milestones. Chronic renal failure occurs in older patients whose disease has been ineffectively treated [13].

Type I glycogenosis can present in adults as hypoglycaemic symptoms and/or hepatomegaly [3].

Hepato-cellular adenomas develop [7]. At least one was found on ultrasound in 75% of 37 patients with type Ia aged 18 years or more [13]; 41% had multiple lesions. There may be pain. Haemorrhage into the tumour is reported. Malignant transition to hepato-cellular carcinoma is recognized [2].

Investigations

Routine liver function tests are usually normal. Occasionally transaminases are raised.

The fasting blood glucose level is low. Ketosis is related to defective glucose metabolism. Hyperlipaemia, hypercholesterolaemia and a fatty liver are common. Plasma uric acid levels are raised and gout develops after puberty. There is chronic lactic acidosis.

Diagnosis depends on showing that the blood glucose fails to rise adequately when hepatic glycogenolysis is stimulated. The pattern of metabolites (glucose, lactate, free fatty acids, ketones and uric acid) in serial blood samples after an oral glucose load or glucagon (around 4h after a meal) is the simplest way to evaluate suspected glycogen storage disease [14]. In type I, there is little or no rise in blood glucose after glucagon, while blood lactate, usually already high, increases further.

If a metabolic test is positive, liver biopsy should be taken for enzyme analysis as well as histology and histochemistry for glycogen quantification. Classification of subtypes of type I requires more specific enzyme analyses.

Around 30 mutations in human liver glucose-6-phosphatase cDNA have been identified in patients with type Ia glycogen storage disease [3, 9]. In some instances this may aid diagnosis and/or prenatal diagnosis.

Ultrasound shows marked parenchymal changes in 40% of patients due to fat, and will identify tumours, usually adenoma [8].

Treatment [14]

Repeated enteral glucose feeds, often given as a continual nocturnal infusion, are needed to prevent hypoglycaemia. Uncooked corn starch, a slow-release source of

glucose, is an alternative regime and can be given with milk feeds every 4 h [15]. Parenteral hyperalimentation may be useful. Allopurinol may be given for the high serum uric acid.

Haemorrhage into an adenoma may necessitate resection.

Hepatic transplantation has been successfully performed both because of poor control of blood glucose with usual therapeutic measures and for hepatic adenomas. With longer survival through improved dietary regimens, adenoma-related complications (haemorrhage, malignant transformation) are clinical problems. Ideally transplantation should predate malignant transformation but data are needed to show when this intervention is most appropriate.

Prognosis

Advances in the management of these patients, with early diagnosis and the prevention of hypoglycaemia, has improved the prognosis. Previously many patients died in early childhood. Despite good glucose control some metabolic abnormalities (raised lipids, uric and lactic acid) may persist. There are great variations in severity and some patients seem to recover completely. The disease tends to become milder after puberty. Later deaths are due to gouty nephropathy or to hepatocellular tumours.

Type II (Pompe's disease)

This primary lysosomal disease is due to deficiency of lysosomal acid α-1,4-glucosidase which normally degrades glycogen within lysosomes.

There is weakness of skeletal muscle, cardiomegaly, hepatomegaly and macroglossia. Mental development is normal. Infantile, childhood and adult onset forms exist. The infantile form is the most severe. Glucagon and adrenaline tests are normal and hypoglycaemia does not occur. Hyperlipidaemia is conspicuous.

All organs show vacuolated cells due to the enlarged lysosomes which contain the glycogen. Vacuolated lymphocytes are found in peripheral blood and marrow. The liver cells at autopsy show particularly prominent vacuoles.

Type III (Cori's disease) (fig. 25.13)

Clinically this resembles type I glycogenosis. Acidosis, hypoglycaemia and hyperlipidaemia may be present. Blood glucose does not rise after glucagon, but galactose and fructose tolerance are normal. Serum transaminases are usually increased. Lactate and uric acid levels are normal because the pathway for gluconeogenesis is normal and hepatic glycolysis not increased. Symptoms may be mild and by adult life only the hepatomegaly may remain. The prognosis is fair to good.

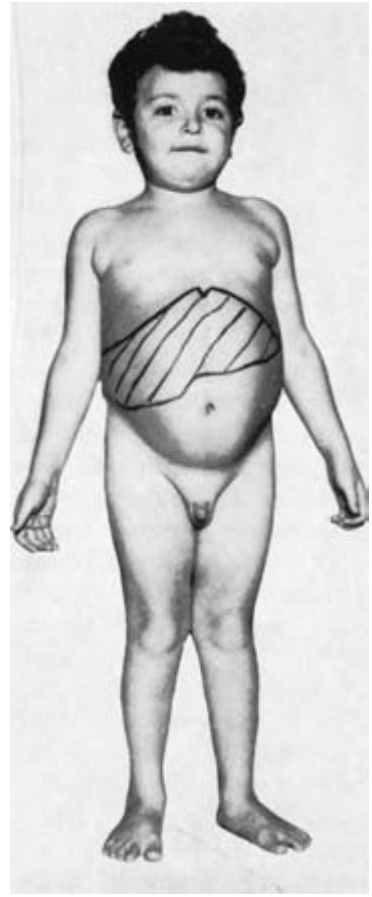


Fig. 25.13. Type III glycogen storage disease (Cori's disease). This boy of 4 years had enormous hepatomegaly but without splenomegaly. At the age of 35 years, he is well.

Peri-portal fibrosis occurs but cirrhosis is rare [5]. Liver biopsy is rarely necessary for diagnosis which is made by measuring debrancher activity in a mixed white blood cell pellet.

There is a single gene for glycogen debranching enzyme, with differential RNA transcription in liver and muscle. Type III glycogen storage disease may effect muscle and liver (IIIA) or only the liver (IIIB), due to mutations in the gene [11]. The enzyme has two functional catalytic sites with different functions necessary for the debranching activity. Loss of one or other of these catalytic sites is rare, giving types IIIC and IIID.

Corn starch therapy may improve growth and liver function.

The prognosis is better for the purely hepatic form of disease (IIIB), because of myopathy and cardiomyopathy in the other groups. Ultrasound shows hepatic adenomas in 25% of patients, less often than that found in type I [7, 8]. Liver transplantation has been done for

cirrhosis and hepato-cellular carcinoma in a 33-year-old patient with a 1-year follow-up [5].

Type IV (Andersen's disease)

This very rare, but usually very severe, form of generalized glycogenosis is associated with low normal tissue levels of glycogen [3]. The glycogen structure is abnormal due to deficiency of the branching enzyme amylo-1,4,1,6-transglucosidase. Hypoglycaemia is rare.

A cirrhosis develops which may be associated with many giant cells. It can resemble that of the alcoholic. The chief distinction is the presence of intra-cellular deposits of abnormal glycogen partially removed by diastase digestion. This may show abnormal staining properties turning purplish with iodine instead of the usual reddish-brown. It stains strongly with PAS. The cirrhosis is presumably due to a reaction to this abnormal glycogen which is found in every organ examined.

The child develops hepatosplenomegaly, ascites and finally liver failure. Enzyme deficiency in skin fibroblasts has been shown and may allow diagnosis and detection of heterozygotes. The features of cirrhosis are present. Hepato-cellular adenoma is reported [1]. Death is in early childhood. Hepatic transplantation has been successful. Because of the persistent metabolic abnormality in extra-hepatic sites, there may be progressive extra-hepatic disease [12] but it is not known why this does not occur in all patients [10].

Type VI (Hers' disease)

This involves only the liver and is caused by deficiency of phosphorylase, which is most frequently caused by a failure to activate the enzyme due to a deficiency of phosphorylase kinase. Kinase deficiency (previously also known as type IX) accounts for about 25% of all cases of glycogen storage disease, and is predominantly X-linked, although there is also an autosomal recessive variant.

The clinical features of phosphorylase kinase deficiency and phosphorylase deficiency itself are identical, with a milder form of disease than types I and III [3]. Patients present in infancy or early childhood with growth retardation and hepatomegaly. Except after prolonged fasting, hypoglycaemia is unusual.

The prognosis is excellent and the clinical course benign. The patient catches up growth and hepatomegaly becomes less. Most adults are asymptomatic.

Phosphorylase and phosphorylase kinase deficiency is detected by measuring their activity in red blood cells, although for definitive diagnosis of the various subtypes liver biopsy is necessary.

Hepatic glycogen synthetase deficiency (type 0)

This very rare condition is characterized by fasting hypoglycaemia and hyperketonaemia, and hyperglycaemia and high blood lactate levels after feeding. The classical presentation is in early infancy with fasting hypoglycaemia/hyperketonaemia. Liver size is normal. Growth may be delayed. Some individuals have few if any symptoms and the condition may be underdiagnosed [4].

Hepatic histology shows small amounts of glycogen and steatosis.

Treatment involves night-time feeds of uncooked corn starch, to prevent hypoglycaemia and ketosis, and frequent daytime feeds with increased protein and reduced carbohydrate to reduce hyperglycaemia and lactic acidosis [14].

References

1 Alshak NS, Cocjin J, Podesta L *et al*. Hepatocellular adenoma in glycogen storage disease type IV. *Arch. Path. Lab. Med*. 1994; **118**: 88.

2 Bianchi L. Glycogen storage disease I and hepatocellular tumours. *Eur. J. Paediatr*. 1993; **152** (Suppl. 1): S63.

3 Burchell A. Glycogen storage diseases and the liver. *Bailliere's Clin. Gastroenterol*. 1998; **12**: 337.

4 Glitzelmann R, Spycher MA, Feil G *et al*. Liver-glycogen synthase deficiency—a rarely diagnosed entity. *Eur. J. Pediatr*. 1996; **155**: 561.

5 Haagsma EB, Smit GPA, Niezen-Koning KE *et al*. Type IIIb glycogen storage disease associated with end-stage cirrhosis and hepatocellular carcinoma. *Hepatology* 1997; **25**: 537.

6 Itoh S, Ishida Y, Matsuo S. Mallory bodies in a patient with type 1a glycogen storage disease. *Gastroenterology* 1987; **92**: 520.

7 Labrune P, Trioche P, Duvaltier I *et al*. Hepatocellular adenomas in glycogen storage disease type I and III: a series of 43 patients and review of the literature. *J. Paediatr. Gastroenterol. Nutr*. 1997; **24**: 276.

8 Lee P, Mather S, Owens C *et al*. Hepatic ultrasound findings in the glycogen storage diseases. *Br. J. Radiol*. 1994; **67**: 1062.

9 Lei KJ, Chen YT, Chen H *et al*. Genetic basis of glycogen storage disease type 1a: prevalent mutations at the glucose-6-phosphatase locus. *Am. J. Hum. Genet*. 1995; **57**: 766.

10 Selby R, Starzl TE, Yunis E *et al*. Liver transplantation for type I and type IV glycogen storage disease. *Eur. J. Paediatr.* 1993; **152** (Suppl. 1): S71.

11 Shen J, Bao Y, Liu HM *et al*. Mutations in exon 3 of the glycogen debranching enzyme gene are associated with glycogen storage disease type III that is differentially expressed in liver and muscle. *J. Clin. Invest*. 1996; **98**: 352.

12 Sokal EM, Van Hoof F, Alberti D *et al*. Progressive cardiac failure following orthotopic liver transplantation for type IV glycogenosis. *Eur. J. Paediatr.* 1992; **151**: 200.

13 Talente GM, Coleman RA, Alter C *et al*. Glycogen storage disease in adults. *Ann. Intern. Med*. 1994; **120**: 218.

14 Wolfsdorf JI, Holm IA, Weinstein DA. Glycogen storage diseases. Phenotypic, genetic and biochemical characteris-

tics, and therapy. *Endocrinol. Metabol. Clin. N. Am.* 1999; **28**: 801.

15 Wolfsdorf JI, Keller RJ, Landy H *et al*. Glucose therapy for glycogenosis type 1 in infants: comparison of intermittent uncooked cornstarch and continuous overnight glucose feedings. *J. Paediatr.* 1990; **117**: 384.

Hereditary fructose intolerance

This autosomal recessive condition is caused by mutations in the gene for aldolase B on chromosome 9. Deficiency of this enzyme impairs the cleavage of fructose-1-phosphate in liver, renal cortex and intestinal epithelium. Exposure to fructose induces cytoplasmic accumulation of fructose-1-phosphate and hence fructose intoxication.

The severity of the disease phenotype appears independent of the type of aldolase B gene mutation, and relates more to the patient's dietary history [1].

The acute syndrome is marked by abdominal pain, vomiting and hypoglycaemia. The chronic syndrome is one of severe metabolic derangement with failure to thrive, vomiting, hepatomegaly and liver and renal tubular dysfunction. Fructosaemia, fructosuria and hypophosphataemia are features. Diagnosis is confirmed by the intravenous fructose tolerance test or by direct assay of fructaldolase activity in tissue biopsy samples. Hepatic histology shows similar findings to galactosaemia with the ultimate development of cirrhosis.

Older children learn to avoid fructose and sucrose and isolated hepatomegaly may be the only abnormality.

Treatment is by a diet without sucrose and fructose. Sometimes the symptoms persist in older children and are marked by growth retardation when even more strict fructose restriction may be necessary.

Reference

1 Ali M, Rellos P, Cox TM. Hereditary fructose intolerance. *J. Med. Genet.* 1998; **35**: 353.

Glutaric aciduria type II

This disturbance of organic acid metabolism presents in infants or adults as recurrent hypoglycaemia with elevated serum free fatty acid. There may be hepatomegaly. The liver often shows fatty change. Peri-portal fibrosis and hypoplastic extra-hepatic ducts are reported [1].

Reference

1 Wilson GN, De Chadarevian J-P, Kaplan P *et al*. Glutaric aciduria type II: review of the phenotype and report of an unusual glomerulopathy. *Am. J. Med. Genet.* 1989; **32**: 395.

Galactosaemia

The liver and red blood cells lack the specific enzyme, galactose-1-phosphate-uridyl transferase (GALT), essential for galactose metabolism. Toxic effects are related to the accumulation in the tissues of galactose-1-phosphate. The mechanism of toxicity is uncertain [3].

Transferase deficiency is inherited as an autosomal recessive with a frequency of between 1 in 10 000 and 1 in 60 000. There are more than 150 mutations reported in the GALT gene [7], and this genetic heterogeneity contributes to the wide phenotypic heterogeneity.

A significant reduction of the transferase is found in heterozygotes.

Clinical picture

The disease starts *in utero*. The infant presents with feeding difficulties, with sepsis, and with vomiting, diarrhoea and malnutrition, often with jaundice. Ascites and hepatosplenomegaly are noted. Cataracts develop. Death may result in the first few weeks, but survivors become mentally retarded and finally show features of cirrhosis, portal hypertension and, later, ascites.

Hepatic changes

Those dying in the first few weeks show diffuse hepatocellular fatty change. In the next few months the liver shows pseudo-glandular or ductular structures around the canaliculi which may contain bile. Regeneration is conspicuous, necrosis scanty and a macronodular cirrhosis results. Giant cells may be numerous.

Diagnosis [5]

The biochemical changes include galactosaemia, galactosuria, hyperchloraemic acidosis, albuminuria and aminoaciduria. Diagnosis is made by finding a urinary reducing substance which is glucose oxidase negative. Definite diagnosis comes from determining GALT levels in the erythrocytes.

The condition should be considered in all young patients with cirrhosis and even in the adult if there are suggestive features such as cataract. Galactosaemia has been diagnosed as late as 63 years [4]. A survey of a group of juvenile cirrhotics for this disease, however, failed to reveal a single case and this must be a rare cause of adult cirrhosis [2].

Prognosis and treatment

Great improvement results from withdrawal of milk and milk products from the diet. If the child survives to 5 years of age, recovery may be complete apart from per-

sistent cataracts or cirrhosis. Delayed puberty, speech abnormalities and reduced intelligence are seen in the longer term [6]. There is endogenous production of galactose explaining the persistence of galactose metabolites despite compliance with dietary restriction [1]. Those living into childhood and adult life without treatment may be only partially enzyme deficient. Alternatively, they may have developed another pathway for handling galactose. The consumption of galactose-containing foods also decreases with age.

References

1 Berry GT, Nissim I, Lin Z *et al*. Endogenous synthesis of galactose in normal men and patients with hereditary galactosemia. *Lancet* 1995; **346**: 1073.
2 Fisher MM, Spear S, Samols E *et al*. Erythrocytic galactose-1-phosphate uridyl transferase levels in hepatic cirrhosis. *Gut* 1964; **5**: 170.
3 Gitzelmann R. Galactose-1-phosphate in the pathogenesis of galactosemia. *Eur. J. Paediatr* 1995; **154** (Suppl. 2): S45.
4 Hsia DY-Y, Walker FA. Variability in the clinical manifestations of galactosaemia. *J. Pediatr.* 1961; **59**: 872.
5 Monk AM, Mitchell AJH, Milligan DWA *et al*. The diagnosis of classical galactosaemia. *Arch. Dis. Child.* 1977; **52**: 943.
6 Schweitzer S, Shin Y, Jakobs C *et al*. Long-term outcome in 134 patients with galactosaemia. *Eur. J. Paediatr.* 1993; **152**: 36.
7 Tyfield L, Reichardt J, Fridovich-Keil J *et al*. Classical galactosemia and mutations at the galactose-1-phosphate uridyl transferase (GALT) gene. *Hum. Mutat.* 1999; **13**: 417.

Mucopolysaccharidoses [2]

These are a group of lysosomal storage diseases, each of which is due to a deficiency of a specific lysosomal enzyme involved in the degradation of dermatin sulphate, heparin sulphate, chondroitin sulphate or keratin sulphate. Hepatosplenomegaly is a feature.

Hepatocyte and Kupffer cell swelling and vacuolization are due to storage of poorly degraded mucopolysaccharide.

In addition, hepatic fibrosis outlining the hepatic lobule (zone 1) may be seen. The mechanism is unknown, but is possibly due to abnormal accumulation of a hepato-toxic metabolite of mucopolysaccharide.

Hurler's syndrome (gargoylism) is inherited as an autosomal recessive and is characterized by deficiency of the lysosomal degrading enzyme, α-L-iduronidase, in liver, cultured skin fibroblasts and leucocytes. It is characterized by coarse facial features, dwarfism, limitation of joint movement, deafness, abdominal hernias, hepatosplenomegaly, cardiac abnormalities and mental retardation.

The liver in the mucopolysaccharidoses is large and firm. Microscopically liver cells are swollen and together with Kupffer cells accumulate glycosaminoglycan, demonstrated by colloidal iron stain. Electron microscopy shows characteristic membrane-bound inclusions in hepatocytes and Kupffer cells. This lysosomal storage material disappears in the majority of patients after bone marrow transplantation [1].

Diagnosis may be made by finding increased urinary or leucocyte mucopolysaccharides. Culture of skin biopsies shows fibroblasts containing mucopolysaccharides.

References

1 Resnick JM, Krivit W, Snover DC *et al*. Pathology of the liver in mucopolysaccharidosis: light and electron microscopic assessment before and after bone marrow transplantation. *Bone Marrow Transplant*. 1992; **10**: 273.
2 Wraith JE. The mucopolysaccharidoses: a clinical review and guide to management. *Arch. Dis. Child*. 1995; **72**: 263.

Familial hypercholesterolaemia

This is an autosomal dominant disease due to absence of a gene which codes for the LDL receptor on cell membranes [2]. The liver contains 60% of such receptors. Sufferers have increased plasma total cholesterol and LDL from birth, cutaneous xanthomas develop and most homozygotes die from coronary artery disease before the age of 30 years.

Hypercholesterolaemia is controlled by reduction in dietary saturated fats and administration of bile acid sequestrants such as cholestyramine. Inhibitors of cholesterol synthesis, given at high dose, lower serum cholesterol. High-dose atorvastatin reduces total cholesterol by 40% [5]. One child has been successfully treated by simultaneous heart transplant for the coronary disease and liver transplant to provide LDL receptors [1]. Follow-up showed decreases in LDL and plasma cholesterol [4].

Gene therapy, using 'transplant' of autologous hepatocytes genetically corrected with recombinant retroviruses carrying the LDL receptor, was successful with 18 months' follow-up [3].

References

1 Bilheimer DW, Goldstein JL, Grundy SM *et al*. Liver transplantation to provide low-density-lipoprotein receptors and lower plasma cholesterol in a child with homozygous familial hypercholesterolemia. *N. Engl. J. Med*. 1984; **311**: 1658.
2 Brown MS, Goldstein JL. Lipoprotein receptors in the liver: control signals for plasma cholesterol traffic. *J. Clin. Invest*. 1983; **72**: 743.
3 Grossman M, Raper SE, Kozarsky K *et al*. Successful *ex vivo* gene therapy directed to liver in a patient with familial hypercholesterolaemia. *Nature Genet*. 1994; **6**: 335.
4 Valdivielso P, Escolar JL, Cuervas-Mons V *et al*. Lipids and lipoprotein changes after heart and liver transplantation in a

patient with homozygous familial hypercholesterolemia. *Ann. Intern. Med.* 1988; **108**: 204.
5 Wierzbicki AS, Lumb PJ, Semra YK *et al*. High-dose atorvastatin therapy in severe heterozygous familial hypercholesterolaemia. *Q. J. Med.* 1998; **91**: 291.

Amyloidosis [6, 8]

Amyloidosis is not a single disease. It is the term used to describe a group of conditions linked by a common feature. This is the extra-cellular deposition of a protein in an abnormal fibrillar form. It is called amyloid because the waxy infiltration of organs resembles starch (Latin: *amylum*) in its staining. It may be hereditary or acquired, systemic or localized, an incidental finding or cause death. Clinical features develop because of the disruption of normal function in kidney, heart and other organs by the deposition of amyloid fibrils.

Classification of amyloidoses is based on the protein involved (table 25.5). Those of particular interest to the hepatologist are AL and AA because of the clinical features, and ATTR because of the role of liver transplantation. Other proteins responsible for amyloidosis include apolipoprotein A1 (AApoA1) and lysozyme (ALys). The spectrum of amyloid-related diseases of general interest includes Alzheimer's disease (Aβ) as well as type 2 diabetes (A1APP) and haemodialysis related ($A\beta_2M$).

The common biochemical feature is that the proteins involved can exist in two stable structures, a normal soluble form and an abnormal fibril. Fibrils form by autoaggregation. This is related to overproduction of the soluble form, but why some individuals develop amyloid and others do not is unclear. All amyloid fibrils share a similar core ultrastructure (β-strands within β-sheets) and many physicochemical properties. All amyloid deposits contain the normal plasma protein serum amyloid P (SAP) component, and this is the basis for radio-labelled SAP scanning currently used in specialist centres to show the distribution and amount of amyloid, and any change during treatment.

Table 25.5. Classification of amyloidosis

Type*	Fibril	Syndrome
AA	Serum amyloid A	Reactive (secondary) amyloid acquired (e.g. rheumatoid) hereditary (FMF)
AL	Monoclonal immunoglobulin light chain	Primary amyloid myeloma associated no association
ATTR	Transthyretin (TTR)	Familial amyloidotic polyneuropathy

FMF, familial mediterranean fever.
* Other types: $A\beta_2M$ (renal failure dialysis), Aβ (Alzheimer's disease), A1APP (diabetes/insulinoma).

In collected series, AL amyloid is the more common type. The contribution of AA, familial and localized amyloid depends on the centre. In a UK study of 484 patients with systemic amyloidosis, AL accounted for 37%, AA 28%, hereditary 20% and dialysis-related 14%. Forty-seven other patients had localized amyloid syndromes [14]. In an American study of 1070 patients with systemic amyloid, 86% had AL [12].

Clinical features

AL amyloid (formerly primary amyloid) is caused by deposition of fibrils from all or part of a monoclonal immunoglobulin light chain, more commonly λ than κ, which usually can be detected in serum or urine. Most patients have a subtle monoclonal gammopathy. Multiple myeloma is diagnosed in only 10–20% of cases. In about 15% of patients a gammopathy cannot be demonstrated. The most common clinical presentations are nephrotic syndrome, cardiomyopathy, carpal tunnel syndrome and a sensory motor neuropathy. Hepatomegaly is found in 25% [12]. Intestinal involvement includes motility disturbances, and malabsorption. Macroglossia or peri-orbital purpura are highly suggestive of AL amyloidosis.

AA amyloid (formerly secondary amyloid) is caused by fibrils of AA protein derived from the circulating acute phase reactant serum amyloid A (SAA) by proteolytic cleavage. SAA is synthesized by hepatocytes, transcriptionally regulated by cytokines, and is an apolipoprotein. Elevated serum SAA is a prerequisite for the development of AA amyloidosis, but not every patient with such levels will develop the disease.

Juvenile and adult rheumatoid arthritis are the commonest underlying inflammatory conditions, although chronic sepsis, tuberculosis, Crohn's disease and malignant neoplasms may be responsible. Presentation is usually with proteinuria, nephrotic syndrome or renal failure, which is the cause of death in half of cases. The spleen is affected early and may be enlarged. Liver involvement, seen in around 25% of patients, is a sign of extensive disease.

Familial Mediterranean fever (FMF) is an autosomal recessive disease, characterized by acute attacks of fever with sterile peritonitis, pleurisy or synovitis. FMF primarily affects non-Ashkenazi Jewish, Armenian, Turkish and Middle-Eastern Arab populations. The gene implicated, *MEFV*, has been cloned, and the protein product called pyrin or marenostrin is a neutophil protein which may be involved in the downregulation of inflammation [1]. Mutations have been identified [10] but diagnosis remains clinical rather than by genotype. Family studies have identified some cases with autosomal dominant

inheritance [3]. One of the most significant complications of FMF is AA amyloidosis, usually affecting the kidneys. Renal insufficiency may progress to end-stage renal disease. Liver, spleen and gastrointestinal tract may be involved.

Familial amyloidotic polyneuropathy (FAP) is caused by the deposition of variant transthyretin (TTR). Normal TTR is mainly produced by the liver and takes part in the transport of thyroid hormones and vitamin A. Over 60 mutations have been found in the *TTR* gene. FAP is characterized by progressive peripheral and autonomic neuropathy. Amyloid may also affect the spleen, heart, eyes, thyroid and adrenals. Other forms of hereditary systemic amyloidosis are extremely rare.

Hepatic involvement

Using SAP scintigraphy, hepatic amyloidosis was shown in 54% of patients with AL amyloid and 18% of those with AA [14]. Hepatic amyloid was only detected in 1 of 53 patients with FAP. SAP scintigraphy correlates with hepatic histology when there are parenchymal or stromal amyloid deposits but not with diffuse vascular deposits [14].

Hepatomegaly in patients with amyloidosis suggests hepatic involvement [7] although occasionally the liver may not be enlarged. An enlarged spleen infiltrated with amyloid may be found. The serum alkaline phosphatase may be raised, but levels overlap between patients (both AA and AL) with and without liver involvement [14].

Percutaneous liver biopsy causes haemorrhage in 4–5% of patients with amyloid [8, 14] and is best avoided. Diagnosis can be made without hepatic histology (see below).

If available, hepatic histology in systemic amyloidosis may show vascular deposition and variable interstitial amyloid, but the pattern is not diagnostically helpful. The amyloid is shown as homogeneous, amorphous, eosinophilic material. It stains with alkaline alcoholic Congo red or methyl violet (fig. 25.14). Polarization microscopy of Congo red stained sections shows the amyloid as apple green birefringent fibrils. Amyloid may also be shown by fluorescent microscopy.

The amyloid is deposited between the columns of liver cells and the sinusoidal wall in the space of Disse. The liver cells are not themselves involved but are compressed to a variable extent. The mid-zone and portal areas are most heavily infiltrated.

Occasionally in AL amyloid the amyloid is found only in the portal tracts in the walls of hepatic arterioles, around the interlobular arteries and lying free in clumps.

Electron microscopy confirms fibrils 10 nm long that do not branch.

Hepato-cellular failure is rare as is portal hypertension, which when present is of the sinusoidal type and has a poor prognosis [2].

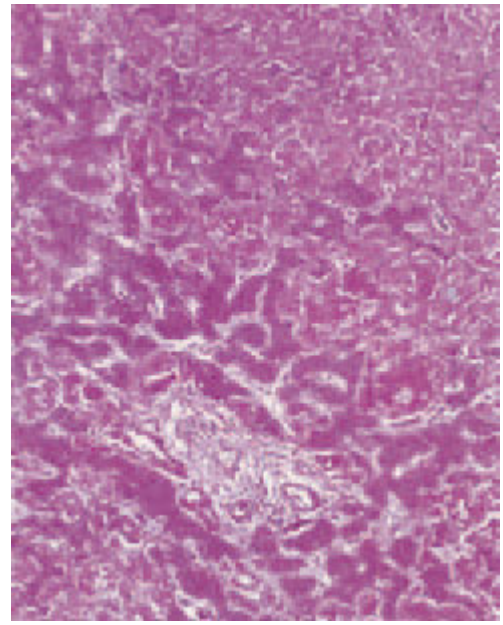


Fig. 25.14. Amyloid is shown as amorphous dark staining material between the liver cells and sinusoids. (Methyl violet, ×40.)

Severe intra-hepatic cholestasis may rarely complicate AL amyloidosis [15]. It is presumably due to the intense amyloid deposition interfering with bile passage into canaliculi and small bile ducts. The prognosis is poor. Light-chain deposition disease of the liver may also be associated with AL-type amyloidosis and produce severe cholestasis [5].

Massive spontaneous hepatic haemorrhage has been reported in a patient with the very rare hereditary lysozyme-associated amyloidosis [11].

Diagnostic approach

A clinical suspicion of amyloidosis will lead to consideration of the best site of biopsy (see below) to obtain tissue for appropriate staining, and a search for evidence of the cause. This may be suggested by a history of chronic inflammation (AA) or a family history (FAP). To identify AL amyloidosis, immunoelectrophoresis of serum and urine for monoclonal protein is done, and bone marrow biopsy with immunohistochemical staining of plasma cells for κ- and λ-chains. Isoelectric focusing of serum samples will show bands of variant and wild-type transthyretin, and analysis of genomic DNA may show a mutant *TTR* gene in FAP.

Although biopsy of the affected tissue is likely to be diagnostic, for example the kidney or heart, other tissues which require a less invasive approach can provide the answer.

Biopsy of the subcutaneous abdominal fat pad, rectal mucosa and labial salivary gland are safe and give a positive result in up to 75–80% of cases depending on expertise in the procedure [8, 12]. Liver biopsy is more invasive and carries a reported risk of bleeding of 4–5% and is best avoided in favour of the less invasive routes.

^{123}I-SAP scintigraphy is a specific and sensitive method for detecting and monitoring amyloidosis during treatment of the underlying cause [14]. This method is, however, at present a specialized tool with restricted availability.

Prognosis

This varies according to the type of amyloidosis, the degree of organ involvement and the response to therapy of the underlying condition.

Patients with AL amyloidosis have a mean survival of 1–2 years [12]. There may be longer survival with intensive chemotherapy compared to low-dose oral regimens [4]. Survival is not effected by liver involvement by amyloid [7, 14]. Survival is less when patients have symptomatic heart disease (median survival 6 months).

The prognosis for AA amyloidosis is affected by the underlying chronic disease. The 5-year survival in those with liver deposits is reduced compared with those without liver involvement (43 vs. 72%) (fig. 25.15) [14]. Surviral is significantly better in those with a serum amyloid A value maintained in the reference range (< 10 mg/l) [9].

Patients with FAP may survive for up to 15 years. Patients with transthyretin mutations associated with a younger age of disease onset have a more rapid progression of neurological and cardiac disease and a shorter survival [6]. The 5-year survival after liver transplantation is 75% [17].

Treatment

AA amyloid is treated by controlling the underlying disease. If tuberculosis is cured then amyloid may disappear. Similarly, clinical improvement in rheumatoid arthritis may be paralleled by disappearance of clinical signs of amyloidosis. There is no specific treatment.

Prophylactic colchicine prevents the development of amyloidosis in all cases of FMF.

The treatment of AL amyloid remains difficult because melphalan combined with prednisone only has a 30% response rate with a mean survival of 18 months [13]. Although the response to higher doses of melphalan with peripheral blood stem cell support is greater (60%) [4], the patients have to be fit enough to tolerate the treatment.

Liver transplantation is the definitive treatment for FAP with a 75% 5-year survival [17]. Liver transplantation results in disappearance of the variant TTR from plasma, and regression of some disease. Recovery from autonomic neuropathy is greater than from peripheral neuropathy. The explanted liver from patients with FAP has been transplanted into selected recipients, on the basis that these livers may be normal apart from the production of variant transthyretin, having only been removed to arrest the build-up of further amyloid and clinical progression of polyneuropathy [16]. This has been termed domino liver transplantation. Follow-up of recipients of a FAP liver was uncomplicated over 18 months, and allowed study of the variant transthyretin protein in donors and recipients.

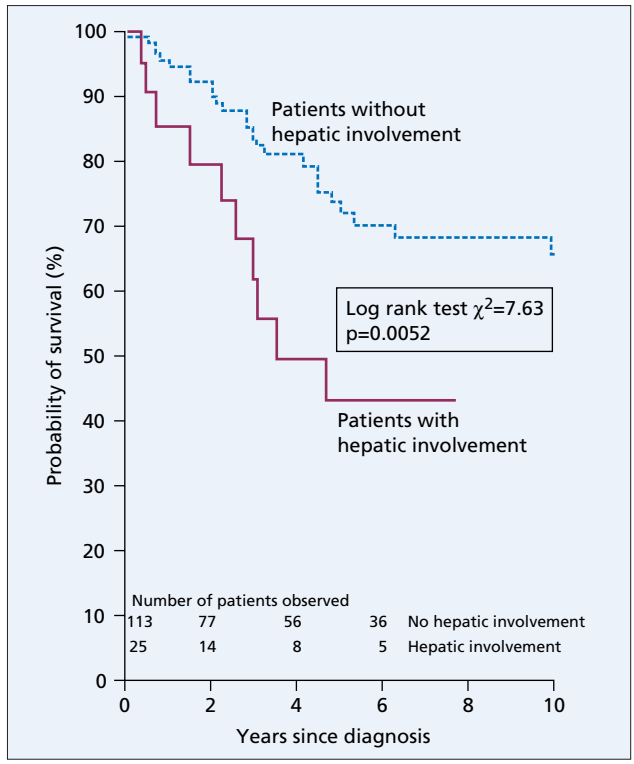


Fig. 25.15. Kaplan–Meier estimate of survival in patients with systemic AA amyloidosis with and without hepatic involvement on ^{123}I-serum amyloid P component. (From [14] with permission.)

References

1 Ben-Chetrit E, Levy M. Familial mediterranean fever. *Lancet* 1998; **351**: 659.
2 Bion E, Brenard R, Pariente EA *et al*. Sinusoidal portal hypertension in hepatic amyloidosis. *Gut* 1991; **32**: 227.
3 Booth DR, Gillmore JD, Lachmann HJ *et al*. The genetic basis of autosomal dominant familial Mediterranean fever. *Q. J. Med*. 2000; **93**: 217.
4 Comenzo RL, Vosburgh E, Falk RH *et al*. Dose-intensive melphalan with blood stem-cell support for the treatment of AL (amyloid light-chain) amyloidosis: survival and responses in 25 patients. *Blood* 1998; **91**: 3662.
5 Faa G, Van Eyken P, De Vos R *et al*. Light chain deposition

disease of the liver associated with AL-type amyloidosis and severe cholestasis. *J. Hepatol.* 1991; **12**: 75.
6 Falk RH, Comenzo RL, Skinner M. The systemic amyloidoses. *N. Engl. J. Med.* 1997; **337**: 898.
7 Gertz MA, Kyle RA. Hepatic amyloidosis: clinical appraisal in 77 patients. *Hepatology* 1997; **25**: 118.
8 Gillmore JD, Lovat LB, Hawkins PN. Amyloidosis and the liver. *J. Hepatol.* 1999; **30**: 17.
9 Gillmore JD, Lovat LB, Persey MR *et al*. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. *Lancet* 2001; **358**: 24.
10 Grateau G, Pêcheux C, Cazeneuve C *et al*. Clinical vs. genetic diagnosis of familial Mediterranean fever. *Q. J. Med.* 2000; **93**: 223.
11 Harrison RF, Hawkins PN, Roche WR *et al*. 'Fragile' liver and massive hepatic haemorrhage due to hereditary amyloidosis. *Gut* 1996; **38**: 151.
12 Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin. Haematol.* 1995; **32**: 45.
13 Kyle RA, Gertz MA, Greipp PR *et al*. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N. Engl. J. Med.* 1997; **336**: 1202.
14 Lovat LB, Persey MR, Madhoo S *et al*. The liver in systemic amyloidosis: insights from ^{123}I serum amyloid P component scintigraphy in 484 patients. *Gut* 1998; **42**: 727.
15 Peters RA, Koukoulis G, Gimson A *et al*. Primary amyloidosis and severe intrahepatic cholestatic jaundice. *Gut* 1994; **35**: 1322.
16 Schmidt HH-J, Nashan B, Pröpsting MJ *et al*. Familial amyloidotic polyneuropathy: domino liver transplantation. *J. Hepatol.* 1999; **30**: 293.
17 Suhr OB, Herlenius G, Friman S *et al*. Liver transplantation for hereditary transthyretin amyloidosis. *Liver Transplant.* 2000; **6**: 263.

α_1-Antitrypsin deficiency [2, 9]

α_1-Antitrypsin is synthesized in the rough endoplasmic reticulum of the liver. It comprises 80–90% of the serum α_1-globulin and is an inhibitor of trypsin and other proteases. Deficiency results in the unopposed action of these enzymes, in particular neutrophil elastase. The lungs are the major target, with damage to alveoli and resulting emphysema.

The gene for α_1-antitrypsin is on chromosome 14. There are about 75 different alleles at this locus which can be distinguished by isoelectric focusing or agarose gel electrophoresis at acid pH, or by PCR analysis. M is the common, normal allele. Z and S are the most frequent abnormal alleles which put the individual at risk of disease. One gene is derived from each parent. The combination results in normal, intermediate, low or zero serum α_1-antitrypsin levels. Protease inhibitor (Pi) MM gives a serum α_1-antitrypsin value of 20–53 µmol/l—the normal state. PiZZ results in a low concentration of 2.5–7 µmol/l and PiNull-Null gives zero levels. Both give a high risk of emphysema. PiSS and PiMZ give levels 50–60% of normal with no increased risk of lung disease. PiSZ gives α_1-antitrypsin levels of 8–19 µmol/l with a mildly increased risk.

Mutation of the gene can give deficiency of circulating α_1-antitrypsin by a number of mechanisms. Liver disease, however, only occurs with mutations where α_1-antitrypsin accumulates in hepatocytes. The classical type is PiZZ but the M_{malton} and M_{duarte} variants may do the same.

Pathogenesis of liver disease [9, 14]

Only the PiZZ phenotype has been clearly associated with liver disease. This is not due to the low circulating levels of α_1-antitrypsin arriving at the liver since other phenotypes with a low circulating level do not develop hepatic damage. Intra-hepatic accumulation of α_1-antitrypsin seems to be responsible. Studies of the molecular structure have shown that with the ZZ mutation there is polymerization of protein units. Normally the reactive loop (fig. 25.16) swings in between the β-helices of the so-called A-sheet of the protein, where it interacts with elastase and other enzymes. In the ZZ mutant protein the

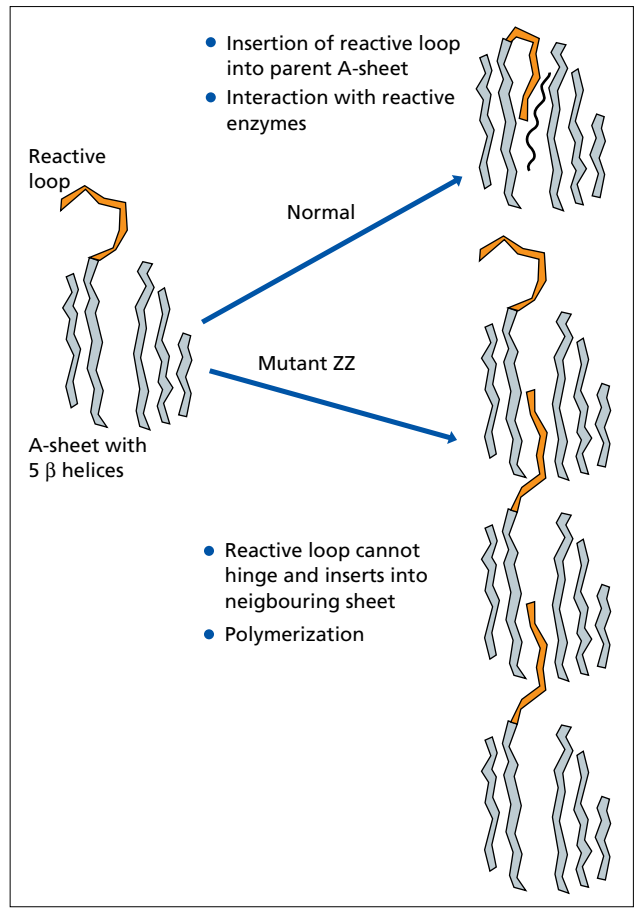


Fig. 25.16. Proposed mechanism of polymerization of ZZ α_1-antitrypsin.

reactive loop cannot do this. It remains on the outside and is then available to insert into the A-sheet of an adjacent ZZ unit [8]. The polymers formed prevent export of most of the protein.

Accumulation is thought to be responsible for liver damage but the mechanism is still unclear. Polymerization of ZZ protein occurs spontaneously or following minor perturbations such as a rise in temperature. However, the mutation of the α_1-antitrypsin protein is not the only reason for its retention. Cells from individuals with α_1-antitrypsin liver disease also have a reduction in the degradatory pathways in the endoplasmic reticulum [14]. The variation in clinical disease therefore appears to depend not only on the abnormal protein produced in PiZZ but also other cellular mechanisms as yet poorly understood.

Clinical picture

α_1-Antitrypsin deficiency has a wide spectrum of disease. The number of patients with recognized liver or lung disease is much less than expected from calculations made from the gene frequency. The spectrum for liver disease stretches from liver failure and the need for transplantation in childhood, to individuals at 18 years old having no evidence of liver disease—the outcome in the majority of patients [13]. The explanation may be environmental and other as yet unknown genetic influences.

Emphysema is the most common manifestation of α_1-antitrypsin deficiency but takes decades to become apparent [1, 13]. There is a threshold of serum α_1-antitrypsin level below which the risk is increased. Cigarette smoking accelerates the development of emphysema and shortens survival. Symptoms of α_1-antitrypsin-related emphysema do not usually begin until the third decade of life. However, there is a wide variation in the incidence and severity of disease, with some smokers remaining asymptomatic or only developing disease in the seventh or eighth decade of life. Overall, patients with α_1-antitrypsin deficiency have a lifespan shortened by 10–15 years compared to the normal population [1].

Most patients with PiZZ develop liver disease at some stage. In the first year of life 75% of infants have an elevated serum alanine transaminase level [13]. Some develop severe hepatitic-cholestatic jaundice in the first few months of life which may be fatal or lead to transplantation.

In a series of 97 children *presenting with disease*, 85% did so in the neonatal period (0–3 weeks) with neonatal hepatitis [4]. The remainder (15%) presented between 11 months and 11 years of age with chronic liver disease without a history of neonatal hepatitis. Poor prognostic factors associated with the need for transplantation were a longer period of jaundice, a higher AST at presentation, and histology showing severe bile duct reduplication, severe fibrosis with bridging septa and cirrhosis. The indication for transplantation was synthetic liver failure (low albumin, coagulopathy, jaundice) in the majority. Median time from presentation to transplantation was 2.5 years in those with neonatal hepatitis, and 4.5 years in those presenting with chronic liver disease.

However, the majority of PiZZ individuals either do not present with disease or recover. In a series of 127 PiZZ Swedish children detected *in a screening programme*, only 22 had clinical liver disease in infancy (neonatal cholestasis or hepatosplenomegaly). Two of these died early in life of cirrhosis. Two died of other causes and liver histology showed cirrhosis/fibrosis. This agrees with a calculation of 3% of α_1-antitrypsin children coming to liver transplantation. Follow-up of the Swedish group at the age of 18 years showed that the remainder were clinically well. Abnormal liver function tests were found in only two patients [13].

The incidence of liver disease in PiZZ individuals at age 50 years is about 15%, more frequent in men. Usually the changes in liver function are subtle [12], but the patient may present with a problem of portal hypertension or ascites. Hepato-cellular carcinoma may complicate cirrhosis, particularly in males [3].

Rarely, both pulmonary and hepatic disease affect the same patient with α_1-Antitrypsin deficiency [5].

An increased prevalence of heterozygotes (MZ) has been found in patients with cryptogenic cirrhosis or chronic hepatitis [6]. The significance is unknown. Hepato-cellular carcinoma can develop in cirrhotic patients heterozygous for α_1-Antitrypsin deficiency but this may be more related to other factors, such as hepatitis C or alcohol, than the carrier state itself [11].

Partial deficiency of α_1-antichymotrypsin, another proteinase inhibitor, may also be associated with liver disease [7].

Liver histology

The acute picture is of neonatal hepatitis except that giant cells are not prominent. After 12 weeks, intracellular globules which are diastase resistant and stain brilliantly with PAS are seen in *peri-portal* liver cells (fig. 25.17). The globules stain positively with the specific α_1-antitrypsin immunoperoxidase method. The liver contains increased amounts of copper.

Electron microscopy shows clumps of α_1-antitrypsin in dilated rough endoplasmic reticulum.

Diagnosis

The condition should be suspected with neonatal jaundice. It should also be considered in any patient with cirrhosis, whatever the age, particularly with a past

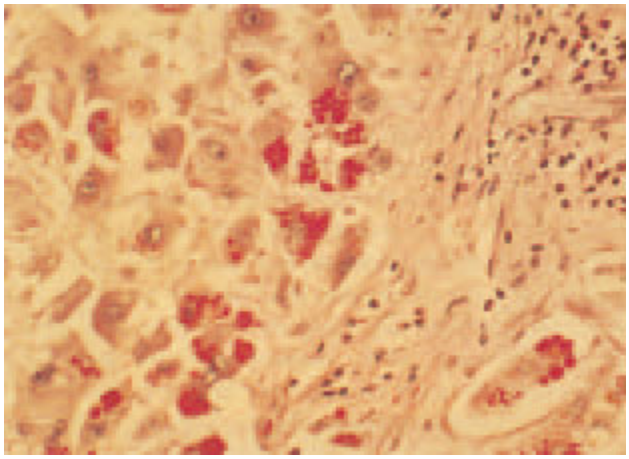


Fig. 25.17. α_1-Antitrypsin deficiency. Liver biopsy showing bright red deposits in peri-portal liver cells when stained by periodic acid–Schiff after diastase digestion. (PAS, ×100.)

history of infantile liver disease or with associated chest infections. α_1-Antitrypsin deficiency can present as cryptogenic cirrhosis in people over the age of 50 [15].

Confirmation comes by measuring serum α_1-antitrypsin. The exact phenotype should be determined by isoelectric focusing.

There is a 75% chance that a subsequent affected child will run the same clinical course.

The deficiency may be diagnosed prenatally by amniotic fluid or cultured amniotic cells using synthetic oligomer probes for DNA analysis.

First trimester prenatal diagnosis is also possible by analysis of fetal DNA. This is justified in families where there is a history of severe disease.

Treatment

Replacement therapy with plasma-derived or synthetic α_1-antitrypsin has been used to treat the pulmonary disease [1].

α_1-Antitrypsin deficiency is the second most common chronic childhood liver disease for which liver transplantation is performed. Survival at 3 years after transplant ranges from 83 to 100% [10]. The recipient's phenotype rapidly changes to that of the donor [16].

Increasing understanding of the molecular mechanism of hepatocyte injury may lead to new approaches to treatment, such as peptides to prevent ZZ polymerization by filling the cleft in the A-sheet, but these remain speculative.

References

1 Crystal RG. α_1-Antitrypsin deficiency, emphysema and liver disease: genetic basis and strategies for therapy. *J. Clin. Invest.* 1990; **85**: 1343.

2 Eriksson S. Alpha$_1$-antitrypsin deficiency. *J. Hepatol.* 1999; **30**: 34.

3 Eriksson S, Carlson J, Velez R. Risk of cirrhosis and primary liver cancer in alpha 1-antitrypsin deficiency. *N. Engl. J. Med.* 1986; **314**: 736.

4 Francavilla R, Castellaneta SP, Hadzic N *et al*. Prognosis of alpha-1-antitrypsin deficiency-related liver disease in the era of paediatric liver transplantation. *J. Hepatol.* 2000; **32**: 986.

5 Glasgow JFT, Lynch MJ, Hercz A *et al*. Alpha$_1$ antitrypsin deficiency in association with both cirrhosis and chronic obstructive lung disease in two sibs. *Am. J. Med.* 1973; **54**: 181.

6 Graziadi IW, Joseph JJ, Wiesner RH *et al*. Increased risk of chronic liver failure in adults with heterozygous α_1-antitrypsin deficiency. *Hepatology* 1998; **28**: 1058.

7 Lindmark B, Eriksson S. Partial deficiency of α-1-antichymotrypsin is associated with chronic cryptogenic liver disease. *Scand. J. Gastroenterol.* 1991; **26**: 508.

8 Lomas DA. Loop-sheet polymerization: the structural basis of Z α_1-antitrypsin accumulation in the liver. *Clin. Sci.* 1994; **86**: 489.

9 Perlmutter DH. Alpha-1-antitrypsin deficiency. *Semin. Liver Dis.* 1998; **18**: 217.

10 Prachalias AA, Kalife M, Francavilla R *et al*. Liver transplantation for alpha-1-antitrypsin deficiency in children. *Transpl. Int*. 2000; **13**: 207.

11 Propst T, Propst A, Dietze O *et al*. Prevalence of hepatocellular carcinoma in α_1-antitrypsin deficiency. *J. Hepatol.* 1994; **21**: 1006.

12 Schönfeld JV, Breuer N, Zotz R *et al*. Liver function in patients with pulmonary emphysema due to severe alpha-1-antitrypsin deficiency (PiZZ). *Digestion* 1996; **57**: 165.

13 Sveger T, Eriksson S. The liver in adolescents with α_1-antitrypsin deficiency. *Hepatology* 1995; **22**: 514.

14 Teckman JH, Qu D, Perlmutter DH. Molecular pathogenesis of liver disease in α_1-antitrypsin deficiency. *Hepatology* 1996; **24**: 1504.

15 Thatcher BS, Winkelman EI, Tuthill RJ. Alpha-1-antitrypsin deficiency presenting as cryptogenic cirrhosis in adults over 50. *J. Clin. Gastroenterol*. 1985; **7**: 405.

16 Van Furth R, Kramps JA, van der Putten AB *et al*. Change in alpha-1-antitrypsin phenotype after orthotopic liver transplant. *Clin. Exp. Immunol.* 1986; **66**: 669.

Hereditary tyrosinaemia [5]

This autosomal recessive disorder is due to lack of the enzyme fumaryl acetoacetate hydrolase, an enzyme that catalyses the last step of tyrosine degradation. Abnormal metabolites of tyrosine accumulate, which are toxic to both liver and kidney. The main clinical features are progressive liver disease and renal tubular abnormalities.

The acute type, usually seen in early infancy, results in death from hepatic failure within the first year of life. The chronic form leads to growth retardation, cirrhosis, severe hypophosphataemic rickets, renal tubular defects and a derangement of tyrosine metabolism with hyperaminoacidaemia. Hepato-cellular carcinoma is a complication occurring in over 40% of patients. Episodes of severe acute peripheral neuropathy are reported [4].

Diagnosis is confirmed by the presence of elevated plasma and urinary tyrosine, phenylalanine and methionine levels and increased levels of succinyl acetone in the urine. The prognosis is related to the time of presentation [5]. Survival when symptoms develop before 2 months of age, between 2 and 6 months, and after 6 months is 38, 74 and 96%, respectively.

The chronic type will respond to dietary avoidance of aromatic amino acids and methionine but this does not prevent the liver disease or the appearance of hepatocellular carcinoma. Without liver transplantation death occurs within the first decade of life. Treatment with an inhibitor of an enzyme preceding the metabolic defect has produced benefit [2] but awaits further study.

CT scanning shows the progression of liver disease from cirrhosis, to macronodular disease and finally hepato-cellular carcinoma.

Liver transplantation for both acute and chronic disease can be successful and virtually corrects the metabolic disease [3]. A mild metabolic abnormality persists, probably due to continued abnormal renal metabolism, but this is not a clinical problem. Because of the difficulty in predicting or preventing complications, including hepato-cellular carcinoma, early liver transplantation has been advocated [1].

References

1 Freese DK, Tuchman M, Schwarzenberg SJ *et al*. Early liver transplantation is indicated for tyrosinemia type I. *J. Paediatr. Gastroenterol. Nutr.* 1991; **13**: 10.
2 Lindstedt S, Holme E, Lock EA *et al*. Treatment of hereditary tyrosinemia type I by inhibition of 4-hydroxyphenylpyruvate dioxygenase. *Lancet* 1992; **340**: 813.
3 Mieles LA, Esquivel CO, Van Thiel DH *et al*. Liver transplantation for tyrosinemia: a review of 10 cases from the University of Pittsburgh. *Dig. Dis. Sci.* 1990; **35**: 153.
4 Mitchell G, Larochelle J, Lambert M *et al*. Neurologic crises in hereditary tyrosinemia. *N. Engl. J. Med.* 1990; **322**: 432.
5 van Spronsen FJ, Thomasse Y, Smit GPA *et al*. Hereditary tyrosinemia type I: a new clinical classification with difference in prognosis on dietary treatment. *Hepatology* 1994; **20**: 1187.

Cystic fibrosis [4]

This condition is inherited with an autosomal recessive pattern. The prevalence is approximately 1 in 2000. The carrier rate is about 5%. The gene responsible, on chromosome 7, has been cloned and the product is a transmembrane protein regulating ion conductance. The mutation in the majority of patients with cystic fibrosis is of three bases, removing phenylalanine 508 from the protein. The result is a secretion containing an abnormal sodium, chloride and calcium content with increased viscidity. Lungs and pancreas are the major targets of pathology.

Postnatal jaundice is associated with meconium ileus.

Approximately 20% of patients develop liver disease including fatty change, focal biliary fibrosis and portal fibrosis followed by multilobular biliary cirrhosis. Those who develop liver disease do so in childhood and follow-up of these cases shows little progression [2, 10]. Of cirrhotic patients 50% bled from varices early in their second decade [6].

The pathogenesis of the liver disease is thought to be the plugging of intra-hepatic bile ducts with inspissated bile. The cystic fibrosis transmembrane regulator (CFTR), normally present in bile ductular cells (cholangiocytes) is absent or expression is aberrant, depending on the mutation [9].

Lack of normal CFTR expression is thought to lead to abnormally concentrated bile and loss of mucous protection. An increase in hepato-toxic bile acids may play a role.

It is not certain why some patients develop liver disease and others do not. Histocompatibility antigens have been implicated, HLA-DQ6 being more frequent in those with liver disease [8].

Cholangitis in patients with clinical evidence of hepatic involvement characteristically shows the changes of sclerosing cholangitis in the intra-hepatic ducts. On magnetic resonance cholangiography 50% of patients without clinical evidence showed similar changes [7]. Biliary scintigraphy with DISIDA may show focal retention of isotope despite normal liver function tests and ultrasound [12].

Pulmonary and pancreatic disease are present in 80–90% of patients with cystic fibrosis. There are no secure predisposing factors for hepato-biliary disease. Liver disease generally runs a mild course. With improved management of the respiratory problems patients are living longer and this may be responsible for the increased recognition of liver disease.

Gallbladder disease, including gallstones, is seen in around 5%. Cholecystectomy is safe.

The prognosis seems to be determined by the respiratory state rather than the liver. Ursodeoxycholic acid therapy is associated with biochemical improvement, but data on long-term improvement in mortality or time to transplantation are needed. Early treatment of all patients with liver disease with ursodeoxycholic acid has been advocated [4] although it is acknowledged that there is a lack of long-term data [1]. Delayed intestinal visualization on scintigraphy may predict a better response [3].

In children with variceal haemorrhage not controlled by injection sclerotherapy, elective surgical portosystemic shunting was successful in those without severe pulmonary failure or poor liver function [6].

Liver transplantation is successful in 70% of patients, either alone for those with end-stage hepatic disease but preserved respiratory function [11] or combined with

lung transplantation for those with late-stage pulmonary disease [5].

References

1 Cheng K, Ashby D, Smyth R. Ursodeoxycholic acid for cystic fibrosis-related liver disease (Cochrane Review). In: *The Cochrane Library*, Issue 3. Oxford: Update Software, 2000.
2 Colombo C, Battezzati PM, Strazzabosco M *et al*. Liver and biliary problems in cystic fibrosis. *Semin. Liver Dis*. 1998; **18**: 227
3 Colombo C, Crosignani A, Battezzati PM *et al*. Delayed intestinal visualization at hepatobiliary scintigraphy is associated with response to long-term treatment with ursodeoxycholic acid in patients with cystic fibrosis-associated liver disease. *J. Hepatol*. 1999; **31**: 672.
4 Colombo C, Crosignani A, Battezzati PM. Liver involvement in cystic fibrosis. *J. Hepatol*. 1999; **31**: 946.
5 Couctil JPA, Houssin DP, Soubrane O *et al*. Combined lung and liver transplantation in patients with cystic fibrosis. *J. Thorac. Cardiovasc. Surg*. 1995; **110**: 1415.
6 Debray D, Lykavieris P, Gauthier F *et al*. Outcome of cystic fibrosis-associated liver cirrhosis: management of portal hypertension. *J. Hepatol*. 1999; **31**: 77.
7 Durieu I, Pellet O, Simonot L *et al*. Sclerosing cholangitis in adults with cystic fibrosis: a magnetic resonance cholangiographic prospective study. *J. Hepatol*. 1999; **30**: 1052.
8 Duthie A, Doherty DG, Donaldson PT *et al*. The major histocompatibility complex influences the development of chronic liver disease in male children and young adults with cystic fibrosis. *J. Hepatol*. 1995; **25**: 532.
9 Kinnman N, Lindlbad A, Housset C *et al*. Expression of cystic fibrosis transmembrane conductance regulator in liver tissue from patients with cystic fibrosis. *Hepatology* 2000; **32**: 334.
10 Lindblad A, Glaumann H, Strandvik B. Natural history of liver disease in cystic fibrosis. *Hepatology* 1999; **30**: 1151.
11 Noble-Jamieson G, Valente J, Barnes ND *et al*. Liver transplantation for hepatic cirrhosis in cystic fibrosis. *Arch. Dis. Child*. 1994; **71**: 349.
12 O'Connor PJ, Southern KW, Bowler IM *et al*. The role of hepatobiliary scintigraphy in cystic fibrosis. *Hepatology* 1996; **25**: 281.

Liver and thyroid

The liver has an important part to play in the transport, storage, activation and metabolism of thyroid hormones. It synthesizes the proteins which transport thyroxine (T_4) in the circulation: T_4-binding globulin, T_4-binding prealbumin and albumin. The liver contains 10–30% of the body's exchangeable T_4, excluding the thyroid, and is the major site for conversion of T_4 to the biologically active tri-iodothyronine (T_3). The liver also removes reverse T_3, the biological inactive product of T_4. Finally around 25% of the daily T_4 secreted by the thyroid is metabolized by oxidative deamination, or excreted into bile after glucuronidation and sulphation. There is also entero-hepatic circulation of unmetabolized T_4 excreted in bile.

Despite all these hepatic contributions to the handling of thyroid hormones, most patients with liver disease are clinically euthyroid, although there may be changes in the serum level of thyroid hormones.

Hypo- and hyperthyroidism may be associated with liver disease, and experimentally influence the severity of experimental liver injury [9].

Thyrotoxicosis

Minor abnormalities of liver function are seen in hyperthyroidism [3]. There is little evidence of significant hepatic functional and structural changes in an otherwise normal liver. However, jaundice in thyrotoxic patients may be due to heart failure [6]. In addition, thyrotoxicosis may cause severe cholestasis in patients without heart failure [2], and result in reversible exacerbation of cholestasis in primary biliary cirrhosis [10].

Thyrotoxicosis may also aggravate an underlying defect in serum bilirubin metabolism, such as Gilbert's syndrome, by decreasing bilirubin UDP–glucuronosyltransferase activity [11].

Liver biopsy is normal in those without jaundice or congestive failure. Electron microscopy shows enlarged mitochondria, hypertrophied smooth endoplasmic reticulum and decreased glycogen.

Myxoedema

Ascites without congestive heart failure in patients with myxoedema has been attributed to centrizonal congestion and fibrosis. The pathogenesis is unknown. It disappears on giving thyroxine. There is a high ascitic protein content of greater than 25 g/l [5].

Jaundice may be related to neonatal thyroid deficiency.

Changes with hepato-cellular disease

Most patients with liver disease are clinically euthyroid, although standard function tests may give misleading results [7]. Serum total T_4 may be raised or decreased in association with varying levels of thyroid hormone binding proteins. The free T_4 index is usually normal. A low T_4 variant of 'sick euthyroid syndrome' is reported in 30% of cirrhotic patients and is associated with reduced short- and long-term survival [4].

In *alcoholic liver disease* raised serum levels of thyrotrophin (TSH) and free T_4 are associated with normal or low T_3 values [8]. The conversion of T_4 to T_3 is reduced. This suggests a compensatory increase in TSH in response to relative T_3 deficiency. The total and free T_3 levels are reduced in proportion to the degree of liver damage. Plasma reverse T_3 levels are high.

In *primary biliary cirrhosis* and *chronic hepatitis* T_4-binding globulins are increased and these may be markers of inflammatory activity. Although total T_4

and T_3 should be increased, the corresponding free hormone concentrations are reduced, probably because of decreased thyroid function associated with the high incidence of thyroiditis in these patients [1].

References

1 Babb RR. Associations between diseases of the thyroid and the liver. *Am. J. Gastroenterol.* 1984; **79**: 421.
2 Barnes SC, Wicking JM, Johnston JD. Graves' disease presenting with cholestatic jaundice. *Ann. Clin. Biochem.* 1999; **36**: 677.
3 Beckett GJ, Kellett HA, Gow SM *et al*. Subclinical liver damage in hyperthyroidism and in thyroxine replacement therapy. *Br. Med. J.* 1985; **291**: 427.
4 Caregaro L, Alberino F, Amodio P *et al*. Nutritional and prognostic significance of serum hypothyroxinemia in hospitalized patients with liver cirrhosis. *J. Hepatol.* 1998; **28**: 115.
5 De Castro F, Bonacini M, Walden JM *et al*. Myxedema ascites: report of two cases and review of the literature. *J. Clin. Gastroenterol.* 1991; **13**: 411.
6 Fong TL, McHutchison JG, Reynolds TB. Hyperthyroidism and hepatic dysfunction. A case series analysis. *J. Clin. Gastroenterol.* 1992; **14**: 240.
7 Huang MJ, Liaw YF. Clinical associations between thyroid and liver diseases. *J. Gastroenterol. Hepatol.* 1995; **10**: 344.
8 Nomura S, Pittman CS, Chambers JB Jr *et al*. Reduced peripheral conversion of thyroxine to triiodothyronine in patients with hepatic cirrhosis. *J. Clin. Invest.* 1975; **56**: 643.
9 Oren R, Dotan I, Papa M *et al*. Inhibition of experimentally induced cirrhosis in rats by hypothyroidism. *Hepatology* 1996; **24**: 419.
10 Thompson NP, Leader S, Jamieson CP *et al*. Reversible jaundice in primary biliary cirrhosis due to hyperthyroidism. *Gastroenterology* 1994; **106**: 1342.
11 Van Steenbergen W, Fevery J, De Vos R *et al*. Thyroid hormones and the hepatic handling of bilirubin. I. Effects of hypothyroidism and hyperthyroidism on the hepatic transport of bilirubin mono- and diconjugates in the Wistar rat. *Hepatology* 1989; **9**: 314.

Liver and adrenal

Undiagnosed Addison's disease can be associated with mild elevation of transminase levels [1]. These return to normal after treatment with corticosteroids. The mechanism is not known.

Reference

1 Boulton R, Hamilton MI, Dhillon AP *et al*. Subclinical Addison's disease: a cause of persistent abnormalities in transaminase values. *Gastroenterology* 1995; **109**: 1324.

Liver and growth hormone

The liver and kidney degrade growth hormone. Basal and stimulated growth hormone concentrations are elevated in cirrhotic patients and correlate with the degree of liver dysfunction [3]. These increased levels may contribute to insulin resistance and glucose intolerance in cirrhosis. Acromegaly does not develop despite the chronic elevation of growth hormone.

Insulin-like growth factor I (IGF-I), which mediates the effects of growth hormone and whose production by the liver is stimulated by growth hormone, is reduced in the serum of cirrhotics [1]. The serum levels of the major binding proteins are also altered, which may affect the bioavailability of IGF-I [5]. Administration of recombinant growth hormone to patients with alcoholic cirrhosis results in a rise in IGF-I, but there appears to be no clinical or biochemical benefit [4]. Experimentally, IGF-I prevents testicular changes associated with cirrhosis [2].

In *acromegaly* the liver enlarges in line with other viscera.

References

1 Blomsma MC, de Knegt RJ, Dullaart RPF *et al*. Insulin-like growth factor-1 in liver disease. *J. Hepatol.* 1997; **27**: 1133.
2 Castilla-Cortazar I, Garcia M, Quiroga J *et al*. Insulin-like growth factor-1 reverts testicular atrophy in rats with advanced cirrhosis. *Hepatology* 2000; **31**: 592.
3 Møller S, Becker U. Insulin-like growth factor I and growth hormone in chronic liver disease. *Dig. Dis.* 1992; **10**: 239.
4 Møller S, Becker U, Gronbaek M *et al*. Short-term effect of recombinant human growth hormone in patients with alcoholic cirrhosis. *J. Hepatol.* 1994; **21**: 710.
5 Møller S, Juul A, Becker U *et al*. The acid-labile subunit of the ternary insulin-like growth factor complex in cirrhosis: relation to liver dysfunction. *J. Hepatol.* 2000; **32**: 441.

Hepatic porphyrias [18, 21]

Porphyrias are caused by defects in the biosynthesis of haem (fig. 25.18). The clinical features are the result of accumulation of porphyrins due to the enzyme defect. In addition the lack of haem increases δ-aminolaevulinic acid (ALA) and porphobilinogen (PBG) production because of loss of negative feedback on ALA-synthetase activity. Accumulation of early precursors (ALA/PBG) results in neurological features, with the acute pattern of attack (table 25.6) including abdominal pain, peripheral neuropathy, autonomic dysfunction and psychosis. Accumulation of substrates later in the pathway gives the cutaneous pattern, in particular photosensitivity. Some types of porphyria give both neurological and cutaneous features.

Most porphyrias are inherited as autosomal dominant, but there is low penetrance. The majority of carriers have latent porphyria and are clinically asymptomatic. Attacks are precipitated by drugs, hormonal factors and endogenous metabolic changes.

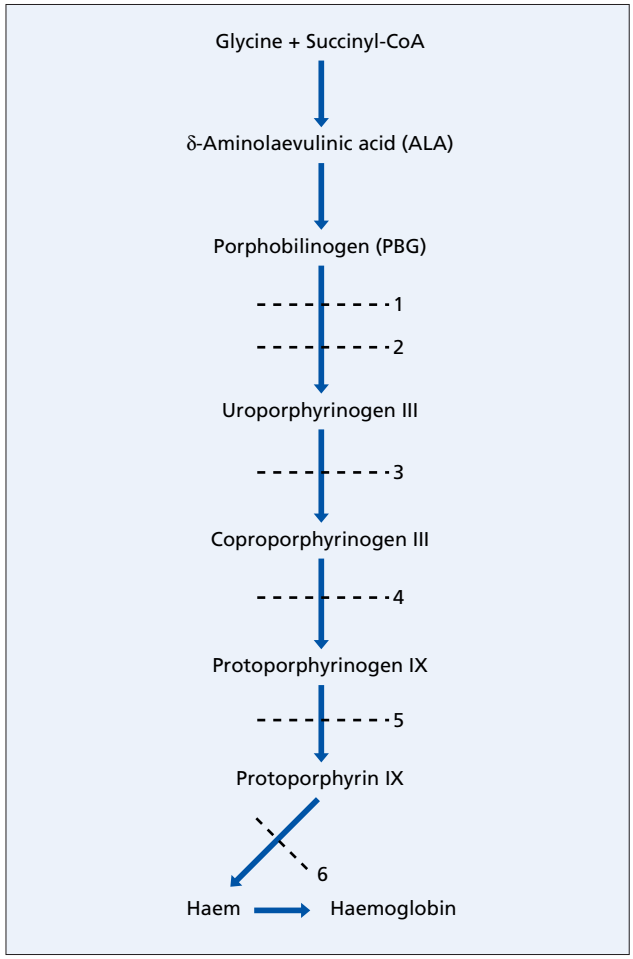


Fig. 25.18. Porphyria and the biosynthesis of porphyrins. Numbers indicate site of enzyme defect leading to:
1 Acute intermittent porphyria
2 Congenital erythropoietic porphyria
3 Porphyria cutanea tarda and hepato-erythropoietic porphyria
4 Hereditary coproporphyria
5 Variegate porphyria
6 Erythropoietic protoporphyria (see text for enzyme deficiency responsible).

The product of this metabolic pathway, haem, is an important component of haemoglobin, myoglobin and haem-requiring enzymes, for example the cytochrome P450 oxidase system. Protoporphyrin synthesis is therefore most pronounced in hepatic cells and erythrocytes, which gives a further classification of hepatic and erythropoietic porphyrias (table 25.6).

The acute hepatic porphyrias include *acute intermittent porphyria*, *hereditary coproporphyria* and *variegate porphyria*. All are marked by neuropsychiatric attacks with vomiting, abdominal colic, constipation and peripheral neuropathy [10]. All are exacerbated by countless enzyme-inducing drugs including barbiturates, sulphonamides, oestrogens, oral contraceptives, griseofulvin, chloroquine and

Table 25.6. Classifications of porphyria

Acute	
neuroporphyria	*Acute intermittent porphyria*
neurocutaneous	*Hereditary coproporphyria*
	Variegate porphyria
Non-acute (cutaneous)	*Porphyria cutanea tarda*
	Erythropoietic protoporphyria
	Congenital erythropoietic porphyria

Hepatic in italic; erythropoietic in roman.

possibly alcohol. A clinical picture similar to acute hepatic porphyria can be the result of severe lead poisoning when ALA dehydratase is markedly reduced. An inherited (recessive) defect in this enzyme has also been reported in four individuals [1].

Hormones are important inducers and women develop attacks in pregnancy and premenstrually.

During the attacks, large amounts of the colourless porphyrin precursors, PBG and ALA, are excreted in the urine. Acute attacks are treated by glucose loading. Infusions of haematin which repress or inhibit hepatic ALA synthetase may also be valuable [3].

Haem arginate which suppresses overproduction of haem precursors and improves hepatic oxidative metabolism may be useful [14].

The fourth type of hepatic porphyria, *porphyria cutanea tarda*, is probably hereditary and may be associated with hepato-cellular disease. It is not exacerbated by barbiturates and acute neurological attacks are not seen.

The erythropoietic porphyrias are congenital erythropoietic porphyria (autosomal recessive) and erythropoietic protoporphyria (dominant).

Differentiation between the various porphyrias depends upon analysis of porphyrin metabolites in urine, faeces and erythrocytes [28].

Acute intermittent porphyria [13]

The basic deficiency is in hepatic PBG deaminase. A diagnostic deficiency may be shown in red cells. The enzyme ALA-synthetase (ALA-S) is secondarily induced in the liver because of loss of the normal negative feedback mechanism due to haem. Overproduction of ALA and PBG follows. The clinical features are of acute porphyria.

Photosensitivity is absent. The urine darkens on standing and gives a positive urobilinogen test. It contains slight increases in ALA and PBG. Latent cases develop acute attacks on various drugs and in the later stages of pregnancy.

General anaesthesia for major surgery can be done safely in known patients with the appropriate choice of drugs; the danger of anaesthesia is in those in whom the diagnosis has not been made [8].

The risk of hepato-cellular carcinoma is increased over 30-fold in acute hepatic porphyrias, although other risk factors including hepatitis virus B and C may be responsible for a proportion [2].

Hereditary coproporphyria [19]

The deficiency is in coproporphyrinogen oxidase. Attacks may be neurological or cutaneous with lesions as in porphyria cutanea tarda. ALA-S activity is increased in the liver. Faecal and urinary coproporphyrin are increased with a corresponding increase in protoporphyrin.

Variegate porphyria [16]

The defect is in protoporphyrinogen oxidase. ALA-S is increased in the liver. This variant is frequently encountered in South Africa and New England. The features are intermediate between acute intermittent porphyria and hereditary coproporphyria. Protoporphyrin and porphyrins may be increased in the stool between attacks. Biliary porphyrin estimation may be diagnostic in the asymptomatic patient [17].

Porphyria cutanea tarda [9]

This is the most common porphyria and is usually latent and the patient symptom-free.

Uroporphyrinogen decarboxylase (URO-D) activity is reduced. Two forms are described: familial (20% of patients) with point mutations in the URO-D gene, and sporadic where there is a URO-D defect restricted to the liver perhaps due to an inhibitor rather than mutation. Sensitivity to drugs such as barbiturates is absent. Exposure to alcohol and oestrogens may precipitate attacks. A background of hepatic siderosis appears necessary for clinical expression of disease [25].

Porphyria cutanea tarda is characterized clinically by photosensitive skin, blistering and scarring, pigmentation and hypertrichosis. Acute neurological attacks with abdominal pain are absent. There is usually evidence of liver dysfunction. Uroporphyrin is increased in the urine.

Liver biopsy usually shows an abnormality, most frequently siderosis, mild steatosis, focal necrosis and portal fibrosis with some inflammation. Less than 15% have cirrhosis. Uroporphyrin can be shown by red fluorescence in ultraviolet light.

Excess hepatic iron can be related to the increased frequency of the C282Y mutation in the *HFE* (haemochromatosis) gene, being over 40% (homozygosity plus heterozygosity) in some studies [5, 24], although hepatitis C and alcohol may also play a role.

A high prevalence of hepatitis C has been found in patients with porphyria cutanea tarda, although varying greatly (8–80%) between different countries [5, 27]. This virus may contribute to the liver disease, but does not necessarily play a role in the pathogenesis of porphyria cutanea tarda.

The incidence of hepato-cellular carcinoma is increased [26].

Exacerbation of symptoms accompanies deterioration of liver function. At this time, porphyrins that would normally be excreted into the bile may be directed via the kidneys to the urine. When the liver is healthy, the porphyrin is excreted harmlessly into the bile; when it is diseased, it is retained in the blood. The porphyrin itself may be hepato-toxic.

Venesection has a good effect, probably related to removal of excess iron.

Erythropoietic protoporphyria [6]

The defect is in ferrochelatase. The inheritance is dominant with variable penetrance. This is explained by the presence of a mutated gene on one chromosome (with no expression of enzyme) and a common low expression variant of the normal gene (found in the normal population) on the other chromosome [12]. Protoporphyrin is increased in tissues and urine.

This type is characterized by skin photosensitivity. Protoporphyrin is increased in tissues and urine.

Liver biopsies examined by fluorescent microscopy or phase microscopy show focal deposits of pigment containing protoporphyrin crystals. Electron microscopy shows abnormalities of nuclei, endoplasmic reticulum and membranes, despite normal light microscopy [22]. Complications include gallstones containing protoporphyrin.

The spectrum of liver involvement ranges from normal liver function in 20%, to mild abnormalities of liver function tests, to chronic liver disease and cirrhosis in 5–10%. The rare but most serious picture is of rapidly progressing photosensitivity, cholestasis and haemolysis [6]. There is severe upper abdominal pain and splenomegaly with rapid deterioration. Emergency treatment is necessary. This includes haematin infusion and red cell transfusion to reduce porphyrin and red cell production. Plasmapheresis may reduce free protoporphyrin. The entero-hepatic circulation of protoporphyrin may be blocked by oral cholestyramine or charcoal. Liver transplantation may be the only ultimate option. Since the red cell is the source of protoporphyrin, bone marrow transplantation is a theoretical therapeutic approach. This has been done in an experimental model, preventing hepato-biliary complications in young animals [11], but has not yet been possible in patients.

In patients with end-stage protoporphyric liver disease neurotoxicity has been reported [23].

Liver transplantation has been successful for severe liver disease [20] although precautions should be taken to reduce the risk of cutaneous reactions at the time of surgery. The metabolic defect is not corrected in bone marrow so that there may be recurrent protoporphyric liver damage [4].

Congenital erythropoietic porphyria [7]

The major clinical problem in this rare type is photosensitivity. Neurological symptoms do not occur. The liver may be enlarged and contain excess iron. Uroporphyrinogen III cosynthase is deficient.

Hepato-erythropoietic porphyria

This very rare type presenting within the first year of life with skin disease is due to homozygous deficiency of URO-D. It is marked by hepatosplenomegaly and cirrhosis. Liver biopsies fluoresce but there is no iron excess. The acute presentation may be preceded by acute viral hepatitis [15].

Secondary coproporphyrias

Heavy metal intoxication, especially with lead, causes porphyria with ALA and coproporphyrin in the urine. Erythrocyte protoporphyrins are increased. Coproporphyrinuria may also be seen with sideroblastic anaemia, various liver diseases, the Dubin–Johnson syndrome and as a complication of drug therapy.

References

1 Akagi R, Shimizu R, Furuyama K *et al*. Novel molecular defects of the δ-aminolevulinate dehydratase gene in a patient with inherited acute hepatic porphyria. *Hepatology* 2000; **31**: 704.

2 Andant C, Puy H, Bogard C *et al*. Hepatocellular carcinoma in patients with acute hepatic porphyria: frequency of occurrence and related factors. *J. Hepatol*. 2000; **32**: 933.

3 Bissell DM. Treatment of acute hepatic porphyria with haematin. *J. Hepatol*. 1988; **6**: 1.

4 Bloomer JR, Rank JM, Payne WD *et al*. Follow-up after liver transplantation for protoporphyric liver disease. *Liver Transplant. Surg*. 1996; **2**: 269.

5 Bonkovsky HL, Poh-Fitzpatrick M, Pimstone N *et al*. Porphyria cutanea tarda, hepatitis C, and HFE gene mutations in North America. *Hepatology* 1998; **27**: 1661.

6 Cox TM, Alexander GJM, Sarkany RPE. Protoporphyria. *Semin. Liver Dis*. 1998; **18**: 85.

7 Desnick RJ, Glass IA, Xu W *et al*. Molecular genetics of congenital erythropoetic porphyria. *Semin. Liver Dis.* 1998; **18**: 77.

8 Dover SB, Plenderleith L, Moore MR *et al*. Safety of general anaesthesia and surgery in acute hepatic porphyria. *Gut* 1994; **35**: 1112.

9 Elder GH. Porphyria cutanea tarda. *Semin. Liver Dis*. 1998; **18**: 67.

10 Elder GH, Hift RJ, Meissner PN. The acute porphyrias. *Lancet* 1997; **349**: 1613.

11 Fontanellas A, Mazurier F, Landry M *et al*. Reversion of hepatobiliary alterations by bone marrow transplantation in a murine model of erythropoietic protoporphyria. *Hepatology* 2000; **32**: 73.

12 Gouya L, Puy H, Lamoril J *et al*. Inheritance in erythropoietic protoporphyria: a common wild-type ferrochelatase allelic variant with low expression accounts for clinical manifestations. *Blood* 1999; **93**: 2105.

13 Grandchamp B. Acute intermittent porphria. *Semin. Liver Dis*. 1998; **18**: 17.

14 Herrick A, McColl KEL, McLellan A *et al*. Effect of haem arginate therapy on porphyrin metabolism and mixed function oxygenase activity in acute hepatic porphyria. *Lancet* 1987; **ii**: 1178.

15 Hift RJ, Meissner PN, Todd G. Hepatoerythropoietic porphyria precipitated by viral hepatitis. *Gut* 1993; **34**: 1632.

16 Kirsch RE, Meissner PN, Hift RJ. Variegate porphyria. *Semin. Liver Dis*. 1998; **16**: 33.

17 Logan GM, Weimer MK, Ellefson M *et al*. Bile porphyrin analysis in the evaluation of variegate porphyria. *N. Engl. J. Med*. 1991; **324**: 1408.

18 McDonagh AF, Bissell DM. Porphyria and porphyrinology—the past 15 years. *Semin. Liver Dis*. 1998; **18**: 3.

19 Martásek P. Hereditary coproporphyria. *Semin. Liver Dis*. 1998; **18**: 25.

20 Mion FBC, Faure J-L, Berger F *et al*. Liver transplantation for erythropoietic protoporphyria. Report of a new case with subsequent medium-term follow-up. *J. Hepatol.* 1992; **16**: 203.

21 Nordmann Y, Puy H, Deybach J-C. The porphyrias. *J. Hepatol*. 1999; **30**: 12.

22 Rademakers LHPM, Cleton MI, Kooijman C *et al*. Early involvement of hepatic parenchymal cells in erythrohepatic protoporphyria? An ultrastructural study of patients with and without overt liver disease and the effect of chenodeoxycholic acid treatment. *Hepatology* 1990; **11**: 449.

23 Rank JM, Carithers R, Bloomer J *et al*. Evidence of neurological dysfunction in end-stage protoporphyric liver disease. *Hepatology* 1993; **18**: 1404.

24 Roberts AG, Whatley SD, Morgan RR *et al*. Increased frequency of the haemochromatosis Cys282Tyr mutation in sporadic porphyria cutanea tarda. *Lancet* 1997; **349**: 321.

25 Siersema PD, Rademakers LHPM, Cleton MI *et al*. The difference in liver pathology between sporadic and familial forms of porphyria cutanea tarda: the role of iron. *J. Hepatol*. 1995; **25**: 259.

26 Siersema PD, ten Kate FJW, Mulder PGH *et al*. Hepatocellular carcinoma in porphyria cutanea tarda: frequency and factors related to its occurrence. *Liver* 1992; **12**: 56.

27 Stölzel U, Köstler E, Koszka C *et al*. Low prevalence of hepatitis C virus infection in porphyria cutanea tarda in Germany. *Hepatology* 1995; **21**: 1500.

28 Thadani H, Deacon A, Peters T. Diagnosis and management of porphyria. *Br. Med. J.* 2000; **320**: 1647.

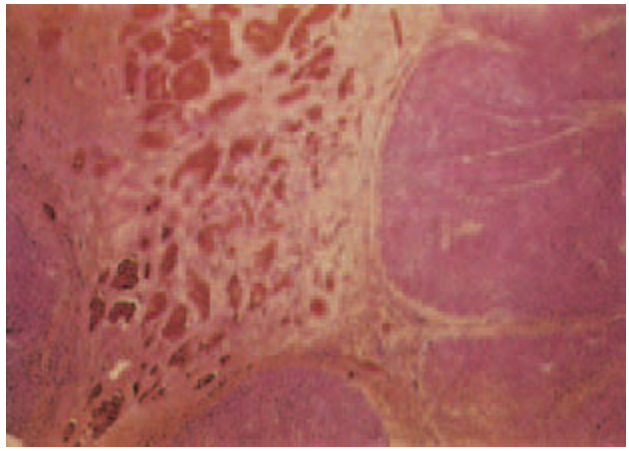


Fig. 25.19. The cirrhosis accompanying hereditary haemorrhagic telangiectasia. Note spaces filled with blood at the periphery of the lobules.

Hereditary haemorrhagic telangiectasia [4]

Hepatomegaly is a common feature of this rare autosomal dominant disease. There are mutations in endothelium-related proteins which may cause vascular dysplasia but the pathogenetic mechanism is uncertain [5]. 25% of patients have vascular malformations which can be demonstrated by Doppler ultrasound [2], dynamic CT or angiography [1]. The majority are asymptomatic.

There are three distinct clinical presentations which overlap: high-output cardiac failure, portal hypertension and biliary disease. In a series of 19 patients, approxiamtely one-third fell into each group [4].

Cardiac failure is due to shunting between the hepatic artery and hepatic vein, which is treated medically as far as possible. Hepatic arterial ligation [6] or embolization [3] are therapeutic but there are complications and a mortality [4].

Portal hypertension with gastrointestinal haemorrhage and ascites appears related to fibrosis or nodular transformation (fig. 25.19), thought to be due to ischaemia or hepatic arterial/portal venous shunts. Previous reports of patients with cirrhosis in the absence of hepatic telangiectasia, are now thought due to post-transfusion hepatitis. Bleeding and ascites are treated conventionally. TIPS placement has not been found beneficial.

Bile duct disease is radiologically similar to Caroli's disease (Chapter 33) or sclerosing cholangitis, and patients present with cholestasis, pain or cholangitis.

Diagnosis of liver involvement can be made by dynamic CT scan or coeliac angiography [1].

References

1 Bernard G, Mion F, Henry L. Hepatic involvement in hereditary haemorrhagic telangiectasia: clinical, radiological, and haemodynamic studies of 11 cases. *Gastroenterology* 1993; **105**: 482.

2 Buscarini E, Buscarini L, Danesino C *et al*. Hepatic vascular malformations in hereditary haemorrhagic telangiectasia: Doppler sonographic screening in a large family. *J. Hepatol.* 1997; **26**: 111.

3 Caselitz M, Wagner S, Chavan A *et al*. Clinical outcome of transfemoral embolization in patients with arteriovenous malformations of the liver in hereditary haemorrhagic telangiectasia (Weber–Rendu–Osler disease). *Gut* 1998; **42**: 123.

4 Garcia-Tsao G, Korzenik JR, Young L *et al*. Liver disease in patients with hereditary haemorrhagic telangiectasia. *N. Engl. J. Med*. 2000; **343**: 931.

5 Johnson DW, Berg JN, Baldwin MA *et al*. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. *Nature Genet*. 1996; **13**: 189.

6 Zentler-Munro PL, Howard ER, Karani J *et al*. Variceal haemorrhage in hereditary haemorrhagic telangiectasia. *Gut* 1989; **30**: 1293.

Dystrophia myotonica

This is an autosomal dominant multi-system disorder that has characteristic neurological features including the slowly relaxing hand grip and failure of upward gaze. More than half of patients have an abnormal liver function test, predominantly alkaline phosphatase or γ-glutaryl-transpeptidase [1]. Ultrasound shows normal liver, biliary system and gallbladder motility. There are no formal data on hepatic histology. The changes have not been found to be clinically significant.

Reference

1 Achiron A, Barak Y, Magal N *et al*. Abnormal liver test results in myotonic dystrophy. *J. Clin. Gastroenterol.* 1998; **26**: 292.

Chapter 26
The Liver in Infancy and Childhood

Biochemical tests in infancy

Fractionation into unconjugated and conjugated *serum bilirubin* is important in neonates. Because of overlap, the proportion of serum bilirubin conjugates does not distinguish between extra-hepatic biliary obstruction and hepato-cellular disease.

Serum bilirubin levels are a guide to the development of kernicterus. Serial levels are useful in the assessment of prolonged jaundice.

Serum cholesterol. Extremely high levels may be recorded in prolonged cholestasis, particularly intra-hepatic cholestasis.

Serum alkaline phosphatase levels are influenced by bone metabolism as well as by cholestasis. Levels are increased in the first month of life and around puberty.

Serum γ-glutamyl transpeptidase (γ-GT) levels are useful indicators of bile duct damage and in the diagnosis of cholestatic syndromes.

Serum transaminase values during the first month of life are about twice the normal adult level.

Bile acid metabolism. Bile acid secretion evolves during the final trimester of pregnancy and in the early neonatal period. In the infant, conjugation and pool size are reduced, as are secretion, intraluminal concentration and ileal active transport. Serum bile acids are increased.

The main bile acid in neonates is glycocholic. After 1–3 months, glycochenodeoxycholic predominates. Secretion of bile acids by the hepatocyte may be reduced and atypical bile acids produced which may not be functionally adequate. A primitive pathway for the synthesis of fetal bile acids may be responsible for excretion of cholestatic bile acids during the immaturity of hepatic excretory function, which lasts in infants from birth until 3 months [46]. This picture of '*physiological cholestasis*' is enhanced in the low birth weight neonate. It may contribute to cholestasis produced by other factors, for instance infection or prolonged parenteral nutrition.

Liver size

Liver span in normal infants and children is measured by percussion of the upper border and percussion/palpation of the lower border (table 26.1) [63].

Circulatory factors and hepatic necrosis

In the fetus the right lobe of the liver is supplied largely by the portal vein whereas the left receives highly oxygenated, placental blood. In the fetal mouse, higher levels of cytochrome P450 gene expression are found in the left lobe [20]. This lobar heterogeneity disappears as the adult pattern of liver circulation develops.

At the time of birth, loss of placental blood can be followed by atrophy of the left lobe of the liver.

Right-sided hepatic necrosis may be seen in post-mature infants dying about the time of birth. This is related to poor placental blood supply and anoxia at the time of delivery.

Disseminated mid-zonal necrosis is found with congenital cardiac defects. This may be due to a decrease in total hepatic blood flow. In others the zone 3 changes of congestive heart failure may be seen. Cholestasis in the first week can be related to congenital cardiac defects and 'shock'.

Localized necrosis of the liver may be due to trapping in defects of the anterior abdominal wall.

Copper is increased in the fetal liver, more so in the left lobe than the right.

Neonatal hyperbilirubinaemia

Unconjugated hyperbilirubinaemia (tables 26.2, 26.3)

Jaundice, reaching its peak within 2–5 days of birth and disappearing in 2 weeks, is common in normal infants

Table 26.1. Approximate mean liver span of infants and children based on four studies on 470 subjects [63]

Age	Span (cm)
Birth	5.6–5.9
2 months	5
1 year	6
2 years	6.5
3 years	7
4 years	7.5
5 years	8
12 years	9

Table 26.2. Unconjugated hyperbilirubinaemia in neonates related to time of onset

Birth to 2 days
Haemolytic disease
3–7 days
Physiological ± prematurity
hypoxia
acidosis
1–8 weeks
Congenital haemolytic disorders
Breast milk jaundice
Hypopituitarism
Crigler–Najjar syndrome
Hypothyroidism
Perinatal complications: haemorrhage, sepsis
Upper gastrointestinal obstruction

Table 26.3. Investigations of the jaundiced newborn

Total and direct serum bilirubin
Blood group
Rhesus status
Coombs' test
Haematocrit
Blood smear for morphology
Blood culture
Urine culture

(*physiological jaundice*). It is a benign self-limited process although it is more serious in low birth weight infants where it may persist for as long as 2 weeks. The urine contains both urobilin and bilirubin and the stools are paler than normal.

Hepatic conjugating and transport systems for bilirubin are delayed in the neonate. Absorption of bilirubin from the intestine is increased. Bilirubin binding to albumin is reduced, particularly in premature infants. The jaundice is enhanced by factors which depress liver function, such as hypoxia and hypoglycaemia. Drugs such as water-soluble vitamin K analogues add to the jaundice.

Serum bilirubin levels may be *lower* in infants with circulatory failure, asphyxia and sepsis. Bilirubin may be a physiological anti-oxidant providing protection against perinatal ischaemia–reperfusion tissue injury [8].

The bilirubinaemia is *not* physiological if the level exceeds 5 mg/dl (86 µmol/l) on the first day, 10 mg (171 µmol/l) on the second day, or 12–13 mg (206–223 µmol/l) at any time.

Unconjugated hyperbilirubinaemia in the neonatal period is complicated by bilirubin encephalopathy (*kernicterus*).

Management

Phototherapy. Hyperbilirubinaemia may be prevented or controlled by exposure of the infant to light with a wavelength near 450 nm. The light converts bilirubin IXα photochemically to a relatively stable geometric isomer. Phototherapy is used if the total serum bilirubin exceeds or is equal to 17 mg/dl (289 mmol/l) during the first 48 h of life. It is discontinued after the serum bilirubin has decreased by more than 2 mg or has fallen to 13 mg or less. *Exchange transfusion* is rarely necessary with the advent of phototherapy. It is indicated if the total serum bilirubin exceeds 20 mg by direct spectrophotometry, or a bilirubin rising at a rate greater than 1 mg/dl/h despite phototherapy.

Enzyme induction using phenobarbital is effective when given to the mother.

Tin mesoporphyrin (Sn mesoporphyrin) inhibits haem-oxygenase and haem analogues [58]. It may be useful in controlling hyperbilirubinaemia if given in one dose intramuscularly to healthy term or pre-term infants. Its use is still experimental.

Haemolytic disease of the newborn

Fetal–maternal incompatibility usually concerns the Rh blood factors and rarely the ABO or other blood groups. The prevalence is falling, now that anti-D immune globulin is given prophylatically to mothers.

Characteristically, the first-born escapes the disease unless the mother's blood has been sensitized by a previous transfusion of Rh-positive blood.

The infant is jaundiced during the first 2 days of life. Serum unconjugated bilirubin is increased. The critical period is in the first few days when the more deeply jaundiced infants may develop *kernicterus*.

Diagnosis may be suspected by antenatal examination of the mother's blood for specific antibodies and confirmed by a positive Coombs' test in the infant and by blood typing on mother and child.

The risk of mental or physical impairment is low until the serum bilirubin increases well above 20 mg/dl (342 µmol/l).

Kernicterus

This grave condition complicates prematurity jaundice, haemolytic disease and neonatal hepatitis. Management with phototherapy, exchange transfusion and phenobarbital has reduced its occurence. However, diagnosis is increasing as neonates are discharged from hospital earlier and recognition is delayed.

It is prevented by early detection of full-term infants at risk. It is rare in pre-term neonates. Very low birth weight infants with a serum bilirubin level of 10 mg/dl, lower

than in full-term babies, may be at risk. Daily transcutaneous serum bilirubin estimations are valuable in management.

Within the first 5 days, the jaundiced infant becomes restless or lethargic and febrile, developing a stiff neck and head retraction which proceeds to opisthotonos. There is stiffness of the limbs with pronated arms, eye squinting, lid retraction, twitching or convulsions and a high-pitched cry.

Death may supervene rapidly in 12 h and 70% of affected infants die within 7 days of onset. The remaining 30% may survive, but are affected by mental defects, cerebral palsy or athetosis, until they eventually die from intercurrent infections.

MRI T_2-weighted images show bilateral high intensity areas in the globus pallidus [87].

Autopsy reveals yellow staining of the basal ganglia and other areas of the brain and spinal cord with unconjugated bilirubin which, being lipid soluble, has an affinity for nervous tissue.

Kernicterus is related to circulating free bilirubin crossing the blood–brain barrier. Reduction of serum bilirubin–albumin binding may play a part and indeed albumin infusions have been used therapeutically.

Mechanisms of bilirubin toxicity and neuron damage are unknown. Bilirubin, however, does inhibit neuronal function [34].

Kernicterus is potentiated by hypoxia, metabolic acidosis and septicaemia [34]. Organic anions which compete for bilirubin binding sites on albumin increase kernicterus although the serum bilirubin level falls. Such anions include salicylates, sulphonamides, free fatty acids and haematin.

Congenital haemolytic disorders

These can all lead to unconjugated hyperbilirubinaemia in the first 2 days of life. They include the red cell enzyme deficiencies (glucose-6-phosphate dehydrogenase and pyruvate kinase) congenital spherocytosis and pyknocytosis.

Glucose-6-phosphate dehydrogenase deficiency. Infants develop jaundice, usually on the second or third day of life. The precipitating haemolytic agent may be a drug such as salicylate, phenacetin or sulphonamides transmitted in the maternal breast milk. This condition is frequent in the Mediterranean area, in the Far East and in Nigeria.

Breast milk jaundice

Hyperbilirubinaemia (serum bilirubin more than 12 mg/dl) affects 34% of newborn breast-fed babies compared with only 15% of those who are formula fed. The aetiology of this breast milk jaundice is unknown. It is diagnosed by exclusion and by showing a fall in serum bilirubin if breast feeding is stopped for 48 h.

The jaundice lasts from 2 weeks to more than 2 months.

Crigler–Najjar hyperbilirubinaemia (Chapter 12)

This may present in the first few days of life. Type I is treated by phototherapy and type II by phenobarbital.

Pituitary or adrenal dysfunction

This is associated with neonatal jaundice in 30%. It is marked by hypoglycaemia, midline facial abnormalities, a low thyroid-stimulating hormone and a free thyroxine level with a low 9.00 a.m. cortisol value. It resolves with hormone replacement, thyroxine and hydrocortisone.

Hypothyroidism

This is more common in girls than boys. Mild anaemia is common and the infant is sluggish. The diagnosis is confirmed by finding low serum thyroxine and triiodothyronine levels with high thyroid-stimulating hormone, and by observing the effects of therapy. The mechanism of the jaundice is unknown.

Perinatal complications

Haemorrhage with release of blood into the tissues provides a bilirubin load which may exacerbate jaundice, particularly in the premature. Anaemia depresses hepato-cellular function. Cephalohaematoma is a common association. The prothrombin time should be measured and vitamin K given.

Sepsis, whether umbilical or elsewhere, leads to unconjugated hyperbilirubinaemia in the first few days of life. Blood, urine and, if necessary, cerebrospinal fluid are cultured and appropriate antibodies given.

Upper gastrointestinal obstruction

About 10% of infants with congenital pyloric stenosis are jaundiced due to unconjugated bilirubin. The mechanism may be similar to that postulated for the increase in jaundice when patients with Gilbert's syndrome are fasted.

Hepatitis and cholestatic syndromes (conjugated hyperbilirubinaemia)

The reaction of the neonatal liver to different insults is similar. Proliferation of giant cells is always a part and this reflects increased regenerative ability. In some instances the condition may be the so-called 'idiopathic'

hepatitis formerly called *giant cell hepatitis*. In others a specific virus such as type B or another infection can be identified. Metabolic disturbances, such as galactosaemia, can cause a giant cell reaction. Cholestatic syndromes are also seen which may be associated with hepatitis and, in these, hepatic histology may include a giant cell reaction. In all these conditions the conjugated 'direct reacting' bilirubin is more than 30% of the total (table 26.4).

Some are immediately treatable, such as congenital syphilis or bacterial infections—which will respond to antibiotics—and galactosaemia or tyrosinosis—which will require exclusion diets. The main bile duct atresias, which may benefit from surgical treatment, must be diagnosed early.

Diagnosis of the hepatitic–cholestatic syndromes (tables 26.4, 26.5) [45]

Family history is important in diagnosing galactosaemia, α_1-antitrypsin deficiency, tyrosinosis, cystic fibrosis and hereditary fructose intolerance.

Virus infections in the mother during pregnancy, such as rubella, hepatitis or genital herpes, must be recorded.

At the onset it is valuable to test the blood of the mother, father and other siblings by appropriate methods and to store the sera for later use. The *routine biochemical tests* of the adult are of little value in the diagnosis of jaundice in infancy and childhood. A serum alkaline phosphatase level three times normal and a serum cholesterol value exceeding 250 mg/100 ml suggest intra-hepatic biliary atresia. A serum γ-GT value exceeding 300 iu/l, particularly if rising, is also suggestive, but not diagnostic, of atresia. A direct reacting bilirubin value exceeding 4 mg/dl (68 μmol/l) suggests extra-hepatic biliary obstruction.

Serum tyrosine is measured if tyrosinosis is suspected and serum α_1-antitrypsin values noted for the diagnosis of α_1-antitrypsin deficiency.

Biliary isotopic scanning (HIDA) is useful in establishing patency of the biliary passages.

Serological methods. The serum is tested for hepatitis B surface antigen (HBsAg), IgM anti-hepatitis B core antigen (anti-HBcAg), IgM anti-hepatitis A virus (anti-HAV), anti-hepatitis C virus (anti-HCV), HCV RNA and for syphilis. Antibodies to herpes simplex, rubella, *Toxoplasma*, cytomegalovirus, adenovirus and Coxsackie viruses are estimated in both baby and mother. Blood cultures are performed if *Escherichia coli* infection is suspected.

Urine tests. Cultures are taken for Gram-negative organisms and for cytomegalovirus infection. Aminoaciduria is noted. Reducing substances are sought if galactosaemia is suspected.

Liver biopsy. Needle biopsy of the liver is easy and well tolerated in neonates, infants and children. Interpretation is always difficult due to the overlap between hepatitis and cholestatic syndromes, both of intra-hepatic and extra-hepatic origin. Neonatal changes in the liver include giant cells and extra-medullary erythropoiesis. These subside by about 3 months.

Portal zone duct proliferation and a biliary type of fibrosis are helpful in diagnosing extra-hepatic atresia. A relative paucity of portal zone bile ducts supports the diagnosis of intra-hepatic cholestasis but is not constant.

Table 26.4. Conjugated hyperbilirubinaemia in neonates

Infection
Viruses (CMV rubella, Coxsackie, herpes, hepatitis, A, B and C) (Chapters 16, 17, and 18)
Syphilis
Bacteria (*Escherichia coli*)
Metabolic (Chapter 25)
Galactosaemia
α_1-Antitrypsin deficiency
Tyrosinosis
Cystic fibrosis
Hereditary fructose intolerance
Total parenteral nutrition
Niemann–Pick disease
Idiopathic
'Neonatal' hepatitis
Congenital hepatic fibrosis
Byler's disease (PFIC 1)
Biliary atresia
Intra-hepatic
Extra-hepatic
Erythroblastosis with cholestasis

Table 26.5. Aetiology of cholestasis in neonates

Week 1
Inspissated bile syndrome (erythroblastosis with cholestasis)
Bacterial infections
Vascular causes
'shock'
congenital heart disease
After week 1
Bile duct anomalies
Genetic
galactosaemia
α_1-antitrypsin deficiency
others
Infections (same as immune deficiency in adults)
TORCH screen (toxoplasmosis, rubella, cytomegala, herpes)
Parenteral hyperalimentation

The PAS-positive bodies of α_1-antitrypsin deficiency may be seen after 2 months.

Electron microscopy is essential if metabolic disease is suspected.

Ultrasonography shows absence of the gallbladder in biliary atresia. It can also diagnose choledochal cyst.

CT scan is also of value.

Percutaneous and endoscopic cholangiography. The percutaneous technique is of great value when liver biopsy findings are equivocal and the HIDA test suggests biliary atresia. Endoscopic cholangiography is employed using suitably sized instruments [13].

Viral hepatitis

Immunity is reduced in the neonate and virus infections are frequent and very liable to persist. Chronic hepatitis and cirrhosis may ensue. Similarly, older children with immunological deficits such as agammaglobulinaemia or who are receiving treatment with immunosuppressive drugs are at risk.

Hepatitis B

This disease develops in babies of mothers who suffer the acute disease during the later part of pregnancy, within 2 months of delivery, or who are chronic carriers, usually, but not always, HBV e antigen positive. Antigenaemia is usually found between 6 weeks and 6 months of birth, suggesting transmission from the mother's blood during delivery or later during her care of the infant. The condition is not spread by breast milk.

Umbilical cord sera may rarely be positive for HBsAg. Placental transmission is rare.

The natural history of hepatitis B contracted at birth and in early life is very variable. Fulminant hepatitis and the precore mutant are rare.

Hepatitis B is a frequent cause of chronic hepatitis, particularly in Italy and the Far East. Spread is perinatal and in the family.

Clinically the disease is mild with high titres of viral replication. Cirrhosis is rare, but viral replication and liver damage may persist for several years [9]. During the first 20 years, the majority of Caucasian children with chronic HBV infection become asymptomatic carriers with normal serum ALT values [11]. In Italy, superinfection with hepatitis delta virus may increase the progression towards cirrhosis.

Liver biopsy in the acute stage shows a giant cell hepatitis (fig. 26.1). Later, the picture is of chronic hepatitis and only occasionally cirrhosis. Histological regression is associated with seroconversion from HBeAg-positive to antibody-HBe positive.

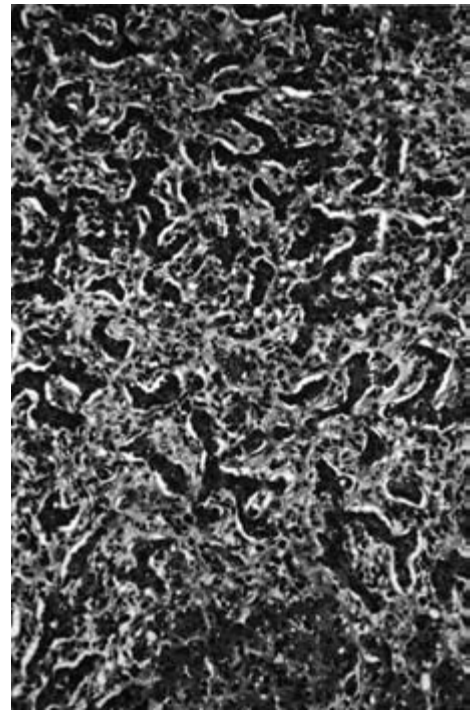


Fig. 26.1. Viral hepatitis in an infant of 3 months. Necrosis of liver cells and multinucleated giant liver cells are seen. (H & E, ×115.)

Prophylaxis (Chapter 17)

Protection persists for 10 years after infancy vaccination [38].

Treatment

Interferon is indicated in children more than 2 years old who are HBeAg and HBV DNA positive and have raised serum transaminase values. Histologically, liver biopsy shows activity.

Cirrhosis or neurological disease are contraindications.

Interferon is given in a dose of 6 million units/m^2 three times a week for 6 months. Serious adverse effects are rare. Results are similar to those reported in adults with a 35% HBeAg to HBeAb sero-conversion 12 months after stopping [77]. Caucasian infants respond much better than Chinese infants [54]. After 5 years, sustained HBV clearance is equal in responders and non-responders and the interferon simply may hasten spontaneous loss [10]. Lamivudine (3 mg/kg) has a shorter life in children and is being investigated.

Hepatic transplantation has a 90% recurrence of HBV in children with more severe liver disease.

Hepatitis A

Asymptomatic hepatitis A can spread in nurseries for neonates. The source may be infected blood or a nurse carrier. The babies spread the hepatitis A to adults in the nursery and to the community.

Hepatitis C

Babies born to anti-HCV positive mothers show passively transmitted antibody for the first 6 months.

Mothers who are HCV RNA positive can transmit HCV RNA positive disease to their infants [70], but this is infrequent [56, 86]. There is probably no difference between transmission from HIV-positive or HIV-negative mothers. Those with a high serum HCV RNA are more likely to transmit the disease (fig. 26.2) [65]. Breast feeding seems safe [53].

In childhood the usual source of HCV infection is perinatal blood transfusion, multiple transfusions in thalassaemics or renal dialysis patients.

Liver biopsy histology is similar to that seen in adults [4]. Necro-inflammatory activity is low, but fibrosis is often severe suggesting possible progression to chronic disease.

Serum transaminases and HCV viral load are low [31].

Cirrhosis and hepato-cellular carcinoma are possibilities [31]. The response to interferon therapy is one-third, similar to that seen in adults [74].

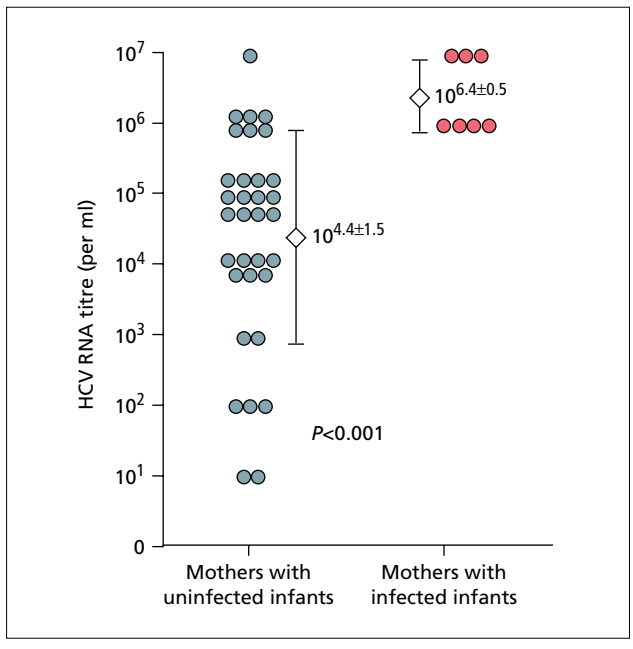


Fig. 26.2. Mean (±SD) serum HCV RNA titres in seven mothers with HCV-infected infants and the 33 mothers with uninfected infants. (From [65] with permission.)

Cytomegalovirus

This is very common (Chapter 16). The incidence in small children is 5–10% in those living in good hygienic conditions, rising to 80% in the underprivileged.

It is usually acquired placentally from an asymptomatic mother. It can also be transmitted in breast milk and from blood products. Many congenital infections are asymptomatic.

The disease may be fulminant with intense jaundice, purpura, hepatosplenomegaly, chorioretinitis, cataracts and pulmonary defects. Survivors may run a long course with persistent jaundice, hepatomegaly and disappearing bile ducts. The prognosis is good although 30% will develop cirrhosis requiring treatment by liver transplantation.

Intra-nuclear viral inclusions are seen in bile duct epithelium and rarely in hepatocytes. Diagnosis is made on urine or tissue *in situ* using PCR [18].

Herpes simplex

The liver may be involved in the course of a fulminating viraemia, contracted at birth from maternal genital herpes. Jaundice is due to viral involvement of the liver. Histologically, necrosis is seen with little or no inflammatory reaction. Giant cells are absent, but inclusion bodies may be found.

Gancyclovir is often given too late, when massive hepatic necrosis and chronic cholestasis have developed and the mortality is 70% [57].

Congenital rubella syndrome

This disease, if contracted in the first trimester of pregnancy, may cause fetal malformations. It may also persist through the neonatal period and into later life. The liver with the brain, lung, heart and other organs are involved in the generalized virus infection.

Jaundice commences within the first 1 or 2 days with hepatosplenomegaly. The picture is sometimes cholestatic. Serum transaminase levels are slightly elevated.

Hepatic histology shows bile in swollen Kupffer cells and ductules with a focal hepato-cellular necrosis and portal fibrosis. Erythroid haemopoietic tissue is relatively increased. A typical giant cell hepatitis can be seen. The virus can be identified from the liver at necropsy or biopsy.

Usually the hepatitis resolves completely.

Intra-uterine *parvovirus* B19 can cause severe giant cell hepatic disease in the neonate, also fulminant liver failure and aplastic anaemia [49].

Adenoviruses

These may disseminate in babies with decreased resistance due to thymic alymphoplasia and agammaglobulinaemia. A marked coagulative necrosis with inclusion-bearing cells may be seen. Under similar circumstances this lesion can also complicate *varicella*.

AIDS

Babies and children with AIDS have a very similar picture to that seen in the adult with the same spectrum of infections, primary lymphoma and Kaposi's sarcoma. Hepatic histology shows more giant cell transformation and fewer granulomas [41]. Diffuse, lymphoplasmocytic infiltration is associated with lymphoid interstitial pneumonia.

Non-viral causes of hepatitis

Congenital syphilis

This is very rare. Visceral involvement is late in acquired syphilis but common in fetal infection. Tremendous numbers of treponemes can be found in the liver. Such involvement leads to a fine peri-cellular cirrhosis with a marked connective tissue reaction. Jaundice is usual. The diagnosis is made serologically.

Congenital toxoplasmosis

Infection is intra-uterine. Jaundice develops within a few hours of birth with hepatomegaly, encephalomyelitis, choroidoretinitis and intra-cerebral calcification. Toxoplasmosis may develop later in the neonatal period. It is diagnosed by finding *Toxoplasma* IgM antibodies.

The liver shows infiltration of portal zones with mononuclear cells. Extra-medullary haemopoiesis with increased stainable iron is conspicuous. Histiocytes containing *Toxoplasma* may be present. The jaundice is difficult to relate to the extent of liver damage and haemolysis may be contributory. The liver disease is generally mild.

Bacterial infection

In the neonate, an immature reticulo-endothelial system with decreased complement and opsonins impairs the ability of the liver and spleen to phagocytose bacteria.

The upsurgence of Gram-negative infections, particularly *Escherichia coli*, in nurseries, has led to an increase in cholestatic jaundice due to this cause.

The origins include umbilical sepsis, pneumonia, otitis media or even gastroenteritis. Diagnosis may be difficult as focal signs are minimal or absent. Jaundice appears suddenly in a baby who does not look ill. Hepatomegaly need not be present and splenomegaly is never great. The leucocyte count exceeds 12000. A blood culture is usually positive. The umbilical stump should be cultured. Liver function tests are of little value.

Hepatic histology is non-contributory. Culture of liver biopsies is usually negative. The jaundice seems to be due to a combination of haemolysis, hepato-cellular dysfunction and even cholestasis, presumably due to endotoxaemia.

Prognosis depends on early treatment and age of onset, the mortality being 80% below the age of 1 week and 25% later. Antibiotics are appropriate.

Portal vein occlusion may be diagnosed years later.

Liver abscesses in older children are associated with blood-spread organisms. A third have acute blastic leukaemia.

Urinary tract infections

Jaundice may be associated both in infants and children. Infants are usually affected in the first week of life. They are often male, but have no underlying renal tract abnormality. Endotoxaemia contributes to the hepatic dysfunction.

The infants fail to thrive, show fever, jaundice, moderate hepatomegaly and bilirubinuria. Liver biopsy is non-specific. Urine culture is essential in any jaundiced child or infant.

Neonatal hepatitis syndrome

This may be due to intra-uterine infections, endocrine causes such as hypothyroidism, or inherited diseases such as chromosomal abnormalities.

Idiopathic neonatal hepatitis

This is diagnosed after exclusion of known causes. The number of cases being diagnosed has diminished. Inheritance is familial and autosomal recessive. Some instances may reflect disturbances in bile acid metabolism (see p. 463).

Clinical features include small gestational age and dysmorphia. The infant may be stillborn or die soon after or before jaundice has time to develop. More usually, a fluctuating jaundice appears during the first 2 weeks or up to 4 months. Hepatosplenomegaly is usual. The stools contain pigment and the urine bilirubin.

Biochemical changes are not diagnostic but transaminases are usually above 800 iu/l. Hypoglycaemia is common.

Liver biopsy histology is non-specific with giant cells, extra-medullary haematopoiesis and zone 3 inflammation. Bile duct proliferation is minimal and there may be canalicular cholestasis.

Prognosis and treatment. The hepatitis resolves slowly over months or may blend with the intra-hepatic cholestases. In a 10-year follow-up of 29 patients, two had died and only two had signs of persisting liver disease [29].

Treatment is symptomatic. Corticosteroid therapy is useless.

Infantile cholangiopathies (fig. 26.3)

A broad classification is made into extra-hepatic, including such lesions as choledochal cyst or biliary atresia, and intra-hepatic, subdivided into neonatal hepatitis and the bile duct diseases such as syndromatic or non-syndromatic biliary atresia. Idiopathic hepatitis and non-syndromatic biliary atresia may overlap.

Biliary atresia

Biliary atresia commences in intra-uterine life (fig. 26.4). It is often classified as congenital, although, in most instances, the abnormality is due to an extraneous, often infectious, cause acting during the normal process of intra-uterine development or shortly after birth. This is supported by the histology of ductular tissue showing acute and chronic inflammation with bile duct obliteration. Reovirus 3 has been invoked, but this could not be confirmed by PCR analysis of preserved tissue from infants with cholestatic liver disease [79]. Another possible cause is cytomegalovirus [35].

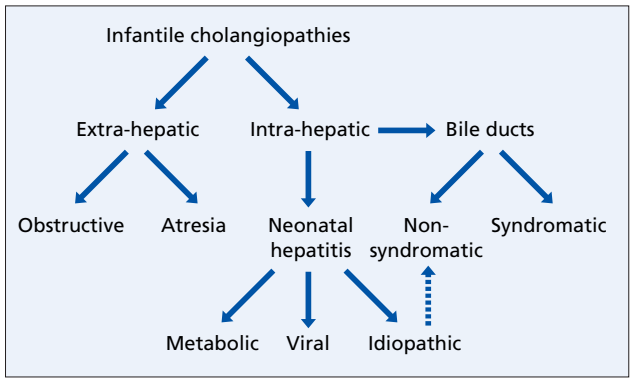


Fig. 26.3. An algorithm for managing infantile cholangiopathies. (After Balistreri, 1985 with permission.).

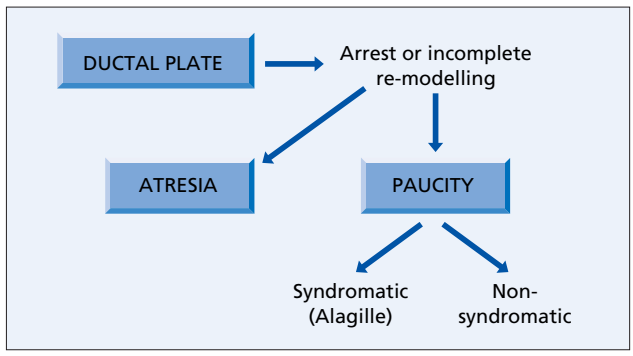


Fig. 26.4. Infantile cholangiopathy. Intra-uterine mechanisms of biliary atresia.

Vascular malformations of the hepatic artery might cause ischaemic fibrosis of the extra-hepatic biliary tree [37].

The biliary atresias are rarely familial [47].

A chromosomal abnormality, namely trisomy 17–18, and Down's syndrome have been associated with neonatal hepatitis and atresia [2], but these are rare.

The atresias result not from the failure of bile ducts to form, but from their destruction at some moment during embryonic development (fig. 26.4). Hepatic histology indicates the stage at which the damage started. At the early stage of the ductal plate with lack of remodelling [27], abnormal cylindrical ducts show atrophy or necrosis of lining cells; later the changes are of regression and involution in normally shaped ducts.

There are grades of destruction from complete absence of bile ducts, termed *atresia*, to drastic reduction of numbers, termed *paucity of bile ducts*. The extent of the process and its continuation into extra-uterine life is reflected in the prognosis. The baby with complete atresia is usually dead by 5 years of age. The baby with paucity of bile ducts may survive into adult life.

Finally, there is the Alagille syndromatic form of paucity of bile ducts [1]. Here the characteristic facies, skeletal defects, cardiovascular and eye changes make the diagnosis.

Extra-hepatic biliary atresia

The abnormality may be in any part of the biliary system; 25% show errors in other organs. In some, bile ducts are absent at birth, but in others the ducts may have been formed but sclerosis starts in the perinatal period and there is a dynamic evolution to bile duct destruction.

Developmental aspects

The biliary passages may fail to develop from the primitive foregut bud. The gallbladder may be absent or the biliary tract represented only by a gallbladder connecting directly with the duodenum. The more usual defect is failure of vacuolation of the solid biliary bud. This is usually partial and rarely extends throughout the biliary tree.

Pathology

The ducts may be absent or replaced by fibrous strands. The site and extent of the atresia are variable. Bile is

absent from the extra-hepatic biliary system including the gallbladder.

The cystic duct only may be involved, the gallbladder becoming a mucous cyst. Involvement of the common bile duct or hepatic duct gives rise to the characteristic syndrome of biliary atresia with deep cholestatic jaundice.

Liver biopsy shows cholestasis with a variable number of giant cells; proliferated bile ductules are conspicuous with biliary-type fibrosis. There is paucity of interlobular ducts. The picture is virtually diagnostic.

Clinical features

Extra-hepatic biliary atresia complicates 1 in 12000 live births. There are more females than males, and all races are affected. The condition is not inherited.

The baby becomes icteric by the first week and this continues unremittingly. Pruritus is severe and increasing. The urine is dark. The stools are pale, although some pigment may reach the intestine, presumably through the intestinal secretions. The diagnosis is confirmed by a serum conjugated bilirubin exceeding 5 mg/dl (100 μmol/l), a serum alkaline phosphatase exceeding 600 iu/l, γ-GT exceeding 100 μ/l. SGPT (ALT) and SGOT (AST) are between 100 and 200 iu/l. Fasting ultrasound shows an absent or contracted gallbladder. Biliary scintigraphy with ^{99M}Tc-TEBIDA shows no excretion of isotope from liver into bowel 24 h after administration. Liver histology shows fibrosis, cholestasis and proliferation of biliary ductules.

Nutrition is well maintained for the first 2 months and then falls off, the child usually dying before 3 years of age. The serum cholesterol level may be very high and skin xanthomas may appear (fig. 26.5). The prolonged steatorrhoea may result in osteomalacia (*biliary rickets*).

Death is usually due to intercurrent infection, liver cell failure, or bleeding related to vitamin K deficiency or oesophageal varices. Ascites is late and terminal.

Prognosis

Prognosis is poor unless the cystic duct only is involved or the bile ducts are not entirely obliterated. Very few patients are amenable to surgical cure.

Surgery

If the proximal bile ducts are patent but end blindly before the duodenum, the condition is *correctable* by Roux-en-Y jejunal anastomosis to the common hepatic duct. This is an exceedingly rare circumstance (<5%). In the vast majority of infants the atresia is *non-correctable* because extra-hepatic ducts are not patent.

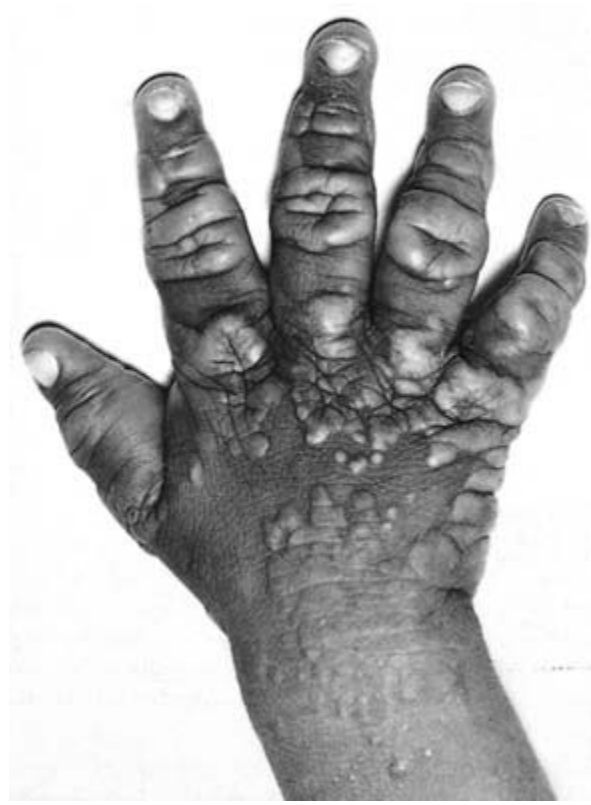


Fig. 26.5. Intra-hepatic biliary atresia (Alagille's syndrome) in a child of 4 years of age. Cholesterol deposits are noted on the hands, particularly on the extensor surfaces. Note also skin pigmentation and white nailbeds. This child spontaneously lost the xanthomas and was alive and reasonably well at 19 years.

Kasai operation (hepatic port enterostomy)

The entire ductal system is resected in the porta hepatis and the proximal, transected, common hepatic duct anastomosed to the intestine. The basis for subsequent biliary drainage is minuscule biliary ductules remaining in the scarred non-patent extra-hepatic bile ducts. These ductules communicate with the intra-hepatic biliary system and, when surgically transected, may drain bile from the liver into the interposed intestine.

The Kasai procedure should only be performed in experienced centres [55]. It must be performed before 2 months of age. After 5 months it is useless as the small hilar bile ducts will have disappeared. If performed early, 86% will develop bile flow.

The Kasai procedure is followed by improved growth and nutrition. Complications include cholangitis, progressive portal hypertension and liver failure. Cirrhosis usually develops even if biliary drainage is achieved. Hepatic transplantation usually becomes necessary although 15–20% will survive long term without the operation. The Kasai procedure delays the need for

transplant so that the prognosis is improved and the child can accept a larger donor liver [19, 73].

Hepatic transplantation

Biliary atresia is the commonest indication for liver transplant in children. The 5-year post-transplant survival is 85%. The operation is not compromised by a previous Kasai procedure provided that complex loops and enterostomies have been avoided.

Alagille's syndrome (arterio-hepatic dysplasia) [1]

This is sometimes called syndromatic or syndromic paucity of intra-hepatic bile ducts. It is seen worldwide.

The condition is related to a deletion, rarely gross, on the short arm of chromosome 20. It is related to mutations in the *Jagged 1* gene which encodes a ligand of *Notch 1*, one of four members of a family of transmembrane receptor proteins [51, 64]. It is inherited as an autosomal dominant, but the mutation is predominately sporadic [23].

Chronic intra-hepatic cholestasis presents in infancy or early childhood. The face is triangular with a prominent broad forehead, deep-set eyes, a flattened nose and a pointed mandible (fig. 26.6). Hepatosplenomegaly is usual. Skeletal changes include short distal phalanges and butterfly vertical bodies. The eyes show various abnormalities, including retinal pigmentation and posterior embryotoxon [12]. Renal abnormalities have been noted [83]. Peripheral pulmonary arterial stenosis is usual.

Liver biopsy shows few, if any, interlobular bile ducts with a reduced number of portal zones [33]. There is little fibrosis, so that neither cirrhosis nor secondary portal hypertension develop. The liver biopsy appearances are not diagnostic.

The patient survives into adult life with varying degrees of growth and mental retardation, xanthomatosis and pruritus (fig. 26.7) [36]. Prolonged survival, even into the 30s or 40s is not unknown [1]. The patient can have children. Hepato-cellular carcinoma may be a complication [43]. This can be familial [68]. On the whole, the condition improves with time.

Hepatic transplantation must be considered, but is usually contraindicated because of multi-system involvement and, in particular, pulmonary stenosis. The 20 years predicted life expectancy is 75% for all patients, 80% for those not requiring liver transplantation and 60% for those who require liver transplantation [30].

Prolonged parenteral nutrition

The cholestasis affects premature low birth weight or severely compromised babies. Diagnosis is made by exclusion as the infants usually have other causes

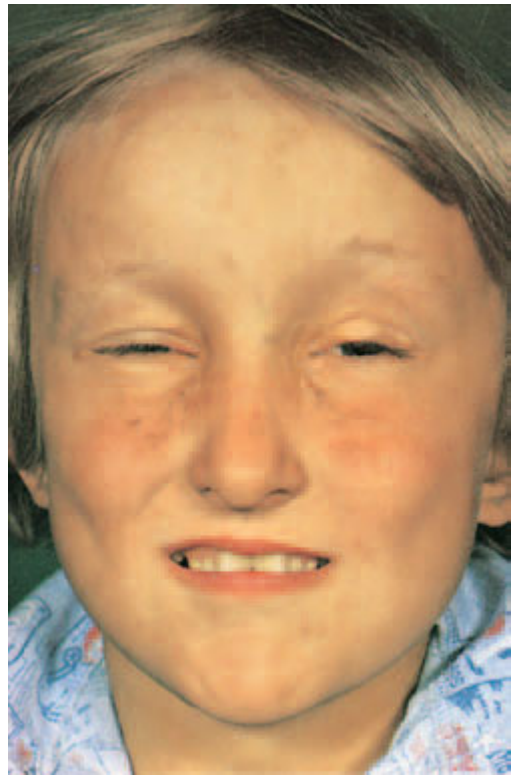


Fig. 26.6. Alagille's syndrome of biliary atresia. A 5-year-old boy showing triangular facies, deep-set eyes and a flattened nose. This patient had poor vision. At 19 years he was well with normal intelligence but dwarfed.

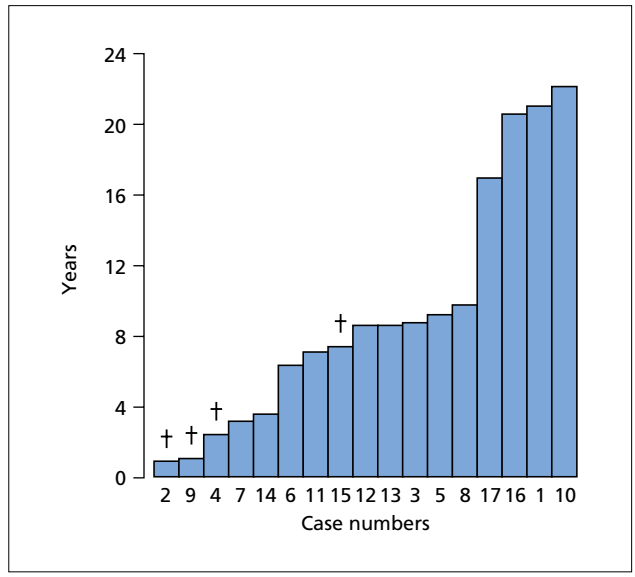


Fig. 26.7. Histogram showing the ages to date of 17 children with chronic intra-hepatic cholestasis. †, patient died [36].

of cholestasis. Diseases with impaired intestinal passage and the presence of infections predispose to hyperbilirubinaemia.

After 1–2 weeks, serum conjugated bilirubin rises steadily, increasing with duration of therapy.

Liver biopsy shows non-specific changes with features of extra-hepatic biliary obstruction. Biliary sludge and gallstones develop.

Cholestasis continues for as long as the parenteral nutrition. It usually resolves within weeks or months of stopping. In some patients, enteral feeding will not halt the liver disease once jaundice develops [60]. If therapy cannot be stopped, biliary cirrhosis develops and this may be fatal. The use of amino acid free parenteral nutrition and enteral whey protein may prevent the cholestasis [14].

The cholestasis is related to loss of the entero-hepatic circulation of bile acids and consequent reduced bile formation, biliary stasis and sludging.

Abnormal bile acid synthesis

Defects in the synthesis of primary bile acids can cause decreased bile flow and abnormal transport and so cholestasis.

Bile acid synthesis defects may resemble progressive familial intra-hepatic cholestasis (PFIC) type 2.

3β-hydroxy-C27-steroid dehydrogenase-isomerase deficiency results in cholestasis without pruritus and with normal serum γ-GT and bile acids [39]. Cholestasis has also resulted from *Δ4-3-oxosteroid-5β-reductase deficiency* [25].

Coprostanic acidaemia results from a defect in the conversion of coprostanic to varinic acid. It is associated with progressive cholestasis and death by 2 years of age.

Zellweger's cerebro-hepato-renal syndrome is a fatal autosomal recessive condition with severe cholestasis. It is probably related to defective peroxisomal β-oxidation.

Treatment. Toxic intermediates are formed which cause cholestasis by interacting with hepatic bile acid transport. Replacement of exogenous bile acids results in the generation of bile acid-dependent flow and a decrease in the synthesis of toxic bile salts. Remarkable benefit has followed the administration of chenodeoxycholic acid, ursodeoxycholic acid and cholic acid [22, 81]. Pruritus is reduced and transaminases and serum bilirubin levels fall.

Genetic cholestatic syndromes

These are being increasingly identified. Formerly they were probably included with idiopathic neonatal hepatitis or with the intra-hepatic paucity of bile duct syndrome [15, 42].

The diseases are related to defects in one of the ATP-binding cassette (ABC) transport superfamily (table 26.6) [3, 40]. They are concerned with the secretion of bile, but are important also in almost every cell organelle. The spectrum of disease caused by these defects is therefore diverse. The molecular basis of severe forms of neonatal cholestatic liver disease has now been defined. Although usually familial with autosomal inheritance, sporadic forms are being identified.

Progressive familial intra-hepatic cholestasis type 1

This was formerly called *Byler's disease* because of the association with the large numbers of an Amish kindred affected in Pennsylvania (Chapter 13). The defect is now being described from many parts of the world, including the Netherlands, Sweden and in Arab populations. Inheritance is autosomal recessive. It presents with infancy cholestasis which eventually progresses to biliary fibrosis and cirrhosis. Liver transplantation is usually necessary in the first decade of life. Characteristically, serum γ-GT is low whereas alkaline phosphatase and serum primary bile acids are increased. Biliary bile acids are reduced.

The genetic defect has been mapped to the FIC 1 locus on chromosome 18q21–q22. It has been mapped to a region encoding the family of P-type ATPases [16] which encode ion transport proteins. There is defective bile acid transport at the canalicular membrane.

Table 26.6. Genetic cholestatic syndromes

Disorder	Clinical	γ-GT	Chromosome	Genetic disorder
PFIC 1	Progressive	Normal	18q21–q22	P-type ATPase
BRIC	Recurrent jaundice, pruritus	Normal	18q21–q22	P-type ATPase
PFIC 2	Progressive	Normal	2q24	Canalicular bile acid transport
PFIC 3	Low phospholipids Bile ductular proliferation	High	7q21	Canalicular phospholipid transport (MDR3)
Dubin–Johnson	Conjugated hyperbilirubin	Normal	10q23q24	cMOAT (MRP2)

PFIC, progressive familial intra-hepatic cholestasis. BRIC, benign recurrent intra-hepatic cholestasis; γ-GT, γ-glutamyl transferase; MDR3, multiple drug resistence 3; MRP2, multidrug resistance protein 2; cMOAT, canalicular multi-specific organic anion transporter

Benign recurrent intra-hepatic cholestasis (BRIC) (Chapter 13)

This presents with recurrent episodes of jaundice and pruritus [85]. The serum γ-GT is not elevated.

The gene involved has been mapped to the FIC 1 locus, the same region as PFIC I—namely chromosome 18q21–q22.

Progressive familial intra-hepatic cholestasis type 2

The disease does not involve the PFIC I locus but has been mapped to a locus on chromosome 2q24. This encodes the bile salt export pump (BSEP) gene [80]. This is a P glycoprotein belonging to class B of the ABC transport super-family. The primary defect is a defective canalicular bile acid transport pump.

Serum γ-GT is normal and bile ductular proliferation is not seen. The disease may start as a giant cell hepatitis but progresses to early cirrhosis and liver transplantation.

Progressive familial intra-hepatic cholestasis type 3

This is marked by an elevated serum γ-GT and bile ductular proliferation. There is a mutation in the multiple drug-resistant gene (MDR3 or P glycoprotein 3) on chromosome 7q21 (Table 26.6). This moves phospholipid from the inner leaflet of the canalicular membrane to the outer leaflet which faces the canalicular lumen [28]. Serum phospholipid is low. Bile acid transport is unimpaired as is bile flow, but in the absence of phospholipid, the bile acids prove toxic to cholangiocytes and hepatocytes. Serum γ-GT is high.

Dubin–Johnson syndrome (Chapter 12)

This is not a cholestatic disease, but is marked by a rise in serum conjugated bilirubin. It is caused by a mutation of an ABC transporter, canalicular multi-specific organic anion transporter (cMOAT) [66].

Symptomatic treatment of cholestatic syndromes

Nutritional support is given by an increased energy intake of 120–150% of the estimated average.

Fat-soluble vitamins are replaced orally by vitamin A 5–15 000 iu/day; vitamin D (α-calcidol) 50 ng/kg/day; and vitamin K 2.5–5 mg/day. The child is encouraged to drink skimmed milk.

Vitamin E deficiency is particularly important. It results in a degenerative neuro-muscular syndrome. Vitamin E at 50–200 mg/day should be given. Once a neurological condition has developed, it may be arrested but not reversed by intramuscular vitamin E.

Medium chain triglyceride (coconut oil) is added to puréed fruit and vegetables and in cooking.

In partial cholestasis, pruritus may be controlled by cholestyramine flavoured with apple purée, tomato juice or chocolate syrup.

Ursodeoxycholic acid (10 mg/kg body weight) is given in one dose after the evening meal. It reduces serum enzyme levels and may relieve pruritus [62].

Other causes of cholestatic jaundice

Neonatal lupus erythematosus syndrome

This presents as neonatal cholestasis and hepatitis [72]. Cutaneous lupus erythematosus and congenital heart block are associated.

Spontaneous perforation of the bile ducts

This occurs between birth and 3 months, usually in the anterior wall of the common bile duct close to the junction with the cystic duct. The child develops non-bile-stained vomiting and acholic stools. Jaundice is mild, intermittent and variable. Abdominal hernias develop and the scrotum becomes green. Cholangiography shows the blocked cystic duct with the hepatic duct leak. The results of surgery are good.

Gallbladder disease and gallstones [69]

Total parenteral nutrition is frequently accompanied by biliary sludge in the gallbladder and cholestasis. Phytosterolaemia may predispose to biliary sludge and liver damage if bile salts are deficient [21]. Bile duct perforation is associated with gallstones secondary to bile stasis.

Pigment gallstones may be found in the lower common bile duct without obvious cause. Acute gastroenteritis with bacterial overgrowth, dehydration or a minor atypical termination of the common bile duct may contribute.

A similar picture may complicate neonatal jaundice due to such conditions as hepatic prematurity or haemolytic disease. This has been termed the *inspissated bile syndrome*.

Surgical or endoscopic washing of the bile ducts is curative without the need for cholecystectomy.

In older children, cholecystitis and gallstones may be associated with blood dyscrasias or congenital anomalies of the biliary tract, such as choledochal cysts or biliary atresia. IgA deficiency has been linked with biliary sludge and gallstones in children [24].

Older children with gallstones often have a strong family history.

Sclerosing cholangitis may present in early infancy as intra-hepatic cholestasis progressing to end-stage biliary

cirrhosis in childhood. There may be an autosomal recessive inheritance. Associations include ulcerative colitis, autoimmune hepatitis, histiocytosis X and immune deficiencies. The prognosis is poor (Chapter 15).

Reye's syndrome

In 1963 Reye and associates described this syndrome of acute encephalopathy and fatty change in the viscera [71]. A marked drop in reported cases has followed recognition of the association with aspirin [7]. In the United States in 1980, 556 children sufferers were reported. Since 1987 no more than 36 cases per year have been identified. The risk also exists in long-term users of aspirin such as those with juvenile rheumatoid arthritis. In view of the decreased prevalence of Reye's syndrome, it becomes even more important to rule out metabolic disorders that can mimic Reye's.

The syndrome can be encountered in epidemic form, often in winter or spring. There are two phases, an infective followed by an encephalopathic phase. Influenza B or A or varicella are the commonest antecedent infections.

Clinical features

Sexes are equally affected, usually below 14 years old; young adults have been described [59]. Three to 7 days after a viral-type illness the child develops intractable vomiting and progressive neurological deterioration. The encephalopathy is marked by erratic behaviour, irritability and listlessness progressing through lethargy to stupor and coma. Jaundice is rare.

Milder (grade 1) Reye's syndrome presents simply as vomiting with abnormal liver function tests after an upper respiratory infection or varicella [52].

In severe cases, medullary coning and brain death result 4–60 h after the onset.

Liver biopsy

This shows microvesicular fat. Electron microscopy shows swelling and distortion of the mitochondria to be followed by showers of peroxisomes.

Other organs

The kidneys show proximal tubular fat. The myocardium is fatty and there is marked cerebral oedema. Electron microscopy of the neurons shows similar mitochondrial changes to those seen in the liver.

Laboratory findings

There is decreased activity of mitochondrial enzymes in the liver. A rise in blood ammonia with low citrulline values can be related to a reduction in Krebs' cycle enzymes. The serum amino acid profile shows a high glutamine, alanine and leucine. Hypoglycaemia is found in about 50%—usually in those seriously ill and less than 2 years old; it may reflect inhibition of the citric acid cycle. Mitochondrial injury also depresses fatty acid oxidation and plasma free fatty acids are increased. Serum transaminases are raised. A prothrombin time prolonged more than 3 s, together with a serum ammonium value greater than 100 μg/dl, predict a serious course. Coagulopathy is constant.

Reye's syndrome is one of the mitochondrial cytopathies (Chapter 25). Some paediatricians doubt the existence of Reye's syndrome and consider that all cases could be due to some underlying metabolic defect.

Treatment

The patient presents as a problem in liver disease, but the cerebral oedema is lethal. Treatment is directed towards this, combined with intense supportive care. There is no specific treatment.

Reye-like syndromes

A number of metabolic defects produce a picture clinically, biochemically and histologically resembling Reye's syndrome [32].

In younger children it is particularly important to exclude urea cycle defects, disturbances in the mitochondrial β-oxidation pathway of fatty acids and, particularly, deficiencies of medium- and long-chain acyl-CoA dehydrogenase [84]. Exclusion of these metabolic defects demands special diagnostic facilities. Specimens of urine and serum should be obtained and frozen so that they may be subsequently analysed in specialist centres. Electron microscopy of a liver biopsy may also be useful, as, in contrast to Reye's syndrome, mitochondrial morphology in the metabolic cases is normal.

Cirrhosis in infancy and childhood

The cirrhosis of infants and children has many aetiologies. Many are cryptogenic.

A number, presenting in later childhood and at puberty, show the picture of *chronic autoimmune hepatitis*. These patients usually respond to prednisolone treatment (Chapter 19).

Neonatal 'giant cell' hepatitis may be followed by cirrhosis and this may also apply to some of the neonatal virus infections such as hepatitis B or C.

Neonatal haemochromatosis is probably of autosomal recessive inheritance. It may be associated with abnormal bile acids and with mitochondrial oxidative phos-

phorylation deficiency. It may present as fulminant liver failure in the newborn.

Iron overload is usually related to transfusion in anaemic children, often thalassaemic. However, inherited haemochromatosis can affect children as early as 2 years. Females and males are equally affected. Cardiac involvement is often fatal. Hypogonadism is frequent.

Wilson's disease, galactosaemia, Fanconi's disease, type IV glycogen disease and fibrocystic disease may be followed by cirrhosis.

In the tropics the kwashiorkor syndrome is not followed by cirrhosis whereas *veno-occlusive disease* is followed by zone 3 fibrosis and finally cirrhosis.

Congenital hepatic fibrosis may cause portal hypertension but the hepatic lesion is not cirrhosis.

Cholestatic syndromes are followed by biliary cirrhosis and this is also true of *α-antitrypsin deficiency*.

Cardiac cirrhosis is unusual in childhood except complicating constrictive pericarditis.

Clinical features

Portal hypertension is usually prominent. The spleen tends to be larger than in the adult. Presentation with splenomegaly and hepatomegaly at a school medical examination or while in hospital for another condition is not unusual. Vascular spiders are conspicuous. Growth is uninterrupted; indeed the adolescent growth spurt may be particularly great so that the child is above normal height (fig. 26.8).

At puberty, both sexes may show acne and facial mooning with cutaneous striae; girls have amenorrhoea and boys gynaecomastia.

This relatively inactive stage can continue for years. Decompensation is followed by deepening jaundice and very high serum globulin and transaminase values. When pre-coma appears it is accompanied by mania, screaming, fits and psychic outbursts. Ascites is usual at this late stage. Sclerotherapy of oesophageal varices is well tolerated.

The prognosis is very variable depending on the aetiology. The outlook is better than for an adult with an equivalent degree of clinical decompensation.

Indian childhood cirrhosis

This condition is seen in rural, middle-class Hindu families throughout India. Both sexes are affected between the ages of 1 and 3 years. The familial incidence suggests genetic factors although it may indicate a common environmental origin. Death is usually due to liver failure and occurs within 1 year of diagnosis.

Hepatic histology shows damaged liver cells which may contain Mallory's hyaline bodies which are surrounded by polymorphs. A micronodular cirrhosis results. The picture resembles acute alcoholic hepatitis but without the fatty change.

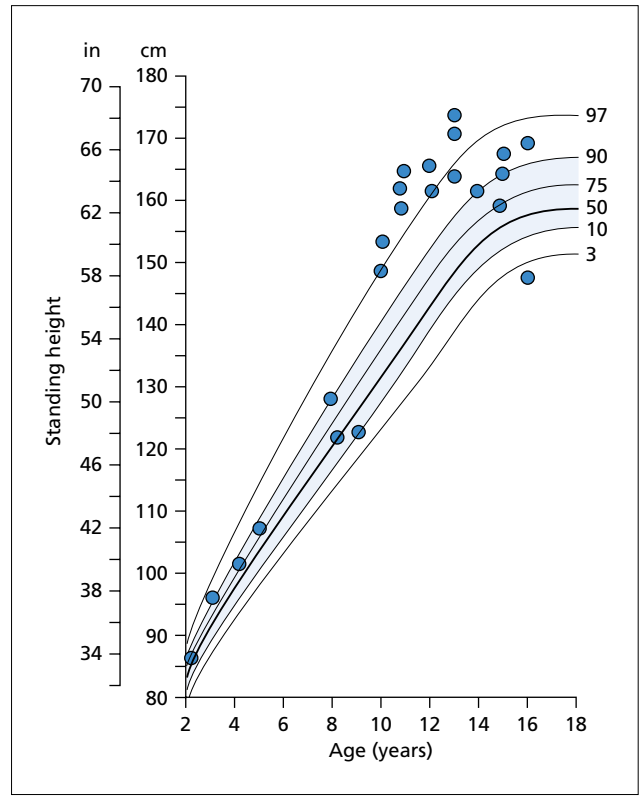


Fig. 26.8. Cirrhosis in female children. Note that children between 10 and 13 years are taller than 90% of the population.

Hepatic copper is markedly increased to more than 250μg/g dry weight. The cytoplasm contains excessive copper. Hepatic nuclei show DNA fragmentation, perhaps the result of copper toxicity [67].

Consanguinity is common but this is frequent in the community [82]. The excess hepatic copper from animal feed prepared in copper and brass utensils has fallen with a marked decline in prevalence.

D-penicillamine results in disease resolution and prolongation of life but does not prevent the development of inactive micronodular cirrhosis.

Wilson's disease is excluded by the absence of Kayser–Fleischer rings and normal serum caeruloplasmin values.

Non-Indian childhood cirrhosis (copper-associated liver disease) [5]

A childhood disorder indistinguishable from Indian childhood cirrhosis has been reported from other countries [50, 61] and termed copper-associated liver disease [5]. It seems not to be related to increased copper ingestion in drinking water. A genetic defect seems likely [75].

Hepatic steatosis

Fetal alcohol syndrome

Hepatomegaly and raised transaminase values may be found. The liver may show fatty changes with portal and peri-sinusoidal fibrosis resembling those seen in the adult with alcoholic liver disease.

Idiopathic steato-hepatitis

This affects obese, peri-pubertal children and is diagnosed by liver biopsy [6].

Tumours of the liver

See also Chapter 31. Primary tumours in infants and children are rare; two-thirds are diagnosed before the second year of life. They may arise from liver cells and/or from supporting structures. Secondary tumours are extremely rare and are usually associated with a neuroblastoma of the adrenals.

Diagnosis

Biochemical tests may be normal. The most usual abnormality is an increase in serum γ-GT and α_2-globulin levels. Serum α-fetoprotein may be increased. The site and extent of the tumour must be defined by ultrasound, CT, MRI and, if necessary, angiography.

Guided liver biopsy is usually a safe method of confirming the diagnosis.

Hamartomas

These benign, congenital lesions present as an abdominal mass in the first 2 years of life. They may be an incidental finding at autopsy and must be distinguished from malignant tumours. They consist of abnormal arrangements of all the cells of the normal liver, particularly bile ducts and fibroblasts. They contain central veins and are nearly always cystic. They require no treatment.

Mesenchymal hamartoma

This is a rare developmental anomaly, largely of bile ducts, seen in children less than 2 years old. It is treated conservatively, or if necessary by surgical excision [26].

Malignant mesenchymoma (undifferentiated sarcoma)

This is seen in older children (6–12 years). Histology is that of sarcoma with PAS-positive intra-cytoplasmic pink globules. The tumour should be resected surgically with subsequent chemotherapy.

Adenomas

These rare tumours do not become malignant, and over the years may even regress. They consist of sheets of liver cells and have a fibrous capsule. They should be treated conservatively.

Hepato-cellular carcinoma

These usually present after 5 years of age. Males are more frequently affected than females. The tumours are often single, large and metastasize late. Cirrhosis may be absent.

Hepatitis B and C are the usual causes especially in the Far East [17]. Hepato-cellular carcinoma may also complicate giant cell hepatitis, biliary atresia and the polycystic diseases (including congenital hepatic fibrosis), tyrosinosis and glycogen storage diseases.

The patients present with weight loss, abdominal swelling in the right upper quadrant, pain, ascites and jaundice. Calcification in the tumour may be noted.

Treatment

Surgical resection is rarely possible. However, following lobectomy, growth and development are normal. Chemotherapy may be useful in reducing tumour size before resection.

The fibro-lamellar form has a much better prognosis and resection is more often possible.

Hepatoblastoma [48]

This rare tumour with epithelial and mesenchymal elements usually presents before 3 years of age and is usually fatal within 5 years.

It has been reported in association with hemihypertrophy, Wilms' tumour, fetal alcohol syndrome and with polyposis coli in the mother. It may produce human chorionic gonadotrophins resulting in precocious puberty.

Hypercholesterolaemia can be associated.

Prognosis has improved with better chemotherapy using cisplatin and desoxyrubicin; 86% respond. Hepatic transplantation has led to falls of human chorionic gonadotrophins.

Infantile haemangio-endothelioma [76]

This, usually benign, vascular tumour of infancy consists of endothelium-lined channels of capillary size. It

may be associated with skin haemangiomas. It presents before 6 months of age as an abdominal mass. Cardiac failure may be related to arteriovenous shunts within the tumour. A systolic bruit may be heard in the epigastrium. Rupture can cause haemoperitoneum. Associated congenital defects are frequent.

Severe anaemia and thrombocytopenia have been attributed to microangiopathic haemolysis related to the abnormal, tortuous, narrow vessels within the tumour.

CT and MRI show typical features of haemangioma. Ultrasound is used to monitor progress [78].

Treatment is symptomatic with hepatic arterial embolization for refractory heart failure or rupture. The prognosis is good.

Treatment

Resection will cure the benign lesions. Cure may even follow in the malignant group, but the tumour is usually single, often large and metastasizes late. Palliation is usual. Subsequent growth and development are normal after hepatic lobectomy. Transplantation must always be considered. The prognosis is very poor if resection is impossible.

Nodular regenerative hyperplasia

The children present with hepatomegaly or splenomegaly. Associations include neoplasms or consumption of drugs such as anti-convulsants.

Hepatic transplantation

This is considered in detail in Chapter 38. Innovative techniques such as split livers and living-related donations have increased the supply of organs [44]. Younger and sicker children are receiving transplants. Early operation is important before the development of significant growth or psycho-social retardation.

References

1 Alagille D, Estrada A, Hadchouel M *et al*. Syndromic paucity of interlobular bile ducts (Alagille syndrome or arteriohepatic dysplasia): review of 80 cases. *J. Paediatr.* 1987; **110**: 195.

2 Alpert LI, Strauss L, Hirschhorn K. Neonatal hepatitis and biliary atresia associated with trisomy 17–18 syndrome. *N. Engl. J. Med.* 1969; **270**: 16.

3 Arrese M, Ananthananarayanan M, Suchy FJ. Hepatobiliary transport: molecular mechanisms of development and cholestasis. *Paediatr. Res*. 1998; **44**: 141.

4 Badizadegan K, Jonas MM, Ott MJ *et al*. Histopathology of the liver in children with chronic hepatitis C viral infection. *Hepatology* 1998; **28**: 1416.

5 Baker A, Gormally S, Saxena R *et al*. Copper-associated liver disease in childhood. *J. Hepatol*. 1995; **23**: 538.

6 Baldridge AD, Perez-Atayde AR, Graeme-Cook F *et al*. Idiopathic steatohepatitis in childhood: a multicentre retrospective study. *J. Pediatr*. 1995; **127**: 700.

7 Belay ED, Bresee JS, Holman RC *et al*. Reye's syndrome in the United States from 1981 through 1997. *N. Engl. J. Med.* 1999; **340**: 1377.

8 Benaron DA, Bowen FW. Variation of initial serum bilirubin rise in new born infants with type of illness. *Lancet* 1991; **338**: 78.

9 Bortolotti F, Cadrobbi P, Cruvellaro C *et al*. Long-term outcome of chronic type B hepatitis in patients who acquire hepatitis B virus infection in childhood. *Gastroenterology* 1990; **99**: 805.

10 Bortolotti F, Jara P, Barbera C *et al*. Long-term effect of alpha interferon in children with chronic hepatitis B. *Gut* 2000; **46**: 715.

11 Bortolotti F, Jara P, Crivellaro C *et al*. Outcome of chronic hepatitis B in Caucasian children during a 20-year observation period. *J. Hepatol.* 1998; **29**: 184.

12 Brodsky MC, Cunniff C. Ocular anomalies in the Alagille syndrome (arteriohepatic dysplasia). *Ophthalmology* 1993; **100**: 1767.

13 Brown CW, Werlin SL, Geenen JE *et al*. The diagnostic and therapeutic role of endoscopic retrograde cholangiopancreatography in children. *J. Paediatr. Gastroenterol. Nutr.* 1993; **17**: 19.

14 Brown MR, Thunberg BJ, Golub L *et al*. Decreased cholestasis with enteral instead of intravenous protein in the very low-birth-weight infant. *J. Paediatr. Gastroenterol. Nutr.* 1989; **9**: 21.

15 Bruguera M, Llach J, Rodés J. Nonsyndromic paucity of intrahepatic bile ducts in infancy and idiopathic ductopenia in adulthood: the same syndrome? *Hepatology* 1992; **15**: 830.

16 Bull LN, van Eijk MJT, Pawlikowska L *et al*. A gene encoding a P-type ATP ase mutated in two forms of hereditary cholestasis. *Nature Genet.* 1998; **18**: 219.

17 Chang M-H, Chen D-S, Hsu H-C *et al*. Maternal transmission of hepatitis B virus in childhood hepatocellular carcinoma. *Cancer* 1989; **64**: 2377.

18 Chang M-H, Huang HH, Huang ES *et al*. Polymerase chain reaction to detect human cytomegalovirus in livers of infants with neonatal hepatitis. *Gastroenterology* 1992; **103**: 1022.

19 Chardot C, Carton M, Spire-Bendelac N *et al*. Prognosis of biliary atresia in the era of liver transplantation: French National Study from 1986 to 1996. *Hepatology* 1999; **30**: 606.

20 Chianale J, Dvorak C, Farmer DL *et al*. Cytochrome P-450 gene expression in the functional units of the fetal liver. *Hepatology* 1988; **8**: 318.

21 Clayton PT, Bowron A, Mills KA *et al*. Phytosterolemia in children with parenteral nutrition-associated cholestatic liver disease. *Gastroenterology* 1993; **105**: 1806.

22 Clayton PT, Mills KA, Johnson AW *et al*. 4–3-Oxosteroid 5β-reductase deficiency: failure of ursodeoxycholic acid treatment and response to chenodeoxycholic acid plus cholic acid. *Gut* 1996; **38**: 623.

23 Crosnier C, Draincourt C, Raynaud N *et al*. Mutations in JAGGED 1 gene are predominantly sporadic in Alagille syndrome. *Gastroenterology* 1999; **116**: 1141.

24 Danon YL, Dinari G, Garty B-Z *et al*. Cholelithiasis in children with immunoglobulin A deficiency: a new gastroenterologic syndrome. *J. Paediatr. Gastroenterol. Nutr.* 1983; **2**: 663.

25 Daugherty CC, Setchell KDR, Heubi JE *et al*. Resolution of liver biopsy alterations in three siblings with bile acid treatment of an inborn error of bile acid metabolism (Δ4–3-oxosteroid 5β-reductase deficiency). *Hepatology* 1993; **18**: 1096.

26 DeMaioribus CA, Lally KP, Sim K *et al*. Mesenchymal hamartoma of the liver. A 35-year review. *Arch. Surg*. 1990; **125**: 598.

27 Desmet VJ. Pathogenesis of ductal plate abnormalities. *Mayo Clin. Proc*. 1998; **73**: 80.

28 DeVree JML, Jacquemin E, Sturm E *et al*. Mutations in the MDR3 gene cause progressive familial intrahepatic cholestasis. *Proc. Natl. Acad. Sci. USA* 1998; **95**: 282.

29 Dick MC, Mowat AP. Hepatitis syndrome in infancy—an epidemiological survey with 10 years follow up. *Arch. Dis. Child*. 1985; **60**: 512.

30 Emerick KM, Rand EB, Goldmuntz E *et al*. Features of Alagille syndrome in 92 patients: frequency and relation to prognosis. *Hepatology* 1999; **29**: 822.

31 Garcia-Monzon C, Jara P, Fernandez-Bermejo M *et al*. Chronic hepatitis C in children: a clinical and immunohistochemical comparative study with adult patients. *Hepatology* 1998; **28**: 1696.

32 Glasgow JFT, Moore R. Reye's syndrome 30 years on. Possible marker of inherited metabolic disorders. *Br. Med. J*. 1993; **367**: 950.

33 Hadchouel M, Hugon RN, Gautier M. Reduced ratio of portal tracts to paucity of intrahepatic bile ducts. *Arch. Pathol. Lab. Med*. 1978; **102**: 402.

34 Hansen TWR. Bilirubin in the brain. Distribution and effects on neurophysiological and neurochemical processes. *Clin. Paediatr.* 1994; **33**: 452.

35 Hart MH, Kaufman SS, Vanderhoof JA *et al*. Neonatal hepatitis and extra-hepatic biliary atresia associated with cytomegalovirus infection in twins. *Am. J. Dis. Child*. 1991; **145**: 302.

36 Heathcote J, Deodhar KP, Scheuer PJ *et al*. Intrahepatic cholestasis in childhood. *N. Engl. J. Med*. 1976; **295**: 801.

37 Ho C-W, Shioda K, Shirosaki K *et al*. The pathogenesis of biliary atresia: a morphological study of the hepatobiliary system and the hepatic artery. *J. Paediatr. Gastroenterol. Nutr.* 1993; **16**: 53.

38 Huang L-M, Chiang B-L, Lee C-Y *et al*. Long-term response to hepatitis B vaccination and response to booster in children born to mothers with hepatitis B e antigen. *Hepatology* 1999; **29**: 954.

39 Jacquemin E, Setchell KDR, O'Connell NC *et al*. A new cause of progressive intrahepatic cholestasis: 3β-hydroxy-C_{27}-steroid dehydrogenase/isomerase deficiency. *J. Paediatr.* 1994; **125**: 379.

40 Jansen PLM. The molecular genetics of familial intrahepatic cholestasis. *Gut* 2000; **47**: 1.

41 Jonas MM, Roldan EO, Lyons HJ *et al*. Histopathologic features of the liver in paediatric acquired immune deficiency syndrome. *J. Paediatr. Gastroenterol. Nutr.* 1989; **9**: 73.

42 Kahn E, Daum F, Markowitz J *et al*. Nonsyndromatic paucity of interlobular bile ducts: light and electron microscopic evaluation of sequential liver biopsies in early childhood. *Hepatology* 1986; **6**: 890.

43 Keeffe EB, Pinson CW, Ragsdale J *et al*. Hepatocellular carcinoma in arteriohepatic dysplasia. *Am. J. Gastroenterol.* 1993; **88**: 1446.

44 Kelly DA. Current results and evolving indications for liver transplantation in children. *J. Pediatr. Gastroenterol. Nutr*. 1998; **27**: 214.

45 Kelly DA. Useful investigations in the assessment of liver disease. In Kelly DA, ed. *Diseases of the Liver and Biliary System in Children*. Blackwell Science, Oxford, 1999, p. 3.

46 Kimura A, Yamakawa R, Ushijima K *et al*. Fetal bile acid metabolism during infancy: analysis of 1β-hydroxylated bile acids in urine, meconium and faeces. *Hepatology* 1994; **20**: 819.

47 Lachaux A, Descos B, Plauchu H *et al*. Familial extrahepatic biliary atresia. *J. Pediatr. Gastroenterol. Nutr.* 1988; **7**: 280.

48 Lack EE, Neave C, Vawter GF. Hepatoblastoma: a clinical and pathologic study of 54 cases. *Am. J. Surg. Pathol.* 1982; **6**: 693.

49 Langnas AN, Markin RS, Cattral MS *et al*. Parvovirus B19 as a possible causative agent of fulminant liver failure and associated aplastic anaemia. *Hepatology* 1995; **22**: 1661.

50 Lefkowitch JH, Honig CL, King ME *et al*. Hepatic copper overload and features of Indian childhood cirrhosis in an American sibship. *N. Engl. J. Med.* 1982; **307**: 271.

51 Li L, Krantz ID, Deng Y *et al*. Alagille syndrome is caused by mutations in human Jagged 1, which encodes a ligand for Notch 1. *Nature Genet.* 1997; **16**: 243.

52 Lichtenstein PK, Heubi JE, Daughterty CC *et al*. Grade I Reye's syndrome: a frequent cause of vomiting and liver dysfunction after varicella and upper respiratory tract infection. *N. Engl. J. Med.* 1983; **309**: 133.

53 Lin H-H, Kao J-H, Hsu H-Y *et al*. Absence of infection in breast-fed infants born to hepatitis C virus-infected mothers. *J. Paediatr.* 1995; **126**: 589.

54 Lok ASF, Lai C-L. A longitudinal follow-up of asymptomatic hepatitis B surface antigen-positive Chinese children. *Hepatology* 1988; **8**: 1130.

55 McKiernan PJ, Baker AJ, Kelly DA. The frequency and outcome of biliary atresia in the UK and Ireland. *Lancet* 2000; **355**: 25.

56 Manzini P, Saracco G, Cerchier A *et al*. Human immunodeficiency virus infection as risk factor for mother-to-child hepatitis C virus transmission; persistence of anti-hepatitis C virus in children is associated with the mother's anti-hepatitis C virus immunoblotting pattern. *Hepatology* 1995; **21**: 328.

57 Marret S, Buffet-Janvresse C, Metayer J *et al*. Herpes simplex hepatitis with chronic cholestasis in a newborn. *Acta Paediatr.* 1993; **82**: 321.

58 Martinez JC, Garcia HO, Otheguy LE *et al*. Control of severe hyperbilirubinemia in full-term newborns with the inhibitor of bilirubin production Sn-mesoporphyrin. *Paediatrics* 1999; **103**: 1.

59 Meythaler JM, Varma RR. Reye's syndrome in adults. Diagnostic considerations. *Arch. Intern. Med.* 1987; **147**: 61.

60 Moss RL, Das JB, Raffensperger JG. Total parenteral nutrition-associated cholestasis: clinical and histopathologic correlation. *J. Paediatr. Surg*. 1993; **28**: 1270.

61 Muller T, Feichtinger H, Berger H *et al*. Endemic Tyrolean infantile cirrhosis: an ecogenetic disorder. *Lancet* 1996; **347**: 877.

62 Narkewicz MR, Smith D, Gregory C *et al*. Effect of ursodeoxycholic acid therapy on hepatic function in children with intrahepatic cholestatic liver disease. *J. Pediatr. Gastroenterol. Nutr.* 1998; **26**: 49.

63 Naveh Y, Berant M. Assessment of liver size in normal infants and children. *J. Paediatr. Gastroenterol. Nutr.* 1984; **3**: 346.

64 Oda T, Elkahloun AG, Pike BL *et al*. Mutations in the human Jagged 1 gene are responsible for Alagille syndrome. *Nature Genet*. 1997; **16**: 235.
65 Ohto H, Terazawa S, Sasaki N *et al*. Transmission of hepatitis C virus from mothers to infants. *N. Engl. J. Med*. 1994; **330**: 744.
66 Paulusma CC, Kool M, Bosma PJ *et al*. A mutation in the human canalicular multispecific organic anion transporter gene causes the Dubin–Johnson syndrome. *Hepatology* 1997; **25**: 1539.
67 Prasad R, Kaur G, Nath R *et al*. Molecular basis of pathophysiology of Indian childhood cirrhosis. Role of nuclear copper accumulation in liver. *Mol. Cell. Biochem*. 1996; **156**: 25.
68 Rabinovitz M, Imperial JC, Schade RR *et al*. Hepatocellular carcinoma in Alagille's syndrome: a family study. *J. Paediatr. Gastroenterol. Nutr.* 1989; **8**: 26.
69 Reif S, Sloven DG, Lebenthal E *et al*. Gallstones in children. Characterization by age, aetiology, and outcome. *Am. J. Dis. Child*. 1991; **145**: 105.
70 Resti M, Azzari C, Lega L *et al*. Mother-to-infant transmission of hepatitis C virus. *Acta. Paediatr.* 1995; **84**: 251.
71 Reye RDK, Morgan G, Baral J. Encephalopathy and fatty degeneration of the viscera. A disease entity in childhood. *Lancet* 1963; **ii**: 749.
72 Rosh JR, Silverman ED, Groisman F *et al*. Intrahepatic cholestasis in neonatal lupus erythematosus. *J. Paediatr. Gastroenterol. Nutr.* 1993; **17**: 310.
73 Rudolph JA, Balistreri WF. Optional treatment of biliary atresia 'halfway' there. *Hepatology* 1999; **30**: 808.
74 Ruiz-Moreno M, Rua MJ, Castillo I *et al*. Treatment of children with chronic hepatitis C with recombinant interferon-α: a pilot study. *Hepatology* 1992; **16**: 882.
75 Scheinberg IH, Sternlieb I. Is non-Indian childhood cirrhosis caused by excess dietary copper? *Lancet* 1994; **344**: 1002.
76 Selby DM, Stocker JT, Waclawiw MA *et al*. Infantile haemangioendothelioma of the liver. *Hepatology* 1994; **20**: 39.
77 Sokal EM, Conjeevaram HS, Roberts EA *et al*. Interferon alfa therapy for chronic hepatitis B in children: a multinational randomized controlled trial. *Gastroenterology* 1998; **114**: 988.
78 Stanley P, Geer GD, Miller JH *et al*. Infantile hepatic haemangiomas. Clinical features, radiologic investigations, and treatment of 20 patients. *Cancer* 1989; **64**: 936.
79 Steele MI, Marshall CM, Lloyd RE *et al*. Reovirus 3 not detected by reverse transcriptase-mediated polymerase chain reaction analysis of preserved tissue from infants with cholestatic liver disease. *Hepatology* 1995; **21**: 697.
80 Strautnieks SS, Bull LB, Knisely AS *et al*. A gene encoding a liver-specific ABC transporter is mutated in progressive familial intrahepatic cholestasis. *Nature Genet*. 1998; **20**: 233.
81 Suchy FJ. Bile acids for babies? Diagnosis and treatment of a new category of metabolic liver disease. *Hepatology* 1993; **18**: 1274.
82 Tanner MS. The role of copper in Indian childhood cirrhosis. *Am. J. Clin. Nutr.* 1998; **67**: 1074S.
83 Tolia V, Dubois RS, Watts FB Jr *et al*. Renal abnormalities in paucity of interlobular bile ducts. *J. Paediatr. Gastroenterol. Nutr.* 1987; **6**: 971.
84 Treem WR, Witzleben CA, Piccoli DA *et al*. Medium-chain and long-chain acyl CoA dehydrogenase deficiency: clinical, pathologic and ultrastructural differentiation from Reye's syndrome. *Hepatology* 1986; **6**: 1270.
85 Tygstrup N, Steig BA, Juijn JA *et al*. Recurrent familial intrahepatic cholestasis in the Faeroe Islands. Phenotype heterogeneity but genetic homogeneity. Hepatology 1999; **29**: 506.
86 Yeung LTF, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus. *Hepatology* 2001; **34**: 223.
87 Yokochi K. Magnetic resonance imaging in children with kernicterus. *Acta Paediatr*. 1995; **84**: 937.

Chapter 27
The Liver in Pregnancy

Normal pregnancy

Physical examination may show palmar erythema and vascular spiders. The liver is impalpable.

A study of biochemical tests in normal pregnant women compared with controls showed little differences [2]. Serum alkaline phosphatase is increased in the last trimester. Serum bilirubin is slightly lower, probably related to haemodilution. This may also account for reduced albumin, urea and uric acid concentrations. Serum transaminases, γ-glutamyl transpeptidease and fasting bile acids remain within normal limits.

Needle liver biopsy in normal pregnancy gives virtually normal histological appearances. Electron microscopy shows some increase in endoplasmic reticulum.

Liver blood flow is within the normal range [25]. In pregnancy, blood volume and cardiac output increase. The liver blood flow comprises 35% of the cardiac output in non-pregnant females and only 28% of the cardiac output in pregnancy. The excess blood volume is shunted through the placenta.

Liver disease in pregnancy

Jaundice may be peculiar to pregnancy, such as acute fatty liver, cholestatic jaundice or jaundice complicating toxaemias. The jaundice may be an intercurrent one affecting the pregnant woman, such as viral hepatitis or gallstones. Finally, the effect of pregnancy on underlying chronic liver disease must be considered (table 27.1).

Hyperemesis gravidarum

This is an extension of the morning sickness of the first trimester [36]. Those severely affected show raised bilirubin, usually to less than four times the upper limit of normal, and transaminase levels as high as 200 iu/l [18]. Liver biopsies are normal or show fatty change. The changes are probably related to malnutrition and return rapidly to normal within a few days of delivery.

The mean birth weight of the offspring is reduced in those women who are severely affected.

Liver diseases of late pregnancy

The three pregnancy-related diseases are fatty liver of pregnancy, pre-eclampsia or eclampsia and the HELLP syndrome. There is considerable overlap between them (fig. 27.1), for instance 40% of sufferers from acute fatty liver of pregnancy show evidence of eclampsia (hypertension, proteinuria and oedema).

The diseases are of unknown cause, they are commoner in twins and there is no chronicity.

Acute fatty liver of pregnancy

The first description is usually attributed to Sheehan [44] who, in 1940, described obstetric acute liver atrophy as a cause of jaundice in pregnancy.

It is still rare, but recognition of milder cases and knowledge of the wide spectrum of illness has resulted

Table 27.1. Liver disease in pregnancy

	Notes
Peculiar to pregnancy	
Acute fatty liver	Rare, presents vomiting, variable prognosis
Toxaemias	Hepatic haemorrhage may be a complication
HELLP syndrome	Haemolysis, Elevated serum, Liver enzymes, Low Platlet count
Recurrent cholestasis	Good prognosis, familial, recurs, fetal wastage
Hyperemesis	Rare cause of jaundice
Intercurrent	
Viral hepatitis	Prognosis as in non-pregnant A—no effect on fetus B—rarely transmitted to fetus C—anti-HCV positive check HCV RNA E—often fatal in Africa and Asia
Gallstones	Rare cause of jaundice, ultrasound diagnosis
Underlying chronic liver disease	Rare to become pregnant, prognosis variable, stillbirths increased

Table 27.2. Clinical and laboratory features of 12 patients with acute fatty liver of pregnancy (data from [7])

	No.
Nausea/vomiting	12
Severe heartburn	4
Abdominal pain	7
Jaundice	11
Leucocytosis	12
Thrombocytopenia	9
Proteinuria	7
Oedema	7
Hypertension	8
Serum urea increased	9

in more patients being diagnosed. The incidence is estimated at 1 per 13 328 deliveries [30]. It is much rarer than pre-eclampsia.

Clinical features

The onset is between the 30th and 38th week and is marked by nausea, repeated vomiting and abdominal pain followed by jaundice (table 27.2). It is commoner with twins and male births and in primiparae.

In those severely affected, the course is marked by encephalopathy, renal failure, pancreatitis, haemorrhages and disseminated intravascular coagulation.

Ascites is found in 50%, perhaps related to portal hypertension.

Polydipsia and polyuria with transient diabetes insipidus have been reported [33].

Serum biochemical changes

Serum ammonia and amino acid levels are increased, reflecting mitochondrial failure. This is also suggested by lactic acidosis. High serum uric acid levels are usual and may be related to the tissue destruction and lactic acidosis [7].

Hypoglycaemia can be profound.

Hyperbilirubinaemia is found without haemolysis in contradistinction to pregnancy toxaemia where jaundice is rare except when there is haemolysis. Serum transaminase values are variable, usually less than 1000 iu/l, and may be normal.

Haematological findings

Leucocytosis and thrombocytopenia are common but the blood film may be leucoerythroblastic [7].

Prothrombin time and partial prothrombin time are increased. Fibrinogen levels are decreased. Severe bleeding is frequent, but disseminated intravascular coagulation is found in only 10%.

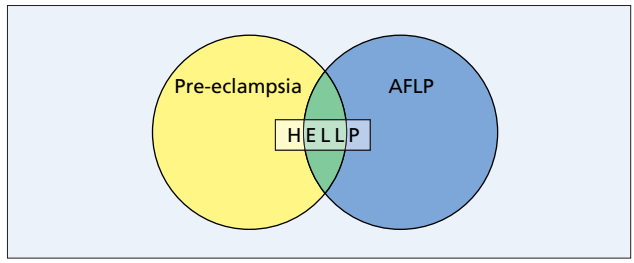


Fig. 27.1. Venn diagram showing the overlap between pre-eclampsia, acute fatty liver of pregnancy (AFLP) and the HELLP syndrome.

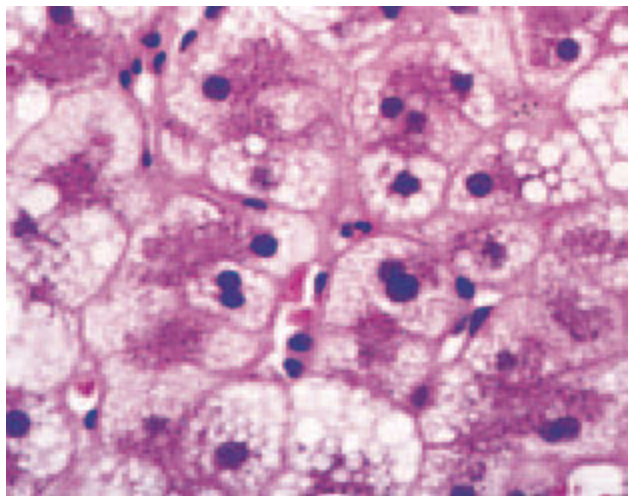


Fig. 27.2. Acute fatty liver of pregnancy. Hepatocytes have a foamy appearance with a central dense nucleus. (H & E, ×120.)

Liver histology

Liver biopsy is not usually necessary but can be performed by the transjugular route. The histological picture is of microvesicular and macrovesicular fat droplets with ballooned hepatocytes containing dense, central nuclei (fig. 27.2). Zone 1 (peri-portal) is relatively spared. The microvacuoles may be clearly recognized only on fresh sections stained for fat with such methods as oil red O (fig. 27.3) [6, 40].

Foci of inflammation and necrosis may be seen; also cholestasis with bile canalicular plugs and bile-stained Kupffer cells. Liver architecture is normal.

Electron microscopy confirms vacuoles and may show a honeycomb appearance in the smooth endoplasmic reticulum. Mitochondria are large and pleomorphic with paracrystalline inclusions [33].

Multi-organ involvement is shown by fatty infiltration of the renal tubules and renal lesions typical of pre-eclampsia. Fatty infiltration of the pancreas and the heart have been reported [40].

Ultrasonography of the liver may show a diffuse increased echogenicity which is very suggestive of acute

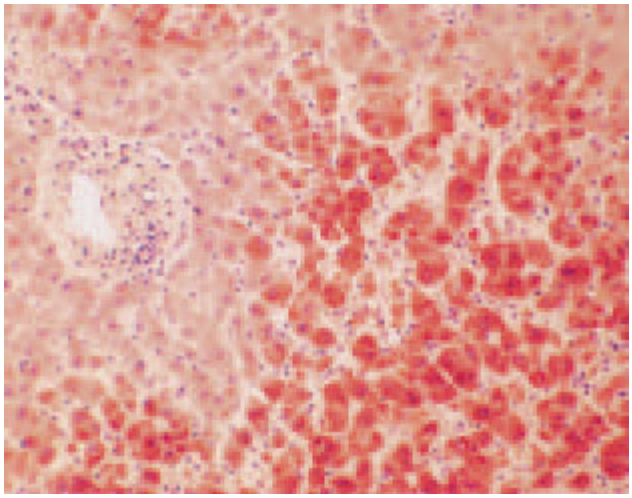


Fig. 27.3. Acute fatty liver of pregnancy: zone 3 hepatocytes are full of microvesicular fat droplets. Portal zones are normal and inflammation is minimal. (Oil red, ×40.)

fatty liver of pregnancy. A normal sonogram does not exclude the diagnosis. CT shows a low attenuation value in 30% [21].

Course and prognosis

Early recognition with prompt treatment has allowed diagnosis of milder cases and the current maternal mortality is 0–15%. The fetal mortality (40–50%) remains high.

Death is usually due to extra-hepatic causes such as disseminated intravascular coagulation with massive haemorrhage, and to renal failure. These features are not seen in the less severe cases.

Recurrences are extremely rare but have been reported. In one such case, a black woman presented with the disease in her fourth and fifth pregnancies [5]. From Australia, a woman had acute fatty liver of pregnancy in her first and second pregnancies [43]. A Chilean report describes the condition in two consecutive pregnancies [33, 34].

Management

The management of the average mild case is careful observation of the mother and fetus in hospital. If the mother's status deteriorates (intractable vomiting, increased jaundice and features of a coagulopathy), the pregnancy should be delivered.

Coagulopathy, renal failure, hypoglycaemia and infections are treated. The prognosis is relatively favourable if intensive care is adequate [29]. Intra-abdominal haemorrhage may necessitate laparotomy for clot evacuation. The intensive care must continue post-partum and intra-abdominal haemorrhage may follow caesarean section. Hepatic transplantation is sometimes necessary [26, 29].

The baby may need corticosteroids to treat lung immaturity.

Oesophagitis with bleeding is a frequent complication and omeprazole or a similar drug should be given.

Table 27.3. The mitochondrial cytopathies

Causes
Acute fatty liver of pregnancy
Reye's syndrome
Genetic defects in mitochondrial function
Drug-related
Features
Vomiting and apathy
Lactic acidosis
Hypoglycaemia
Hyperammonaemia
Microvesicular fat in organs

Aetiology

Acute fatty liver of pregnancy can be regarded as a member of the *mitochondrial cytopathy family* (table 27.3) [45]. Members include Reye's syndrome, genetic defects in mitochondrial enzymes and drug reactions, especially to sodium valproate and nucleoside analogues (e.g. FIAU).

Apart from the breakdown of carbohydrate, nearly all the reactions involved in energy production take place in mitochondria. Some oxidative phosphorylation includes the oxidation of fuel molecules by oxygen and simultaneous energy transduction into ATP. Fatty acids are broken down in the mitochondria into shorter derivative fatty acids and acyl-CoA. This cycle of repeated fatty acid cleavage requires a series of specific enzymes.

The mitochondrial cytopathies are marked by vomiting and weakness. Lactic acidosis and metabolic acidosis are related to defective mitochondrial energy supply and defects in oxidative phosphorylation. Hypoglycaemia may be related to failure of mitochondrial citric acid cycle function. Raised blood ammonia relates to defects in mitochondrial Krebs' cycle enzymes. Microvesicular fat is seen in the organs.

Young people are predominantly affected in Reye's disease and in genetic defects of mitochondrial enzymes. Patients with acute fatty liver of pregnancy are usually reasonably young. Adverse hepatic effects of sodium valproate are roughly twice as frequent in children than in adults. This has led to the hypothesis that these diseases primarily affect patients having an underlying defect in mitochondrial function. A proportion of women with acute fatty liver of pregnancy are heterozy-

gous for long-chain 3-hydroxy-CoA dehydrogenase deficiency which leads to impaired fatty acid oxidation [51]. Their infants may show hypoglycaemic coma and hepatic steatosis, and have a similar but homozygous defect in fatty acid oxidation. As this defect is autosomal recessive and the mothers are heterozygotes, some of the spouses must be heterozygous. In another report, 11 pregnancies, complicated by features of fatty liver and, HELLP syndrome, were followed by six babies with long-chain 3-hydroxy acyl coenzyme dehydrogenase deficiency [54]. The mothers might be heterozygous for this deficiency because they have had subsequent uneventful pregnancies when the fetus was unaffected.

Pregnancy *per se* may affect mitochondrial function. In mice, late pregnancy is associated with failure of mitochondrial oxidation of fatty acids as a consequence of both decreased mitochondrial β-oxidation of medium-chain fatty acids and decreased activity of the tricarboxylic acid cycle [12].

The mode of initiation of the mitochondrial cytopathies, apart from the genetic enzyme defects, is uncertain. It might be viral, as speculated in Reye's syndrome. It might be toxic and acute fatty liver of pregnancy has followed exposure to toluene [27]. Nutritional factors have also been suggested.

Acute fatty liver of pregnancy should be regarded as part of a systemic mitochondrial dysfunction affecting particularly liver, muscle, nervous system, pancreas and kidneys.

Pregnancy toxaemias

These conditions are characterized by hypertension, proteinuria and fluid retention. The term 'pregnancy toxaemia' includes a spectrum of conditions (table 27.4). The target organs are the uterus, kidney and brain. Hepatic damage is only seen in patients with severe pre-eclampsia and eclampsia.

The aetiology of pre-eclampsia is unknown. It is marked by generalized vasospasm with increased systemic vascular resistance and enhanced pressor responses to endogenous vaso-constrictors. Endothelial cell injury may decrease endothelial-dependent vasodilators and increase production of vaso-constrictors coming from both endothelial cells and platelets. Serum from pre-eclamptic patients contains factors that increase endothelial cell permeability [13]. The vascular endothelium may be a target for blood-borne products of reduced placental perfusion [39].

Vascular endothelial damage leads to platelet deposition, thrombocytopenia and fibrin deposition in sinusoids. The resultant ischaemia accounts for the focal and diffuse hepato-cellular necrosis and haemorrhages in zone 1 (fig. 27.4).

In mild cases increases in serum alkaline phosphatase and transaminase values are frequent. Minor signs of disseminated intravascular coagulation, such as a reduction in platelets, are also common.

Jaundice is infrequent and often terminal. It is usually haemolytic with disseminated intravascular coagulation. Failure of renal bilirubin excretion may contribute. Serum bilirubin is less than 6 mg/dl (100 μmol/l).

Severe toxaemia may present with epigastric pain, nausea, vomiting, right upper quadrant tenderness and hypertension.

Hepatic histology. Peri-portal (zone 1) fibrin deposits [37] and haemorrhage progress to small necrotic foci, infarcts and haematomas. Zone 3 necrosis and haemorrhage represent shock. An inflammatory reaction is characteristically absent (fig. 27.5). Capillary and hepatic arterial thrombi and, rarely, intra-hepatic portal venous thrombi may be noted. *Serum transaminases* are usually more than 10 times elevated.

Rupture of the liver is associated with shock.

Ultrasound and CT show focal filling defects.

The *treatment* of severe toxaemia is by delivering the pregnancy and by supportive care.

Table 27.4. Spectrum of pregnancy toxaemias

Pre-eclampsia
HELLP syndrome
Infarction
Bleeding and rupture

The HELLP syndrome

This is a rare variant of pre-eclampsia [42]. It consists of haemolysis, elevated liver enzymes and low platelet

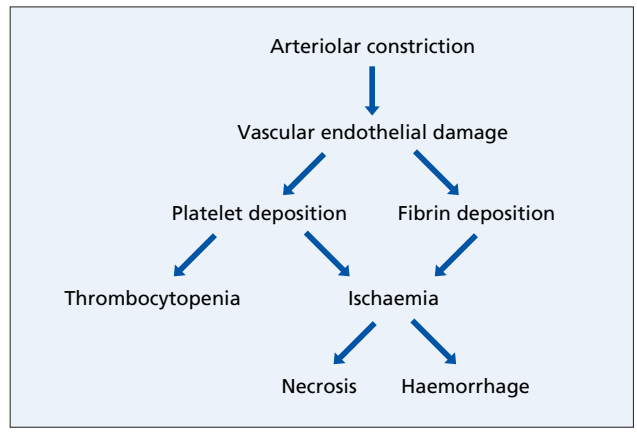


Fig. 27.4. The liver in eclampsia. Hepato-cellular necrosis and haemorrhage follow ischaemia related to vascular endothelial damage.

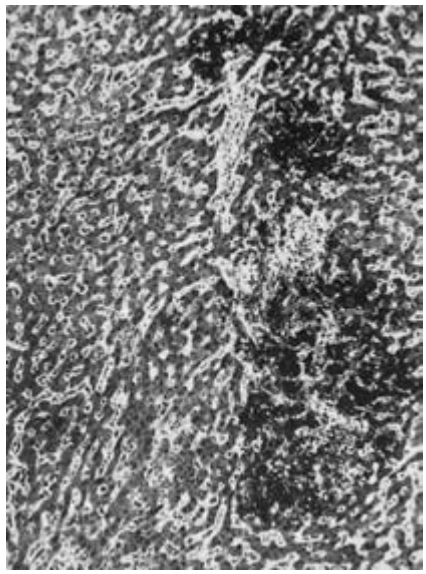


Fig. 27.5. The liver in eclampsia. Focal peri-portal necrosis of liver cells; the lesion contains fibrin. (Mallory's phosphotungstic acid, ×80.)

Table 27.5. Acute fatty liver of pregnancy and toxaemias contrasted: overlaps exist

	Acute fatty liver	Toxaemia
Abdominal pain	50%	100%
Jaundice	100%	40%
Serum transaminases (× normal)	<10	>10
Scans	Diffuse change	Focal abnormalities
Liver biopsy	Microvesicular fat	Fibrin (peri-sinusoidal)
Liver failure	Present	Absent

count [52]. It often affects multipara. The blood pressure may be normal and proteinuria may be absent.

Liver histology shows fibrin deposition [4]. This suggests severe pre-eclamptic liver disease and calls for immediate delivery. The laboratory results do not reflect hepatic histology [4]. Perinatal mortality is 10–60% and the maternal mortality 1.5–5% [46].

Management is supportive, as for eclampsia [49].

Toxaemia and the HELLP syndrome

There is considerable overlap between acute fatty liver of pregnancy, the pregnancy toxaemias and the HELLP syndrome (fig. 27.1, table 27.5). The features include proteinuria and even some peri-sinusoidal fibrin deposition, but hypertension is unusual. The patient with clear pregnancy toxaemia may lack proteinuria and hypertension and yet the liver biopsy, in addition to fibrin deposition, shows some microvesicular fat. Multiparous patients with acute fatty liver of pregnancy often have a history of pre-eclampsia.

Hepatic haemorrhage

This usually complicates pre-eclampsia or eclampsia and the HELLP syndrome with accompanying disseminated intravascular coagulation and intra-hepatic vascular lesions [11]. The picture includes infarction [19], subcapsular haemorrhage and ruptured liver. Clinically this catastrophe is suspected by sudden constant right upper quadrant or epigastric pain with vomiting and circulatory collapse. The diagnosis is confirmed by ultrasound, CT and angiography. Treatment varies with the severity. Subcapsular haemorrhage is usually treated conservatively. Surgery may be required or even transplant [29]. Hepatic arterial embolization with gelfoam can be used to control haemorrhage.

Hepatic adenomas, often with peliosis hepatis, and often associated with oral contraceptives, may rupture during pregnancy (see Chapters 20 and 30).

Cholestasis of pregnancy

This intra-hepatic cholestasis appears in the last trimester of pregnancy [31].

In its mildest form, pruritus is the only abnormality. It usually commences in the last trimester, but can start as early as the second or third month. Jaundice is rarely deep. The urine is dark and the stools pale. General health is preserved and there is no pain. Weight loss may be great. The liver and spleen are impalpable. After delivery, jaundice disappears and within 1–2 weeks the pruritus has ceased. The condition usually recurs with subsequent pregnancies. Consecutive pregnancies in multiparous patients are associated with variability in the severity and in the time of onset.

Laboratory changes

Serum shows an increase in conjugated bilirubin and alkaline phosphatase values. Serum transaminases are normal or slightly increased, although occasionally very high values are found. These changes return to normal after delivery. Serum bile acids are increased and the primary bile acids (cholic and chenodeoxycholic acids) predominate [1].

Steatorrhoea is usual. It correlates with the severity of the cholestasis.

The prothrombin time is prolonged due to vitamin K deficiency. Cholestyramine enhances the hypoprothrombinaemia.

Hepatic histology shows mild focal and irregular cholestasis. Electron microscopy shows the changes in the

microvilli of the bile canaliculi common to all forms of cholestasis.

Aetiology

Multiple factors probably interact with the genetic predisposition to alter the canalicular and hepatic membranes so changing their transport of sex steroids. Hormonal factors are suggested by worsening with multiple pregnancies and recurrences with menstruation or oestrogen therapy. The administration of progesterone has been reported shortly before the development of cholestasis [1]. A primary change may be in the reproductive metabolism of progesterone with a selective defect in the biliary excretion of sulphated metabolites, particularly disulphates [23]. A heterozygous non-sense mutation of the MDR3 biliary transporter has been shown [16].

The condition is particularly common in Scandinavia, northern Europe, Chile, Bolivia and China. It is very rare in Asiatic or Black women [31]. Prevalence varies but is increasing worldwide.

Nutritional support is essential. Vitamin K supplements are necessary as post-partum haemorrhage is increased.

Ursodeoxycholic acid (15 mg/kg/day) stimulates the excretion of biliary steroid sulphates [22]. It suppresses pruritus and resolves deranged biochemistry.

Epidemiology

Cholestasis of pregnancy is often familial, and has been reported in mothers, sisters and daughters, some of whom develop pruritus when given oral contraceptives. Male family members may show the cholestatic tendency when given oestrogens [32]. Findings support a Mendelian dominant inheritance.

In Chile, cholestasis seems to be associated with Araucarial Indian descent, rather than with Chilean Caucasians.

Family history is associated with increased frequency of HLA-B8 and HLA-Bw16 [35].

Diagnosis

In the first pregnancy, the differentiation from viral hepatitis and other conditions causing jaundice may be difficult. Absence of constitutional symptoms, prominent pruritus and biochemical tests suggesting cholestasis are helpful. Ultrasound helps to exclude obstruction to main bile ducts. Liver biopsy is rarely necessary, but the appearances are diagnostic. Failure of the pruritus to stop after delivery, with continuing high serum alkaline phosphatase values, suggests underlying primary biliary cirrhosis, and liver biopsy and serum mitochondrial antibody tests should be performed. After delivery, the woman may show a cholestatic response to a small dose of oestrogen.

Prognosis and management

Prognosis for the mother is excellent. The fetus, however, is at increased risk of distress, prematurity and death [38]. The fetus must be carefully monitored and termination is indicated for distress [8]. The mother should be delivered at 38 weeks, or at 36 weeks if the cholestasis is severe.

The mother is warned that the condition will usually return in a subsequent pregnancy and that she may develop pruritus if she takes oral contraceptive drugs.

Budd–Chiari syndrome (Chapter 11)

Pregnancy is a pro-coagulant state as shown by increased fibrinogen levels and increased values for factor VIII, factor IX (Christmas) and factor XII (Hagemann). Rarely, venous thrombosis, particularly the Budd–Chiari syndrome and hepatic microthrombi, complicate pregnancy, especially in patients having an underlying defect in blood coagulation. This may be the lupus anticoagulant and anticardiolipin antibodies, which favour repeated abortions [28], antithrombin III deficiency or factor V Leiden mutation [10]. Factors precipitating the actual thrombosis are unclear but may be infections.

Intercurrent jaundice

Viral hepatitis

Viral hepatitis causes about 50% of jaundice in pregnancy [47]. It is particularly serious in developing countries with a mortality ranging from 10 to 45%. In Ethiopia it ranks among the leading causes of maternal mortality, coming third to septic abortion and puerperal sepsis [20]. In developed countries, the course and mortality of acute hepatitis in pregnancy are about the same as in the non-pregnant. Fetal abnormalities are not recorded, but stillbirths may be increased.

Hepatitis A

The disease is passed to the mother by contact with the excreta of older children attending nursery schools.

Pregnant women exposed should receive immunoglobulin and vaccine immediately. The course is similar to that in the non-pregnant even in the last trimester. It is rarely transmitted to the fetus.

Hepatitis B

Pregnant women in close contact with persons carrying hepatitis B must receive hepatitis B vaccine, which is safe

in pregnancy, and also hepatitis B immunoglobulin. An acute attack of hepatitis B usually runs the same course in the pregnant as in the non-pregnant woman. The chances of the disease progressing to chronic hepatitis are less than 10%. In underdeveloped countries the mortality is high and fetal wastage and stillbirths are increased. The effect on the baby of a mother carrying hepatitis B is very serious (Chapter 17).

Screening of mothers for hepatitis B viral markers should be universal and not simply directed to those at increased risk of hepatitis B carriage, such as drug abusers, those of Chinese and African origin and those working in the health-care professions.

The *hepatitis delta virus* can be transmitted to the fetus from a mother who is carrying both hepatitis B and delta. This results in more serious hepatitis. A baby vaccinated against hepatitis B will be protected from delta virus infection.

Hepatitis C

The chances of a hepatitis C carrier mother transmitting the disease to her baby are very small. They are increased if the mother has a high titre of circulating hepatitis C virus RNA or is HIV positive. Maternal blood hepatitis C virus RNA should be checked if the mother is antibody positive. If the result is repeatedly negative, vertical transmission has not been reported [15]. Antibody to hepatitis C virus passes the placenta and values may be positive for 6 months, the lifespan of circulating maternal antibody. The infant should be checked by measuring serum hepatitis C virus RNA. Breast feeding has not been associated with vertical transmission of hepatitis C virus infection [15].

Hepatitis E

Hepatitis E has a 16% mortality in the last trimester and fetal mortality is 50% [14]. The diagnosis from acute fatty liver may be difficult, but can be made by the IgM antibody to hepatitis E virus.

Herpes simplex virus (HSV type II)

This infection is usually reported in the immunocompromised, but has been reported in pregnant women [17]. This might be related to a defect in cell-mediated immunity thought to exist in pregnancy. The hepatitis can mimic acute fatty liver of pregnancy. It is marked by very high serum transaminase levels but without jaundice. Herpetic lesions can usually be detected on the vulva or cervix. Liver biopsy shows extensive hepato-cellular necrosis and intra-nuclear herpetic inclusions (fig. 27.6). The treatment is with ganciclovir.

Biliary tract disease

During pregnancy the bile becomes more lithogenic and gallbladder emptying is impaired. Gallstones form [9]. Immediately post-partum, gallbladder ultrasound examinations have shown sludge in 26.2% and gallstones in 5.2%. One year later, only two of 45 patients with sludge and 13 of 15 with gallstones still had abnormal ultrasound findings. In spite of these observations, symptoms of gallbladder disease during pregnancy are rare.

Patients with choledocholithiasis can be successfully relieved by ERCP and sphincterotomy. This may be performed as early as the second trimester [3]. Cholecystectomy, whether by open operation [50] or the laparoscopic technique [24] is safe during pregnancy.

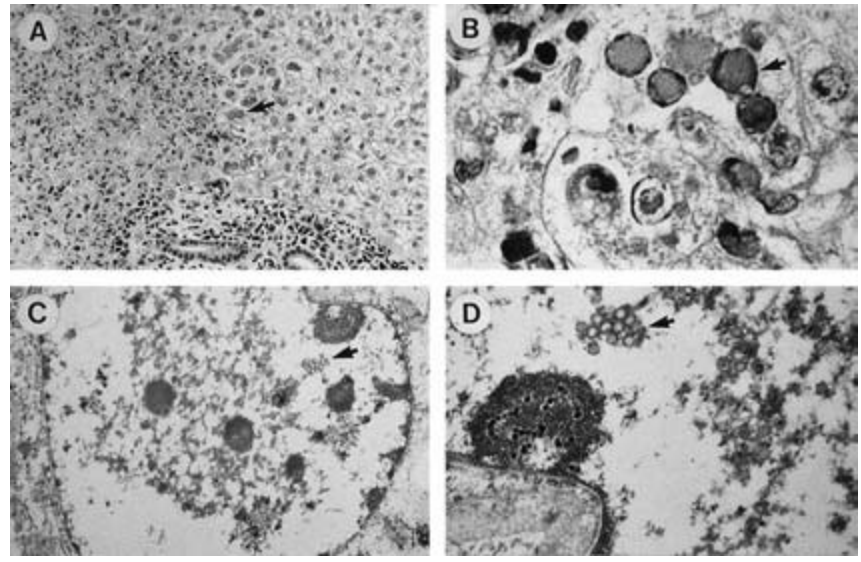


Fig. 27.6. Herpes simplex hepatitis in the third trimester of pregnancy. (A, B) Light microsocopy: (A) shows moderate portal inflammation with periportal necrosis. Both (A), and (B) (high power), show classic Cowdry A inclusions in nuclei (arrows). (C, D) Electron micrographs show aggregates of 106 nm viral particles (arrows) in the nucleus of an infected hepatocyte. The biopsy grew herpes simplex. (Courtesy of Dr Caroline Riely.)

Hepato-toxic drugs and the pregnant woman

The pregnant woman can react to drugs causing jaundice in a similar fashion to the non-pregnant. Drugs may potentiate jaundice or kernicterus in the newborn. In particular, drugs such as sulphonamides which displace bilirubin from its binding site to serum albumin should be avoided. Drugs such as phenacetin given to the mother may precipitate jaundice in an infant with glucose-6-phosphate dehydrogenase deficiency.

Effect of pregnancy on pre-existing chronic liver disease

The full-time parturition of a woman suffering from hepatic cirrhosis is unusual. It is rare for such a patient to conceive. The liver disease *per se* is not an indication for termination. Patients with chronic hepatitis (autoimmune hepatitis) are younger, often physically attractive, women. Amenorrhoea is usual at the onset but, as the disease becomes less active with corticosteroid therapy, fertility is regained [53]. Liver function may deteriorate during pregnancy, but after delivery soon returns to its previous level. The fetal loss rate is about 33% and babies may be born prematurely, but will be normal. Corticosteroids and azathioprine must be continued. Management in a specialist obstetric unit with hepatological back-up is essential. The disease may exacerbate after delivery.

Bleeding from oesophageal varices is a risk in those with portal hypertension, whether due to cirrhosis or a portal vein obstruction. Patients who have previously bled are at particular risk. It is treated along similar lines to those adopted in the non-pregnant.

Pregnancy is not contraindicated in those with well-treated Wilson's disease, and penicillamine does not pose an undue risk to the fetus [48].

Primary biliary cirrhosis may present as cholestatic jaundice in, or shortly after, pregnancy.

Successful pregnancy has been reported in a patient with Alagille's syndrome [41].

Pregnancy in liver transplant recipients

Pregnancy can be allowed 1 year post-transplant, and if the condition of the graft is stable. Successful outcomes are recorded, but the pregnancy must be regarded as high risk. Immunosuppression must be continued and monitored particularly carefully. There is a high risk of premature delivery and of low birth weight infants. Rarely, the mother loses the graft and re-transplantation is necessary.

References

1 Bacq Y, Myara A, Brechot M-C *et al*. Serum conjugated bile acid profile during intrahepatic cholestasis of pregnancy. *J. Hepatol*. 1996; **22**: 66.

2 Bacq Y, Zarka O, Brechot J-F *et al*. Liver function tests in normal pregnancy: a prospective study of 103 pregnant women and 103 matched controls. *Hepatology* 1996; **23**: 1030.

3 Baillie J, Cairns SR, Putnam WS *et al*. Endoscopic management of choledocholithiasis during pregnancy. *Surg. Gynecol. Obstet*. 1990; **171**: 1.

4 Barton JR, Riely CA, Adamec TA *et al*. Hepatic histopathologic condition does not correlate with laboratory abnormalities in HELLP syndrome (haemolysis, elevated liver enzymes, and low platelet count). *Am. J. Obstet. Gynecol*. 1992; **167**: 1538.

5 Barton JR, Sibai BM, Mabie WC *et al*. Recurrent acute fatty liver of pregnancy. *Am. J. Obstet. Gynecol*. 1990; **163**: 534.

6 Bernuau J, Degott C, Nouel O *et al*. Non-fatal acute fatty liver of pregnancy. *Gut* 1983; **24**: 340.

7 Burroughs AK, Seong NH, Dojcinov DM *et al*. Idiopathic acute fatty liver of pregnancy in 12 patients. *Q. J. Med*. 1982; **51**: 481.

8 Davis MH, da Silva RCMA, Jones SR *et al*. Fetal mortality associated with cholestasis and the potential benefit of therapy with ursodeoxycholic acid. *Gut* 1995; **37**: 580.

9 Everson GT. Pregnancy and gallstones. *Hepatology* 1993; **17**: 159.

10 Fickert P, Ramschak H, Kenner L *et al*. Acute Budd–Chiari syndrome with fulminant hepatic failure in a pregnant woman with factor V Leiden mutation. *Gastroenterology* 1996; **111**: 1670.

11 Greenstein D, Henderson JM, Boyer TD. Liver haemorrhage: recurrent episodes during pregnancy complicated by preeclampsia. *Gastroenterology* 1994; **106**: 1668.

12 Grimbert S, Fromenty B, Fisch C *et al*. Decreased mitochondrial oxidation of fatty acids in pregnant mice: possible relevance to development of acute fatty liver of pregnancy. *Hepatology* 1993; **17**: 628.

13 Haller H, Hempel A, Homuth V *et al*. Endothelial-cell permeability and protein kinase C in pre-eclampsia. *Lancet* 1998; **351**: 945.

14 Hamid SS, Jafri SMW, Khan H *et al*. Fulminant hepatic failure in pregnant women: acute fatty liver or acute viral hepatitis. *J. Hepatol*. 1996; **25**: 20.

15 Hunt CM, Carson KL, Sharara AI. Hepatitis C in pregnancy. *Obstet. Gynecol*. 1997; **89**: 883.

16 Jacquemin E, Crestell D, Manouvrier S *et al*. Heterozygous non-sense mutation of the MDR3 gene in familial intrahepatic cholestasis of pregnancy. *Lancet* 1999; **353**: 210.

17 Klein NA, Mabie WC, Shaver DC *et al*. Herpes simplex virus hepatitis in pregnancy: two patients successfully treated with acyclovir. *Gastroenterology* 1991; **100**: 239.

18 Knox TA, Olans LB. Liver disease in pregnancy. *N. Engl. J. Med*. 1996; **335**: 569.

19 Krueger KJ, Hoffman BJ, Lee WM. Hepatic infarction associated with eclampsia. *Am. J. Gastroenterol*. 1990; **85**: 588.

20 Kwast BE, Stevens JA. Viral hepatitis as a major cause of maternal mortality in Addis Ababa, Ethiopia. *Int. J. Gynaecol. Obstet*. 1987; **25**: 99.

21 Mabie WC, Dacus JV, Sibai BM *et al*. Computed tomography

in acute fatty liver of pregnancy. *Am. J. Obstet. Gynecol.* 1988; **158**: 142.
22 Meng L-J, Reyes H, Axelson M *et al*. Progesterone metabolites and bile acids in serum of patients with intrahepatic cholestasis of pregnancy: effect of ursodeoxycholic acid therapy. *Hepatology* 1997; **26**: 1573.
23 Meng L-J, Reyes H, Palma J *et al*. Profiles of bile acids and progesterone metabolites in the urine and serum of women with intrahepatic cholestasis of pregnancy. *J. Hepatol.* 1997; **27**: 346.
24 Morrell DG, Mullins JR, Harrison PB. Laparoscopic cholecystectomy during pregnancy in symptomatic patients. *Surgery* 1992; **112**: 856.
25 Munnell EW, Taylor HC Jr. Liver blood flow in pregnancy—hepatic vein catheterization. *J. Clin. Invest.* 1947; **26**: 952.
26 Ockner SA, Brunt EM, Cohn SM *et al*. Fulminant hepatic failure caused by acute fatty liver of pregnancy treated by orthotopic liver transplantation. *Hepatology* 1990; **11**: 59.
27 Paraf F, Lewis J, Jothy S. Acute fatty liver of pregnancy after exposure to toluene. A case report. *J. Clin. Gastroenterol.* 1993; **17**: 163.
28 Pelletier S, Landi B, Piette JC *et al*. Antiphospholipid syndrome as the second cause of non-tumorous Budd–Chiari syndrome. *J. Hepatol.* 1994; **21**: 76.
29 Pereira SP, O'Donoghue J, Wendon J *et al*. Maternal and perinatal outcome in severe pregnancy-related liver disease. *Hepatology* 1997; **26**: 1258.
30 Pockros PJ, Peters RL, Reynolds TB. Idiopathic fatty liver of pregnancy: findings in 10 cases. *Medicine (Baltimore)* 1984; **63**: 1.
31 Reyes H. The enigma of intrahepatic cholestasis of pregnancy: lessons from Chile. *Hepatology* 1982; **2**: 87.
32 Reyes H, Ribalta J, Gonzáles MC *et al*. Sulfobromophthalein clearance tests before and after ethinyl estradiol administration, in women and men with familial history of intrahepatic cholestasis of pregnancy. *Gastroenterology* 1981; **81**: 226.
33 Reyes H, Sandoval L, Wainstein A *et al*. Acute fatty liver of pregnancy: a clinical study of 12 episodes in 11 patients. *Gut* 1994; **35**: 101.
34 Reyes H, Simon FR. Intrahepatic cholestasis of pregnancy: an oestrogen-related disease. *Semin. Liver Dis.* 1993; **13**: 289.
35 Reyes H, Wegmann ME, Segovia N *et al*. HLA in Chileans with intrahepatic cholestasis of pregnancy. *Hepatology* 1982; **2**: 463.
36 Riely CA. Hepatic disease in pregnancy. *Am. J. Med.* 1994; **96**: 117.
37 Riely CA, Romero R, Duffy TP. Hepatic dysfunction with disseminated intravascular coagulation in toxaemia of pregnancy: a distinct clinical syndrome. *Gastroenterology* 1981; **80**: 1346.
38 Rioseco AJ, Ivankovic MB, Manzur A *et al*. Intrahepatic cholestasis of pregnancy: a retrospective case–control study of perinatal outcome. *Am. J. Obstet. Gynecol.* 1994; **170**: 890.
39 Roberts JM, Redman CWG. Pre-eclampsia: more than pregnancy-induced hypertension. *Lancet* 1993; **341**: 1447.
40 Rolfes DB, Ishak KG. Acute fatty liver of pregnancy: a clinicopathologic study of 35 cases. *Hepatology* 1985; **5**: 1149.
41 Romero R, Reece EA, Riely C *et al*. Arteriohepatic dysplasia in pregnancy. *Am. J. Obstet. Gynecol.* 1983; **147**: 108.
42 Saphier CJ, Repke JT. Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: a review of diagnosis and management. *Semin. Perinatol.* 1998; **22**: 118.
43 Schoeman MN, Batey RG, Wilcken B. Recurrent acute fatty liver of pregnancy associated with a fatty-acid oxidation defect in the offspring. *Gastroenterology* 1991; **100**: 544.
44 Sheehan HL. The pathology of acute yellow atrophy and delayed chloroform poisoning. *J. Obstet. Gynaecol. Br. Emp.* 1940; **47**: 49.
45 Sherlock S. Acute fatty liver of pregnancy and the microvesicular fat diseases. *Gut* 1983; **24**: 265.
46 Sibai BM, Taslimi MM, El-Nazer A *et al*. Maternal–perinatal outcome associated with the syndrome of haemolysis, elevated liver enzymes, and low platelets in severe preeclampsia-eclampsia. *Am. J. Obstet. Gynecol.* 1986; **155**: 501.
47 Simms J, Duff P. Viral hepatitis in pregnancy. *Semin. Perinatol.* 1993; **17**: 384.
48 Sternlieb I. Wilson's disease and pregnancy. *Hepatology* 2000; **31**: 531.
49 Stone JH. HELLP syndrome: haemolysis, elevated liver enzymes, and low platelets. *JAMA* 1998; **280**: 559.
50 Swisher SG, Schmit PJ, Hunt KK *et al*. Biliary disease during pregnancy. *Am. J. Surg.* 1994; **168**: 576.
51 Treem WR, Shoup ME, Hale DE *et al*. Acute fatty liver of pregnancy, hemolysis, elevated liver enzymes, and low platelets syndrome, and long chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency. *Am. J. Gastroenterol.* 1996; **91**: 2293.
52 Weinstein L. Syndrome of haemolysis, elevated liver enzymes, and low platelet count: a severe consequence of hypertension in pregnancy. *Am. J. Obstet. Gynecol.* 1982; **142**: 159.
53 Whelton MJ, Sherlock S. Pregnancy in patients with hepatic cirrhosis. Management and outcome. *Lancet* 1968; **ii**: 995.
54 Wilcken B, Leung K-C, Hammond J *et al*. Pregnancy and fetal long-chain 3-hydroxyacylcoenzyme A dehydrogenase deficiency. *Lancet* 1993; **341**: 407.

Chapter 28
The Liver in Systemic Disease, Granulomas and Hepatic Trauma

The liver in collagen diseases

If hepatomegaly is present, it is probably due to amyloidosis in chronic rheumatoid arthritis, or to cardiac failure with or without systemic lupus erythematosus (SLE). Splenomegaly reflects reticulo-endothelial hyperplasia rather than portal hypertension.

Biochemistry

Serum α- and β-globulins may be elevated and serum albumin values slightly depressed. Serum bilirubin, transaminase and alkaline phosphatase levels are normal or mildly disturbed.

Rheumatoid arthritis

The liver shows non-specific changes such as mild fatty infiltration, focal necroses, sinusoidal dilatation or complicating amyloidosis. Kupffer cells are hyperplastic. Serum alkaline phosphatase increases. Serum bilirubin and transaminases are normal [9].

In chronic rheumatoid arthritis, and particularly Felty's syndrome, nodular regenerative hyperplasia is related to obliterative vasculitis of small portal veins (see figs 30.16, 30.17).

Arthropathy associated with liver disease

Systemic lupus erythematosus

Liver enzyme increases are seen in about a quarter of patients, but in only 8% are they unexplained and possibly related to the SLE itself.

Liver biopsy shows no serious lesions, only rarely has chronic hepatitis been described [6]. Rarely, a severe hepatic arteritis is present. Jaundice with SLE is usually haemolytic.

'Autoimmune lupoid' chronic hepatitis is not SLE, but belongs in the spectrum of active chronic hepatitis.

Type 1 autoimmune chronic hepatitis (Chapter 19)

This is associated with arthralgias presumably related to immune complex vascular injury. The arthralgias affect 25% and are polyarticular and transient. Rheumatoid factor is present in 95% and antinuclear antibody in 80% [3]. The patient is usually HLA-DR4 positive and there is a good response to corticosteroids.

Primary biliary cirrhosis (PBC) (Chapter 14)

Non-rheumatoid polyarteritis is seen in about 9%. It is frequently symmetrical and involves large and small joints. Attacks last weeks to months and may recur after a symptom-free interval. Rheumatoid arthritis is seen in 5–10%. Sclerodactyly is part of the CREST syndrome. Sjögren's syndrome may be associated.

Genetic haemochromatosis (Chapter 23)

This is present in 1–5% of attendees at rheumatism clinics. Arthropathy affects 40–60% of sufferers, usually involving the second or third metacarpophalangeal joints. The condition may be related to pyrophosphate crystal deposition. Venesection is ineffective.

Hepatitis B virus (HBV) associations

An arthritis syndrome resembling serum sickness is seen in 25% of patients during the prodromal stages [3]. It usually recovers fully. It is due to circulating immune complexes containing HBV DNA, immunoglobulin M (IgM) and complement. A rash is commonly associated. The arthritis usually disappears with the onset of jaundice, but the rash may last days to weeks [3].

Of cases with polyarteritis nodosa, 10–50% are associated with chronic HBV infection. The disease is autoantibody driven and of immune complex type. The underlying liver disease is mild, and the treatment given is interferon. Results with lamivudine are not yet available.

Table 28.1. Immune complexes in HCV-related cryoglobulinaemia

Composition
HCV and anti-HCV
Monoclonal IgM rheumatoid factor
Polyclonal IgG
Complement
Clinical associations
Vasculitis
Palpable purpura
Polyarthritis
Non-Hodgkin's lymphoma
Glomerulonephritis
Sjögren's syndrome
Treatment
Interferon-α (with ribavirin)
80% relapse

Hepatitis C virus (HCV) associations

Vasculitis may complicate the cryoglobulinaemia of chronic HCV infection. A classical triad is asthenia, palpable purpura and arthralgia. Eighty per cent of essential cryoglobulinaemia is HCV related (table 28.1) [1]. It can present after liver transplant related to an increase in HCV RNA levels [4]. The vasculitis may affect the kidney as a membranous glomerulonephritis [5].

The chronic HCV antigenic stimulation results in polyclonal B-cell activation and immune complex formation. HCV is several times more concentrated in the complexes than in corresponding serum.

The cryoglobulinaemia may evolve into occult, low-grade B-cell non-Hodgkin's lymphoma [8].

Therapy with interferon is effective in 50%. Both the vasculitis and renal function improves; HCV and cryoglobulin levels fall [2]. Unfortunately 80% relapse.

Chronic HCV infection may be associated with sialoadenitis, similar to that seen with primary Sjogren's syndrome, but with less severe symptoms [7].

Post-liver transplant peri-biliary vasculitis

Post-transplant peri-biliary vasculitis leads to segmental hepatic infarction and ischaemic biliary strictures. The end result may be the disappearing bile duct syndrome.

References

1 Agnello V, Chung RT, Kaplan IM. A role for hepatitis C virus infection in Type II cryoglobulinaemia. *N. Engl. J. Med.* 1992; **327**: 1490.

2 Cresta P, Musset L, Cacoub P *et al*. Response to interferon alpha treatment and disappearing of cryoglobulinaemia in patients infected by hepatitis C virus. *Gut* 1999; **45**: 122.

3 Duffy J. Arthritis and hepatitis. *Bull. Rheum. Dis.* 1998; **47** (2): 1.

4 Gourlay J, Ferrell LD, Roberts JP *et al*. Cryoglobulinaemia presenting after liver transplantation. *Gastroenterology* 1996; **110**: 265.

5 Jefferson JA, Johnson RJ. Treatment of hepatitis C-associated glomerular disease. *Semin. Nephrol.* 2000; **20**: 286.

6 Matsumoto T, Yoshimine T, Shimouchi K *et al*. The liver in systemic lupus erythematosus: pathologic analysis of 52 cases and review of the Japanese Autopsy Registry Data. *Hum. Pathol.* 1992; **23**: 1151.

7 Ramos-Casals M, Garcia-Carpasco M, Cevera R *et al*. Sjögren's syndrome and hepatitis C virus. *Clin. Rheumatol.* 1999; **18**: 93.

8 Rasul I, Shepherd FA, Kamel-Reid S *et al*. Detection of occult low-grade B-cell non-Hodgkin's lymphoma in patients with chronic hepatitis C infection and mixed cryoglobulinaemia. *Hepatology* 1999; **29**: 543.

9 Thompson PW, Houghton BJ, Clifford C *et al*. The source and significance of raised serum enzymes in rheumatoid arthritis. *Q. J. Med.* 1990; **76**: 869.

Hepatic granulomas

Granuloma formation is the end result of a complex interplay of many factors including invading antigen, prolonged antigenaemia, macrophage presentation, T_4-helper response, B-cell overactivity, circulating immune complexes and numerous biological mediators. Finally, a cascade of chemical mediators, particularly IL2 and interferon-γ, contributes to granuloma formation and ultimately fibrosis [17]. Granulomas are always part of generalized disease in which the liver participates [24].

All granulomas represent a response to antigenic stimuli. The liver is particularly involved because of the very large number of sinusoidal cells. These include the *Kupffer cells* which endocytose old cells, foreign particles, tumour cells, bacteria, yeasts, viruses and parasites. The Kupffer cell has specific membrane receptors which are important for antigen presentation. When Kupffer cells are activated by generalized infections or trauma, they specifically endocytose endotoxin and, in response, secrete a series of cytokines [28]. *Endothelial* cells clear macro-molecules and small particles from the circulation by receptor-mediated endocytosis. Endothelial cells act as scavengers removing harmful enzymes and pathogens. Hepatic *stellate cells* in hepatocyte injury change to myofibroblasts and produce collagen. It is not surprising therefore that the liver is involved in almost all types of granuloma. The reaction is rarely organ-specific except where a definite antigen, such as *Schistosoma* ovum, can be identified. The antigenic stimuli fall into common categories: drugs, infections, chemicals and a whole group where the antigen is unrecognized. These include sarcoidosis, PBC and granulomatous hepatitis.

Hepatic granulomas are found in 4–10% of needle liver biopsies. In 10% no cause is found even after a search for specific histological characteristics, staining for possible causative organisms and culture of the specimen [8].

Hepatic granulomas are of varying size, between 50

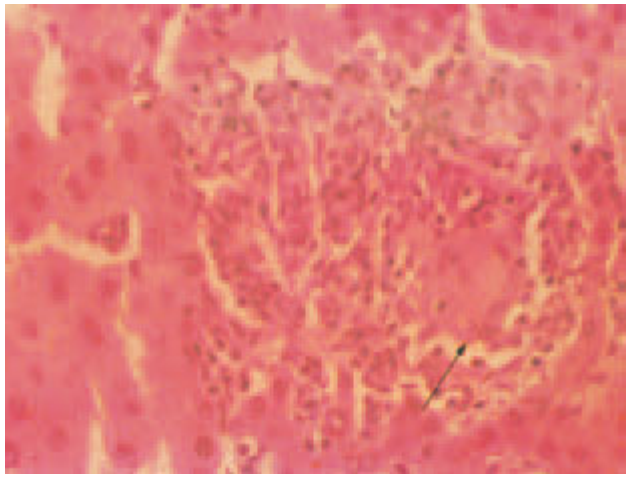


Fig. 28.1. A well-demarcated hepatic granuloma in zone 1 shows a giant cell (arrow), pale-staining epithelioid cells and a rim of lymphocytes. (H & E,×160.)

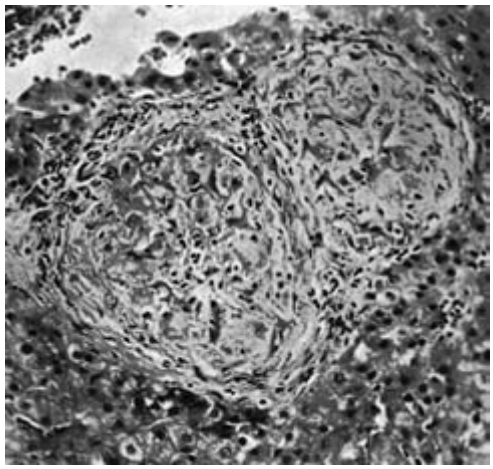


Fig. 28.2. Healing hepatic sarcoid. Two adjacent lesions are acquiring a structureless hyaline appearance and are surrounded by a connective tissue capsule. (H & E,×90.)

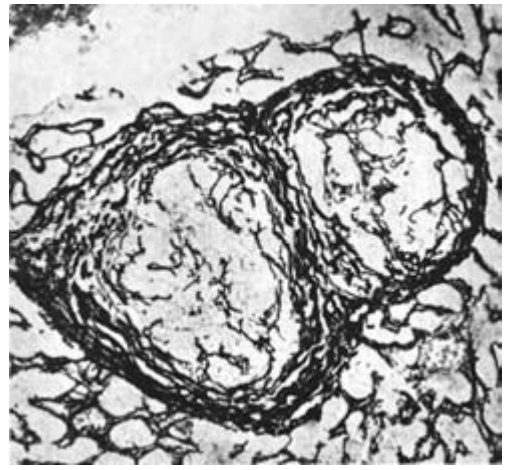


Fig. 28.3. Same section as in fig. 28.2 stained to show reticulin formation around the granulomas. (Modified silver,×90.)

Table 28.2. Differential diagnosis of some diseases with hepatic granulomas

Disease	Diagnostic aids
Sarcoidosis	Chest X-ray, SACE, broncho-alveolar lavage
Tuberculosis	Tuberculin skin test; broncho-alveolar lavage; isolation of organism; acid-fast staining
Brucellosis	Blood culture; agglutinin titre
Berylliosis	Industrial exposure; chest X-ray
Syphilis	*Treponema* test
Leprosy	Race; lepromin skin test
Histoplasmosis	Complement fixation test; chest X-ray
Infectious mononucleosis	Blood film; monospot; IgM EBV antibodies
AIDS	Poorly formed granulomas; acid-fast and fungal stains
Primary biliary cirrhosis	Mitochondrial antibody
Lymphomas	Chest X-ray; lymph node biopsy; CT scan
Drug reaction	History

and 300 µm in diameter. Serial sections must be cut and stained if granulomas are to be identified. Granulomas are found anywhere in the liver, but most frequently near portal tracts. They are sharply defined and do not disturb the normal pattern of the liver. Classically, they consist of pale staining, epithelioid cells with surrounding lymphocytes (figs 28.1, 28.2). Giant cells, central caseation and necrosis may be present. Older lesions may be surrounded by a fibrous capsule and healing is accompanied by hyaline change (fig. 28.3). In the liver, granulomas may present the classical appearance, but more often they may be seen only as six or less histiocytes; these probably represent a non-specific reaction to cell necrosis.

Granulomas have many causes (table 28.2) [6]. They may be found by chance in a needle biopsy specimen and this can lead to over-investigation. Many of these patients may be suffering from sarcoidosis or tuberculosis, but in many the cause will never be found. In symptomless patients, the granulomas must be ignored, but the patient should be observed over the next year or so.

Necrotizing or caseating granulomas are small to large, well formed with a necrotic centre. The histiocytic rim often has a palisade pattern and fibrosis is variable. They are associated with fungal infections and rarely with tuberculosis or Hodgkin's lymphoma [13].

A hepatitis-like background should be sought and, in particular, note made of infections including AIDS and hepatitis A, B and C [8].

Clinical syndrome of hepatic granulomas

Granulomas are often asymptomatic. Overt hepatic

insufficiency is rare. The liver is palpable in only 20% of patients. Very rarely the picture is of active liver disease with marked hepatic functional abnormalities and liver cell destruction and fibrosis on liver biopsy. In general, however, the evidence of hepatic involvement arises from the results of the liver biopsy.

Serum IgG and alkaline phosphatase may be raised. Serum bilirubin level is normal. Serum angiotensin-converting enzyme (SACE) is increased.

'Granulomatous hepatitis'

Hepatic granulomas may be associated with a prolonged, febrile syndrome [25]. Some patients are eventually diagnosed as having an infection, such as tuberculosis, histoplasmosis or Q fever or a lymphoma. Those that defy diagnosis are labelled 'granulomatous hepatitis'. They accounted for 50% of hepatic granulomas in one series [23]. The sufferer is often a middle-aged or elderly male. The granulomas are not widespread and pulmonary involvement is unusual. Biochemical tests of liver function are moderately impaired with increases in serum alkaline phosphatase, and slight increases in serum transaminases and globulins. Serum bilirubin is normal. The condition may subside spontaneously or necessitate short- or long-term prednisolone treatment. The ultimate prognosis is excellent [33]. Those not responding to, or unwilling to take, corticosteroids may benefit from low-dose, oral pulse methotrexate [15].

Sarcoidosis

Sarcoidosis is a disease of unknown aetiology, characterized by granulomatous lesions involving most organs [11]. Involvement of lungs, lymph nodes, eyes, skin and the neurological system may be associated with well-recognized clinical features, although this is not always so.

The liver is frequently affected, although granulomas are often asymptomatic [12]. Overt hepatic insufficiency is rare. The liver is palpable in only 20% of patients. Occasionally the picture is of active liver disease with marked hepatic functional abnormalities and liver cell destruction, and fibrosis on liver biopsy. The evidence of hepatic involvement arises not by the clinical picture but from the result of liver biopsy. This technique confirms sarcoidosis in about 60%. This agrees with autopsy figures showing hepatic involvement in about two-thirds [19].

Liver biopsy is indicated when another more accessible tissue, such as lymph gland or skin, is not available.

Hepatic histology

Rounded, well-demarcated lesions are most often in the portal zones. The pallor makes them distinctive even in haematoxylin and eosin stained sections.

The granulomas are repetitively monotonous, all being at the same stage of development. Classically, the granuloma is small and well formed with clusters of histiocytes with ill-defined cell cytoplasm. Multinucleated giant cells may be present (see fig. 28.1). In the liver, these rarely contain asteroid bodies, Schaumann bodies or crystalline inclusions. Occasionally, there is a central area of eosinophilic necrosis. Lymphocytes often surround or mix with the histiocytes. Caseation is absent. Granulomas can coalesce to form large aggregates. As the granuloma heals, reticulin fibres are deposited and it is replaced or surrounded by a fibrous reaction (see fig. 28.2). The granuloma may only be seen as a nodule of collagen (see fig. 28.3).

Proliferation of Kupffer cells demonstrates the widespread reticulo-endothelial activity.

The granuloma is converted into an acellular mass of hyaline material with a fibrous capsule (see figs 28.2, 28.3); many disappear.

Since the hepatic lesions are focal, and fibrosis is restricted to healing lesions, sarcoidosis does not produce the diffuse fibrosis and nodular regeneration of cirrhosis. It is therefore difficult to accept the occasional reports of cirrhosis following sarcoidosis, and a fortuitous combination seems more likely. The association with jaundice and hepatic failure is very rare and unexpected.

Corticosteroid therapy seems to have little effect on the liver biopsy appearances.

Biochemical changes. Serum IgG is raised and alkaline phosphatase may be slightly raised. Serum bilirubin level is normal. SACE is increased.

CT scanning shows discrete upper abdominal glandular enlargement in about 60% of patients with sarcoidosis (fig. 28.4) [4]. Hepatic CT changes are found only in 38% of those with known hepatic involvement. This is shown by multiple, small low-attenuation areas on a bolus contrast-enhanced CT scan. CT may be useful in confirming hepatosplenomegaly.

MRI shows multiple, diffuse, densely packed islands of iso-intense or slightly hyper-intense parenchyma on proton density images and corresponding foci of hypo-intensity on T_2-weighted images. This finding effectively excludes metastatic or inflammatory disease which would exhibit hyper-intense signals on T_2-weighted images.

Broncho-alveolar lavage shows lymphocyte excess with activated macrophages [26].

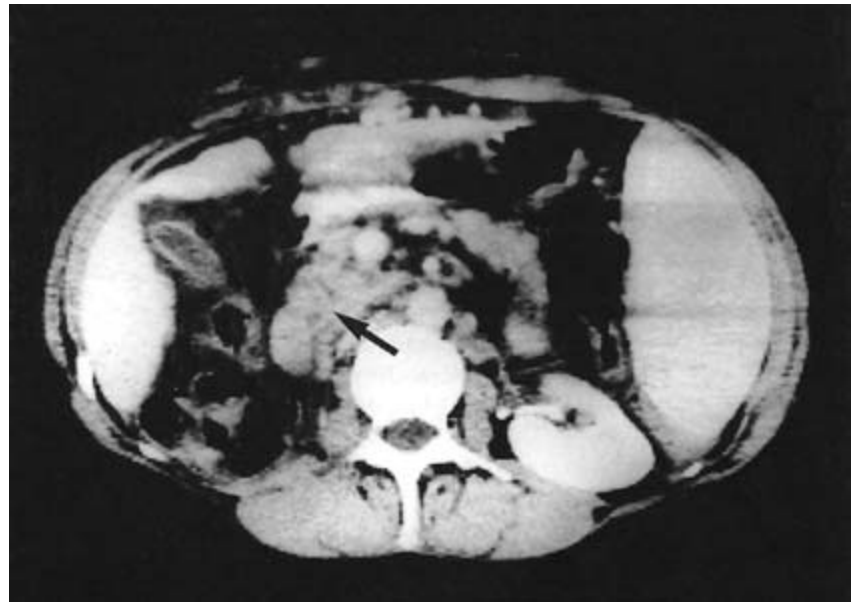


Fig. 28.4. Contrast-enhanced CT scan from a patient with chronic sarcoidosis showing retroperitoneal lymphadenopathy (arrow).

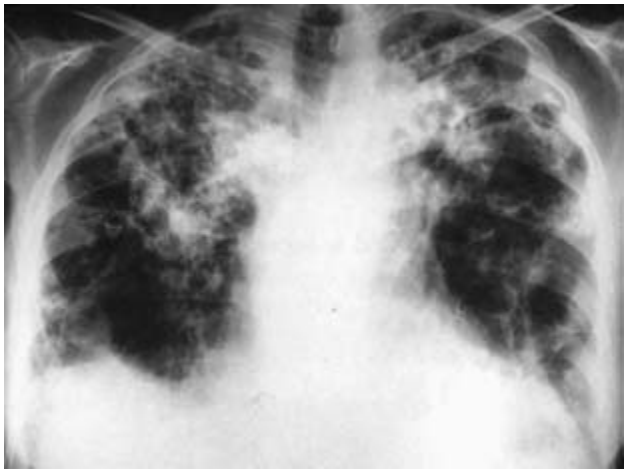


Fig. 28.5. Chronic sarcoidosis with portal hypertension. Chest X-ray of a woman aged 45 shows bilateral, severe, end-stage pulmonary fibrosis.

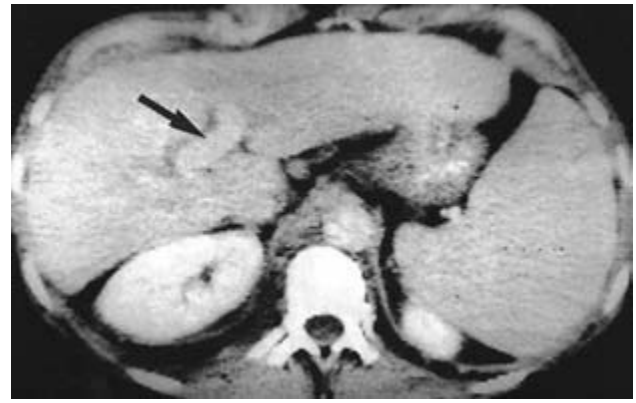


Fig. 28.6. Contrast-enhanced abdominal CT scan from same patient as in fig. 28.5 shows a patent portal vein (arrow) and a large spleen.

Portal hypertension

The patients are usually young, black people of both sexes, or females greater than 40 years of age. The portal hypertension is pre-sinusoidal due to portal (zone 1) granulomas (figs 28.5, 28.6). Sinusoidal block may be superimposed due to fibrosis [29]. Corticosteroids do not prevent the portal hypertension.

In some, thrombotic occlusion of a portal or splenic vein may be found. Rarely, oesophageal bleeding is a real problem. These patients tolerate surgical shunts well.

Budd–Chiari syndrome

Sarcoidosis has been reported in association with hepatic vein occlusion. The hepatic veins are narrowed by sarcoid granulomas leading to venous stasis and extensive thrombotic occlusions [22]. A similar Budd–Chiari syndrome has been caused by idiopathic granulomatous venulitis involving hepatic vein radicles [31].

Cholestasis

Rarely patients with sarcoidosis, usually male and black, show features of chronic intra-hepatic cholestasis [1]. They present with fever, malaise, weight loss, jaundice and usually pruritus. Serum alkaline phosphatase levels are very high and transaminases increased about two to five times. Hepatosplenomegaly is usual. Liver biopsy usually shows granulomas. Portal areas contain hepatic arteries but show damaged or even absence of bile ducts (fig. 28.7). The ductopenia can be related to the extent of

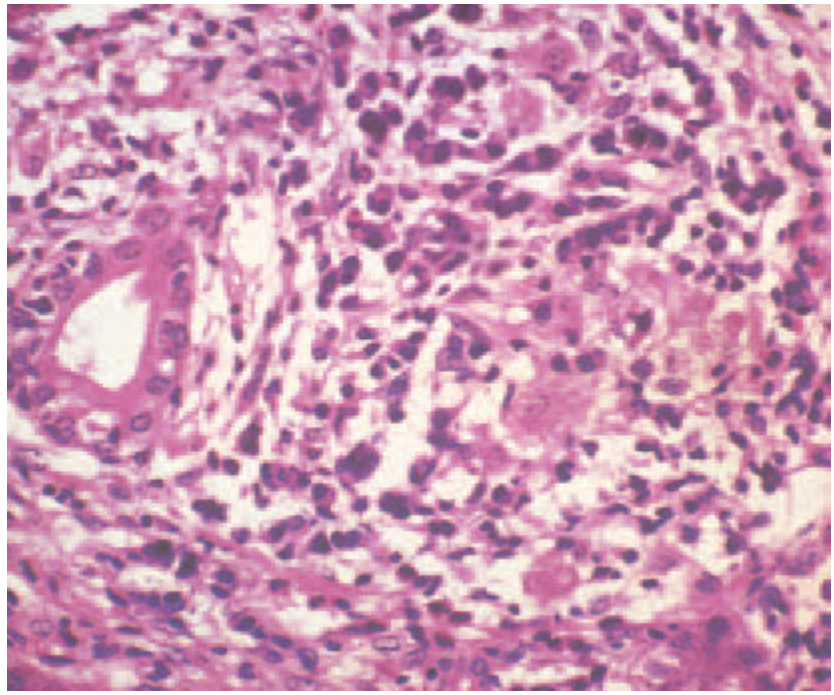


Fig. 28.7. Chronic cholestasis in sarcoidosis. A damaged bile duct is surrounded by an inflammatory infiltrate including lymphocytes. (H & E, ×160.)

the fibrosis which may be massive. Sequential liver biopsies show relentless progression of the fibrosis and bile duct loss.

ERCP shows tortuous stretched ducts due to the disturbed liver architecture. Rarely the common hepatic duct is involved [16].

The prognosis is poor. The patients usually die within 2–18 years from the onset.

Corticosteroids are not helpful. Ursodeoxycholic acid may be used to control pruritus [2]. Liver transplantation may be necessary [5]. However, post-transplant multiple hepatic granulomas can recur, but without clinical deterioration [9].

The condition may resemble, and even be indistinguishable from, PBC (see table 14.2).

Granulomatous drug reactions

Drugs are rare causes of hepatic granulomas. However, the identification of a granuloma in a liver biopsy always raises the possibility that it is drug-related. The granuloma may be a reaction to the therapy and not due to the underlying disease. Typically the granuloma is part of a general hypersensitivity reaction. It develops 10 days to 4 months after starting the drug. It may be associated with rash, lymphadenopathy and arthritis. Fever may be related to cytokines from activated macrophages and lymphocytes.

Serum biochemistry shows increases in alkaline phosphatase and γ-glutamyl transpeptidase. Transaminases may be modestly increased. A rise in serum bilirubin is unusual with a simple granulomatous reaction.

Liver biopsy histology shows predominant granulomas. Caseation is absent. Tissue eosinophilia is found in about 70%. Fatty change, portal zone inflammation and bile duct injury are occasionally present. The lesion heals without concentric fibrosis.

Nevertheless, a liver biopsy showing the appearance of granulomas, eosinophils, fatty change, bile duct injury and cholestasis always suggests a granulomatous drug reaction.

Prognosis is usually excellent with recovery within 6 weeks of withdrawing the drug. Rarely, severe reactions may lead to consideration of corticosteroid therapy.

Drug associations

An enormous number of drugs have been linked with a granulomatous hepatic reaction. In most instances the granulomas are not the predominant lesion. In some, the evidence of a causal association is anecdotal and dechallenge has not been recorded. Re-challenge is usually unjustifiable on ethical grounds.

Drugs which can cause a predominantly granulomatous reaction are listed in table 28.3. Allopurinol, carbamazepine, glibenclamide and sulphonamides are the most common culprits. They are all rare, but the reactions can be fatal. In all, the clinicopathological picture is a mixed one with granulomatous, hepato-cellular, cholangitic and vasculitic elements. Carbamazepine and allopurinol are associated with fibrin-ring granulomas

Table 28.3. Important causes of granulomatous drug reactions

Allopurinol
Carbamazepine
Diltiazem
Glibenclamide
Hydralazine
Quinidine/quinine
Sulphonamides

Table 28.4. Hepatic granulomas associated with infections

Mycobacteria	*M. tuberculosis*
	M. avium-intracellulare
	Leprosy
Bacteria	*Brucella*
Spirochaetes	*T. pallidum*
Fungi	Histoplasmosis
	Coccidioidomycosis
	Blastomycosis
Protozoa	Toxoplasmosis
Helminths	Schistosomiasis
	Toxocara canis
	Fasciola hepatica
	Ascaris lumbricades
Rickettsiae	Q fever
Viruses	Hepatitis A
	Hepatitis C
	Cytomegalovirus

[30]. Corticosteroids may be considered in severe granulomatous drug reactions.

Granulomas associated with infections

Granulomas can be found with almost all types of infection. The most frequent are tuberculosis, brucellosis, toxoplasmosis, atypical mycobacteriosis, fungal diseases, syphilis, leishmaniasis and the infestations, schistosomiasis and toxocariasis (table 28.4). In many instances, the granulomas are ill-formed and histologically can be distinguished with ease from the classical epithelioid granulomas of sarcoidosis.

Mycobacteria

Tuberculosis

Miliary dissemination accompanies the primary complex, and is also common with chronic adult tuberculosis. Aspiration liver biopsies in patients with tuberculosis have shown positive results in about 25%.

Aspiration biopsy has been used in the diagnosis of tuberculous meningitis when other methods have failed, and also in miliary tuberculosis at the stage of an indeterminate pyrexia. In such cases, Ziehl–Neelsen stains should be performed, and an unfixed portion of the biopsy cultured for tubercle bacilli.

Table 28.5. Hepatic granulomas in tuberculosis and sarcoidosis*

	Tuberculosis	Sarcoidosis
Caseation	Present	Absent
Acid-fast bacilli	Present in 10%	Absent
Reticulin framework	Destroyed	Intact
Numbers	Few	Many
Coalescence	Frequent	Rare

*The granulomas may be indistinguishable.

The distinction between these granulomas and those of sarcoidosis may be impossible to make. Distinctive features of tuberculosis are the presence of acid-fast bacilli and caseation with destruction of the reticulin framework. There is irregularity of the contour with a particularly dense cuff of lymphocytes. Less numerous lesions with a tendency to coalesce also suggest tuberculosis (table 28.5).

Capillary granulomas are found after BCG vaccination, especially in the immunosuppressed.

Rarely, fulminant liver failure can result from tuberculosis [10].

Lepromatous leprosy

Hepatic granulomas indistinguishable from those of sarcoidosis may be found in 62% of patients compared with the tuberculoid form when only 21% are positive. *Mycobacterium leprae* bacilli are sometimes present.

Bacteria

Brucella abortus infection may be complicated by hepatic granulomas. Hepatic tenderness and mild elevations of transaminases and alkaline phosphatase may be found in the acute stage. Hepatic histology shows a non-specific reactive hepatitis. Granulomas cannot be distinguished from those of sarcoidosis although they tend to be smaller and less clearly demarcated (fig. 28.8). Healing results in scarring. Necrotizing microgranulomas may be found in the bone marrow.

The presence of circulating autoantibodies indicate that the *Brucella* antigen can be responsible for a β-lymphocyte activation of the immune system [3].

Spirochaetes

In the secondary septicaemic stage of *syphilis*,

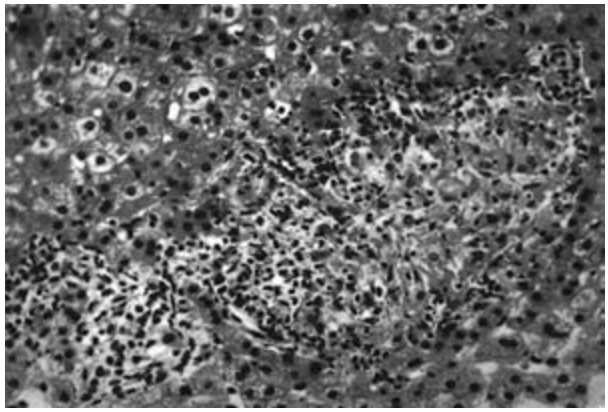


Fig. 28.8. Brucellosis. Granulomas in the liver; the smaller is little more than a collection of round cells. (H & E,×170.)

spirochaetes invade the liver with the production of miliary granulomas.

Fungal infections

In *histoplasmosis* the liver is second only to the spleen in frequency of involvement. In the granulomatous form, the lesions are histologically identical with those of sarcoidosis, except for the presence of intra-cellular fungus in the Kupffer cells. Liver biopsy can be used for diagnosis. Sections should be stained for *Histoplasma capsulatum* and a small portion of the biopsy should be cultured. Histoplasmosis leads to discrete hepatic calcification.

Coccidioidomycosis and *blastomycosis* also produce sarcoid-like granulomas and the organism may be demonstrated.

Protozoa

Toxoplasmosis may be associated with granulomas usually without giant cells [18].

Helminths

The hepatic granulomatous reaction to the *Schistosoma* ovum is of delayed hypersensitivity type, related to antigen released by the egg (Chapter 29). TH0- and TH2-type helper lymphocytes play an important role in granuloma formation [32]. α_2-Macroglobulin may be synthesized in the egg granulomas. This is a major proteinase inhibitor which affects binding of cytokines such as TGF-β and platelet-derived growth factor [27]. Earlier, cytokines formed from granulomas around ova may play a central role in fibrogenesis [21].

Eggs or their remnants are seen in 94% of liver biopsies from those with faecal eggs (see fig. 29.13). The remnants of eggs are of diagnostic importance.

Toxocara canis is spread by cats and dogs. The second stage can infect the liver of man forming granulomas [14]. Hepatomegaly, recurrent pneumonia, eosinophilia and hypergammaglobulinaemia are associated findings.

Fasciola hepatica. The clinical picture in the acute stage is of cholangitis with fever, right upper quadrant pain and hepatomegaly. Eosinophilia and raised serum alkaline phosphatase are noted. Hepatic granulomas and ova in the liver may occasionally be seen.

Ascariasis is particularly common in the Far East, India and South Africa. Ova of the round worm *Ascaris lumbricoides* arrive in the liver by retrograde passage up the bile ducts. They exert an immunological reaction and eggs, giant cells and granulomas are surrounded by a dense eosinophil infiltrate. The adult worm may lodge in the common bile duct producing partial bile duct obstruction and secondary cholangitic abscesses.

Rickettsia

Q fever has predominantly pulmonary manifestations. Occasionally, hepatitis may be prominent and the clinical features may mimic anicteric viral hepatitis. The liver shows a granulomatous hepatitis. The granulomas have a characteristic ring of fibrinoid necrosis surrounded by lymphocytes and histiocytes. In the centre of the granuloma is a clear space giving a doughnut appearance.

Viruses

Hepatitis A. The histological picture is of an acute hepatitis, but occasionally fibrin-ring granulomas may be found [20].

Hepatitis C. Epithelioid granulomas have been found in 10% of surgical transplant liver specimens from patients with hepatitis C-related cirrhosis. They had no other cause of granulomatous hepatitis and granulomas were not found in the transplanted livers of patients with hepatitis B-related cirrhosis [7].

Acute cytomegalovirus infection produces a mononucleosis syndrome. Transient well-formed hepatic granulomas may be associated.

Hepatic granulomas in the patient with AIDS

Granulomas are frequent and have multiple causes (table 28.6).

Liver biopsy is particularly helpful in showing granulomas of mycobacterial infection whether *M. tuberculosis* or *M. avium-intracellulare*. The granulomas tend to be poorly formed without lymphocyte cupping, giant cells or central caseation. Acid-fast bacilli are present in large numbers in clusters of foamy histiocytes or

Table 28.6. Hepatic granulomas in patients with AIDS

Infections	*Mycobacterium avium-intracellulare*
	Mycobacterium tuberculosis
	Cytomegalovirus
	Histoplasmosis
	Toxoplasmosis
	Cryptococcosis
Neoplasms	Hodgkin's and non-Hodgkin's lymphoma
Drugs	Sulphonamides
	Antibiotics
	Antifungals
	Isoniazid
	Tranquillizers

within Kupffer cells. Cytomegalovirus and herpes simplex infections may also be associated with hepatic granulomas.

Fungal infections are usually part of disseminated disease. They can all be related to granuloma formation. They include *Cryptococcus neoformans*. Similarly, histoplasmosis, coccidiomycosis and *Candida albicans* may involve the liver.

The granulomas may be related to drug therapy. Trimethoprim-sulfamethoxazole is a common offender causing granulomatous hepatitis and jaundice.

Industrial causes

Beryllium poisoning leads to pulmonary granulomas. Hepatic involvement consists of miliary granulomas resembling those of sarcoidosis. Pulmonary and hepatic granulomas may be due to inhalation of *cement* and *mica dust*, and to *copper* in vineyard sprayers.

Other conditions with hepatic granulomas

In the early stages of PBC the liver may show widespread hepatic granulomas. This histological picture may be indistinguishable from sarcoidosis.

Whipple's disease may be accompanied by hepatic granulomas with bacillary inclusions negative for PAS staining after protein digestion.

Non-specific reticulo-endothelial proliferations: 'reactive hepatitis' [8]

Focal accumulations of mononuclear and epithelioid cells are found in a great variety of diseases. They are perhaps most frequent in viral infections, including infectious mononucleosis, during the recovery phase of viral hepatitis when they contain iron, and in influenza. Occasionally, they are noted in pyogenic infections and septicaemias where polymorphonuclear leucocytes are also present.

Their distinction from small sarcoid granulomas may be difficult, especially since they may also be seen in sarcoidosis. If such an accumulation of cells is found in a liver biopsy section, the whole block should be sectioned serially to identify typical granulomas.

Generalized proliferation of Kupffer cells is another frequent finding occurring in infections and in malignant disease arising in any part of the body. Generalized Kupffer cell proliferation is also seen in a liver containing local lesions—such as malignant deposits or an amoebic abscess.

The *lipogranuloma* consists of poorly formed perivenular aggregates of histiocytes and macrophages, some containing fat which can be identified in the granuloma. It is often associated with fatty liver. They are due to deposition of mineral oils used in the food industry.

Microgranulomas consist only of a cluster of six or less histiocytes. They have many associations and probably represent a non-specific reaction to cell necrosis.

Fibrin-ring granulomas are typical of Q fever, but are also seen as a drug reaction to such agents as carbamazepine and allopurinol [30]. They are also described with acute hepatitis A [20].

Necrotizing or caseating granulomas are small to large, well formed with a necrotic centre. The histiocytic rim often has a palisade pattern and fibrosis is variable. They are associated with fungal infections and rarely with tuberculosis.

References

1 Bass NM, Burroughs AK, Scheuer PJ *et al*. Chronic intrahepatic cholestasis due to sarcoidosis. *Gut* 1982; **23**: 417.
2 Becheur H, Dall'osto H, Chatellier G *et al*. Effect of ursodeoxycholic acid on chronic intrahepatic cholestasis due to sarcoidosis. *Dig. Dis. Sci.* 1997; **42**: 789.
3 Bourantas KL, Christou LG, Dalekos GN *et al*. A 54-year-old stockbreeder with ascites. *Lancet* 1997; **349**: 994.
4 Britt AR, Francis IR, Glazer GM *et al*. Sarcoidosis: abdominal manifestations at CT. *Radiology* 1991; **178**: 91.
5 Casavilla FA, Gordon R, Wright HI *et al*. Clinical course after liver transplantation in patients with sarcoidosis. *Ann. Intern. Med.* 1993; **118**: 865.
6 Denk H, Scheuer PJ, Baptista A *et al*. Guidelines for the diagnosis and interpretation of hepatic granulomas. *Histopathology* 1994; **25**: 209.
7 Emile JF, Sebagh M, Feray C *et al*. The presence of epithelioid granulomas in hepatitis C virus-related cirrhosis. *Hum. Pathol.* 1993; **24**: 1095.
8 Ferrell LD. Hepatic granulomas: a morphologic approach to diagnosis. *Surg. Pathol.* 1990; **3**: 87.
9 Fidler HM, Hadziyannis SJ, Dhillon AP *et al*. Recurrent hepatic sarcoidosis following liver transplantation. *Transplant. Proc.* 1997; **29**: 2509.
10 Hussain W, Mutimer D, Harrison R *et al*. Fulminant hepatic failure caused by tuberculosis. *Gut* 1995; **36**: 792.

11 James DG. Definition and classification. In James DG, ed. *Sarcoidosis and Other Granulomatous Disorders.* Marcel Dekker, New York, 1994. p. 19.
12 Johns CJ, Michele TM. The clinical management of sarcoidosis. A 50-year experience at the Johns Hopkins Hospital. *Medicine (Baltimore)* 1999; **78**: 65.
13 Johnson LN, Iseri O, Knodell RG. Caseating hepatic granulomas in Hodgkin's lymphoma. *Gastroenterology* 1990; **99**: 1837.
14 Kaushik SP, Hurwitz M, McDonald C *et al*. *Toxocara canis* infection and granulomatous hepatitis. *Am. J. Gastroenterol.* 1997; **92**: 1223.
15 Knox TA, Kaplan MM, Gelfand JA *et al*. Methotrexate treatment of idiopathic granulomatous hepatitis. *Ann. Intern. Med.* 1995; **122**: 592.
16 Kusielewicz D, Duchatelle V, Valeyre D *et al*. Obstructive jaundice by granulomatous stenosis of the extrahepatic biliary tract due to sarcoidosis. *Gastroenterol. Clin. Biol.* 1988; **12**: 664.
17 Lefkowitch JH. Hepatic granulomas. *J. Hepatol.* 1999; **30**: 40.
18 Ortego TJ, Robey B, Morrison D *et al*. Toxoplasma chorioretinitis and hepatic granulomas. *Am. J. Gastroenterol.* 1990; **85**: 1418.
19 Perry A, Vuitch F. Causes of death in patients with sarcoidosis. A morphologic study of 38 autopsies with clinicopathologic correlations. *Arch. Pathol. Lab. Med.* 1995; **119**: 167.
20 Ponz E, García-Pagán JC, Bruguera M *et al*. Hepatic fibrin-ring granulomas in a patient with hepatitis A. *Gastroenterology* 1991; **100**: 288.
21 Prakash S, Postlethwaite AE, Wyler D. Alterations in influence of granuloma-derived cytokines on fibrogenesis in the course of murine *Schistosoma mansoni* infection. *Hepatology* 1991; **13**: 970.
22 Russe EW, Bansky G, Pfaltz M *et al*. Budd–Chiari syndrome in sarcoidosis. *Am. J. Gastroenterol.* 1986; **81**: 71.
23 Sartin JS, Walker RC. Granulomatous hepatitis: a retrospective review of 88 cases. *Mayo Clin. Proc.* 1991; **66**: 914.
24 Sherlock S. Granulomatous liver disorders. In James DG, Zumla A, eds. *The Granulomatous Disorders*. Cambridge University Press, Cambridge, 1999, p. 418.
25 Simon HB, Wolff SM. Granulomatous hepatitis and prolonged fever of unknown origin: a study of 13 patients. *Medicine (Baltimore)* 1973; **52**: 1.
26 Spiteri MA, Johnson M, Epstein O *et al*. Immunological features of lung lavage cells from patients with primary biliary cirrhosis may reflect those seen in pulmonary sarcoidosis. *Gut* 1990; **31**: 208.
27 Tiggelman AM, Boers W, Moorman AF *et al*. Localization of alpha-2 macroglobulin protein and messenger RNA in rat liver fibrosis: evidence for the synthesis of alpha-2-macroglobulin within *Schistosoma mansoni* egg granulomas. *Hepatology* 1996; **23**: 1260.
28 Toth CA, Thomas P. Liver endocytosis and Kupffer cells. *Hepatology* 1992; **16**: 255.
29 Valla D, Pessegueiro-Miranda H, Degott C *et al*. Hepatic sarcoidosis with portal hypertension. A report of seven cases with a review of the literature. *Q. J. Med.* 1987; **63**: 531.
30 Vanderstigel M, Zafrani ES, Lejonc JL *et al*. Allopurinol hypersensitivity syndrome as a cause of hepatic fibrin-ring granulomas. *Gastroenterology* 1986; **9**: 188.
31 Young ID, Clark RN, Manley PN *et al*. Response to steroids in Budd–Chiari syndrome caused by idiopathic granulomatous venulitis. *Gastroenterology* 1988; **94**: 503.
32 Zhu Y, Lukacs NW, Boros DL. Cloning of TH0 and TH2-type helper lymphocytes from liver granulomas of *Schistosoma mansoni*-infected mice. *Infect. Immun*. 1994; **62**: 994.
33 Zoutman DE, Ralph ED, Frei JV. Granulomatous hepatitis and fever of unknown origin. An 11-year experience of 23 cases with three years' follow-up. *J. Clin. Gastroenterol.* 1991; **13**: 69.

Hepato-biliary associations of inflammatory bowel disease

In one large clinic over half the patients with ulcerative colitis showed liver functional abnormalities.

The surgeon sees acute fatty liver when operating on patients with fulminant colitis, biliary strictures in those with sclerosing cholangitis, or gallstones in patients with ileal resection. In treating ulcerative colitis the physician sees chronic active (autoimmune) hepatitis or chronic cholestasis in those with pericholangitis and sclerosing cholangitis. The pathologist may encounter hepatic granulomas or amyloidosis in a liver biopsy from a patient with inflammatory bowel disease. Involvement of the liver in patients with malnutrition has been discussed in Chapter 25.

Sclerosing cholangitis (Chapter 15) presents in many forms. *Gallstones* are present in up to a third of patients with Crohn's disease of the terminal ileum.

Ulcerative colitis, rarely, has been complicated by the *Budd–Chiari syndrome* [1].

Fatty change. This is very frequent. As with other types of fatty infiltration, the incidence is higher when autopsy rather than biopsy material is used for diagnosis. It may be focal but usually starts in zone 1 and spreads to zone 3. Cirrhosis is not a sequel.

This change is related to the anorexia, anaemia, faecal protein loss and malnutrition of severe colitis.

Carcinoma of the bile ducts (Chapter 37). This has been reported in ulcerative colitis, usually with sclerosing cholangitis. The ulcerative colitis is usually of long standing. The bile duct carcinoma develops independently of the extent and severity of the colitis. It may develop many years after proctocolectomy. It must be considered in any patient with ulcerative colitis developing persistent cholestatic jaundice.

Chronic active hepatitis and cirrhosis. Five per cent of cirrhotic patients have ulcerative colitis, a greater incidence than in the general population. In some the cirrhosis is of chronic autoimmune type. The colitis is then part of the general spectrum of this *multi-system disease*. In these patients, and in contrast to sclerosing cholangitis, the colitis tends to present with the cirrhosis and to be severe but often not subsequently relapsing. The recognition of the cirrhosis may precede the diarrhoea.

In others the cirrhosis is inactive and is diagnosed

after many years of chronic relapsing colitis. Initially the colitis is predominant and the cirrhosis mild, but as the years pass the positions reverse.

The cirrhosis might be related to the long course of the illness, many hospital attendances, injections, infusions and blood transfusions, all carrying the hazard of viral hepatitis. This cannot be the whole answer because the cirrhosis may precede the colitis.

Later pericholangitis and sclerosing cholangitis may be associated with piecemeal necrosis of liver cells and scar formation. This can proceed to biliary cirrhosis.

Primary sclerosing cholangitis is a much more common association than is autoimmune chronic hepatitis.

Liver abscess. Patients with Crohn's disease may develop liver abscesses, usually multiple and with a predisposing abdominal focus of infection rather than a biliary one. Streptococci, especially *S. milleri*, are often responsible.

Coeliac disease. Non-specific liver lesions are frequent and improve with a gluten-free diet [2]. Chronic hepatitis is also found and shows no dietary response. Steatosis may be massive.

References

1 Chesner IM, Muller S, Newman J. Ulcerative colitis complicated by Budd–Chiari syndrome. *Gut* 1986; **27**: 1096.

2 Jacobsen MB, Fausa O, Elgjo K *et al*. Hepatic lesions in adult coeliac disease. *Scand. J. Gastroenterol.* 1990; **25**: 656.

Hepatic trauma

This is usually due to road traffic accidents, to penetrating wounds from stabbing or to gun shots. It may follow birth injury. Spontaneous rupture can complicate the last trimester of pregnancy usually with toxaemia.

Blunt injury may be due to deceleration (leading to splits and tears from shearing) or to direct violence causing contusion or disruption of the liver substance. It may complicate cardio-pulmonary resuscitation [1].

Injury to the hepatic parenchyma is the main problem, and injuries to portal vein, hepatic artery, hepatic vein or retro-hepatic vena cava are rare.

Extra-hepatic bile duct injuries are rare, but all types can follow both blunt and penetrating abdominal trauma [4] and, of course, laparoscopic or conventional cholecystectomy.

Diagnosis

This may be difficult as physical signs may be minimal. Pattern bruising of the abdominal wall indicates severe abdominal compression.

Diagnostic peritoneal aspiration [5], ultrasonography and CT scanning are invaluable [13]. CT may show laceration, subcapsular fluid (blood or bile) and fragmentation (fig. 28.9). Hepatic parenchymal gas may indicate infection but may also be seen simply after blunt trauma.

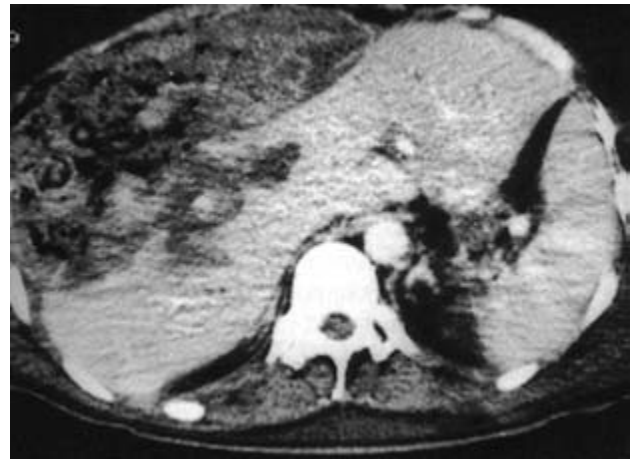


Fig. 28.9. Intravenous contrast-enhanced CT of a patient with a gun shot injury to the anterior part of the liver. A low-attenuation haematoma with disorganized liver tissue and gas indicates infection. Successful treatment was by drainage of pus, debridement and gel foam angiographic embolization of a feeding hepatic artery branch.

The possibility of other organs being damaged, such as spleen, intestines, lungs or kidneys, or the coincidence of head injuries and fractures, must be remembered.

Blunt abdominal trauma may lead to haemobilia, usually secondary to hepatic arterial aneurysm [12]. Angiography is a necessary investigation.

HIDA biliary scans show bile leaks (Chapter 32).

In children, blunt abdominal trauma results in injury to the liver, usually the right lobe and frequently posteriorly [15]. Associated thoracic injuries are common.

Management

This depends on the type of injury, the extent and the haemodynamic stability of the patient (table 28.7) [2, 11]. Gun shot wounds require abdominal exploration. Stable patients with anterior stab wounds require local exploration followed by laparotomy if the anterior fascia is violated. Indications for surgery following blunt trauma include positive peritoneal lavage, abnormal CT scan and abdominal tenderness. Surgery can be avoided in some patients if observation is close and the patient haemodynamically stable [3].

Most liver injuries require only minor therapy. Mild splits, lacerations and penetrating wounds can usually be managed by simple haemostasis and drainage. If CT shows minimal or absent haemoperitoneum and an intact or nearly intact hepatic capsule, surgical interven-

Table 28.7. Severity of liver injury graded according to the American Association for the Surgery of Trauma hepatic injury scale [2]

Grade*	Injury description†	
I	Haematoma	Subcapsular, non-expanding, <10% surface area
	Laceration	Capsular tear, non-bleeding, <1 cm parenchymal depth
II	Haematoma	Subcapsular, non-expanding, 10–50% surface area
	Laceration	Capsular tear, active bleeding; 1–3 cm parenchymal depth, <10 cm in length
III	Haematoma	Subcapsular, >50% surface area or expanding; ruptured subcapsular haematoma with active bleeding; intra-parenchymal haematoma >2 cm or expanding
	Laceration	>3 cm parenchymal depth
IV	Haematoma	Ruptured intra-parenchymal haematoma with active bleeding
	Laceration	Parenchymal disruption involving 25–50% of hepatic lobe
V	Laceration	Parenchymal disruption involving >50% of hepatic lobe
	Vascular	Juxta-hepatic venous injuries, i.e. retro-hepatic vena cava/major hepatic veins
VI	Vascular	Hepatic avulsion

* Advance one grade for multiple injuries to the same organ.
† Based on most accurate assessment at autopsy, laparotomy or radiological study.

tion will not be necessary. Deeper lacerations with tearing of intra-hepatic vessels and bile ducts are treated by ligating the bleeding vessels and repairing the liver with deep sutures. Omental packing may be helpful, and gauze used when omentum is unavailable.

If surgical treatment is impossible at a local centre, the patient should be transferred immediately to a specialized unit where definitive operative treatment can be carried out. In general, packing should be avoided as this increases the mortality, particularly from abscess [8].

Portahepatis injuries are rare and control of bleeding is of prime importance [14]. Bleeding is controlled by digital compression of the hepatic artery and portal vein in the lesser omentum. Selective hepatic arteriography is useful in defining treatment. Hepatic arterial embolization with gel foam must be considered.

Repair of major venous injuries requires adequate exposure. The mid-line abdominal incision is extended, cephalad, and a median sternal split made. This allows control of the hepatic vein and any tear of the subdiaphragmatic inferior vena cava. Repairs of the inferior vena cava or hepatic vein are sutured or side-clamped. Portal vein injuries are rare and are nearly always associated with pancreatic rupture [6]. They have the worst prognosis. They are treated by suture or end-to-side porta-caval anastomosis or, if necessary, acute portal vein ligation [14].

In the majority of cases, hepatic trauma can be managed by local pressure and aggressive debridement with hepatic segmentectomy. With the damaged liver exposed, ragged areas of questionable viability can be excised, local haemostasis obtained and efficient drainage established. Excellent results have been noted after resection of as much as 400 g of liver tissue. Hepatic resection and lobectomy are required in only a small number of cases.

Repeated ultrasound examinations are important in following the patient.

Post-operative complications include coagulopathy, sepsis, biliary fistula and stricture and late haemorrhage [9]. Abscess is a late and often fatal complication. Diagnosis of bile duct injuries is difficult and may be delayed [4]. Endoscopic therapy with sphincterotomy and biliary stenting is usually effective, but more serious injuries require surgical relief [10].

Prognosis

The overall mortality is 10.5% with 78.1% of all deaths occurring in the post-operative period from shock or coagulopathies. Penetrating wounds have a lower mortality than blunt ones. This is largely due to the greater magnitude of associated injury [2]. The mortality following major penetrating liver injury in an urban setting is 17% [9].

The prognosis depends on the extent of the injury and the number of organs involved. Injuries to the hepatic veins, portal vein or retro-hepatic inferior vena cava are highly lethal. Hepatic venous injuries, usually due to blunt trauma, have a 61% mortality usually due to blood loss [7].

Abscess is related to increase in severity of trauma and to transfusion requirements [2].

Rupture of the gallbladder

Rupture or contusion of the gallbladder can follow blunt trauma. It is rare because the gallbladder is cushioned by

surrounding bony and visceral structures. The gallbladder is usually distended at the time of rupture. Early diagnosis is difficult. The condition is recognized by fever, jaundice, increasing distension and ascites. Paracentesis shows bile-stained fluid. Later, encysted bile accumulations are recognized by ultrasound and CT scanning. The perforation is confirmed by percutaneous or endoscopic cholangiography. HIDA scanning is useful.

Treatment is by cholecystectomy.

References

1 Adler SN, Klein RA, Pellechia C *et al*. Massive hepatic haemorrhage associated with cardiopulmonary resuscitation. *Arch. Intern. Med.* 1983; **143**: 813.

2 Fabian TC, Croce MA, Stanford GG *et al*. Factors affecting morbidity following hepatic trauma. A prospective analysis of 482 injuries. *Ann. Surg.* 1991; **213**: 540.

3 Federico JA, Horner WR, Clark DE *et al*. Blunt hepatic trauma: nonoperative management in adults. *Arch. Surg.* 1990; **125**: 905.

4 Feliciano DV. Biliary injuries as a result of blunt and penetrating trauma. *Surg. Clin. North Am.* 1994; **74**: 897.

5 Feliciano DV, Bitondo CG, Steed G *et al*. Five hundred open taps or lavages in patients with abdominal stab wounds. *Am. J. Surg.* 1984; **148**: 772.

6 Henne-Bruns D, Kremer B, Lloyd DM *et al*. Injuries of the portal vein in patients with blunt abdominal trauma. *HPB Surg.* 1993; **6**: 163.

7 Hollands MJ, Little JM. Hepatic venous injury after blunt abdominal trauma. *Surgery* 1990; **107**: 149.

8 Ivatury RR, Nallathambi M, Gunduz Y *et al*. Liver packing for uncontrolled haemorrhage: a reappraisal. *J. Trauma* 1986; **26**: 744.

9 Knudson MM, Lim RC, Olcott EW. Morbidity and mortality following major penetrating liver injuries. *Arch. Surg.* 1994; **129**: 256.

10 Kozarek RA. Endoscopic techniques in management of biliary tract injuries. *Surg. Clin. North Am.* 1994; **74**: 883.

11 Moore EE, Shackford SR, Pachter HL *et al*. Organ injury scaling: spleen, liver, and kidney. *J. Trauma* 1989; **29**: 1664.

12 Samuels RS, Shriver M, Patel NH. Hemobilia after a gunshot injury to the liver. *Am. J. Roentgenol.* 1996; **166**: 1204.

13 Shangmuganathan K, Mirvis SE. CT scan evaluation of blunt hepatic trauma. *Radiol. Clin. North Am.* 1998; **36**: 399.

14 Sheldon GF, Lim RC, Yee ES *et al*. Management of injuries to the porta hepatis. *Ann. Surg.* 1985; **202**: 539.

15 Stalker HP, Kaufman RA, Towbin R. Patterns of liver injury in childhood: CT analysis. *Am. J. Roentgenol.* 1986; **147**: 1199.

Chapter 29
The Liver in Infections

Pyogenic liver abscess

Over the past 30 years there has been a marked change in the aetiology of pyogenic liver abscess (fig. 29.1) [7]. Abscesses secondary to biliary disease, particularly malignant, have continued to increase. The immunosuppressive states have increased the number due to opportunistic infections.

Earlier diagnosis has followed increased use of scanning and cholangiographic techniques.

Aetiology

Underlying biliary disease is the most frequent cause. Septic cholangitis can complicate any form of biliary obstruction, especially if partial. More cases are related to surgical or invasive non-surgical treatment of hepatobiliary disease, despite the use of prophylactic antibiotics. Biliary stenting for malignant biliary and pancreatic disease is a particular association. Abscess may follow sclerosing cholangitis and congenital biliary anomalies, especially Caroli's disease.

Portal pyaemia may follow pelvic or gastrointestinal infection resulting in portal pylephlebitis or septic emboli. It can follow appendicitis, empyema of the gallbladder, diverticulitis, regional enteritis [14], *Yersinia* ileitis [9], perforated gastric or colonic ulcers, leaking anastomoses, pancreatitis [1] or infected haemorrhoids.

Neonatal umbilical sepsis may spread to the portal vein with subsequent liver abscesses.

Injury to the *hepatic arterial system* may lead to liver abscesses. This can follow cholecystectomy. In liver transplant patients, abscess may be diagnosed 2 weeks postoperatively associated with technical complications, particularly hepatic arterial thrombosis. Abscesses may follow local treatment of liver tumours by trans-hepatic chemo-embolization or percutaneous tumour injections [5]. Abscess may follow therapeutic hepatic arterial catheterization to treat colonic cancer metastases [15].

Increase in liver abscesses may also be related to the numbers of severely *immunosuppressed patients*. These include those post-transplant, with HIV infection or with leukaemia receiving chemotherapy [3].

Traumatic causes include penetrating wounds or blunt trauma from automobile accidents.

A solitary liver abscess may follow *direct spread* from an adjacent septic focus such as a perinephric abscess. Diabetics may develop a liver abscess with gas-forming organisms (*Klebsiella*) [16].

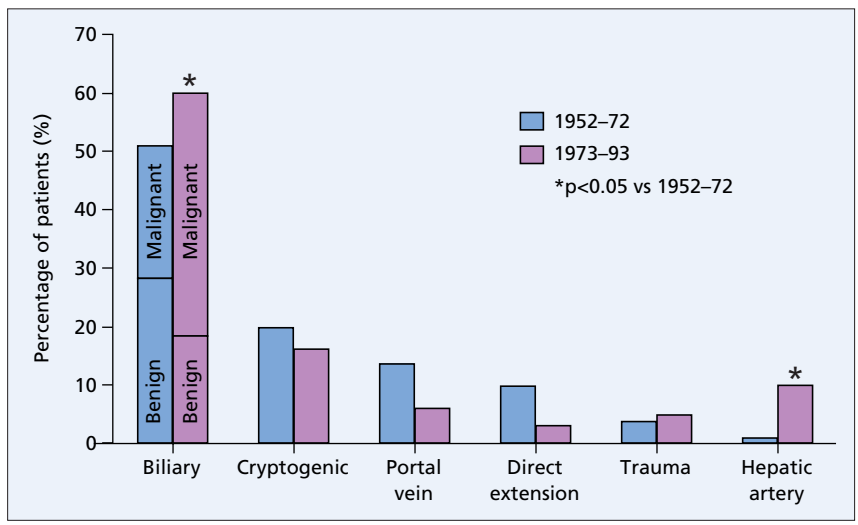


Fig. 29.1. Aetiology of pyogenic hepatic abscesses from 1952 to 1993 (from [7]).

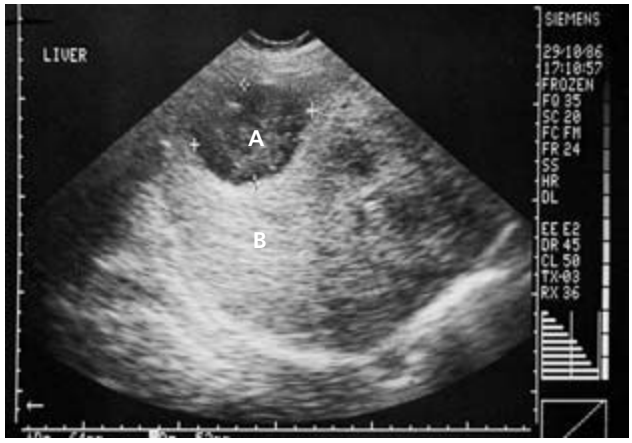


Fig. 29.2. US of a pyogenic liver abscess shows a low-density lesion (A) containing echogenic material which is pus and necrotic tissue. Acoustic enhancement (B) beyond the lesion is characteristic.

About one half of abscesses are *cryptogenic*. This is especially so in the elderly.

Infecting agents

The commonest are Gram-negative *Escherichia coli*, *Streptococcus faecalis*, *Klebsiella* and *Proteus vulgaris*. Recurrent pyogenic cholangitis may be due to *Salmonella typhi*.

Streptococcus milleri, which is neither a true anaerobe nor a micro-anaerobe is a very common cause [13]. Anaerobes are particularly important. Infections are liable to be mixed and often antibiotic resistant. Superinfection is common.

Liver abscesses associated with biliary stents are often due to resistant *Klebsiella*, enterobacter and *Pseudomonas*, *Candida* may be found in the bile. Fungal infections may be associated with underlying malignancy. Staphylococci, usually resistant, are found especially in those who have received chemotherapy. *Klebsiella pneumoniae*, *Pseudomonas* and *Clostridium welchii* may also be found.

Rare causes include *Yersinia enterocolitica* [9] and septicaemic melioidosis. The abscess may be sterile, but this is usually due to lack of adequate, particularly anaerobic, culture techniques or to previous antibiotics.

Pathology

The enlarged liver may contain multiple yellow abscesses, 1 cm in diameter or a single abscess encased in fibrous tissue and usually found in the right lobe. With pylephlebitis, the portal vein and its branches contain pus and blood clots. There may be peri-hepatitis or adhesion formation. A chronic liver abscess may persist for as long as 2 years before death or diagnosis. In biliary-associated cases, multiple foci correspond to the bile duct system.

Small pyaemic abscesses may be found in lung, kidney, brain or spleen. Direct extension may lead to sub-phrenic or pleuro-pulmonary suppuration. Extension to the peritoneum or rupture of a sinus pointing under the skin are rare. A small amount of ascites may be present.

Histologically, areas remote from the abscess show portal zone infection and surrounding disintegrating hepatocytes being infiltrated by polymorphs.

Clinical features

Features such as diabetes, biliary disease, malignancy or immunosuppressive states are recorded.

Presentation is with abdominal pain and fever with features of a space-occupying lesion in the liver.

The onset may be insidious and diagnosis delayed for at least 1 month. A single abscess is often insidious and cryptogenic especially in the elderly. Multiple abscesses are more acute and the cause is more often identified. Sub-diaphragmatic irritation or pleuro-pulmonary spread leads to right shoulder pain and to an irritable cough. The liver is enlarged and tender and the pain is accentuated by percussion over the lower ribs.

Jaundice is late unless there is biliary disease. It is more common than with amoebic abscess.

Recovery may be followed by portal hypertension due to thrombosis of the portal vein.

Serum alkaline phosphatase is usually raised. Polymorph leukocytosis is usual.

Blood cultures may show the causative organism or organisms [2].

Localization of the abscess

Ultrasound (US) distinguishes a solid from a fluid-filled lesion (fig. 29.2). *CT scanning* is particularly valuable although false negatives can be due to lesions near the dome of the liver and to micro-abscesses (figs 29.3–29.5). Multiple small abscesses aggregate, suggesting the beginning of coalescence into single larger abscesses (*cluster sign*) [8].

Endoscopic or *percutaneous cholangiography* may be used to diagnose cholangitic abscesses.

MRI shows a raised lesion with sharp borders, hypointense on T_1-weighting, and hyper-intense on a T_2-weighted image. Appearances are not specific or diagnostic of biliary or haematogenous origin [11].

Aspirated material is positive in 90% [2]. It should be cultured aerobically, anaerobically and in carbon dioxide-enriched media for *Streptococcus milleri*.

Treatment

Management has been revolutionized by the wide-

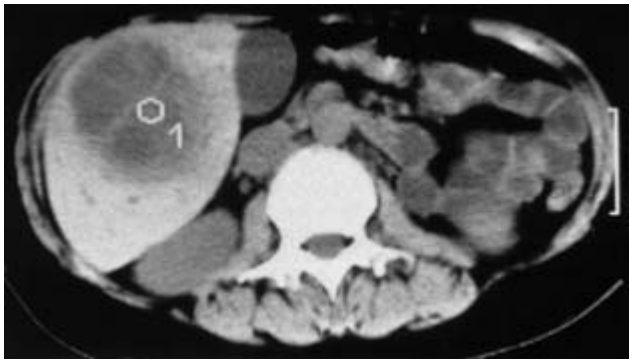


Fig. 29.3. Thalassaemic Greek patient post-splenectomy. CT scan shows a filling defect in the right lobe of the liver with marker over it (labelled 1).

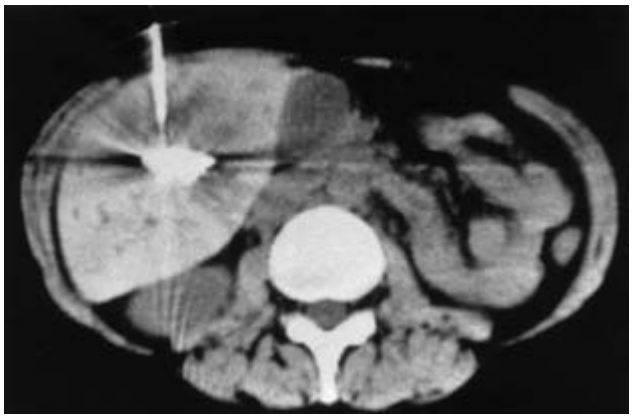


Fig. 29.4. Same patient as in fig. 29.3 with directed puncture of the abscess which resolved without surgery.

spread use of imaging, especially US, allowing localization and easy aspiration for both diagnostic and therapeutic purposes (fig. 29.4). The majority of abscesses can be managed by systemic antibiotics and aspiration, which may need to be repeated [4]. Intravenous antibiotics are rarely effective alone. Drainage is indicated if signs of sepsis persist. Open surgical drainage is rarely indicated. However, solitary left-sided abscess may require surgical drainage, especially in children [12].

With multiple abscesses, the largest is aspirated and the smaller lesions usually resolve with antibiotics. Occasionally, percutaneous drainage of each is necessary.

If amoebiasis is suspected, metronidazole should be given before aspiration [6].

Biliary obstruction must be relieved, usually by ERCP, papillotomy and stone removal. If necessary, a biliary stent is inserted (Chapter 32). Even with eventual cure, fever may continue for 1–2 weeks [2].

Prognosis

Needle aspiration and antibiotic therapy have lowered the mortality [3]. The prognosis is better for a unilocular abscess in the right lobe where survival is 90%. The outcome for multiple abscesses, especially if biliary, is very poor. The prognosis is worsened by delay in diagnosis, associated disease, particularly malignant [17], hyperbilirubinaemia, hypo-albuminaemia, pleural effusion and old age [10].

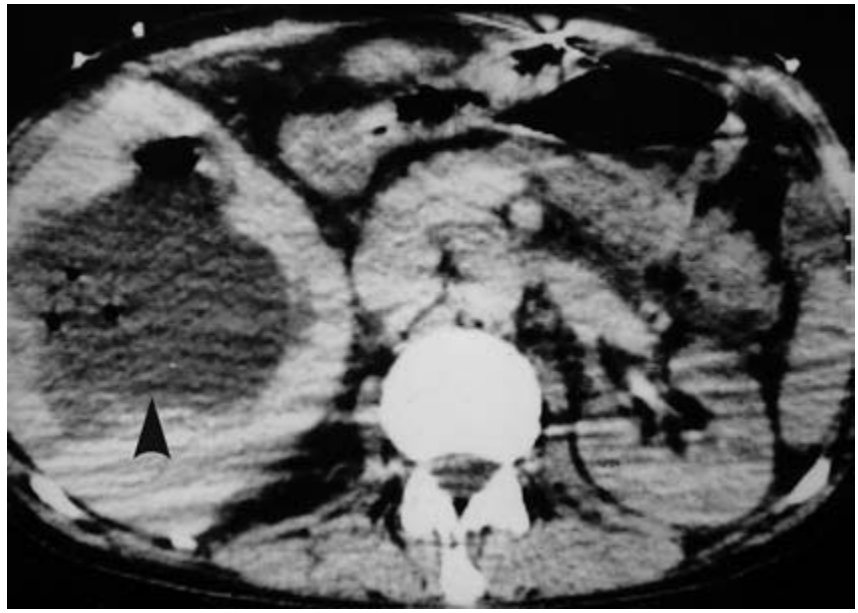


Fig. 29.5. CT shows a large pyogenic abscess with thick shaggy walls in the inferior part of the right lobe of the liver (arrowhead). The abscess contains gas.

References

1 Ammann R, Münch R, Largiadèr F *et al*. Pancreatic and hepatic abscesses: a late complication in 10 patients with chronic pancreatitis. *Gastroenterology* 1992; **103**: 560.
2 Barnes PF, DeCock KM, Reynolds TN *et al*. A comparison of amebic and pyogenic abscesses of the liver. *Medicine (Baltimore)* 1987; **66**: 472.
3 Branum GD, Tyson GS, Branum MA *et al*. Hepatic abscess. Changes in aetiology, diagnosis, and management. *Ann. Surg*. 1990; **212**: 655.
4 Ch Yu S, Hg Lo R, Kan PS *et al*. Pyogenic liver abscess: treatment with needle aspiration. *Clin. Radiol*. 1997; **52**: 912.
5 De Baere T, Roche A, Amenabar JM *et al*. Liver abscess formation after local treatment of liver tumours. *Hepatology* 1996; **23**: 1436.
6 Giorgio A, Tarantino L, Mariniello N *et al*. Pyogenic liver abscesses: 13 years of experience in percutaneous needle aspiration with US guidance. *Radiology* 1995; **195**: 122.
7 Huang CJ, Pitt HA, Lipsett PA *et al*. Pyogenic hepatic abscess. Changing trends over 42 years. *Ann. Surg*. 1996; **223**: 600.
8 Jeffrey RB Jr, Tolentino CS, Chang FC *et al*. CT of small pyogenic hepatic abscesses: the cluster sign. *Am. J. Roentgenol*. 1988; **151**: 487.
9 Khanna R, Levendoglu H. Liver abscess due to *Yersinia enterocolitica*: case report and review of the literature. *Dig. Dis. Sci*. 1989; **34**: 636.
10 Lee K-T, Sheen P-C, Chen J-S *et al*. Pyogenic liver abscess: multivariate analysis of risk factors. *World J. Surg*. 1991; **15**: 372.
11 Méndez RJ, Schiebler ML, Outwater EK *et al*. Hepatic abscesses: MR imaging findings. *Radiology* 1994; **190**: 431.
12 Moore SW, Millar AJ, Cywes S. Conservative initial treatment for liver abscesses in children. *Br. J. Surg*. 1994; **81**: 872.
13 Moore-Gillon JC, Eykyn SJ, Phillips I. Microbiology of pyogenic liver abscess. *Br. Med. J*. 1981; **283**: 819.
14 Vakil N, Hayne G, Sharma A *et al*. Liver abscess in Crohn's disease. *Am. J. Gastroenterol*. 1994; **89**: 1090.
15 Wong E, Khadori N, Carrasco CH *et al*. Infectious complications of hepatic artery catheterization procedures in patients with cancer. *Rev. Infect. Dis*. 1991; **13**: 583.
16 Yang CC, Chen CY, Lin XZ *et al*. Pyogenic liver abscess in Taiwan: emphasis on gas-forming liver abscess in diabetics. *Am. J. Gastroenterol*. 1993; **88**: 1911.
17 Yeh TS, Jan YY, Jeng LB *et al*. Pyogenic liver abscesses in patients with malignant disease: a report of 52 cases treated at a single institution. *Arch. Surg*. 1998; **133**: 242.

Other infections

Giardiasis is rarely associated with hepatic granulomas and cholangitis [3].

Campylobacter colitis can be related to a non-specific acute hepatitis [2].

Cat scratch disease is due to *Bartonella henselae*. It causes hepatic nodules, biopsy of which reveals necrotizing granulomas containing the organism [4]. CT shows focal hepatic defects and mediastinal and peri-portal lymphadenopathy.

Listeria monocytogenes can cause hepatic abscesses [1].

References

1 Jenkins D, Richards JE, Rees Y *et al*. Multiple listerial liver abscesses. *Gut* 1987: **28**: 1661.
2 Reddy KR, Farnum JB, Thomas E. Acute hepatitis associated with *Campylobacter* colitis. *J. Clin. Gastroenterol*. 1983; **5**: 259.
3 Roberts-Thomas JC, Anders RF, Bhathal PS. Granulomatous hepatitis and cholangitis associated with giardiasis. *Gastroenterology* 1982; **83**: 480.
4 Tompkins LS. Of cats, humans and *Bartonella*. *N. Engl. J. Med*. 1997; **337**: 1916.

Hepatic amoebiasis

Entamoeba histolytica exists in a vegetative form and as cysts, which survive outside the body and are highly infectious. The cystic form passes unharmed through the stomach and small intestine and changes into the vegetative, trophozoite form in the colon. Here, it invades the mucosa, forming typical flask-shaped ulcers. Amoebae are carried to the liver in the portal venous system. Occasionally, they pass through the hepatic sinusoids into the systemic circulation with the production of abscesses in lungs and brain.

Amoebae multiply and block small intra-hepatic portal radicles with consequent focal infarction of liver cells. They contain a proteolytic enzyme which destroys the liver parenchyma. The lesions produced are single or multiple and of variable size.

The amoebic abscess is usually about the size of an orange. The most frequent site is in the right lobe, often supero-anteriorly, just below the diaphragm. The centre consists of a large necrotic area which has liquefied into thick, reddish-brown pus. This has been likened to anchovy or chocolate sauce. It is produced by lysis of liver cells. Fragments of liver tissue may be recognized in it. Initially, the abscess has no well-defined wall, but merely shreds of shaggy, necrotic liver tissue. Histologically, the necrotic areas consist of degenerate liver cells, leucocytes, red blood cells, connective tissue strands and debris. Amoebae may be identified in scrapings. Hepatocyte death is by apoptosis, but not proceeding through Fas or tumour necrosis factor as pathways [6].

Small lesions heal with scars, but larger abscesses show a chronic wall of connective tissue of varying age.

The lesion is focal and liver away from the abscess or micro-abscesses is normal.

Only 10% of those harbouring the parasite develop invasive amoebiasis. Two species of entamoebae are found and one is non-pathogenic. The pathogenic may be distinguished from the non-pathogenic by DNA markers for antigens on the surface of the amoeba [4].

Secondary bacterial infection of the abscess occurs in about 20%. The pus then becomes green or yellow and foul smelling.

Epidemiology

Colonic amoebae have a worldwide distribution, but hepatic amoebiasis is a disease of the tropics and subtropics. Endemic areas are Africa, south-east Asia, Mexico, Venezuela and Colombia.

In temperate climates, symptomless carriers of toxic strains are found but colonic ulcers are not seen. It is a frequent commensal in homosexual men [3].

In the tropics a new arrival is heavily exposed, especially when sanitation is poor. Locals are less prone, presumably because of partial immunity induced by repeated contact.

The latent period between the intestinal infection and hepatic involvement has not been explained.

Clinical features

Residence in tropical or subtropical areas is noted. Amoebic dysentery is found in only 10% and cysts in the stool in only 15%. Past history of dysentery is rare. Hepatic amoebiasis has been recorded as long as 30 years after the primary infection. It is most frequent in young males. Multiple abscesses are frequent in such areas as Mexico and Taiwan.

The onset is usually *sub-acute* with symptoms lasting up to 6 months. Rarely it may be *acute* with rigors and sweating and a duration of less than 10 days. Fever is variously intermittent, remittent or even absent unless an abscess becomes secondarily infected; it rarely exceeds 40°C. Deep abscesses may present simply as fever without signs referable to the liver.

Jaundice is unusual and, if present, mild. Bile duct compression is rare.

The patient looks ill, with a peculiar sallowness of the skin, like faded suntan.

Pain in the liver area may commence as a dull ache, later becoming sharp and stabbing. If the abscess is near the diaphragm, there may be referred shoulder pain accentuated by deep breathing or coughing. Alcohol makes the pain worse, as do postural changes. The patient tends to lean to the left side; this opens up the right intercostal spaces and diminishes the tension on the liver capsule. The pain increases at night.

A swelling may be visible in the epigastrium or bulging the intercostal spaces. Hepatic tenderness is virtually constant. It may be elicited over a palpable liver edge or by percussion over the lower right chest wall. The spleen is not enlarged.

The lungs may show consolidation of the right lower zone, pleurisy or an effusion. Pleural fluid may be blood stained.

Examination of faeces. Cysts and vegetative forms are rare.

Serological tests

The fluorescent antibody test is positive and remains so for some time after clinical cure. Amoebic abscess is unlikely if the test is negative. Current tests do not distinguish acute from chronic amoebiasis. This may be possible using antibody responses to recombinant *E. histolytica* antigens [8].

Biochemical tests

In chronic cases, serum alkaline phosphatase values are usually about twice normal. Increases in transaminases are found only in those who are acutely ill or with severe complications. A rise in serum bilirubin is unusual except in those with superinfection or rupture into the peritoneum.

Radiological features

A chest X-ray may show a high right diaphragm, obliteration of the costophrenic and cardiophrenic angles by adhesions, pleural effusions or right basal pneumonia (fig. 29.6). A right lateral abscess may cause widening of the intercostal spaces. The liver shadow may be enlarged with a raised immobile right diaphragm. The abscess commonly causes a bulge in the antero-medial part of the right diaphragm.

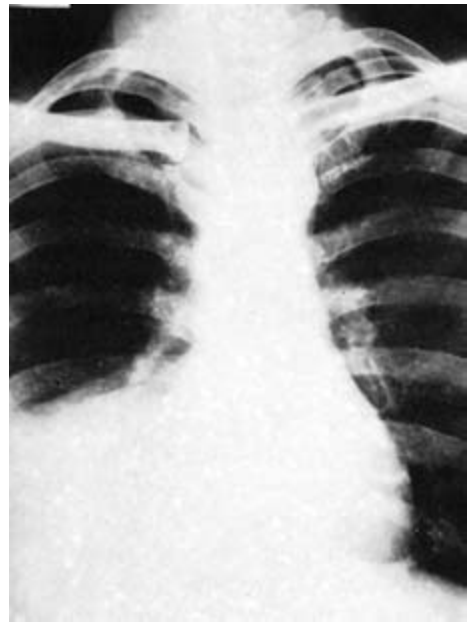


Fig. 29.6. Amoebic abscess of liver. Note the elevated right diaphragm with overlying reaction in the lung field.

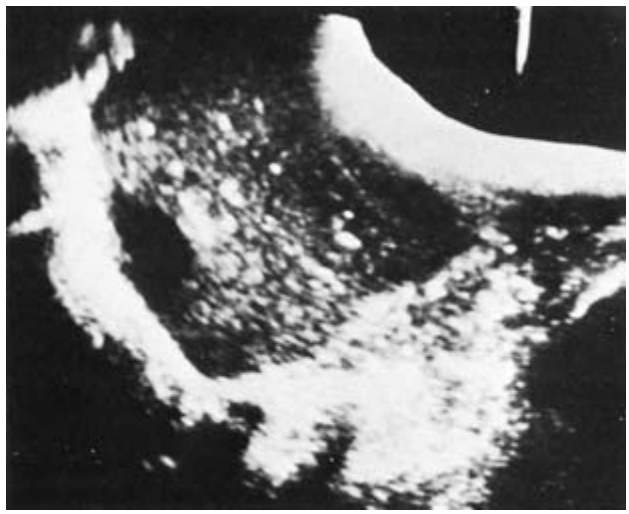
An abscess in the left lobe of the liver may show a crescentic deformity of the lesser curve of the stomach.

US is the most useful (fig. 29.7). *CT* shows the abscess with a somewhat irregular edge and low attenuation. It is more sensitive than US for small abscesses. It may show extra-hepatic involvement, for instance in the lung [5].

MRI can be used for diagnosis and to follow treatment [2]. Liquefaction of the cavity may be shown as early as 4 days after starting treatment [2].

Diagnostic criteria

- History of residence in an endemic area.
- An enlarged tender liver in a young male.
- Response to metronidazole.
- Leucocytosis without anaemia in those with a short history, and less marked leucocytosis and anaemia with a long history.
- Suggestive postero-anterior and lateral chest X-ray.
- Scanning showing a filling defect.
- A positive amoebic fluorescent antibody test.



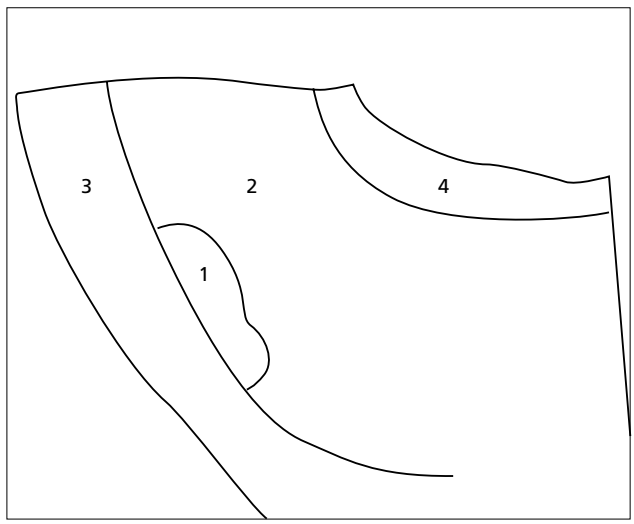


Fig. 29.7. Amoebic liver abscess. US demonstrates an amoebic abscess (1) in the liver (2), lying posteriorly against the diaphragm (3). The anterior abdominal wall (4) is also shown.

Complications

Rupture into the lungs or pleura causes empyema, hepato-bronchial fistula or pulmonary abscess. The patient coughs up pus, develops pneumonitis or lung abscess or a pleural effusion.

Rupture into the pericardium is a complication of amoebic abscess in the left lobe.

Intra-peritoneal rupture results in acute peritonitis. If the patient survives the initial effect, long-term results are good. Abscesses of the left lobe may perforate into the lesser sac.

Rupture into the portal vein, bile ducts or gastrointestinal tract is rare.

Secondary infection is suspected if prostration is particularly great, and fever and leucocytosis high. Aspiration reveals yellowish, often fetid, pus and culture reveals the causative organism.

Treatment

Metronidazole, 750 mg three times a day for 5–10 days, has a 95% success rate. An intravenous preparation is available. The time to defervescence is 3–5 days [1]. Failures may be related to the persistence of intestinal amoebiasis, drug resistance or inadequate absorption.

The time taken for the abscess to disappear depends on its size and varies from 10 to 300 days [7].

Aspiration is rarely necessary even with very large abscesses. It should be done under US or CT guidance. A tense abscess in the left lobe that is likely to rupture into the peritoneum demands aspiration. The mortality from amoebic liver abscess should be zero [1].

A course of oral amoebocide should be given to cover amoebae persisting in the gut.

References

1 Barnes PF, De Cock KM, Reynolds TB *et al*. A comparison of amebic and pyogenic abscess of the liver. *Medicine* 1987; **66**: 472.

2 Elizondo G, Weissleder R, Stark DD *et al*. Amebic liver abscess: diagnosis and treatment evaluation with MR imaging. *Radiology* 1987; **165**: 795.

3 Goldmeier D, Sargeaunt PG, Price AB *et al*. Is *Entamoeba histolytica* in homosexual men a pathogen? *Lancet* 1986; **i**: 641.

4 Katwinkel-Wladarsch S, Lascher T, Rinder H. Direct amplification and differentiation of pathogenic and nonpathogenic *Entamoeba histolytica* DNA from stool specimens. *Am. J. Trop. Med. Hyg*. 1994; **51**: 115.

5 Radin DR, Ralls PW, Colletti PM *et al*. CT of amebic liver abscess. *Am. J. Roentgenol*. 1988; **150**: 1297.
6 Seydel KB, Stanley SL Jr. *Entamoeba histolytica* induces host cell death in amoebic liver abscess by a non-Fas-dependent, nontumour necrosis factor alpha-dependent pathway of apoptosis. *Infect. Immun*. 1998; **66**: 2980.
7 Simjee AE, Patel A, Gathiram V *et al*. Serial ultrasound in amoebic liver abscess. *Clin. Radiol*. 1985; **36**: 61.
8 Stanley SL Jr, Jackson TF, Foster L *et al*. Longitudinal study of the antibody response to recombinant *Entamoeba histolytica* antigens in patients with amoebic liver abscess. *Am. J. Trop. Med. Hyg*. 1998; **58**: 414.

Tuberculosis of the liver

Abdominal tuberculosis is suspected in immigrants from developing countries and also increasingly in patients with AIDS [4].

The liver may be involved as part of miliary tuberculosis or as local tuberculosis where evidence of extra-hepatic disease is not obvious. Rarely, hepatic tuberculosis can cause fulminant liver failure [5].

The basic lesion is the *granuloma* which is very frequent in the liver in both pulmonary and extrapulmonary tuberculosis (fig. 29.8) (Chapter 28). The lesions usually heal without scarring but sometimes with focal fibrosis and calcification.

Pseudo-tumoral hepatic *tuberculomas* are rare [1]. There may be no evidence of extra-hepatic tuberculosis [2]. The tuberculomas may be multiple, consisting of a white, irregular, caseous abscess surrounded by a fibrous capsule (fig. 29.9). Their naked eye distinction from Hodgkin's disease, secondary carcinoma or actinomycosis may be difficult. Occasionally, the necrotic area calcifies.

Tuberculous cholangitis is extremely rare, resulting from spread of caseous material from the portal tracts into the bile ducts.

Biliary stricture is a rare complication [3].

Tuberculous pylephlebitis results from rupture of caseous material. It is usually rapidly fatal although chronic portal hypertension can result [8].

Tuberculous glands at the hilum may lead rarely to biliary obstruction.

Clinical features

These may be few or absent. The condition may present as a pyrexia of unknown origin. Jaundice may appear in overwhelming miliary tuberculosis, particularly in the racially susceptible. Rarely, multiple caseating granulomas lead to massive hepatosplenomegaly and death in liver failure [5].

Biochemical tests

Serum globulin is increased so that the albumin/globulin ratio is reduced. Alkaline phosphatase is disproportionately elevated [2].

Diagnosis

This is difficult. Tuberculomas in liver and spleen are difficult to differentiate from lymphoma. Liver biopsy is essential. The indications are unexplained fever and weight loss with hepatomegaly or hepatosplenomegaly. A portion of the biopsy should be stained for acid-fast bacilli and cultured. Positives are obtained in about 50%.

A *plain X-ray* of the abdomen may reveal hepatic calcification. This may be multiple and confluent in tubercu-

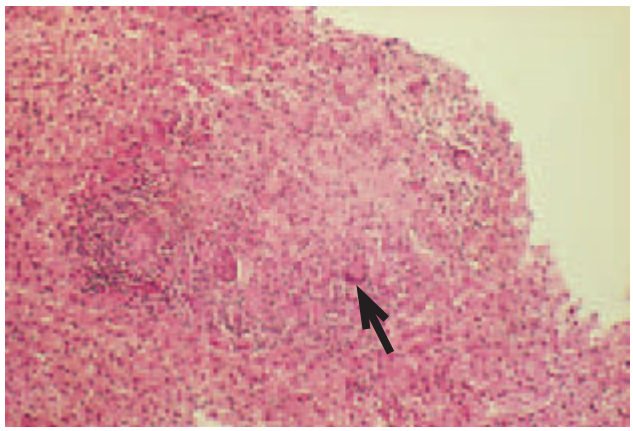


Fig. 29.8. Miliary tuberculosis: a caseating granuloma contains lymphocytes, epithelial cells and numerous giant cells (arrow). There is central caseation.

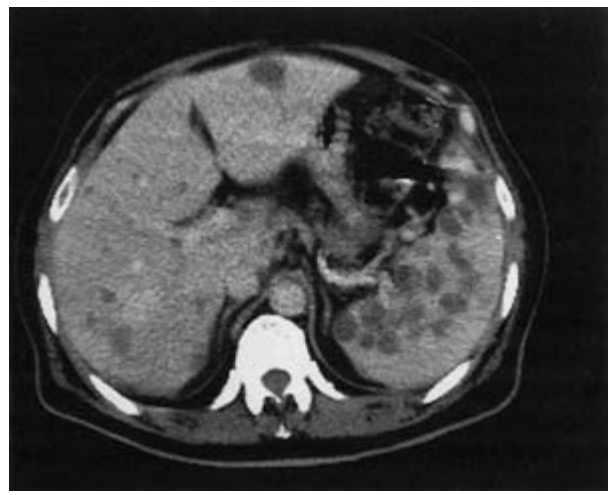


Fig. 29.9. Hepato-splenic tuberculosis. CT scan showing scattered filling defects in the liver and spleen. Aspirate showed acid-fast bacilli and the culture was positive.

loma, discrete and scattered and of uniform size, or large and chalky adjoining a stricture in the common bile duct [6].

CT may show a lobulated mass or multiple filling defects in liver and spleen (fig. 29.9).

Extra-hepatic features of tuberculosis may not be obvious.

Treatment is that for haematogenous tuberculosis.

The effect on the liver of tuberculosis elsewhere

Amyloidosis may complicate chronic tuberculosis. Fatty change is due to wasting and toxaemia. Drug jaundice may follow therapy, especially with isoniazid, rifampicin and pyrazinamide.

Other mycobacteria

Atypical mycobacteria can produce a granulomatous hepatitis, particularly as part of the AIDS syndrome (see p. 26). *Mycobacterium scrofulaceum* can cause a granulomatous hepatitis, characterized by a rise in alkaline phosphatase, tiredness and low-grade fever. Liver biopsy culture produces the organism [7].

References

1 Achem SR, Kolts BE, Grisnik J *et al*. Pseudotumoral hepatic tuberculosis. Atypical presentation and comprehensive review of the literature. *J. Clin. Gastroenterol*. 1992; **14**: 72.
2 Chien R-N, Lin P-Y, Liaw Y-F. Hepatic tuberculosis: comparison of miliary and local form. *Infection* 1995; **23**: 5.
3 Fan ST, Ng IOL, Choi TK *et al*. Tuberculosis of the bile duct: a rare cause of biliary stricture. *Am. J. Gastroenterol*. 1989; **84**: 413.
4 Guth AA, Kim U. The reappearance of abdominal tuberculosis. *Surg. Gynecol. Obstet*. 1991; **172**; 432.
5 Hussain W, Mutimer D, Harrison R *et al*. Fulminant hepatic failure caused by tuberculosis. *Gut* 1995; **36**: 792.
6 Maglinte DDT, Alvarez SZ, Ng AC *et al*. Patterns of calcifications and cholangiographic findings in hepatobiliary tuberculosis. *Gastrointest. Radiol*. 1988; **13**: 331.
7 Patel KM. Granulomatous hepatitis due to *Mycobacterium scrofulaceum*: report of a case. *Gastroenterology* 1981; **81**: 156.
8 Ruttenberg D, Graham S, Burns D *et al*. Abdominal tuberculosis—a cause of portal vein thrombosis and portal hypertension. *Dig. Dis. Sci*. 1991; **36**: 112.

Hepatic actinomycosis

Hepatic involvement due to *Actinomyces israeli* is a sequel to intestinal actinomycosis, especially of the caecum and appendix. It spreads by direct extension or, more often, by the portal vein, but can be primary. Large greyish-white masses, superficially resembling malignant metastases, soften and form collections of pus, separated by fibrous tissue bands, simulating a honeycomb. The liver becomes adherent to adjacent viscera and to the abdominal wall, with the formation of sinuses. These lesions contain the characteristic 'sulphur granules', which consist of branching filaments with eosinophilic, clubbed ends.

Clinical features

The patient is toxic, febrile, sweating, wasted and anaemic. There is local, sometimes irregular, enlargement of the liver with tenderness of one or both lobes. The overlying skin may have the livid, dusky hue seen over a taut abscess that is about to rupture. Multiple irregular sinus tracks develop. Similar sinuses may develop from the ileo-caecal site or from the chest wall if there is pleuro-pulmonary extension.

Diagnosis

The diagnosis is obvious at the stage of sinus tracts, because the organism can be isolated from the pus. If actinomycosis is suspected before this stage, percutaneous liver biopsy may reveal sulphur granules with organisms [1].

Early presentation is as pyrexia, hepatosplenomegaly and anaemia. It may be months before multiple abscesses are detected, often by US, CT [3] or MRI [4]. Anaerobic blood cultures may be positive.

Treatment

Intravenous penicillin is given in massive doses. Because of the thick capsule, the penicillin may reach the abscess with difficulty. Surgical resection may be necessary [2].

References

1 Bhatt BD, Zuckerman MJ, Ho H *et al*. Multiple actinomycotic abscesses of the liver. *Am. J. Gastroenterol*. 1990; **85**: 309.
2 Kasano Y, Tanimura H, Yamaue H *et al*. Hepatic actinomycosis infiltrating the diaphragm and right lung. *Am. J. Gastroenterol*. 1996; **91**: 2418.
3 Mongiardo N, De Rienzo B, Zanchetta G *et al*. Primary hepatic actinomycosis. *J. Infect*. 1986; **12**: 65.
4 Nazarian LN, Spencer JA, Mitchell DG. Multiple actinomycotic liver abscesses: MRI appearances with aetiology suggested by abdominal radiography. Case report. *Clin. Imaging* 1994; **18**: 119.

Other fungal infections

These usually affect the immunocompromised, including sufferers from AIDS, acute leukaemia [6], cancer [10] and following liver transplant.

The liver is involved, together with other organs, particularly kidney, spleen, heart, lungs and brain. Fever

with a raised serum transaminase or alkaline phosphatase indicates needle liver biopsy.

US shows multiple hypoechoic areas throughout the liver and spleen, often with a target (bull's eye) configuration [8]. *CT* shows multiple, non-enhancing, low-attenuation lesions [6]. The scanning appearances are not diagnostic.

The histological picture is usually granulomatous and the causative organism can be identified by appropriate stains and cultures, so allowing selection of appropriate antifungal treatment [4, 5].

Candidiasis. The liver is affected in up to three-quarters of those with disseminated *Candida albicans* infection who come to autopsy [5]. Hepatic granulomas and micro-abscesses are the commonest histological lesions. *Candida* can be demonstrated in the liver [2]. The treatment is with fluconazole.

Disseminated aspergillosis may attack the immunocompromised patients with respiratory, renal or hepatic failure [7].

Hepatic cryptococcosis usually affects the immunocompromised but sometimes it may be seen in the otherwise normal. Liver biopsy shows granulomas with yeast-like organisms.

The picture may resemble sclerosing cholangitis when bile is positive for the fungus (Chapter 15).

Disseminated coccidioidomycosis may involve the liver and be diagnosed by liver biopsy [3].

Torulopsis glabrata hepatic abscesses and fungaemia have developed in a severely diabetic patient with biliary stricture due to chronic pancreatitis [1].

Blastomyces dermatitidis can cause cholangitis in the elderly or immunocompromised [9].

References

1 Friedman E, Blahut RJ, Bender MD. Hepatic abscesses and fungemia from *Torulopsis glabrata*. Successful treatment with percutaneous drainage and amphotericin B. *J. Clin. Gastroenterol*. 1987; **9**: 711.

2 Gordon SC, Watts JC, Veneri RJ *et al*. Focal hepatic candidiasis with perihepatic adhesions: laparoscopic and immunohistologic diagnosis. *Gastroenterology* 1990; **98**: 214.

3 Howard PF, Smith JW. Diagnosis of disseminated coccidioidomycosis. *Arch. Intern. Med*. 1983; **143**: 1335.

4 Korinek JK, Guarda LA, Bolivar R *et al*. *Trichosporon* hepatitis. *Gastroenterology* 1983; **85**: 732.

5 Lewis JH, Patel HR, Zimmerman HJ. The spectrum of hepatic candidiasis. *Hepatology* 1982; **2**: 479.

6 Maxwell AJ, Mamtora H. Fungal liver abscesses in acute leukaemia—a report of two cases. *Clin. Radiol*. 1988; **39**: 197.

7 Park GR, Drummond GB, Lamb D *et al*. Disseminated aspergillosis occurring in patients with respiratory, renal and hepatic failure. *Lancet* 1982; **i**: 179.

8 Pastakia B, Shawker TH, Thaler M *et al*. Hepatosplenic candidiasis: wheels within wheels. *Radiology* 1988; **166**: 417.

9 Ryan ME, Kirchner JP, Sell T *et al*. Cholangitis due to *Blastomyces dermatitidis*. *Gastroenterology* 1989; **96**: 1346.

10 Thaler M, Pastakia FB, Shawker TH *et al*. Hepatic candidiasis in cancer patients: the evolving picture of the syndrome. *Ann. Intern. Med*. 1988; **108**: 88.

Syphilis of the liver

Congenital

The liver is heavily infected by any trans-placental infection. It is firm, enlarged and swarming with spirochaetes. Initially, there is a diffuse hepatitis, but gradually fibrous tissue is laid down between the liver cells and in the portal zones, and this leads to a true peri-cellular cirrhosis.

Since hepatic involvement is but an incident in a widespread spirochaetal septicaemia, the clinical features are seldom those of the liver disease. The fetus may be stillborn or die soon after birth. If the infant survives, other manifestations of congenital syphilis are obvious, apart from the hepatosplenomegaly and mild jaundice. Syphilis nowadays rarely causes neonatal jaundice.

In older children who have survived without this florid neonatal picture, the hepatic lesion may be a gumma.

Diagnosis can be confirmed by blood serology which is always positive.

Secondary

In the secondary septicaemic stage, spirochaetes produce miliary granulomas [1].

Fifty per cent of sufferers have raised serum enzyme levels [4]. Clinical hepatitis is rare. However, sometimes the picture is of severe cholestatic jaundice [2].

Serology is positive. Serum alkaline phosphatase levels are high. The M1 cardiolipin fluorescent anti-mitochondrial antibody is positive and becomes normal with recovery [2].

Liver biopsy shows non-specific changes with moderate infiltration with polymorphs and lymphocytes, and some hepato-cellular disarray, but cholestasis is absent or mild except in the severely cholestatic patients [2]. Portal-to-central zone necrosis can be seen (fig. 29.10). Spirochaetes are sometimes detected in the liver biopsy.

Tertiary

Gummas may be single or multiple. They are usually in the right lobe. They consist of a caseous mass with a fibrous capsule. Healing is followed by deep scars and coarse lobulation (*hepar lobatum*).

Hepatic gummas are usually diagnosed incidentally, by US or CT, at surgery or at autopsy. US-guided biopsy

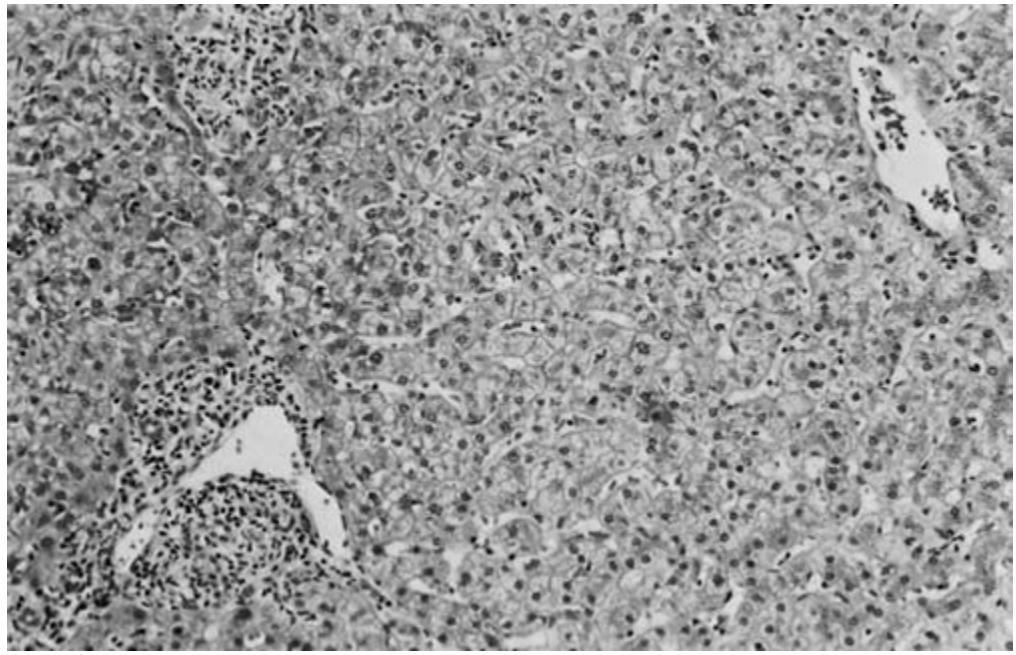


Fig. 29.10. Liver in secondary syphilis. Mononuclear cell infiltration can be seen in portal zones and in the sinusoids. (H & E, ×160.)

of a nodule shows aseptic necrosis, granulomas and spirochaetes [3]. Serology is positive. Antibiotic treatment is successful.

Jaundice complicating penicillin treatment

Rarely, the patient shows an idiosyncrasy to penicillin. Jaundice, chills and fever, often with a rash (*erythema of Milan*), occur about 9 days after starting therapy. This is part of the Herxheimer reaction. The mechanism of the jaundice is unclear.

References

1 Case Records of the Massachusetts General Hospital. Case 27, 1983. *N. Engl. J. Med*. 1983; **309**: 35.
2 Comer GM, Mukherjee S, Sachdev RK *et al*. Cardiolipin-fluorescent (M1) antimitochondrial antibody and cholestatic hepatitis in secondary syphilis. *Dig. Dis. Sci*. 1989; **34**: 1298.
3 Maincent G, Labadie H, Fabre M *et al*. Tertiary hepatic syphilis. A treatable cause of multinodular liver. *Dig. Dis. Sci*. 1997; **42**: 447.
4 Schlossberg D. Syphilitic hepatitis: a case report and review of the literature. *Am. J. Gastroenterol*. 1987; **82**: 552.

Leptospirosis

Pathogenic *Leptospira* related to human disease can be classified by DNA typing into at least 200 serovarieties belonging to 23 subtypes [9]. The disease due to *Leptospira icterohaemorrhagiae* was described by Weil in 1886 [8]. It is a severe infection spread by the urine of infected rats. The whole group of leptospiral infections should be designated leptospirosis.

Weil's disease

Mode of infection

Living *Leptospira* are continually excreted in the urine of infected rats and survive for months in pools, canals, flood water or damp soil. The patient is infected by contaminated water or by direct occupational contact with infected rats. Those affected include agricultural and sewer workers and fish cutters. Deteriorating cities in Europe and Asia, where rat populations are expanding, provide a source of infection [6].

Pathology

Histopathological changes are slight in relation to the marked functional impairment of kidneys and liver. The damage is at a subcellular level. An endotoxin-like substance in the wall of spirochaetes has been suggested. Plasma tumour necrosis factor-α (TNF-α) levels have been related to the severity of organ involvement [5].

Liver [2] necrosis is minimal and focal. Zone 3 necrosis is absent. Active hepato-cellular regeneration, shown by mitoses and nuclear polyploidy, is out of proportion to cell damage. Swollen Kupffer cells contain leptospiral debris. Leukocyte infiltration and bile thrombi are prominent in the deeply jaundiced. Cirrhosis is not a sequel.

Kidney shows tubular necrosis. *Skeletal muscle* shows punctate haemorrhages and focal necrosis.

Heart may show haemorrhages in all layers.

Haemorrhages into tissues, especially skin and lungs, is due to papillary injury and thrombocytopenia.

Jaundice is related to hepatocyte dysfunction magnified by renal failure impairing urinary bilirubin excretion. Tissue haemorrhages and haemolysis increase the bilirubin load on the liver. Hypotension with diminished hepatic blood flow contributes.

Kidney failure is related to impaired renal perfusion.

Clinical features (fig. 29.11)

The clinical picture is not pathognomonic and the disease is heavily underdiagnosed. It is more often anicteric than icteric. The disease is most prevalent in late summer and autumn. The incubation period is 6–15 days. The course may be divided into three stages: the first or septicaemic phase lasts for about 7 days, the second or toxic stage for a similar period, and the third or convalescent period begins in the third week.

The first or septicaemic stage is marked by the presence of the spirochaete in the circulating blood.

The onset is abrupt, with prostration, high fever and even rigors. The temperature rises rapidly to 39.5–40.5°C and falls by lysis within 3–10 days.

Abdominal pain, nausea and vomiting may simulate an acute abdominal emergency, and severe muscular pains, especially in the back or calves, are common.

Central nervous system involvement is shown by severe headache, mental confusion and sometimes meningism. The cerebrospinal fluid confirms the meningeal infection. If jaundice is present, there is xanthochromia.

The eyes show a characteristic suffusion.

In those with a severe attack, bleeding may occur from nose, gut or lung, with skin petechiae or ecchymoses.

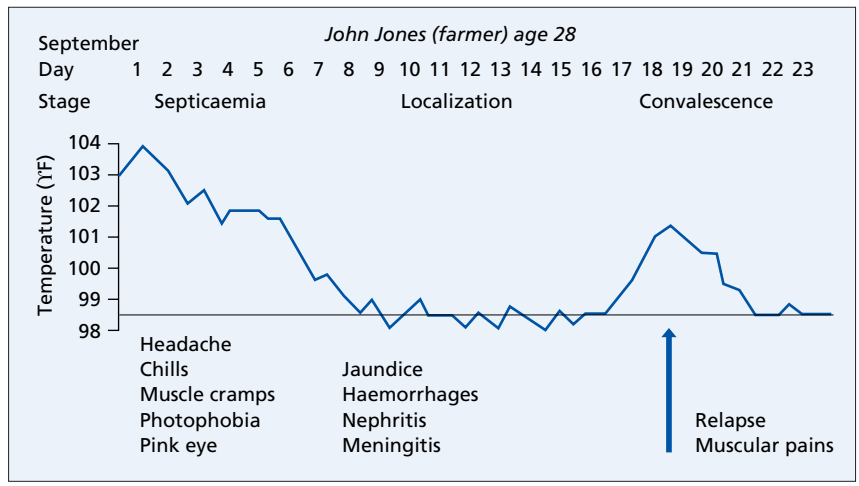
Pneumonitis with cough, sore throat and rhonchi occurs in 40% of sufferers.

Jaundice appears between the fourth and seventh day in 80% of patients. It is a grave sign, for the disease is never fatal in the absence of icterus. The liver is enlarged, but not the spleen.

The urine shows albumin and bile pigment. The stools are well coloured.

There is a leucocytosis of 10 000–30 000/mm^3 with a relative increase in polymorphs. Thrombocytopenia may be profound.

The second or immune stage in the second week is char-



Blood							
organisms	+ + + + + + ± 0						
antibodies			1:75	1:300		1:2400	
WBC	18 000 (80% polys)						8000
Bilirubin (mg)	2	5	10	14	3	2	0.5
Urea (mg)	30	70	130	210	50	40	30
BP	130/60	130/70	100/60	90/50	110/60	120/70	
Urine							
volume (ml)	700	800	500	100	1100	900	1500
albumin	+	++	+++	+++	++	+	++
organisms			0	+	++	+	0

Fig. 29.11. The clinical course of a patient with Weil's disease.

acterized by a normal temperature but without clinical improvement. This is the stage of deepening jaundice, with increasing renal and myocardial failure. Albuminuria persists, there is a rising blood urea, and oliguria may proceed to anuria. Death may be due to renal failure. A markedly elevated creatinine phosphokinase level reflects myositis.

Severe prostration is accompanied by a low blood pressure and a dilated heart. There may be transient cardiac dysrhythmias and electrocardiograms may show a prolonged P–R or Q–T interval, with T-wave changes. Death may be due to circulatory failure.

During this stage, the *Leptospira* can be found in the urine, and rising antibody titres demonstrated in the serum.

The third or convalescent stage starts at the beginning of the third week. Clinical improvement is shown by a brightening of the mental state, fading of the jaundice, a rise in blood pressure and an increased urinary volume, with a drop in the blood urea concentration. Albuminuria is slow to disappear.

Temperature may rise during the third week (fig. 29.11), associated with muscle pains. Such relapses occur in 20% of cases.

There is great variation in the clinical course ranging from a mild illness, clinically indistinguishable from influenza, to a prostrating, fatal disease with anuria.

Diagnosis

Before the appearance of antibodies, PCR demonstration of *Leptospira* is the best method of diagnosis [3].

Rising titres of antibodies are sought by Dot-ELISA [4] or immunofluoroscence [1]. The microscopic agglutination test is too complex for routine use.

Leptospira may be cultured from blood during the first 10 days. Urine cultures are positive during the second week and persist for several months.

Liver function tests are non-contributory.

Differential diagnosis

In the early stages, Weil's disease is confused with septicaemic bacterial infections or typhus fever. When jaundice is evident acute viral hepatitis must be excluded (table 29.1). Important distinguishing points are the sudden-onset increased polymorph count and albuminuria of Weil's disease.

Spirochaetal jaundice would be diagnosed more often if blood samples for antibodies were taken from patients with obscure icterus and fever.

Prognosis

Mortality is about 5%. This depends on the depth of jaundice, renal and myocardial involvement, and the extent of haemorrhages. Death is usually due to renal failure. The mortality is negligible in non-icteric patients, and is lower in those under 30 years old. Since many mild infections are probably unrecognized, the overall mortality may be considerably less.

Although transient relapses in the third and fourth weeks are common, final recovery is complete.

Table 29.1. The differential diagnosis of Weil's disease from viral hepatitis during the first week of illness

	Weil's disease	Viral hepatitis
Onset	Sudden	Gradual
Headache	Constant	Occasional
Muscle pains	Severe	Mild
Conjunctival injection	Present	Absent
Prostration	Great	Mild
Disorientation	Common	Rare
Haemorrhagic diathesis	Common	Rare
Nausea and vomiting	Present	Present
Abdominal discomfort	Common	Common
Bronchitis	Common	Rare
Albuminuria	Present	Absent
Leucocyte count	Polymorph leucocytosis	Leucopenia with lymphocytosis

Prevention

Protective clothing should be provided for workers in industries with a high incidence of Weil's disease, and adequate measures taken to control rodents. Bathing in stagnant water should be avoided.

Treatment

Early, mild leptospirosis is treated by doxycycline (100 mg by mouth) twice daily for 1 week. More seriously ill patients, particularly with vomiting, are given intravenous penicillin G 6 million units/day for 1 week [7].

Prognosis is improving with earlier diagnosis, attention to fluid and electrolyte balance, renal dialysis, antibiotics and circulatory support.

Other types of leptospirosis

In general these infections are less severe than those due to *L. icterohaemorrhagiae*. *L. canicola* infection, for instance, is characterized by headache, meningitis and conjunctival infection. Albuminuria is only found in 40%, and jaundice in only 18% of patients. The frequent presentation is that of 'benign aseptic meningitis'. The disease affects young adults who have usually been in close

contact with an infected dog. Fatalities in man are virtually unknown.

Diagnosis is confirmed in a similar way to Weil's disease. A convenient method is rising antibody titres. The spinal fluid shows a lymphocytic picture in most cases.

References

1 Appassakij H, Silpapojakul K, Wansit R *et al*. Evaluation of the immunofluorescent antibody test for the diagnosis of human leptospirosis. *Am. J. Trop. Med. Hyg.* 1995; **52**; 340.
2 Arean VM. The pathologic anatomy and pathogenesis of fatal human leptospirosis (Weil's disease). *Am. J. Pathol*. 1962; **40**: 393.
3 Brown PD, Gravekamp C, Carrington DG *et al*. Evaluation of the polymerase chain reaction for early diagnosis of leptospirosis. *J. Med. Microbiol*. 1995; **43**: 110.
4 Ribeiro MA, Souza CC, Almeida SH *et al*. Dot-ELISA for human leptospirosis employing immunodominant antigen. *J. Trop. Med. Hyg*. 1995; **98**: 452.
5 Tajiki H, Salomao R. Association of plasma levels of tumour necrosis factor alpha—with severity of disease and mortality among patients with leptospirosis. *Clin. Infect. Dis.* 1996; **23**: 1177.
6 Vinetz JM, Glass GE, Flexner CE *et al*. Sporadic urban leptospirosis. *Ann. Intern. Med*. 1996; **125**: 794.
7 Watt G, Padre LP, Tuazon ML *et al*. Placebo-controlled trial of intravenous penicillin for severe and late leptospirosis. *Lancet* 1988; **i**: 433.
8 Weil A. Über eine eigenthumliche mit Milztumour, Icterus and Nephritis einhergehene, acute Infektionskrankheit. *Dtsch. Arch. Klin. Med*. 1886; **39**: 209.
9 Zuerner RL, Alt D, Bolin CA. IS*1533*-based PCR assay for identification of *Leptospira interrogans* sensu lato serovars. *J. Clin. Microbiol*. 1995; **33**: 3284.

Relapsing fever

This arthropod-borne infection is caused by spirochaetes of the species *Borrelia recurrentis*. It is encountered throughout the world except in New Zealand, Australia and some parts of the west Pacific.

The *Borrelia* multiply in the liver, invading liver cells and causing focal necrosis. Just before the crisis the *Borrelia* roll up and are ingested by reticulo-endothelial cells. This effect is related to immunologically competent lymphocytes. Surviving *Borrelia* remain in the liver, spleen, brain and bone marrow until the next relapse [2].

Clinical features [1]

The incubation period is 3–15 days. The onset is acute with chills, a continuous high temperature, headache, muscle pains and profound prostration. The patient is flushed, sometimes with injected conjunctivae, and epistaxes. In severe attacks, tender hepatosplenomegaly and jaundice develop. The jaundice is similar to that of Weil's disease. Sometimes a rash develops on the trunk. There may be bronchitis.

These symptoms continue for 4–9 days and then the temperature falls, often with collapse of the patient. This peripheral collapse may be fatal, but more usually the symptoms and signs then rapidly abate, the patient remains afebrile for about 1 week, when there is a relapse. There may be a second or even a third milder relapse before the disease ends.

Diagnosis

Spirochaetes can rarely be found in thick blood films. Agglutination and complement fixation tests are available [2]. Organisms may be identified by lymph node aspiration, or from the insect bite site.

Treatment

Tetracyclines and streptomycin are more effective than penicillin. Mortality is 5%.

References

1 Bryceson ADM, Parry EHO, Perine PL *et al*. Louse-born relapsing fever: a clinical and laboratory study of 62 cases in Ethiopia and a reconsideration of the literature. *Q. J. Med*. 1970; **39**: 129.
2 Felsenfeld O, Wolf RH. Immunoglobulins and antibodies in *Borrelia turicetae* infections. *Acta Trop*. 1969; **26**: 156.

Lyme disease

This is due to a tick-borne spirochaete *Borrelia burgdorferi*. It has caused hepatitis with numerous liver cell mitoses [1]. Mild liver function test abnormalities are frequent in the early erythema migrans stage, but these resolve with antibiotic treatment [2]. Lyme disease does not seem to cause permanent hepatic sequelae.

References

1 Goellner MH, Agger WA, Burgess JH *et al*. Hepatitis due to recurrent Lyme disease. *Ann. Intern. Med*. 1988; **108**: 707.
2 Horowitz HW, Dworkin B, Forseter G *et al*. Liver function in early Lyme disease. *Hepatology* 1996; **23**: 1412.

Q fever

This rickettsial disease has predominantly pulmonary manifestations. Occasionally hepatitis may be prominent and clinical features may mimic anicteric viral hepatitis [2, 3].

The liver shows a granulomatous hepatitis. Portal areas contain abundant lymphocytes and the limiting plate is destroyed. Kupffer cells are hypertrophied. The

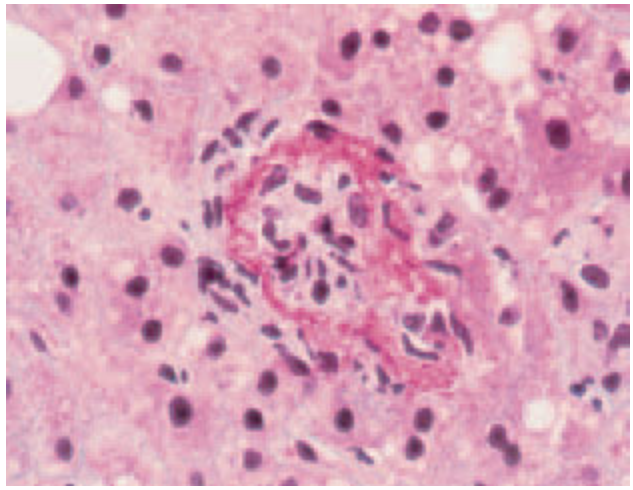


Fig. 29.12. Liver biopsy in Q fever showing a granuloma with fibrin rings having a clear centre. (Martius scarlet blue, ×350.)

granulomas have a characteristic ring of fibrinoid necrosis surrounded by lymphocytes and histiocytes. In the centre of the granuloma is a clear space giving a 'doughnut' appearance (fig. 29.12). The diagnosis is made by showing a rising titre of complement-fixing antibodies to *Coxiella burnetii* 2–3 weeks after the infection.

Rocky mountain spotted fever

Jaundice and rises in serum enzymes sometimes occur. Liver histology shows portal zone inflammation with large mononuclear cells. Hepato-cellular necrosis is inconspicuous but erythrophagocytosis is marked. Rickettsiae may be demonstrated in the portal zones by immunofluorescence microscopy [1].

References

1 Adams JS, Walker DH. The liver in rocky mountain spotted fever. *Am. J. Clin. Pathol*. 1981; **75**: 156.
2 Dupont HL, Hornick RB, Levin HS *et al*. Q fever hepatitis. *Ann. Intern. Med*. 1971; **74**: 198.
3 Tissot-Dupont H, Raoult D, Brouquil P *et al*. Epidemiologic features and clinical presentation of acute Q fever in hospitalized patients: 323 French cases. *Am. J. Med*. 1992; **93**: 427.

Schistosomiasis (bilharziasis)

Hepatic schistosomiasis is usually a complication of the intestinal disease, since emboli of *Schistosoma* ova reach the liver from the intestines via the mesenteric veins. *S. mansoni* and *S. japonicum* affect the liver. *S. haematobium* can sometimes involve the liver.

Schistosomiasis affects more than 200 million people in 74 countries. *S. japonicum* is prevalent in Japan, China, Indonesia and the Philippines. *S. mansoni* is found in Africa, the Middle East, the Caribbean and Brazil [4].

Pathogenesis

Eggs, excreted in the faeces, hatch out in water to release free-swimming embryos which enter appropriate snails and develop into fork-tailed cercariae. These re-enter human skin in contact with infected water. They burrow down to the capillary bed, whence there is widespread haematogenous dissemination. Those reaching the mesenteric capillaries enter the intra-hepatic portal system, where they grow rapidly.

The extent and severity of chronic liver disease correlates with the intensity and duration of egg production and hence with the number of eggs excreted. Adult male and female worms can exist for about 5 years producing 300–3000 eggs daily in portal venules. If liver disease is advanced, faecal egg counts may fall because of senescence of adult worms or previous therapy.

S. japonicum is more pathogenic than *S. mansoni* and produces hepatosplenic schistosomiasis more often and faster.

In the liver, the ova penetrate and obstruct the portal branches and are deposited either in the large radicles, producing the coarser type of bilharzial hepatic fibrosis, or in the small portal tracts, producing the fine diffuse form.

The granulomatous reaction to the *Schistosoma* ovum is of delayed hypersensitivity type, related to antigen released by the egg. TH0- and TH2-type helper lymphocytes play an important role in granuloma formation [10].

Portal fibrosis is related to the adult worm load. The classic, clay-pipestem cirrhosis is due to fibrotic bands originating from the granulomas.

Early on, cytokines, formed from granulomas around ova, may play a central role in fibrogenesis [7]. Fibrosis may be slowly reversible with treatment.

Wide, irregular, thin-walled arteriolar spaces are found in 85% of cases in the thickened portal tracts. These angiomatoids are useful in distinguishing the bilharzial liver from other forms of hepatic fibrosis. Remnants of ova are also diagnostic. There is little or no bile duct proliferation. Nodular regeneration and disturbance of the hepatic architecture is not sufficient to justify the term 'cirrhosis'.

In areas where schistosomiasis, hepatitis virus B and C coexist, a mixed picture of schistosomal fibrosis with cirrhosis may be seen.

Splenic enlargement is mainly due to portal venous hypertension and reticulo-endothelial hyperplasia. Very few ova are found in the spleen. Portal-systemic collateral channels are numerous.

There are associated bilharzial lesions in the intestines

and elsewhere. Fifty per cent of patients with rectal schistosomiasis have granulomas in the liver.

Clinical features

Schistosomiasis shows three stages. Itching follows the entry of the cercariae through the skin. This is followed by a stage of fever, urticaria and eosinophilia. Finally, the third stage of deposition of ova results in intestinal, urinary and hepatic involvement.

Initially, the liver and spleen are firm, smooth and easily palpable. This is followed by hepatic fibrosis and eventually portal hypertension which may appear years after the original infection.

Oesophageal varices develop. Bleeding episodes are recurrent but rarely fatal.

The liver shrinks in size and the spleen becomes much larger. Dilated abdominal wall veins and a venous hum over the liver are indications of the portal venous obstruction. Ascites and oedema may develop. The blood shows leucopenia and anaemia. The faeces at this stage contain few, if any, parasites.

Patients tolerate blood loss well and hepatic encephalopathy is unusual. Hepato-cellular function remains good although there is a large porto-systemic collateral circulation.

Aspiration liver biopsy (fig. 29.13). Eggs or their remnants are seen in 94% of livers from those with faecal eggs.

Remnants of ova may be seen but appearances are not usually diagnostic and the liver biopsy mainly excludes other types of liver disease.

Diagnostic tests

Detection of ova in urine, stool or rectal mucosal biopsy (rectal 'snip') is still the accepted method of diagnosing active infection (fig. 29.14). Bleeding may be a complication of rectal biopsy in those with portal hypertension. *Serological antibody tests* indicate past exposure without specifying the time.

Detection of circulating schistosomal antigen indicates active disease. An ELISA for detecting circulating soluble egg antigens in serum correlates with egg output. A reagent strip assay is based on glycoconjugates for adult schistosomes [9].

CT shows dense bands following the portal vein to the liver edge; these enhance with contrast [5].

US shows greatly thickened portal veins (fig. 29.15). It may be used to grade fibrosis [1]. Liver, spleen, periportal and pancreatic lymph nodes are diffusely enlarged without evidence of portal hypertension.

Colour Doppler shows an increase in blood flow

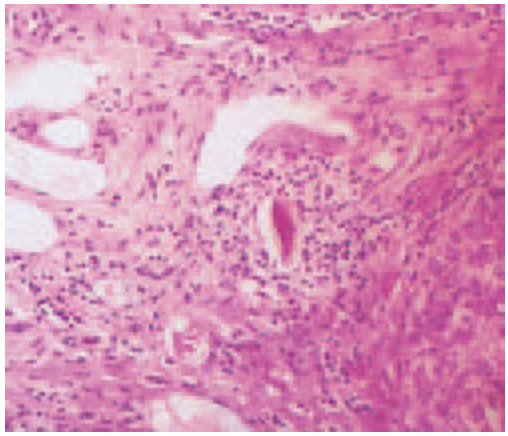


Fig. 29.13. Bilharzial liver. An ovum of *S. mansoni* has lodged in a portal tract which shows a granulomatous reaction. (H & E, ×64.)

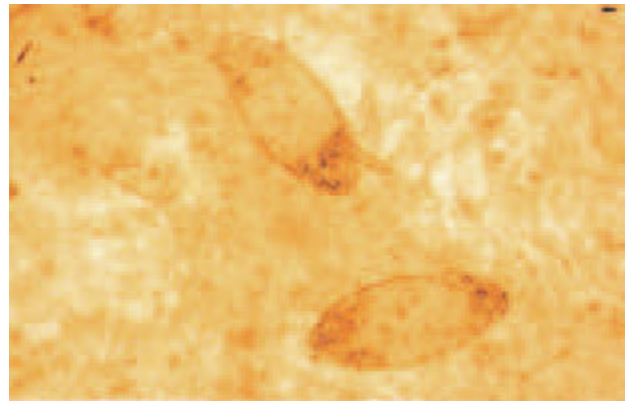


Fig. 29.14. Rectal ('snip') biopsy in schistosomiasis mansoni. A 'squash' preparation in glycerol reveals the ova of *S. mansoni*.

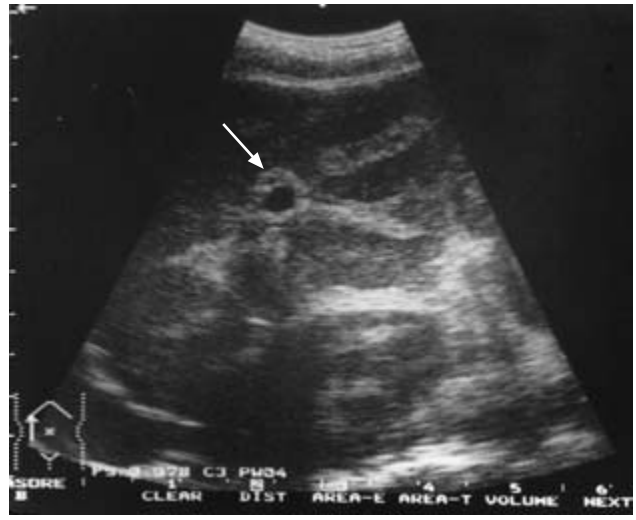


Fig. 29.15. Schistosomiasis: US shows bright portal tracts and a portal vein with greatly thickened walls (arrow).

velocity in the portal and superior mesenteric varices and the development of collaterals [8].

Portal hypertension

This is pre-sinusoidal and related to the portal granulomas. As the portal venous blood flow falls, hepatic arterial blood flow increases so that total hepatic blood flow is not significantly reduced. Retrograde flow develops in the portal vein [2].

At the stage of haemorrhage from varices the granulomatous reaction may have subsided and the picture is predominantly that of fibrosis.

Biochemical changes

Serum alkaline phosphatase may be raised. Hypoalbuminaemia can be related to poor nutrition and to the effects of repeated gastrointestinal haemorrhages. Serum transaminases are virtually normal.

Disease association

The prognosis is worsened by concomitant hepatitis B or hepatitis C infection.

When associated with an immunosuppressed state, granuloma formation is reduced and egg output decreases sharply.

Treatment

Chemotherapy aims to relieve symptoms and prevent further deposition of the eggs which will produce further fibrosis. If egg excretion is stopped, the life cycle of the parasite is blocked. Chemotherapy reduces community transmission of disease.

Metriphonate is an organophosphate compound, effective only in *S. haematobium* infection. It is given orally and has negligible toxicity. It is cheap and useful.

Oxamniquine 20 mg/kg/day for 3 days is effective only against *S. mansoni*. South American strains are less sensitive than North or South African and larger doses may be required. It is expensive and well tolerated. Side-effects include dizziness, drowsiness and headache.

Praziquantel has high therapeutic activity against all species of *Schistosoma*. It is safe and non-toxic in a single dose of 40–75 mg orally. The drug paralyses the worm which migrates in the blood stream to the liver where it is attacked by phagocytes, granulocytes and cell-mediated immune cells. It decreases messenger RNA levels of the major proteins associated with fibrosis [6].

Disease control

This is by health education and reducing contamination of water. Attacks on the snails are limited by cost, the need to repeat over long periods and the effects on fish.

Mass treatment by drugs such as metrifonate is limited by cost and poor compliance. Praziquantel would be the ideal drug but the cost is too high.

Vaccines

Schistosomal antigens have been identified and used as the basis of vaccines, but so far none has proved effective in man [3].

Bleeding oesophageal varices

This is rarely fatal and is usually controlled by sclerotherapy or variceal banding (Chapter 10). Distal spleno-renal shunt preferred over total shunts. Gastro-oesophageal devascularization with splenectomy may be the procedure of choice [6] as it has a low mortality and encephalopathy rate. TIPS may be a satisfactory alternative, but post-shunt jaundice is enhanced.

References

1 Abdel-Wahab MF, Esmat G, Farrag A *et al*. Grading of hepatic schistosomiasis by the use of ultrasonography. *Am. J. Trop. Med. Hyg*. 1992; **46**: 403.

2 Alves CAP, Alves AR, Abreu ION *et al*. Hepatic artery hypertrophy and sinusoidal hypertension in advanced schistosomiasis. *Gastroenterology* 1977; **72**: 126.

3 Bergquist NR. Controlling schistosomiasis by vaccination: a realistic option. *Parasitol. Today* 1995; **11**: 191.

4 El-Garem AA. Schistosomiasis. *Digestion* 1998; **59**: 589.

5 Fataar S, Bassiony H, Satyanath S. CT of hepatic schistosomiasis mansoni. *Am. J. Roentgenol*. 1985; **145**: 63.

6 Kresina TF, Qing HE, Esposti SD *et al*. Gene expression of transferring growth factor β1 and extra-cellular matrix proteins in murine *Schistosoma mansoni* infection. *Gastroenterology* 1994; **107**: 773.

7 Prakash S, Postlethwaite AE, Wyler DJ. Alterations in influence of granuloma-derived cytokines on fibrogenesis in the course of murine *Schistosoma mansoni* infection. *Hepatology* 1991; **13**: 970.

8 Salama ZA, El Dorry AK, Soliman MT *et al*. Doppler sonography of the portal circulation in cases with portal hypertension. *Med. J. Cairo Univ.* 1997; **65**: 347.

9 Van Etten L, Folman CC, Eggeltte TA *et al*. Rapid diagnosis of schistosomiasis by antigen detection in urine with a reagent strip. *J. Clin. Microbiol*. 1994; **32**: 2404.

10 Zhu Y, Lukacs NW, Botos DL. Cloning of TH0- and TH2-type helper lymphocytes from liver granulomas of *Schistosoma mansoni*-infected mice. *Infect. Immun.* 1994; **62**: 994.

Malaria [1]

In the *erythrocytic stage*, the parasite is engulfed by reticulo-endothelial cells. The liver suffers from the general effects of the toxaemia and pyrexia [2].

In the *pre-erythrocytic* (exo-erythrocytic) stage, schizogony takes place in the liver without obvious effect on its function. The hepatocyte is invaded by the sporozoite. The nucleus divides many times and, at last (in about 6–12 days), a spherical or irregular body containing thousands of ripe merozoites is formed. This schizont bursts and the merozoites are discharged into the sinusoids and invade erythrocytes. In quartan or benign tertian malaria, a few merozoites return to the liver cells to initiate the exo-erythrocytic or relapse cycle. In malignant tertian this does not happen and there are no true relapses. So far only *Plasmodium falciparum* and *P. vivax* have been found in the liver of man. The tissue stage of human malaria is confined to the liver cells.

Pathology

The liver shows reticulo-endothelial proliferation, both of Kupffer cells and in zone 1. Focal, non-specific granulomas may be seen in the sinusoids. Brown 'malarial' pigment (iron and haemofuscin) is seen in Kupffer cells. Malarial parasites are not shown. Hepatocyte damage is slight with nuclei of variable size and shape and increased mitoses.

In *P. falciparum* malaria sinusoids may contain parasitized, clumped erythrocytes.

Reaction to the malarial parasite is reticulo-endothelial, with minor effects on the liver cells and no fibrosis. The high incidence of cirrhosis in malarial areas is due to other factors.

Clinical features

There are usually no specific hepatic features. Occasionally, in acute malignant malaria, there may be mild jaundice, hepatomegaly and tenderness over the liver.

Hepatic function

Increases in serum bilirubin are rarely above 3 mg/dl (50 µmol/l). Serum transaminases increase slightly and serum globulin concentrations rise.

References

1 Cook GC. Malaria in the liver. *Postgrad. Med. J.* 1994; **70**: 780.
2 Hollingdale MR. Malaria and the liver. *Hepatology* 1985; **5**: 327.

Kala-azar (leishmaniasis)

Leishmaniasis is a reticulo-endothelial disease. Periportal cellular infiltrations and macrophage accumulations are scattered throughout the liver and within them the Leishman–Donovan bodies may be identified (fig. 29.16). There is some portal zone fibrosis [1]. The picture is similar in the American, Mediterranean and Oriental types [1].

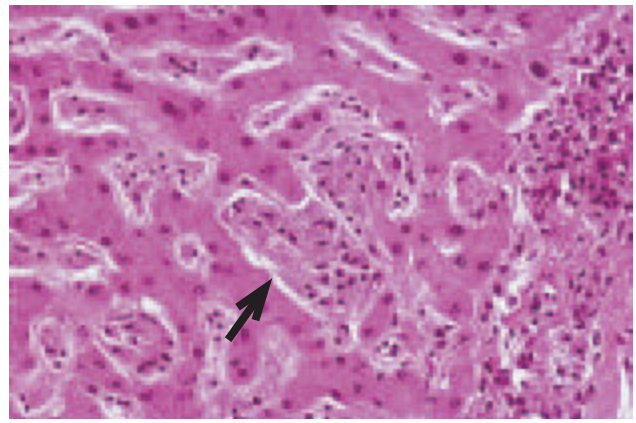


Fig. 29.16. Kala-azar. Liver biopsy shows enlarged Kupffer cells (arrow) distending the sinusoids. These contain Leishman–Donovan bodies. (H & E, ×100.)

Kala-azar presents with fever, splenomegaly, a firm, tender liver, pancytopenia, anaemia and very high serum globulins. Aspiration of the bone marrow is usually positive. Treatment is with paromomycin [2].

References

1 Da Silva JR, De Paola D. Hepatic lesions in American kala-azar: a needle-biopsy study. *Ann. Trop. Med. Parasitol.* 1961; **55**: 249.
2 Jha TK, Olliaro P, Thakur CP *et al*. Randomized controlled trial of aminosidine (paromomycin) v. sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India. *Br. Med. J.* 1998; **316**: 1200.

Hydatid disease

Hydatid disease is due to the larval or cyst stage of infection by the tapeworm, *Echinococcus granulosus*, which lives in dogs. Man, sheep and cattle are intermediate hosts.

Biology (fig. 29.17)

Man is infected by the excreta of dogs, often during childhood. The dog is infected by eating the viscera of sheep, which contain hydatid cysts. Scolices, contained in the cysts, adhere to the small intestine of the dog and become adult worms which attach to the intestinal wall. Each worm sheds 500 ova into the bowel. The infected faeces of the dog contaminate grass and farmland, and the contained ova are ingested by sheep, pigs, camels or man. The ova adhere to the coats of dogs, so man is

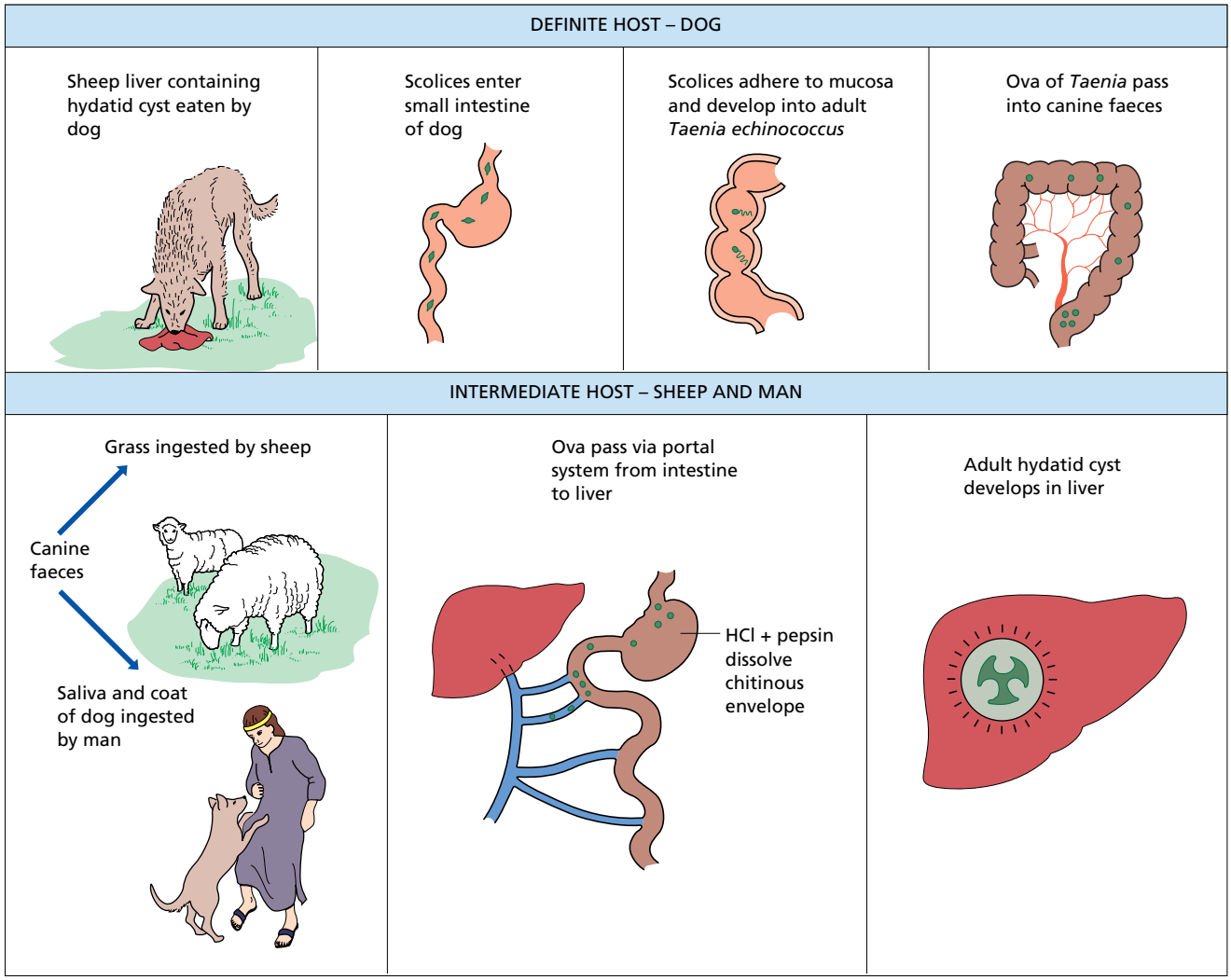


Fig. 29.17. The life cycle of the hydatid parasite.

infected by handling dogs, as well as by eating contaminated vegetables.

The ova have chitinous envelopes which are dissolved by gastric juice. The liberated ovum burrows through the intestinal mucosa and is carried by the portal vein to the liver, where it develops into an adult cyst. Seventy per cent of hydatid cysts form in the liver. A few ova pass through the liver and heart, and are held up in the lungs causing pulmonary cysts. A few ova reach the general circulation causing spleen, brain and bone cysts.

Development of the hepatic cyst (fig. 29.18)

The adult cyst develops slowly from the ovum and provokes a cellular response in which three zones can be distinguished: a peripheral zone of fibroblasts, an intermediate layer of endothelial cells and an inner zone of round cells and eosinophils. The peripheral zone, derived from the host tissues, becomes the *adventitia* or ectocyst, a thick layer which may calcify. The intermediate and inner zones become hyalinized (the *laminated layer*). Finally, the cyst becomes lined with the *germinal layer*, which gives rise to pedunculated nodes of multiplying cells which project into the lumen of the cyst as *brood capsules*. Scolices develop from the brood capsules and eventually indent it. The attachment of the brood capsules to the germinal layer becomes progressively thinner until the capsule bursts, releasing the scolices into the cyst fluid. These fall to the bottom and are termed *hydatid sand*.

All hydatid cysts start as purely cystic type I structures [10]. When they develop daughter cysts or a gelatinous matrix, they are termed type II. When formed, elements deprive the type II lesion of its nourishing hydatid fluid, it dies and becomes a calcified and biologically inert type

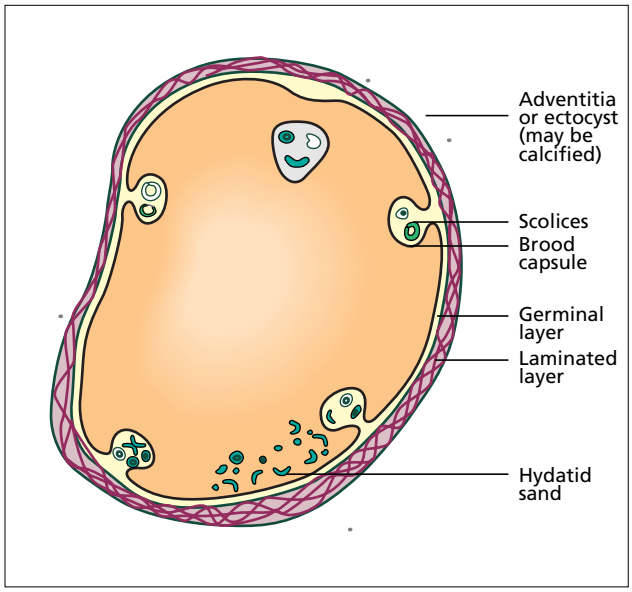


Fig. 29.18. The basic constitution of a hydatid cyst.

III lesion. The course is modified by rupture, infection or anaphylaxis.

Daughter and even grand-daughter cysts develop by fragmentation of the germinal layer. The majority of cysts in adult patients are thus multilocular. The cyst fluid is a transudate of serum. It contains protein and is antigenic. If released into the circulation, eosinophilia or anaphylaxis may result.

Endemic regions

The disease is common in sheep-raising countries, where dogs have access to infected offal. These include South Australia, New Zealand, Africa, South America, southern Europe, especially Cyprus, Greece and Spain, and the Middle and Far East. The disease is rare in Britain, apart from some areas in Wales.

Clinical features

These depend on the site, the stage and whether the cyst is alive or dead. The rest of the liver hypertrophies and hepatomegaly results.

The *uncomplicated hydatid cyst* may be silent and found incidentally. It should be suspected if a rounded smooth swelling, continuous with the liver, is found in a patient who is not obviously ill. The only complaints may be a dull ache in the right upper quadrant and sometimes a feeling of abdominal distension. The tension in the cyst is high and fluctuation is never marked.

Complications

Rupture. Intra-peritoneal rupture is frequent and leads to multiple cysts throughout the peritoneal cavity with intestinal obstruction and gross abdominal distension.

The pressure in the cyst greatly exceeds that in bile and rupture into bile ducts is frequent. This may lead to cure or to cholestatic jaundice with recurrent cholangitis.

Colonic rupture leads to elimination per rectum and to secondary infection.

The cysts may adhere to the diaphragm, rupture into the lungs and result in expectoration of daughter cysts. Pressure on and rupture into the hepatic veins leads to the Budd–Chiari syndrome. Secondary involvement of the lungs may follow.

Infection. Secondary invasion by pyogenic organisms follows rupture into biliary passages, giving the picture of a pyogenic abscess; the parasite dies. Occasionally, the entire cyst content undergoes aseptic necrosis and again the parasite dies. This amorphous yellow debris must be distinguished from the pus of secondary infection.

Other organs. Cysts can occur in lung, kidney, spleen, brain or bone, but mass infestation is rare; the liver is usually the only organ involved. If a hydatid cyst is found elsewhere, there is always concomitant infestation of the liver.

Hydatid allergy. Cyst fluid contains a foreign protein which sensitizes the host. This may lead to severe anaphylactic shock but more commonly to recurrent urticaria or 'hives'.

Membranous glomerulonephritis may be related to glomerular deposits of hydatid antigen [7].

Diagnosis

Serological tests

Hydatid fluid contains specific antigens, leakage of which sensitizes the patient with the production of antibodies.

ELISA gives positive results in about 85% [2].

Results may be negative for all tests if the cyst has never leaked, if it contains no scolices or if the parasite is dead.

Eosinophilia of greater than 7% is found in about 30% of patients.

Imaging

Radiology shows a raised, poorly moving right diaphragm and hepatomegaly. Calcium is laid down in the ectocyst as a distinct round or oval opacity (fig. 29.19) or merely as shreds.

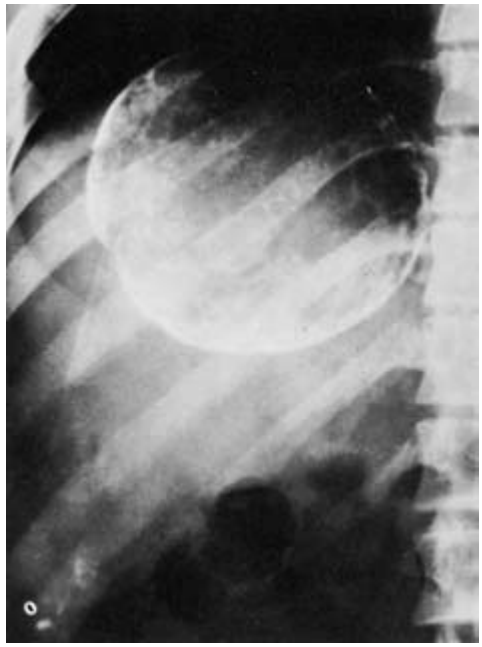


Fig. 29.19. X-ray of the abdomen shows a calcified hydatid cyst in the liver.

Floating bodies indicate the presence of free-moving daughter cysts. Infected gas-containing cysts may show a fluid level.

Hepatic cysts may displace the stomach or hepatic flexure of the colon. Characteristic radiological changes may be seen in the lungs, spleen, kidney or bone.

US or *CT scanning* demonstrates single or multiple cysts which may be uni- or multiloculated, and thin or thick walled (figs 29.20, 29.21, 29.22). US and CT are highly sensitive for diagnosis: 97.7% for US and 100% for CT.

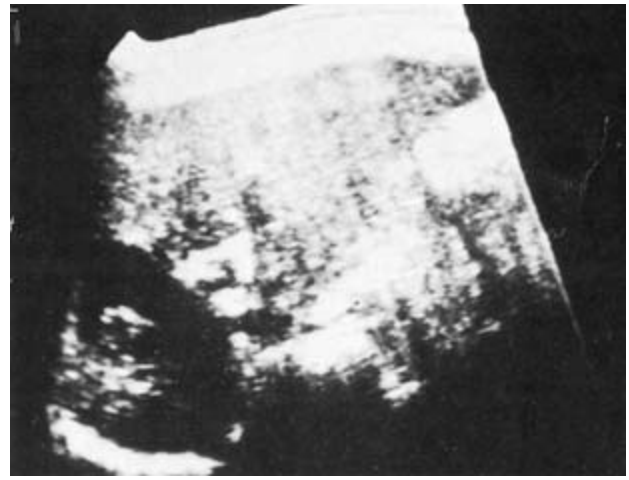
US changes provide the basis for classification (table 29.2) [6]. WHO classification is into active, transitional and inactive cysts. Infected cysts are poorly defined [17].

MRI may show a characteristic intense rim, daughter cysts and detachment of the membranes [12]. Intra-hepatic and extra-hepatic rupture can be defined.

ERCP may show cysts in the bile ducts (figs 29.23, 29.24).

Prognosis

The uncomplicated hepatic hydatid cyst carries a reasonably good prognosis. The risk of complications is, however, always present. Intra-peritoneal or intra-pleural rupture is grave, but rupture into the biliary tree is not so serious because spontaneous cure may follow the biliary colic. Infection is controlled by antibiotics.



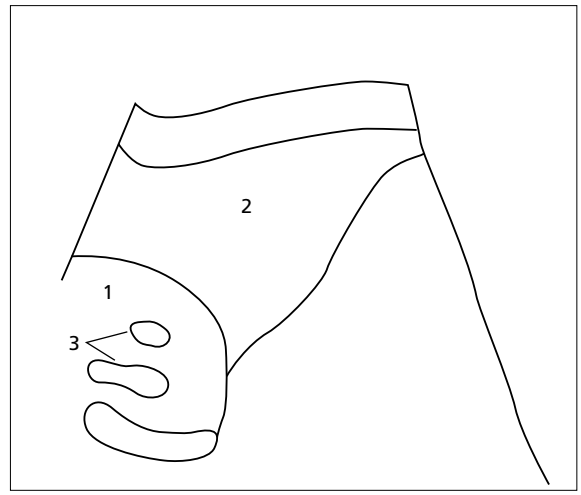


Fig. 29.20. US shows a hydatid cyst (1) in the right lobe of the liver (2). Daughter cysts (3) can be seen inside the larger cyst.

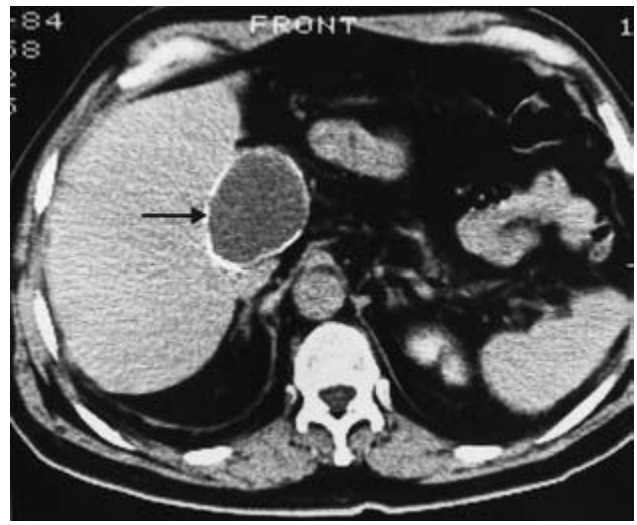


Fig. 29.21. CT scan shows calcified hydatid cyst (arrowed) in a quadrate lobe of the liver (contrast-enhanced scan).

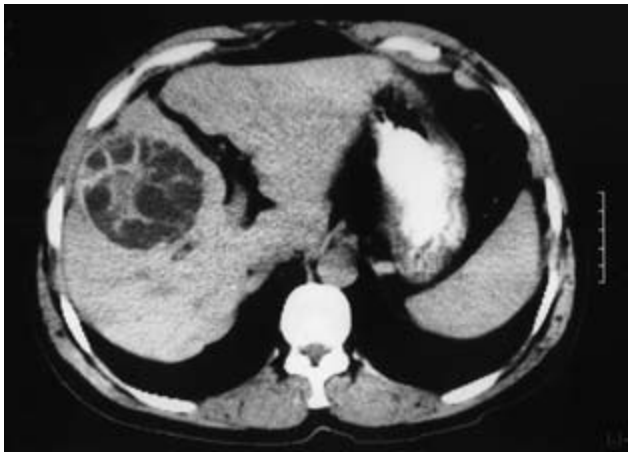


Fig. 29.22. CT scan. Hydatid cyst in right lobe of liver showing patchy calcification of the wall and containing multiple septae produced by daughter cysts (contrast-enhanced scan).

Table 29.2. Classification of ultrasound appearances in hydatid disease [6]

Type	Description
I	Purely cystic
II	Detached membrane
III	Undulating in cyst cavity
	Multiseptate cyst
IV	Heterogenous complex mass (dead parasite)
	Calcified mass (eggshell) (dead parasite)

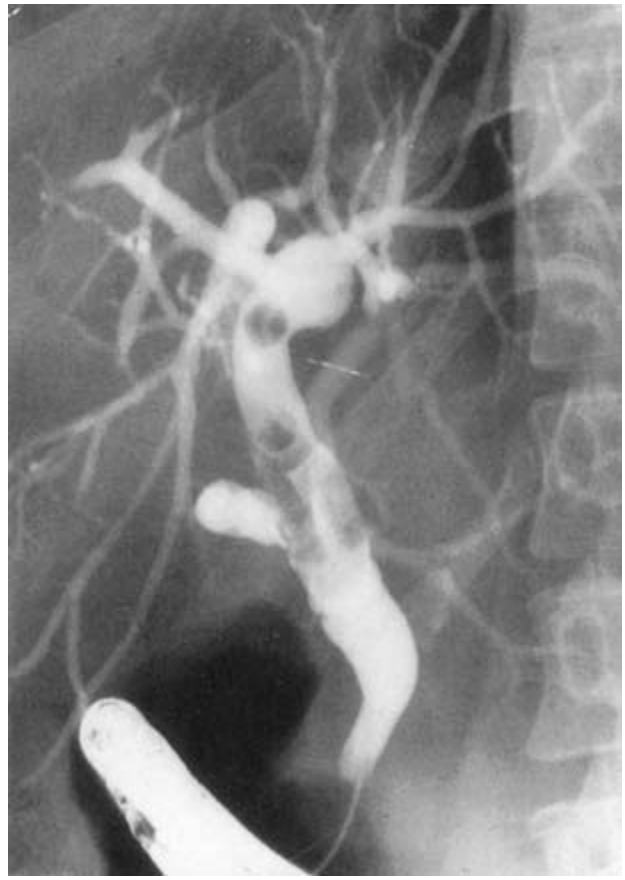


Fig. 29.23. Endoscopic cholangiography showing hydatid cysts in the common bile duct.

Fig. 29.24. Four glistening hydatid cysts (arrow) were removed surgically from the common bile duct of the patient shown in fig. 29.23.

Treatment

Dogs are denied access to infected offal and hands are washed after handling dogs [5]. Dogs in affected areas must be regularly de-wormed.

Medical treatment

Mebendazole perfuses through the cyst membrane and interferes with microtubular function. It is poorly absorbed.

Albendazole is better absorbed and cyst levels equal that achieved in plasma. It is more satisfactory than mebendazole.

Medical therapy cannot be regarded as definitive. Albendazole can be given in a 6 to 24-month course for those unsuitable for surgery, with disseminated disease or with rupture. About 30% of cysts disappear, 30–50% degenerate or become smaller and 20–40% of cysts are unchanged [13].

Mebendazole is particularly useful if given 10–14 days

Table 29.3. Treatment of hydatid liver cysts [4]

Percutaneous puncture
Aspirate
Inject 25% alcohol
Re-aspirate

before and for several weeks after surgery or percutaneous puncture to prevent recurrence [9].

Percutaneous drainage

US-guided percutaneous drainage is as effective as surgery [4, 9]. The 'PAIR' routine is used (table 29.3) [4]. Care must be taken that sclerosing solutions such as formalin are not injected as these may induce sclerosing cholangitis [15]. The cyst fluid must not be bile stained as a fall in pressure might prevent closure of a biliary fistula.

Surgery

The object is to remove the cyst completely, without soiling and infecting the peritoneum and with complete obliteration of the resulting dead space. Complete removal of the cyst with its adventitia is ideal to avoid spillage. The usual operation is cystectomy with removal of the germinal and laminated layers and preservation of the host-derived ectocyst [11]. Surgical pericystectomy includes removal of the pericyst and has a high mortality. The mortality for these operations is 2.2% and the morbidity rate is 23.7% [11]. Cure rates are up to 22%.

Hemi-hepatectomy or segmentectomy are occasionally performed. Cholangitis is treated by biliary drainage, usually by ERCP, papillotomy and cyst removal. Surgical biliary drainage may be necessary. The technical problem is great.

Rupture into the peritoneal cavity

The cyst contents are removed from the peritoneal cavity as far as possible by sucking and swabbing. The scolices, however, usually settle down in the peritoneal cavity and form daughter cysts so that recurrence is almost inevitable.

Urgent surgery has a substantial morbidity and mortality [14]. Chemotherapy is essential.

***Echinococcus multilocularis* (alveolar echinococcosis)**

This is found in the northern hemisphere. Rodents are intermediate hosts and foxes are definitive hosts. The larvae grow indefinitely and produce liver necrosis and a major granulomatous reaction. It may be diagnosed by PCR [8]. The disease behaves like a locally malignant tumour. The *Echinococcus* invades liver and biliary tissue, hepatic veins, inferior vena cava and diaphragm. Chemotherapy is effective but not curative [1]. It is fatal unless completely removed by surgery [16]. Hepatic transplant may be necessary [3].

References

1 Ammann RW, Ilitsch N, Marincek B *et al*. Effect of chemotherapy on the larval mass and the long-term course of alveolar echinococcosis. *Hepatology* 1994; **19**: 735.
2 Babba H, Messedi A, Masmoudi S *et al*. Diagnosis of human hydatidosis: comparison between imaging and six serologic techniques. *Am. J. Trop. Med. Hyg*. 1994; **50**: 64.
3 Bresson-Hadni S, Franza A, Miguet JP *et al*. Orthotopic liver transplantation for incurable alveolar echinococcosis of the liver: report of 17 cases. *Hepatology* 1991; **13**: 1061.
4 Filice C, Pirola F, Brunetti E *et al*. A new therapeutic approach for hydatid liver cysts. Aspiration and alcohol injection under sonographic guidance. *Gastroenterology* 1990; **98**: 1366.
5 Gemmell MA, Lawson JR, Roberts MG. Control of echinococcosis/hydatidosis: present status of worldwide progress. *Bull. WHO* 1986; **64**: 333.
6 Gharbi HA, Hassine W, Brauner MW *et al*. Ultrasound examination of the hydatic liver. *Radiology* 1981; **139**: 459.
7 Ibarrola AS, Sobrini B, Guisantes J *et al*. Membranous glomerulonephritis secondary to hydatid disease. *Am. J. Med*. 1981; **70**: 311.
8 Kern P, Frosch P, Helbig M *et al*. Diagnosis of *Echinococcus multilocularis* infection by reverse-transcription polymerase chain reaction. *Gastroenterology* 1995; **109**: 596.
9 Khuroo MS, Wani NA, Javid G *et al*. Percutaneous drainage compared with surgery for hepatic hydatid cysts. *N. Engl. J. Med*. 1997; **337**: 881.
10 Lewall DB. Hydatid disease: biology, pathology, imaging and classification. *Clin. Radiol*. 1998; **53**: 863.
11 Magistrelli P, Masetti R, Coppola R *et al*. Surgical treatment of hydatid disease of the liver. A 20-year experience. *Arch. Surg*. 1991; **126**: 518.
12 Marani SA, Canossi GC, Nicoli FA *et al*. Hydatid disease: MR imaging study. *Radiology* 1990; **175**: 701.
13 Nahmias J, Goldsmith R, Soibalman M *et al*. Three to 7 years follow-up after albendazole treatment of 68 patients with cystic echinococcosis (hydatid disease). *Ann. Trop. Med. Parasitol*. 1994; **88**: 295.
14 Schaefer JW, Khan MY. Echinococcosis (hydatid disease): lessons from experience with 59 patients. *Rev. Infect. Dis*. 1991; **13**: 243.
15 Teres J, Gomez-Moli J, Bruguera M *et al*. Sclerosing cholangitis after surgical treatment of hepatic echinococcal cysts: report of three cases. *Am. J. Surg*. 1984; **148**: 694.
16 Wilson JF, Rausch RL, Wilson FR *et al*. Alveolar hydatid disease. Review of the surgical experience in 42 cases of active disease among Alaskan Eskimos. *Ann. Surg*. 1995; **221**: 315.
17 WHO Informal Working Group on Echinococcosis. Guidelines for the treatment of cystic and alveolar echinococcosis in humans. *Bull. WHO* 1996; **74**: 231.

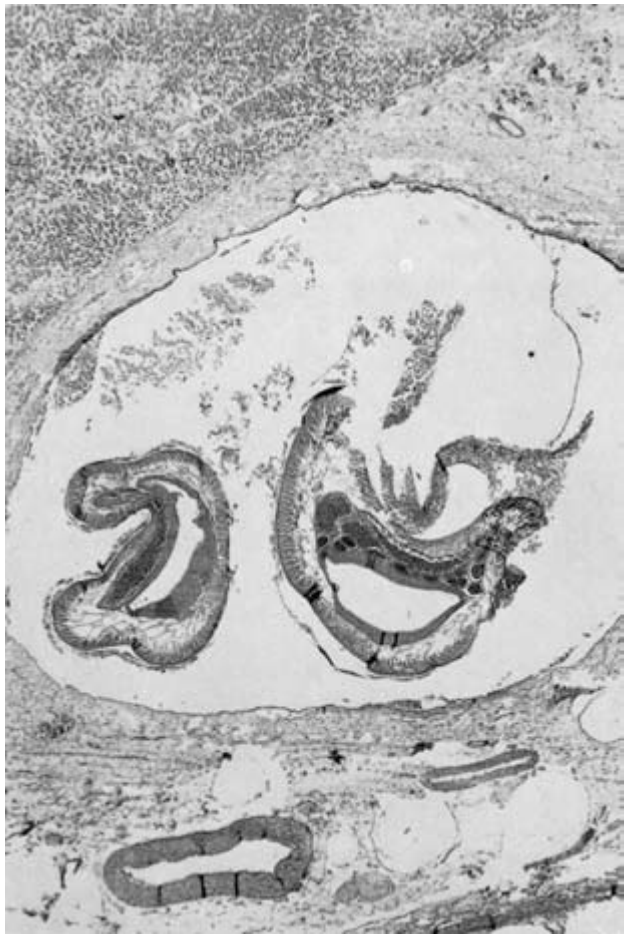


Fig. 29.25. Section shows a dead *Ascaris* in an intra-hepatic blood vessel in a portal zone. There is surrounding fibrous tissue reaction. (H & E, ×40.)

Ascariasis

Ascaris infection is particularly common in the Far East, India and South Africa. Ova of the roundworm *Ascaris lumbricoides* arrive in the liver by retrograde flow in the bile ducts. They exert an immunological reaction and eggs, giant cells and granulomas are surrounded by a dense eosinophil infiltrate (fig. 29.25). The adult worm is 10–20 cm long but occasionally may lodge in the common bile duct producing partial bile duct obstruction, and secondary cholangitic abscesses [2]. The *Ascaris* may be a nucleus for intra-hepatic gallstones [4]. Biliary colic is a complication.

A *plain abdominal X-ray* may show calcified worms.

Clinical presentation is as acute cholecystitis, acute cholangitis, biliary colic, acute pancreatitis and, rarely, hepatic abscess [2].

US shows long linear echogenic structures or strips which characteristically move. It can be used to monitor migration of the worms. It cannot diagnose duodenal ascariasis.

ERCP shows the *Ascaris* as a linear filling defect (fig. 29.26). Worms can be seen moving into and out of the biliary tree from the duodenum [1].

Treatment is by ERCP with endoscopic worm extraction with or without sphincterotomy [3]. Failures need surgical treatment.

Treatment with piperazine citrate, mebendazole or albendazole will usually kill *Ascaris* but it remains in the bile ducts. Re-invasion is common.

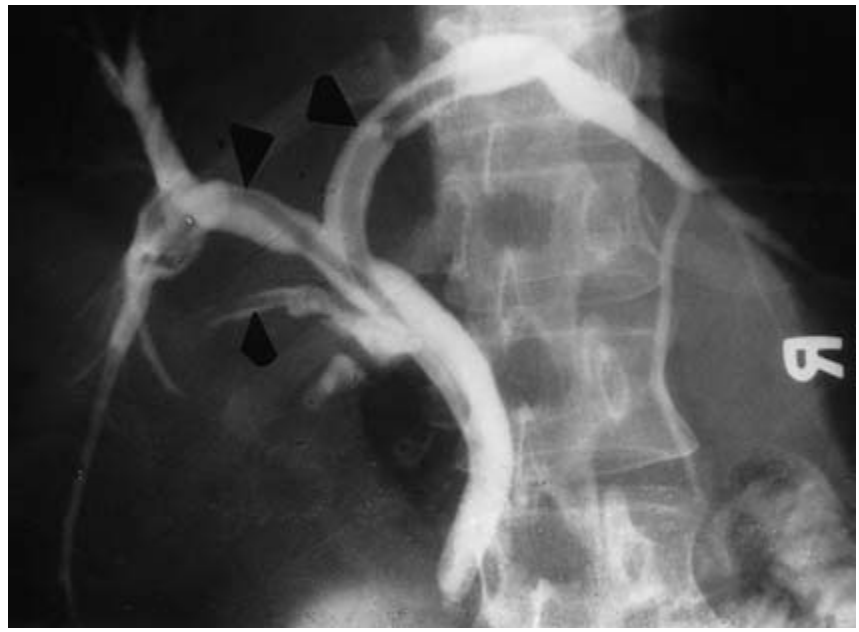


Fig. 29.26. Ascariasis: endoscopic cholangiography shows linear filling defects in the bile ducts due to *Ascaris* worms (arrowheads).

References

1 Kamath PS, Joseph DC, Chandran R *et al*. Biliary ascariasis: ultrasonography, endoscopic retrograde cholangiopancreatography, and biliary drainage. *Gastroenterology* 1986; **91**: 730.
2 Khuroo MS, Zargar SA, Mahajan R. Hepatobiliary and pancreatic ascariasis in India. *Lancet* 1990; **335**: 1503.
3 Manialawi MS, Khattar NY, Helmy MM *et al*. Endoscopic diagnosis and extraction of biliary *Ascaris*. *Endoscopy* 1986; **18**: 204.
4 Shulman A. Non-Western patterns of biliary stones and the role of ascariasis. *Radiology* 1987; **162**: 425.

Strongyloides stercoralis

This soil-transmitted intestinal nematode is common in tropical countries. It is usually asymptomatic but can cause biliary obstruction due to biliary stenosis [1]. Thiabendazole is effective treatment.

Reference

1 Delarocque Astagneau E, Hadengue A, Degottc C *et al*. Biliary obstruction resulting from *Strongyloides stercoralis* infection: report of a case. *Gut* 1994; **35**: 705.

Trichiniasis

This disease is caused by eating raw, infected pork with subsequent dissemination of *Trichinella* larvae throughout the body.

Hepatic histology may show invasion of hepatic sinusoids by *Trichinella* larvae and fatty change [1].

Diagnosis is difficult unless in an epidemic. Eosinophilia is suggestive. Muscle pain and tenderness may warrant muscle biopsy.

Treatment. ERCP is indicated if the biliary tract is obstructed. Treatment is unsatisfactory. Mebendazole may be effective in the migratory stage but is of doubtful value later.

Reference

1 Guattery JM, Milne J, House RK. Observations on hepatic and renal dysfunction in trichinosis. Anatomic changes in these organs occurring in cases of trichinosis. *Am. J. Med*. 1956; **21**: 567.

Toxocara canis (visceral larva migrans)

This parasite is spread by cats and dogs. The second stage can infect the liver of man, forming granulomas [1]. Hepatomegaly, recurrent pneumonia, eosinophilia and hypergammaglobulinaemia are associated findings. The serum fluorescent antibody test is positive.

Treatment may be tried with diethyl carbamazine or thiabendazole.

Reference

1 Zinkham WH. Visceral larva migrans. *Am. J. Dis. Child*. 1978; **132**: 627.

Liver flukes

Cysts are consumed and larvae develop in the duodenum and eventually reach the bile ducts. The flukes probably invade the liver through its peritoneal coat and are carried via the parenchyma to the bile ducts. During the migratory phase they cause fever and eosinophilia. When they reach the biliary passages they may cause obstruction with complicating suppurative cholangitis.

Clonorchis sinensis

The Chinese liver fluke is found mainly in eastern Asia. It can present years after the patient has left their country of origin as the biliary flukes persist for decades. Cysts are ingested with improperly cooked or raw, fresh-water fish. The cyst wall is destroyed by trypsin in the duodenum and the larvae migrate from the duodenum into the peripheral intra-hepatic bile ducts where they mature to adult worms. In uncomplicated cases, the changes are confined to the bile duct walls with abundant adenomatous formation; fibrosis increases with time [4]. Cholangiocarcinoma is a serious complication [8].

Clinical manifestations depend on the number of flukes, the period of infestation and the complications. With heavy infestation, the patient suffers weakness, epigastric discomfort, weight loss and diarrhoea. Jaundice is due to obstruction to the intra-hepatic biliary tree by worms or inflammation. Infection leads to fever, chills and abdominal pain. Cholangiocarcinoma is marked by progressive jaundice and pruritus.

Diagnosis is based on finding ova in the stool or aspirated bile. Laboratory findings include eosinophilia and an increased serum alkaline phosphatase.

ERCP shows filamentous filling defects in the bile ducts which have blunted tips [7]. The defects are of uniform size and change in position.

US and *CT* changes are based on flukes within dilated ducts and peri-ductal changes without evidence of extra-hepatic biliary obstruction [1, 7].

The *therapeutic response* to praziquantel is poor and relapses may follow bithionol.

The bile ducts must be cleared of stones by endoscopic or percutaneous cholangiography or surgery [5, 6].

Fasciola hepatica

The common sheep fluke is found mostly in mid- and western Europe and in the Caribbean. The animal infestation rate in Britain is high: 30–90% of all sheep and cattle excrete the ova. This increases in wet summers when the intermediate host, the snail *Lymnaea trunculata*, is also more numerous. The encysted cercariae from these snails survive on herbage and patients are usually infected by eating contaminated watercress.

The clinical picture in the acute stage is of cholangitis with fever, right upper quadrant pain and hepatomegaly. Eosinophilia and a raised serum alkaline phosphatase are noted. The picture may simulate choledocholithiasis.

ERCP shows several irregular linear or rounded filling defects in the bile ducts or segmental stenosis, with an inflammatory pattern. Worms can be aspirated.

Liver biopsy shows infiltration of the portal zones with histiocytes, eosinophils and polymorphs. Hepatic granulomas and ova in the liver may occasionally be seen.

Diagnosis is suspected by finding the clinical picture of biliary tract disease with eosinophilia. It is confirmed by finding ova in the faeces. These, however, may not be detected until 12 weeks after the infection when parasites have attained sexual maturity. They disappear later.

The diagnosis may be confirmed by ELISA testing of circulating antibodies to *Fasciola hepatica* excretory-secretory antigens [2, 3].

CT shows peripheral filling defects, sometimes crescentic, in the liver due to the migrating fluke (fig. 29.27) [9].

Treatment of all liver flukes is by praziquantel, bithionol or albendazole.

Recurrent pyogenic cholangitis

This is a common disease in south-east Asia. The initial cause is uncertain, but may be *Clonorchis* or enteric microorganisms. Biliary stone and stricture formation follow recurrent bacterial infections. Treatment is by antibiotics following biliary drainage either endoscopic or surgical.

References

1 Choi BI, Kim HJ, Han MC *et al*. CT findings of clonorchiasis. *Am. J. Roentgenol*. 1989; **152**: 281.

2 Cordova M, Herrera P, Nopo L *et al*. *Fasciola hepatica* cysteine proteinases: immunodominant antigens in human fascioliasis. *Am. J. Trop. Med. Hyg*. 1997; **57**: 660.

3 Espino AM, Marcet R, Finlay CM. Detection of circulating excretory secretory antigens in human fascioliasis by sandwich enzyme-linked immunosorbent assay. *J. Clin. Microbiol*. 1990; **28**: 2637.

4 Hou PC, Pang LSC. *Clonorchis sinensis* infestation in man in Hong Kong. *J. Pathol. Bact*. 1964; **87**: 245.

5 Jan YY, Chen MF. Percutaneous trans-hepatic cholangioscopic lithotomy for hepatolithiasis: long-term results. *Gastrointest. Endosc*. 1995; **42**: 1.

6 Jan YY, Chen MF, Wang CS *et al*. Surgical treatment of hepatolithiasis: long-term result. *Surgery* 1996; **120**: 509.

7 Lim JH. Radiologic findings of clonorchiasis. *Am. J. Roentgenol*. 1990; **155**: 1001.

8 Ona FV, Dytoc JNT. Clonorchis-associated cholangiocarcinoma: a report of two cases with unusual manifestations. *Gastroenterology* 1991; **101**: 831.

9 Pagola Serrano MA, Vega A, Ortega E *et al*. Computed tomography of hepatic fascioliasis. *J. Comp. Assist. Tomogr*. 1987; **11**: 269.

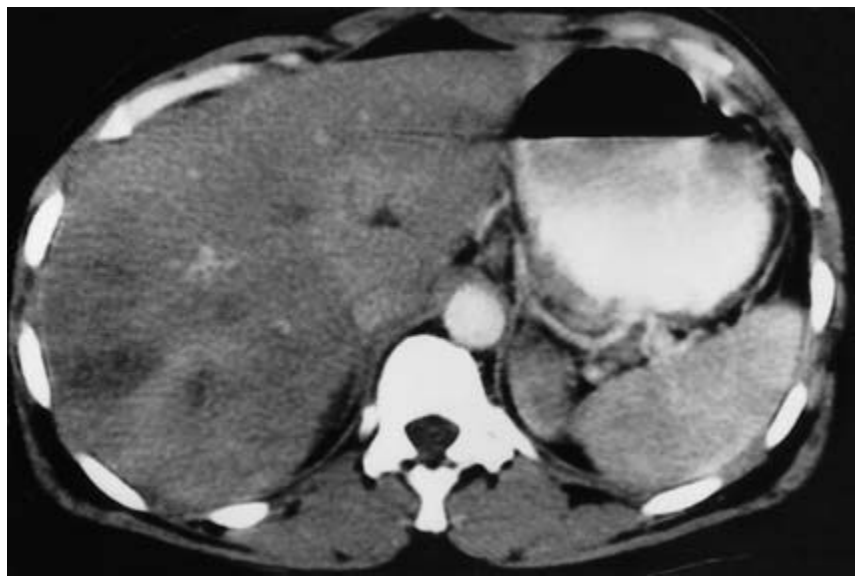


Fig. 29.27. *Fasciola hepatica*. CT in the migratory stage shows multiple, sometimes linear, filling defects at the periphery of the liver. (Courtesy of P.A. McCormick.)

Peri-hepatitis

This upper abdominal peritonitis is associated with genital infections, particularly *Chlamydia trachomatis* and less often with *Neisseria gonorrhoeae* [2]. It affects young, sexually active women and simulates biliary tract disease. Diagnosis is by laparoscopy. The liver surface shows white plaques, tiny haemorrhagic spots and 'violin string' adhesions.

CT may also show 'violin string' adhesions (fig. 29.28) [1]. Treatment is with tetracycline.

References

1 Haight JB, Ockner SA. *Chlamydia trachomatis* perihepatitis with ascites. *Am. J. Gastroenterol*. 1988; **83**: 323.
2 Simson JNL. Chlamydial perihepatitis (Curtis–Fitz Hugh syndrome) after hydrotubation. *Br. Med. J*. 1984; **289**: 1146.

Hepato-biliary disease in HIV infection

HIV does not seem to exert any direct effect on the liver. Many diseases, however, affect the immunodeficient and provide a confusing picture [23, 31]. All parts of the hepato-biliary system can show changes and may be involved in more than one process (table 29.4). Hepatomegaly is seen in at least two-thirds and 50% of patients show abnormal liver function tests. A blood culture is usually more helpful than a liver biopsy.

Hepatic histology is seldom normal, showing macrovesicular fat and mild zone 1 lymphocytes [18].

The causes of hepato-biliary disease differ depending on the extent of immunocompromise [32]. In earlier stages where the CD4 cell count exceeds $500\,10^9$/l, hepatic complications are largely liver-specific, such as drug-related, primary neoplasm or infection with hepato-trophic viruses such as hepatitis B and C. With progression of immunodeficiency to CD4 cell counts of less than 200, the liver is generally involved as part of systemic opportunistic infections due to *Mycobacterium avium intracellulare* (MAI), fungi or cytomegalovirus (CMV). The liver is only one site involved in AIDS; liver disease is rarely the primary cause of death.

A high serum alkaline phosphatase level is an indication for US or CT (fig. 29.29). Those with dilated bile ducts should proceed to ERCP to confirm biliary obstruction. Those with a focal lesion should have a guided liver biopsy. In the absence of a focal or bile duct

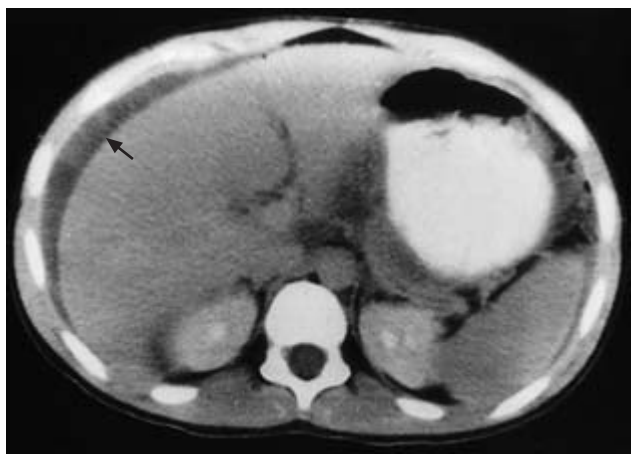


Fig. 29.28. CT in chlamydial peri-hepatitis shows 'violin string' adhesions between liver and anterior abdominal wall (arrowed) and ascites.

Table 29.4. Hepato-biliary changes in AIDS

Non-specific
Hepatomegaly
Abnormal biochemistry
Histology
fatty change
portal inflammation
Kupffer cell iron
diminished lymphocytes
Infections
Mycobacterium avium intracellulare
Mycobacterium tuberculosis
Cytomegalovirus*
Herpes simplex virus
Epstein–Barr virus
*Cryptococcus neoformans**
Histoplasmosis
*Candida albicans**
Coccidiomycosis
Microsporidia*
Toxoplasmosis
Bacillary peliosis
Hepatitis B virus
Impaired response to vaccine and antiviral therapy
Fulminant (rare)
Hepatitis C virus
Tumours
Hodgkin's and non-Hodgkin's lymphoma
Kaposi's sarcoma (rare)
Hepato-toxic drugs
Sulphonamides
Antibiotics
Isoniazid
Antifungals
Tranquillizers
Zidovudine

*Associated biliary tract disease.

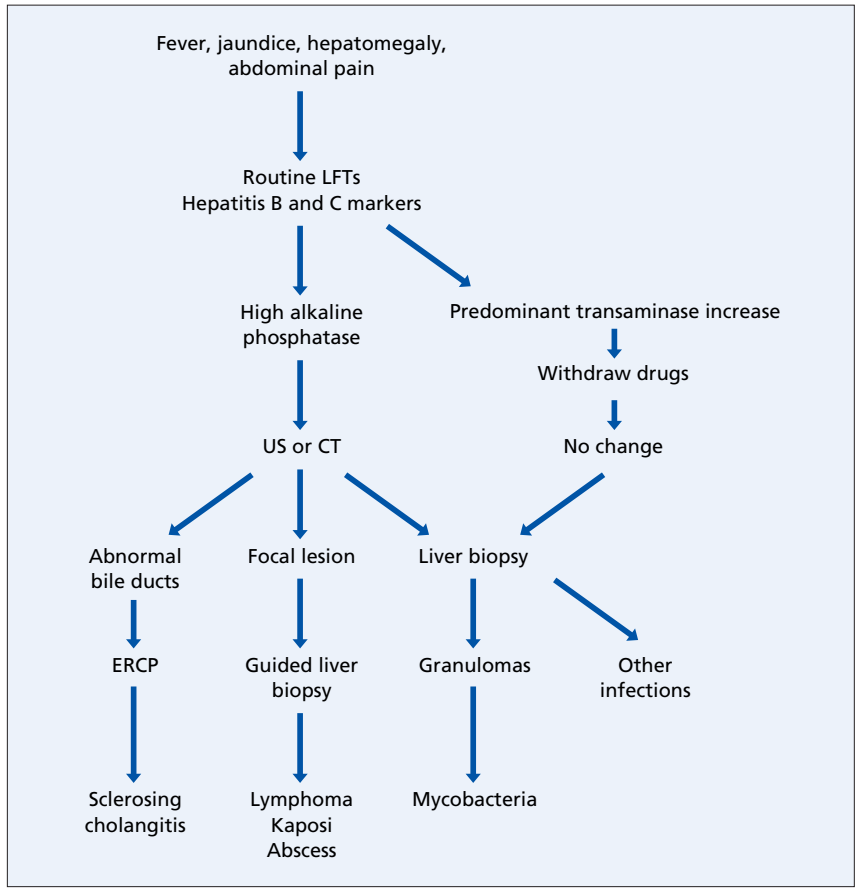


Fig. 29.29. The management of the patient with hepato-biliary AIDS.

lesion a liver biopsy should be performed to exclude mycobacteria (fig. 29.29).

Infections

These are largely opportunistic and part of generalized infection. Liver biopsy in patients with hepatomegaly, fever and abnormal biochemical tests gives the cause in about 25%.

MAI infection is a late complication. It presents with fever, night sweats, weight loss and diarrhoea. Hepatic histology shows poorly formed granulomas without lymphocyte cuffing, giant cells or central caseation. Acid-fast bacilli are present in large numbers in clusters of foamy histiocytes or within Kupffer cells (figs 29.30, 29.31). If MAC is seen in liver biopsies, the mean survival is only 69 days.

Mycobacterium tuberculosis can occur at an earlier stage and is more prevalent in injection drug users than in other categories. When the CD4 count exceeds 200, infection is pulmonary whereas atypical presentations, including hepatic involvement, are seen in patients with more severe immunodeficiency.

CMV is late and part of generalized disease. It is associated with fever and weight loss. Diagnosis is made by demonstrating nuclear and cytoplasmic inclusions in Kupffer cells, bile duct epithelium and occasionally hepatocytes.

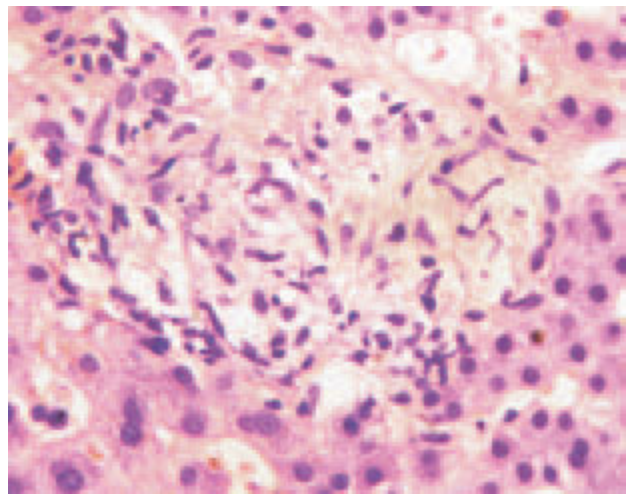


Fig. 29.30. An ill-defined poorly cellular granuloma in the liver of a patient with AIDS. (H & E, ×220.)

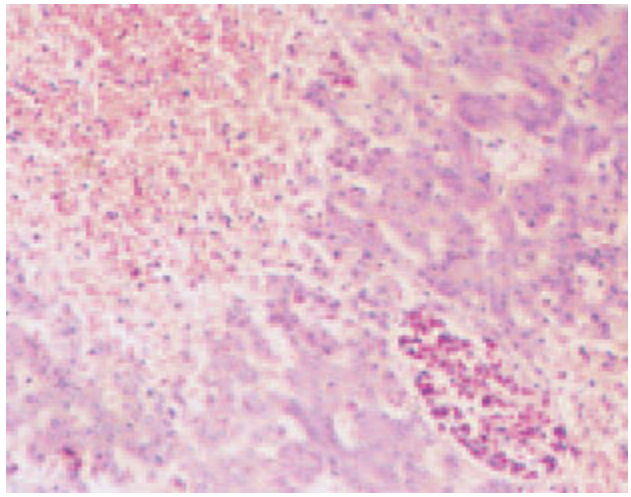


Fig. 29.31. Same patient as in fig. 29.30. Liver stained for acid-fast bacilli shows two granulomas containing many red-staining bacilli (*Mycobacterium avium intracellulare*).

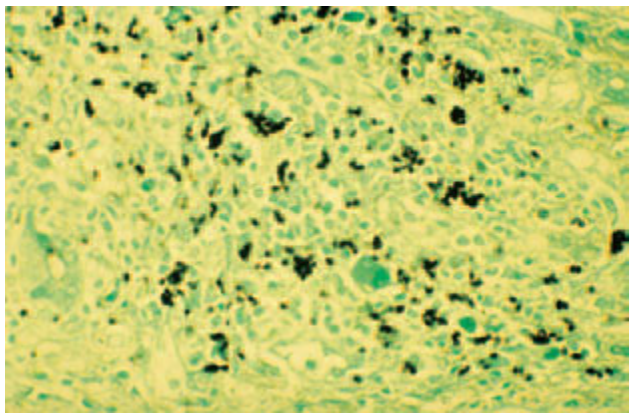


Fig. 29.32. Cryptococcal hepatitis in a patient with AIDS. Many yeast forms of *Cryptococcus neoformans* are stained black. (Methenamine silver, ×350.)

Bacillary peliosis hepatitis. The angioproliferative lesions in the liver resemble Kaposi's sarcoma. It is due to *Bartonella henselae*, a tiny Gram-negative organism which is difficult to cultivate [16, 29]. Systemic features include fever, lymphadenopathy, hepatosplenomegaly and cutaneous and bony lesions. It is treated by erythromycin.

Fungal infections are usually part of late disseminated disease. They include *Cryptococcus neoformans* where yeast can be shown in the liver (fig. 29.32) [4]. Similarly, histoplasmosis (fig. 29.33), coccidiomycosis [27] and *Candida albicans* may involve the liver. Those with low CD4 counts exposed to *Cryptosporidium* are at risk of biliary disease and death within 1 year [30]. *Pneumocystis carinii* can rarely cause hepatitis [20].

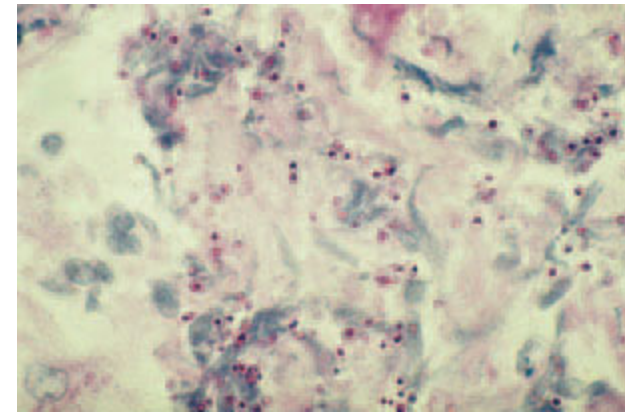


Fig. 29.33. Histoplasmosis hepatitis in a patient with AIDS. Many intracellular forms of *Histoplasma capsulatum* are stained red. (PAS diastase, ×500.)

Hepatitis B, C and D co-infection

Markers of past or present HBV infection are found in approximately 90% of homosexual men or drug abusers with AIDS. In late stage disease, the HBV may activate with conversion to HBe antigen positivity and an increase in HBV polymerase [15]. However, the HBV seems to have little effect on liver histology or survival [24]. Patients respond poorly to HBV vaccination, and to interferon therapy [19, 33]. Hepatitis delta virus (HDV) is present, depending on the location [25].

In contrast, HIV accelerates the course and reduces the survival of HCV-infected patients. The co-infection is particularly frequent in drug absuers and in haemophiliacs where the liver disease is particularly severe [12, 21, 28]. Antibodies to HCV can disappear despite persistent HCV viraemia [26]. Interferon therapy may be tried, but will have the greatest benefit only in those with higher CD4 counts. With the modern therapy of HIV, the number of doubly infected patients with good immune function will increase and combined ribavirin/interferon therapy can be tried.

Neoplasms

Non-Hodgkin's lymphoma is usually metastatic, but can be primary (fig. 29.34). It usually appears late, but may appear at any stage of the disease and can be a primary presentation. It presents as fever, weight loss, night sweats and abdominal pain, with a rise in serum transaminases and especially serum alkaline phosphatase. Large hepatic lesions present with jaundice and pruritus.

US and *CT* show large, usually multifocal solid space-occupying lesions. Guided liver biopsy is diagnostic.

Survival is short and response to chemotherapy poor.

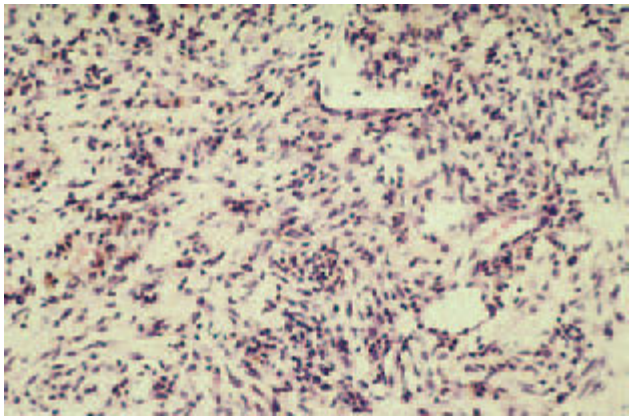


Fig. 29.34. B-cell lymphoma in a patient with AIDS. Sinusoids are infiltrated with large pleomorphic lymphoid cells. (H & E, ×350.)

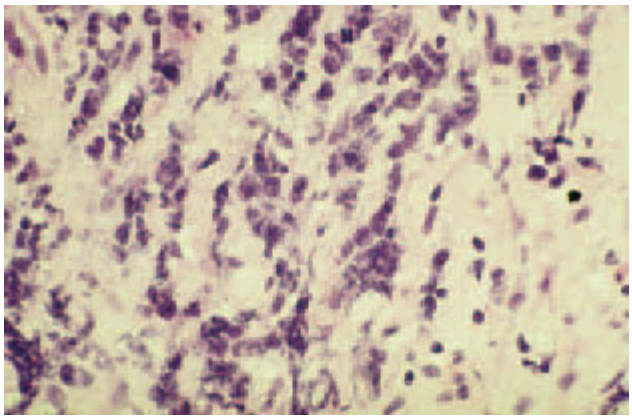


Fig. 29.35. Kaposi's sarcoma in a patient with AIDS. Portal zones show expansion with spindle cell tumour cells which are forming vascular clefts. (H & E, ×150.)

The prognosis depends on the degree of immunocompromise.

Kaposi's sarcoma largely affects homosexual men and is decreasing in prevalence. The patient is usually asymptomatic. It frequently involves the liver as purple–brown, soft nodules. Histology shows multifocal areas of vascular endothelial proliferation with pleomorphic spindle cells and extravasated erythrocytes (fig. 29.35). US shows small hyperechoic nodules and dense peripheral bands. *CT* shows hypoattenuated lesions enhancing after contrast.

Drug-induced HIV-infected patients are exposed to many potential hepato-toxins. Any agent should be considered at fault. Drug interactions must always be considered. Drug reactions are the commonest cause of *jaundice* in AIDS [8]. Anti-mycobacterials are most commonly at fault, especially isoniazid and rifampicin.

Trimethoprim-sulfamethoxasole is a common offender, causing granulomatous hepatitis and jaundice [17].

Hepatomegaly and steatosis may be related to nucleoside-analogue retroviral therapy [14]. Zidovudine and dideoxyinosine can cause severe, sometimes fatal, liver failure. The picture is of mitochondrial failure [3].

Hepato-biliary disease

This includes intra- and extra-hepatic sclerosing cholangitis [6], papillary stenosis and acalculous cholecystitis [31]. It is termed *AIDS cholangiopathy*. It is associated with severe immunodeficiency with CD4 lymphocytes counts of less than 200.

Cryptosporidia are the single most common pathogens identified. *Cryptosporidium parvum* is cytopathic for cultured human biliary epithelia via an apoptotic mechanism (fig. 29.36) [9].

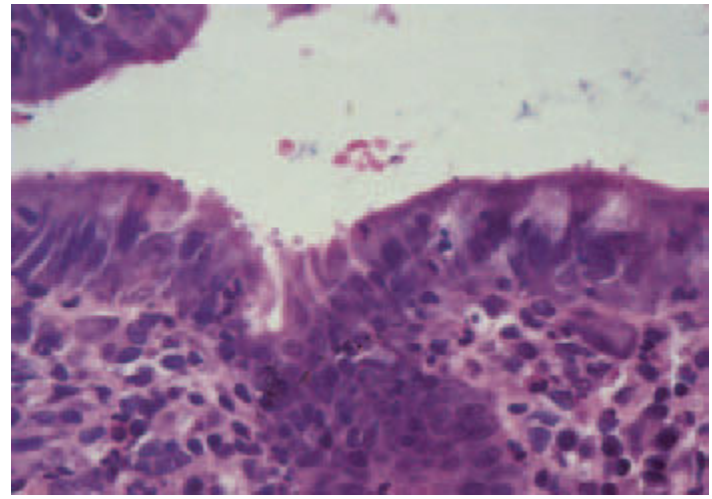


Fig. 29.36. Cryptosporidiosis of the gallbladder in a patient with AIDS. (H & E, ×160.)

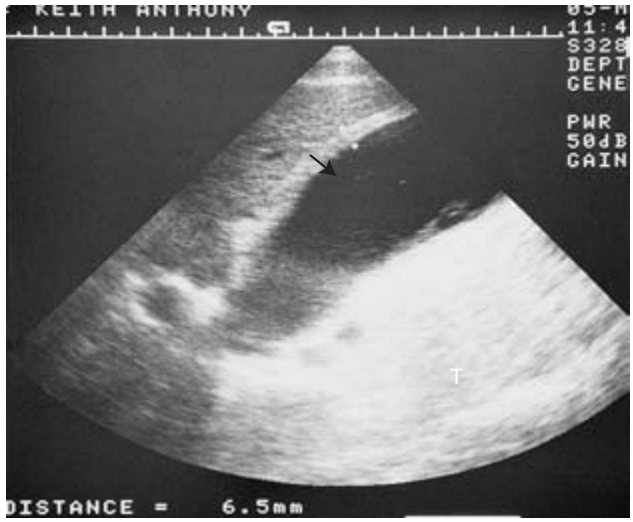


Fig. 29.37. Cryptosporidial biliary infection in a patient with AIDS. US showing a greatly thickened gallbladder wall (arrowed) and bile ducts.

Microsporidia or *cytomegalovirus* may be causative [5, 22]. The agent can be found in biliary or gallbladder wall and in bile. The patient presents with intermittent right upper abdominal pain and tenderness. Serum alkaline phosphatase may be strikingly high, but serum bilirubin is usually normal. Presentation may also be as painless cholestasis or as acute bacterial cholangitis.

US is the best initial diagnostic tool. It shows bile duct thickening or biliary dilatation or both (fig. 29.37). A hyperechoic nodule may be seen as the distal end of the common bile duct and represent an oedematous papilla [10].

Endoscopic US is useful in demonstrating papillary stenosis [2].

ERCP is the diagnostic gold standard, but gives little additional information if the US is normal [11]. It shows an irregularly dilated common bile duct with papillary stenosis (fig. 29.38). Better yield of the causative agent is obtained if multiple (duodenal and papillary) biopsies are taken and the bile sampled [5].

Prognosis and treatment

The outcome (mean survival 7.5 months) is similar to that of matched AIDS controls [13]. Only 14% survive 1 year [5]. Prognosis depends on the stage of immunosuppression.

Treatment is primarily endoscopic. Sphincterotomy gives striking relief of pain or cholangitis [7]. Balloon dilatation and stents may be necessary. Medical treatment of cryptosporidial or microsporidial infection has failed to relieve biliary symptoms.

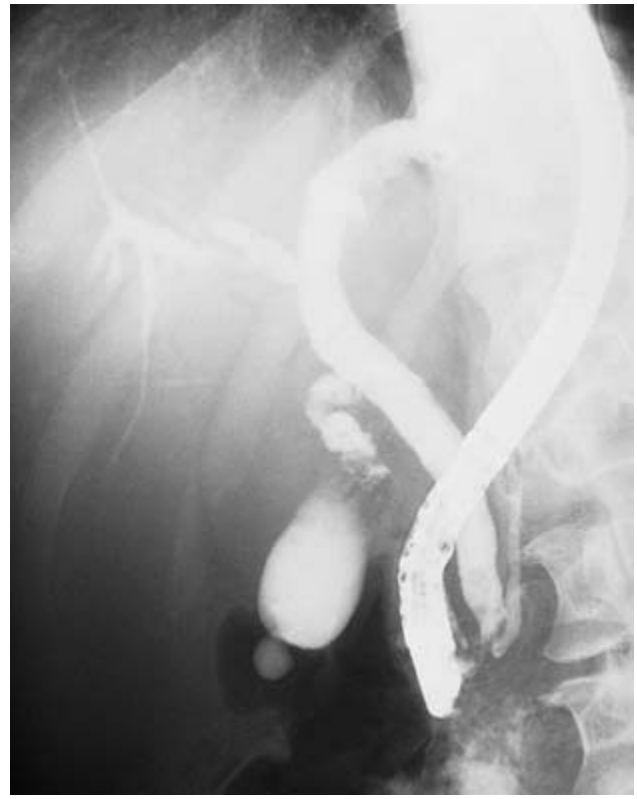


Fig. 29.38. Ampullary stenosis and sclerosing cholangitis due to cytomegalovirus infection in a patient with AIDS.

Acalculous cholecystitis

This is primarily infectious and due to the same causes as AIDS cholangiopathy. It can be gangrenous. US shows a thickened gallbladder wall, air in the gallbladder and pericholecystic fluid [1]. Acute cholecystitis must be treated surgically. Results for laparoscopic cholecystectomy are not encouraging.

References

1 Aaron JS, Wynter CD, Kirton OC *et al*. Cytomegalovirus associated with acalculous cholecystitis in a patient with acquired immune deficiency syndrome. *Am. J. Gastroenterol*. 1988; **83**: 879.

2 Benhamou Y, Caumes E, Gerosa Y *et al*. AIDS-related cholangiopathy. Critical analysis of a prospective series of 26 patients. *Dig. Dis. Sci*. 1993; **38**: 1113.

3 Bissuel F, Bruneel F, Habersetzer F *et al*. Fulminant hepatitis with severe lactate acidosis in HIV-infected patients on didanosine therapy. *J. Intern. Med*. 1994; **235**: 367.

4 Bonacini M, Nussbaum J, Ahluwalia C. Gastrointestinal, hepatic, and pancreatic involvement with *Cryptococcus neoformans* in AIDS. *J. Clin. Gastroenterol*. 1990; **12**: 295.

5 Bouche H, Housset C, Dumont J-L *et al*. AIDS-related cholangitis: diagnostic features and course in 15 patients. *J. Hepatol*. 1993; **17**: 34.

6 Cello JP. Acquired immunodeficiency syndrome cholangiopathy: spectrum of disease. *Am. J. Med*. 1989; **86**: 539.

7 Cello JP, Chan MF. Long-term follow-up of endoscopic retrograde cholangiopancreatography sphincterotomy for patients with acquired immune deficiency syndrome papillary stenosis. *Am. J. Med.* 1995; **99**: 600.
8 Chalasani N, Wilcox CM. Etiology, evaluation and outcome of jaundice in patients with acquired immunodeficiency syndrome. *Hepatology* 1996; **23**: 728.
9 Chen X-M, Levine SA, Tietz P *et al*. *Cryptosporidium parvum* is cytopathic for cultured human biliary epithelia via an apoptotic mechanism. *Hepatology* 1998; **28**: 906.
10 Da Silva F, Boudghene F, Lecomte I *et al*. Sonography in AIDS-related cholangitis: prevalence and cause of an echogenic nodule in the distal end of the common bile duct. *Am. J. Roentgenol*. 1993; **160**: 1205.
11 Daly CA, Padley SP. Sonographic prediction of a normal or abnormal ERCP in suspected AIDS related sclerosing cholangitis. *Clin. Radiol.* 1996; **51**: 618.
12 Eyster ME, Diamondstone LS. Natural history of hepatitis C virus infection in multitransfused haemophiliacs: effect of coinfection with human immunodeficiency virus. *J. AIDS* 1993; **6**: 602.
13 Forbes A, Blanshard C, Gazzard B. Natural history of AIDS-related sclerosing cholangitis: a study of 20 cases. *Gut* 1993; **34**: 116.
14 Fortgang IS, Belitsos PC, Chaisson RE *et al*. Hepatomegaly and steatosis in HIV-infected patients receiving analogue antiretroviral therapy. *Am. J. Gastroenterol*. 1995; **90**: 1433.
15 Housset C, Pol S, Carnot F *et al*. Interactions between human immunodeficiency virus-1, hepatitis delta virus and hepatitis B virus infections in 260 chronic carriers of hepatitis B virus. *Hepatology* 1992; **15**: 578.
16 Koehler JE, Quinn FD, Berger TG *et al*. Isolation of *Rochalimaea* species from cutaneous and osseous lesions of bacillary angiomatosis. *N. Engl. J. Med*. 1992; **327**: 1625.
17 Kreisberg R. Clinical problem-solving. We blew it. *N. Engl. J. Med*. 1995; **332**: 945.
18 Lefkowitch JH. Pathology of AIDS-related liver disease. *Dig. Dis. Sci*. 1994; **12**: 321.
19 McDonald JA, Caruso L, Karayiannis P *et al*. Diminished responsiveness of male homosexual chronic hepatitis B carriers with HTLV-III antibodies to recombinant alpha interferon. *Hepatology* 1987; **7**: 719.
20 Poblete RB, Rodriguez K, Foust RT *et al*. *Pneumocystis carinii* hepatitis in the acquired immunodeficiency syndrome (AIDS). *Ann. Intern. Med*. 1989; **110**: 737.
21 Pol S, Lamorthe B, Thi NT *et al*. Retrospective analysis of the impact of HIV infection and alcohol use on chronic hepatitis C in a large cohort of drug users. *J. Hepatol.* 1998; **28**: 945.
22 Pol S, Romana CA, Richard S *et al*. Microsporidia infection in patients with the human immunodeficiency virus and unexplained cholangitis. *N. Engl. J. Med*. 1993; **328**: 95.
23 Poles MA, Lew EA, Dieterich DT. Diagnosis and treatment of hepatic disease in patients with HIV. *Gastroenterol. Clin. North Am.* 1997; **26**: 291.
24 Scharschmidt BF, Held MJ, Hollander HH *et al*. Hepatitis B in patients with HIV infection: relationship to AIDS and patient survival. *Ann. Intern. Med.* 1992; **117**: 837.
25 Soloman RE, Kaslow RA, Phair JP *et al*. Human immunodeficiency virus and hepatitis delta virus in homosexual men. A study of four cohorts. *Ann. Intern. Med*. 1988; **108**: 51.
26 Spengler U, Rockstroh JK. Hepatitis C in the patient with human immunodeficiency virus infection. *J. Hepatol.* 1998; **29**: 1023.
27 Stevens DA. Current concepts. Coccidiomycosis. *N. Engl. J. Med*. 1995; **332**: 1077.
28 Telfer P, Sabin C, Devereux H *et al*. The progression of HCV-associated liver disease in a cohort of haemophilic patients. *Br. J. Haematol*. 1994; **87**: 555.
29 Tomkins LS. Of cats, humans and *Bartonella*. *N. Engl. J. Med.* 1997; **337**: 1916.
30 Vakil NB, Schwartz SM, Buggy BP *et al*. Biliary cryptosporidiosis in HIV-infected people after the water borne outbreak of cryptosporidiosis. *N. Engl. J. Med*. 1996; **334**: 19.
31 Wilcox CM, Monkemuller KE. Hepatobiliary diseases in patients with AIDS: focus on AIDS cholangiopathy and gallbladder disease. *Dig. Dis.* 1998; **16**: 205.
32 Wilcox CM, Rabeneck L, Friedman S. AGA technical review: malnutrition and cachexia, chronic diarrhea, and hepatobiliary disease in patients with human immunodeficiency virus infection. *Gastroenterology* 1996; **111**: 1724.
33 Wong DK, Yim C, Naylor CD *et al*. Interferon alfa treatment of chronic hepatitis B: randomised trial in a predominantly homosexual male population. *Gastroenterology* 1995; **108**: 165.

Jaundice of infections

Bacterial pneumonia

Jaundice is an unusual complication of pneumonia. It is, however, still frequent in Africans, where it may be related partly to haemolysis in those deficient in glucose-6-phosphate dehydrogenase [5]. The jaundice is also both hepato-cellular and cholestatic.

Liver biopsy shows non-specific changes; electron microscopy shows cholestasis. There is also evidence of toxic liver injury. Increased numbers of fat-storing lipocytes are seen during the acute stage.

Septicaemia and septic shock

Liver function abnormalities, including modest increases in serum alkaline phosphatase, transaminases and bile salts, are not uncommon in patients with severe infections, septicaemia, toxic shock and endotoxaemia [1, 4]. In two-thirds, jaundice is a feature and, if it persists, carries a bad prognosis.

Hepatic histology shows non-specific hepatitis including mid-zonal and peripheral necrosis. Cholestasis may be marked and in severe cases is shown as inspissated bile within dilated and proliferated portal and periportal bile ductules [2]. Cultures of the liver are sterile.

The causes are multifactorial. Hepatic hypoperfusion plays a part. The cholangiolar lesions might be related to interference with canalicular exchange of water and electrolytes, to endotoxaemia, to staphylococcal exotoxin [3] or to interference with the peri-biliary vascular plexus as a result of shock [1]. TNF-α may mediate endotoxin-

induced cholestasis [6]. Endotoxin interferes with bile acid transport.

The syndrome of jaundice associated with extrahepatic infection is functional and reversible upon control of the infection.

References

1 Gourley GR, Chesney PJ, Davis JP *et al*. Acute cholestasis in patients with toxic-shock syndrome. *Gastroenterology* 1981; **81**: 928.

2 Lefkowitch JH. Bile ductular cholestasis: an ominous histopathologic sign related to sepsis and 'cholangitis lenta'. *Hum. Pathol*. 1982; **13**: 19.

3 Quale JM, Mandel LJ, Bergasa NV *et al*. Clinical significance and pathogenesis of hyperbilirubinemia associated with *Staphylococcus aureus* septicemia. *Am. J. Med*. 1988; **85**: 615.

4 Sikuler E, Guetta V, Keynan A *et al*. Abnormalities in bilirubin and liver enzyme levels in adult patients with bacteremia. *Arch. Intern. Med*. 1989; **149**: 2246.

5 Tugwell P, Williams AO. Jaundice associated with lobar pneumonia. *Q. J. Med*. 1977; **46**: 97.

6 Whiting JF, Green RM, Rosenbluth AB *et al*. Tumor necrosis factor-alpha decreases hepatocyte bile salt uptake and mediates endotoxin-induced cholestasis. *Hepatology* 1995; **22**: 1273.

Chapter 30
Nodules and Benign Liver Lesions

The increased use of radiological imaging, particularly ultrasound examination, has led to much more frequent identification of nodules in the liver. Patient management is vastly different depending on the different causes (figs 30.1, 30.2).

Diagnosis and management depend on whether the patient has underlying liver disease, usually cirrhosis, when hepato-cellular cancer (HCC) has to be excluded, or whether the lesion is a benign nodule or metastasis. Hepatitis B and C markers should be sought and a routine serum α-fetoprotein level determined.

Small hepato-cellular cancer (Chapter 31)

The patient is well aware of the significance of the small nodule. Considerable anxiety is present in both patient and physician and a definitive diagnosis should be made if at all possible, particularly as the survival rate (of resection or transplant) is much greater with tumours only 1–2 cm in diameter (fig. 30.3).

Cirrhosis may or may not have been diagnosed previously. The tumour is usually asymptomatic and there are no additional physical signs. The serum α-fetoprotein level is usually less than 200 ng/ml. The level may be normal or modestly raised due to non-malignant regeneration nodules. Serial records showing an increasing α-fetoprotein level over the last few months and years may be particularly helpful as well as any records of past ultrasound or other imaging results.

Difficulty exists in distinguishing a dysplastic or macro-regenerative nodule from a cancer (figs 30.4, 30.5). Indeed all three may coexist. Imaging and histological characteristics may be inconclusive.

The percentage of diagnostic success using imaging depends on the size of the lesion, particularly if it is larger than 2 cm in diameter.

Ultrasound usually detects lesions less than 2 cm. The lesion is hypoechoic with ill-defined margins.

CT shows a hypodense lesion. It frequently fails to detect the size and number of lesions. Intravenous contrast enhancement is essential.

Hepatic angiography is not reliable diagnostically and has largely been replaced by MRI.

MRI is better than CT for showing focal lesions. T_2-weighted images show focal lesions, vascular invasion and satellites. Contrast such as gadolinium or supermagnetic iron oxide are safe and useful.

Guided nodule biopsy. This is done under ultrasound control. Success depends on the size of the lesion and its position. It is important to sample tissue away from the nodule so that the underlying cirrhosis may be diagnosed. There is a possibility of needle-tract seeding of tumour [15]. The specimen may be fully diagnostic of HCC, but more often the appearances are suspicious and suggestive. The picture in nodules having a high risk for evolution to HCC include an increased number of hepa-

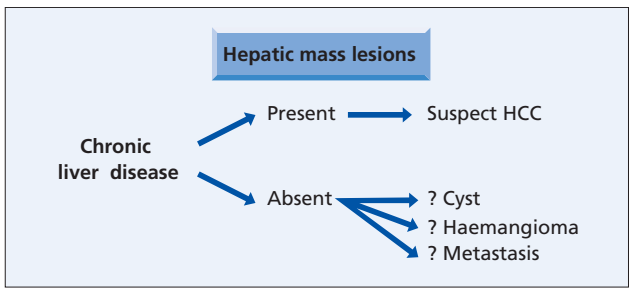


Fig. 30.1. Algorithm for the management of hepatic mass lesion (nodule) in a patient with underlying chronic liver disease.

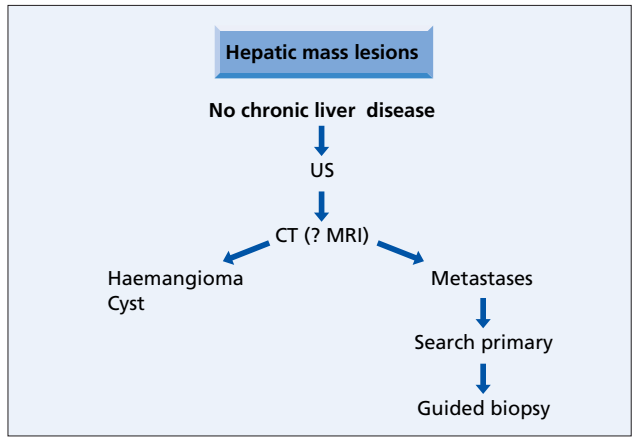


Fig. 30.2. Algorithm for the management of a hepatic mass lesion (nodule) in a patient without underlying chronic liver disease.

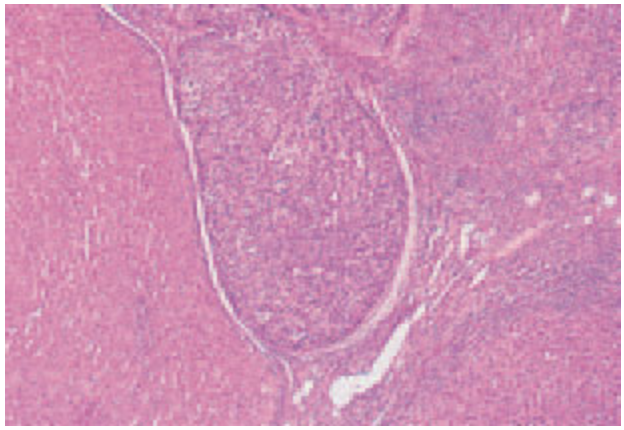


Fig. 30.3. Cirrhosis and a very small hepato-cellular carcinoma.

Fig. 30.4. Explant liver of chronic hepatitis C virus cirrhosis: note nodularity. Larger nodules with green/tan appearance are dysplastic.

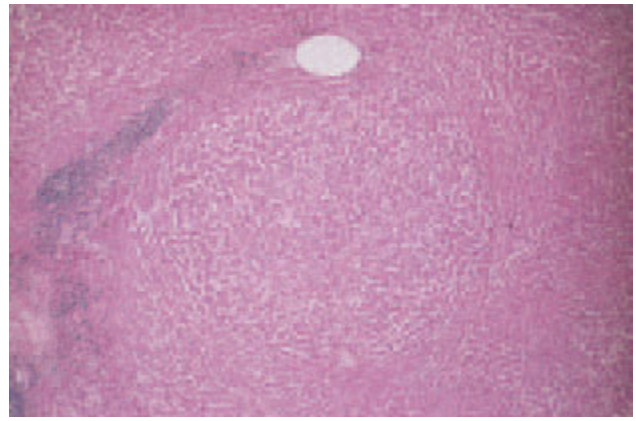


Fig. 30.5. Same patient as in fig. 30.4. Part of a dysplastic nodule: the central nodule (nodule-in-nodule) shows thick trabeculae and focal cholestasis. It is probably a minute hepato-cellular carcinoma. (H & E, × 10.) (Courtesy of Professor A.P. Dhillon.)

tocyte nuclei compared with surrounding tissue, clear cell change, small cell dysplasia and fatty change [18]. Features in a dysplastic nodule favouring HCC include nuclear atypia, high nuclear/cytoplasm density, absence of portal tracts, unaccompanied arteries and reduction of reticulin and mitoses [7].

Conclusions. Any focal lesion in a cirrhotic liver must be regarded as suspicious of HCC or of its impending development [14]. Macro-regenerative nodules which are at least 1 cm in diameter and are hypoechoic, are particularly precancerous [5,19]. Screening of focal lesions by ultrasound and α-fetoprotein at 6-monthly intervals at least is mandatory.

Nodules in the absence of underlying liver disease (fig. 30.2)

Discovery of the lesion is followed by the usual detailed history and clinical examination, routine biochemical tests, hepatitis B and C viral markers and an α-fetoprotein level. A family history is taken for cystic disease.

Simple cysts (Chapter 33)

The hepatic cyst may be simple or multiple and may be accompanied by renal or other cysts.

On ultrasound, simple cysts have smooth walls and echo-free contents with through transmission of the sound waves. The CT scan shows a low attenuation value of the centre equivalent to water. There is no enhancement with contrast. MRI with T_2-weighted images shows the cysts as fluid.

Haemangioma

This is the commonest benign tumour of the liver, being found in about 5% of autopsies. Diagnosis is increasing with the greater use of scanning. It is usually single and small, but occasionally may be multiple or very large. The tumour is commonly subcapsular, on the convexity of the right lobe and is occasionally pedunculated. On section it appears round or wedge shaped, dark red in colour and has a honeycomb pattern, with a fibrous capsule which may be calcified. Histologically, a communicating network of spaces contains red corpuscles. Factor VIII may be expressed. The tumour is lined by flat endothelial cells and contains scanty fibrous tissue. Occasionally, there is a marked fibrous component.

Clinical features. The majority are asymptomatic and discovered incidentally. Symptoms from giant tumours (>4 cm diamater) include abdominal mass and pain due to thrombosis. Symptoms may be due to pressure on adjacent organs. Rarely, a vascular hum is heard over the lesion.

Radiology. A plain X-ray may show a calcified capsule.

Ultrasound shows a solitary echogenic spot with

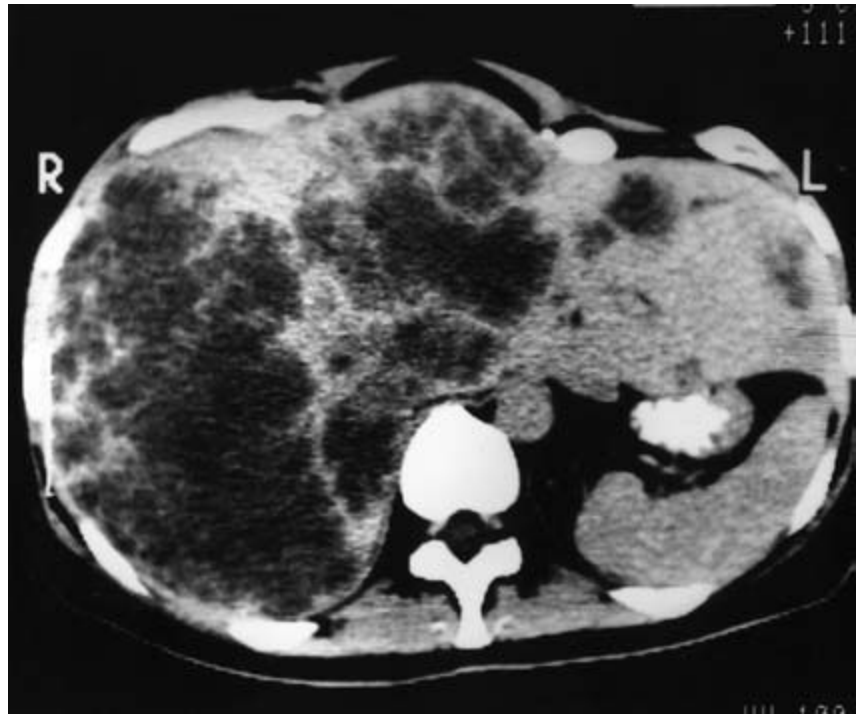


Fig. 30.6. Haemangioma. CT shows a giant benign haemangioma in the right lobe. A few small lesions are seen in the left lobe. The lesions filled in completely after intravenous contrast.

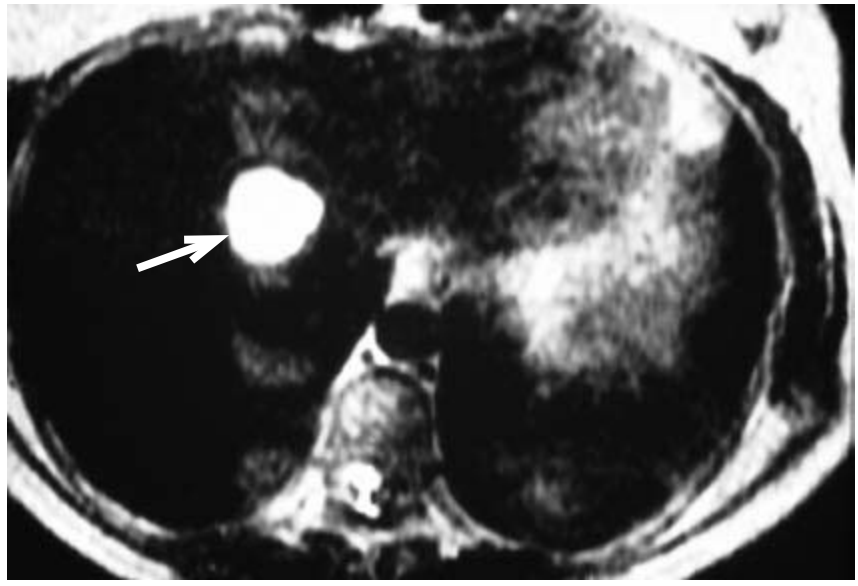


Fig. 30.7. Haemangioma. MRI using long T_2-weighting shows a very bright lesion (arrow). This reflects a profuse and very sluggish circulation usually due to a haemangioma.

smooth well-defined borders. Posterior acoustic enhancement, due to increased sound transmission through the blood of cavernous sinuses, is characteristic.

CT scan enhanced by contrast shows distinctive puddling of contrast in venous channels (fig. 30.6). The contrast fills in the lesion from the periphery to the centre, until opacification is homogeneous after 30–60 min. Foci of globular enhancement are seen after dynamic bolus CT. Calcification may be seen due to previous bleeding or thrombus formation.

MRI shows the tumour as a markedly high intensity area. T_2 is prolonged over 8 ms (fig. 30.7). MRI is of special value in diagnosing small haemangiomas.

SPECT with ^{99m}Tc-labelled red blood cells shows persistent blood pool activity within the lesion.

Arteriography is rarely necessary. Large arterial branches are displaced. The hepatic arteries divide to form small vessels before filling the vascular space. Prolonged, up to 18 s, opacification of the lesion may be shown.

Needle liver biopsy. Using a fine needle this is safe, but unnecessary in view of the diagnostic imaging.

Treatment is usually unnecessary as the lesions do not increase in size [11] or in clinical manifestations. The possibility of rupture is not an indication for surgery. Resection (usually lobectomy or segmentectomy) is safe if pain is severe or expansion rapid [1, 17].

Focal nodular hyperplasia

Focal nodular hyperplasia (FNH) is defined as a nodule composed of benign-appearing hepatocytes in a liver which is otherwise histologically normal or nearly normal (fig. 30.8). It is commonly subcapsular, but can be pedunculated and in either lobe. The lesions vary in size between 1 and 15 cm and may be multiple. The lesion is supported by large arteries accompanied by fibrous stroma containing ductules. The stroma is usually prominent, forming a stellate scar [7]. A central stellate scar (stalk) contains a large artery from which blood flows to the periphery of the lesion. The scar is dense and contains bile ductules, but no portal vein radical. It may represent a vascular anomaly as it is associated with haemangiomas elsewhere. Studies using X-chromosome inactivation showed a random pattern consistent with a polyclonal lesion, thus confirming a reactive disorder related to pre-existing vascular malformation [13]. It does not have an association with sex hormones [10]. It affects both sexes, but especially women in their reproductive years, some of whom have never taken sex hormones. It may present with pain or an abdominal mass. Serum biochemical tests are normal in the uncomplicated case.

The diagnosis is made by imaging with demonstration of the central scar (figs 30.9, 30.10) [14]. Ultrasound shows a nodule of varying echogenicity from patient to patient. The central scar is rarely seen. Colour Doppler shows arterial signals peripherally and centrally.

Contrast-enhanced CT shows a hypervascular mass with a central hypodense stellate scar (fig. 30.9) [2].

MRI shows a mass iso-intense or hypo-intense on T_1-weighted images and slightly intense on T_2-weighted images. The central scar is not usually seen. MRI with

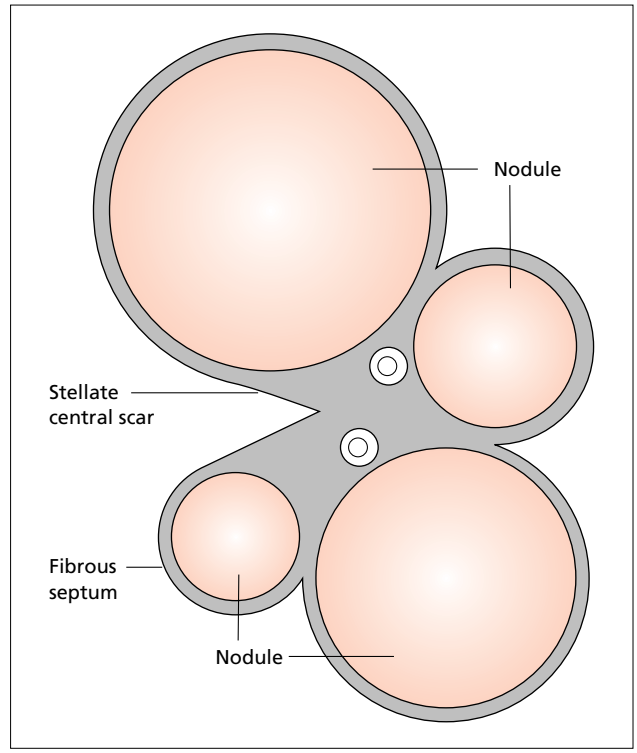


Fig. 30.8. The structure of focal nodular hyperplasia.

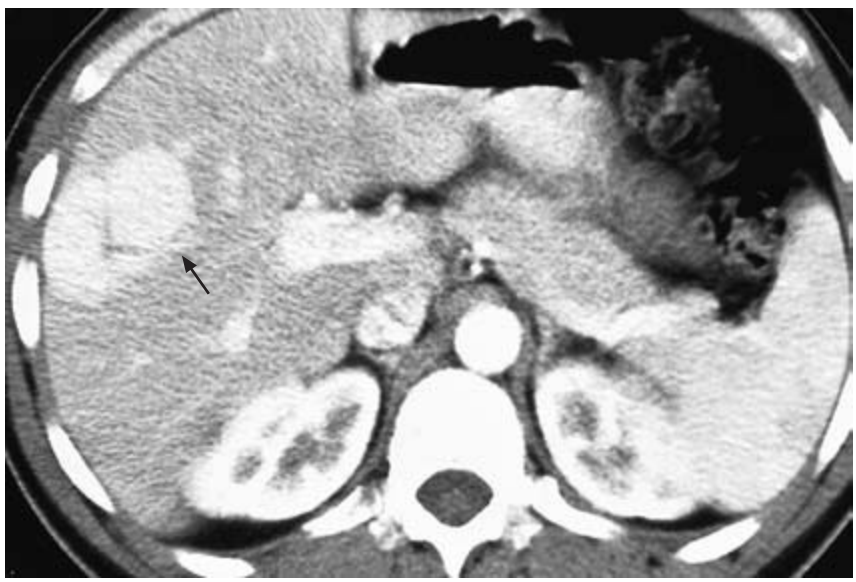


Fig. 30.9. Focal nodular hyperplasia. CT scan, enhanced with intravenous contrast, shows a focal hepatic lesion 5.8 cm in diameter with a central scar (arrow) in the right lobe.

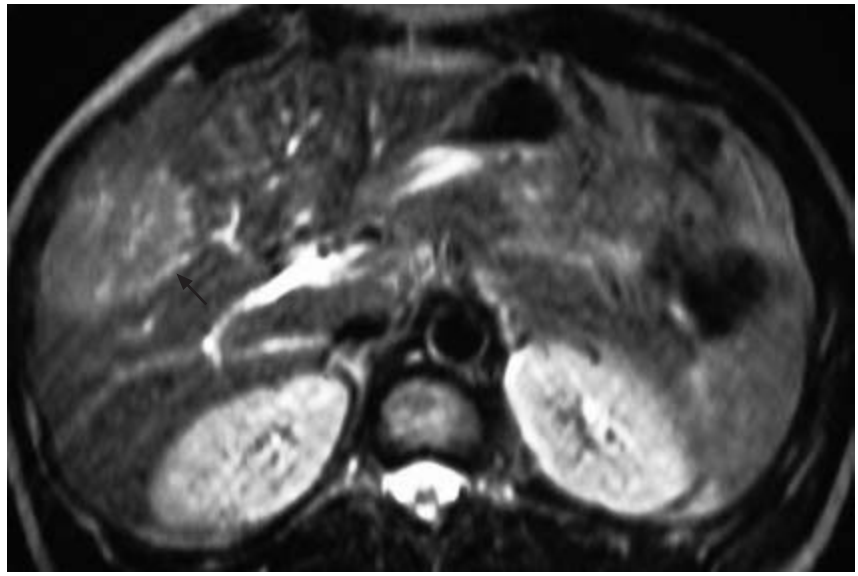


Fig. 30.10. Focal nodular hyperplasia. MRI shows a liver mass in the right lobe (arrow), homogeneously hypervascular after intravenous gadolinium and with a hypo-intense central area.

intravenous gadolinium at the early stages shows a central hypodense area, whereas 4 min later, high signal intensity is present showing that the central scar is vascularized. MRI with gadolinium is the best diagnostic procedure for FNH, having a sensitivity of 70% and a specificity of 98% [3]. Angiography confirms the supply is directed centrally to the scar and is then distributed to the periphery of the lesion like the spokes of a wheel. In most instances, angiography is not considered necessary as CT and MRI are usually diagnostic.

Histologically, the lesion consists of normal hepatocytes and Kupffer cells. The central core is composed of fibrous tissue and proliferating bile ducts (fig. 30.11). Liver biopsy is not usually necessary for diagnosis.

Interpretation may be difficult on the small specimen provided.

FNH is a static lesion, increasing only slowly, if at all, with time. It should be treated conservatively without surgery. Pregnancy may be allowed and any oral hormone therapy continued safely [10, 21].

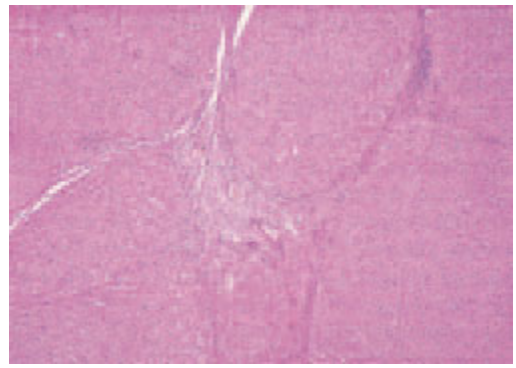


Fig. 30.11. Focal nodular hyperplasia. The central core is composed of fibrous tissue containing a thick-walled artery and proliferating bile ducts. (H & E, ×160.)

Hepatic adenoma

Hepato-cellular adenoma is defined as a benign neoplasm composed of hepatocytes in a liver that is otherwise histologically normal or nearly normal (figs 30.12, 30.13). There are no portal tracts or central veins. Bile ducts are conspicuously absent. There is no central scar or predominant arterial supply. Kupffer cells are scarce. Signs of necrosis and infarction may be present and fatty change can be seen in some sections. Large arteries and veins are present in excess, sinusoids may be focally dilated and peliosis may be present (Chapter 20).

There is an association with oral contraceptive use, particularly over many years and in older women. A

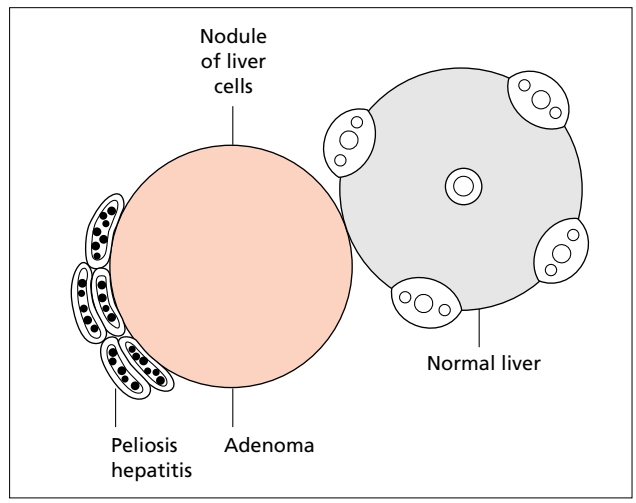


Fig. 30.12. Structure of hepatic adenoma and peliosis hepatis compared with normal liver.

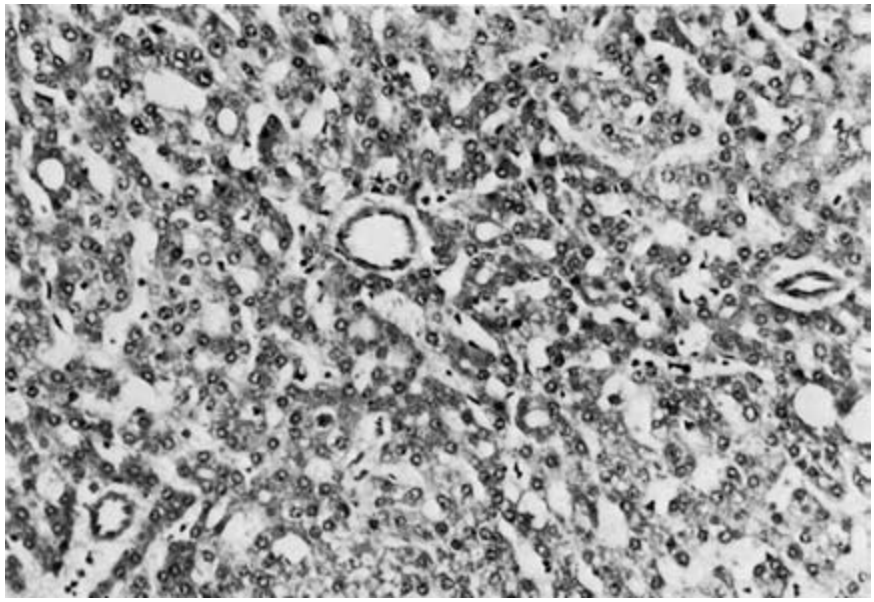


Fig. 30.13. Hepatic adenoma. The appearance is of sheets of near-normal liver cells without portal tracts. (H & E, ×185.)

decreasing prevalence can be related to the reduction in the content of oestrogens and especially progesterone in birth control pills and the increasing use of other methods of contraception.

Tumour may be discovered incidentally at autopsy, surgery or hepatic imaging performed for another condition.

The patient may *present* with a right upper quadrant mass. Haemorrhage into the tumour, or infarction, leads to abdominal pain and the lesion is tender. Rupture is associated with the symptoms and signs of acute intra-peritoneal bleeding.

Serum biochemical tests may be normal. Necrosis and rupture lead to increases in transaminases and alkaline phosphatase. Serum α-fetoprotein is normal.

Other associations. These include type 1a glycogen storage disease [9], danazol therapy [4], diabetes mellitus and galactosaemia.

Localization

Ultrasound usually shows the filling defect although this may not be so when it closely resembles normal liver. Colour Doppler gives venous signals.

CT shows diffuse arterial enhancement. Occasional hyperdense areas may represent haemorrhage and low density areas necrosis or fat.

MRI may confirm haemorrhages as hyper-intense areas on T_1- and T_2-weighted images. Hypo-intense areas corresponding to hyper-intense areas on T_2 represent necrosis [3]. There is no accumulation of gadolinium contrast in the lesion.

Arteriography (fig. 30.14) shows stretching of the feeding arteries around the mass with branches penetrating from the periphery. Irregular vessels course through the lesion. Areas of haemorrhage may be shown. There is a marked capillary blush.

Management

Adenoma is a stimulated lesion. The stimulus may be hormonal, type 1 glycogenesis or familial diabetes. Complications such as haemorrhage with subsequent necrosis may cause symptoms and very rarely the tumour may rupture. Progression to hepato-cellular carcinoma has been reported, especially with glycogen storage disease, but is very rare [9]. In one-third of patients, the nodules are multiple. In the absence of complications, it is safe to observe the patient with 6-monthly ultrasounds for 2 years. Regression has been reported [8]. Sex hormones must be stopped. Surgical resection may be required in the younger woman, especially where pregnancies are desired. Resection is safe and well tolerated [12].

Focal nodular hyperplasia and adenoma contrasted (fig. 30.15, table 30.1) [14]

Differential diagnosis of these common lesions, often found by chance, can be difficult. The central scar in FNH is important. Adenoma is more often symptomatic and complicated and treatment is more often necessary.

Liver metastases

These are considered in more detail in Chapter 31.

The history of primary tumour, especially of breast, lung, colon or stomach, is clearly important. Physical examination includes a search for the primary lesion.

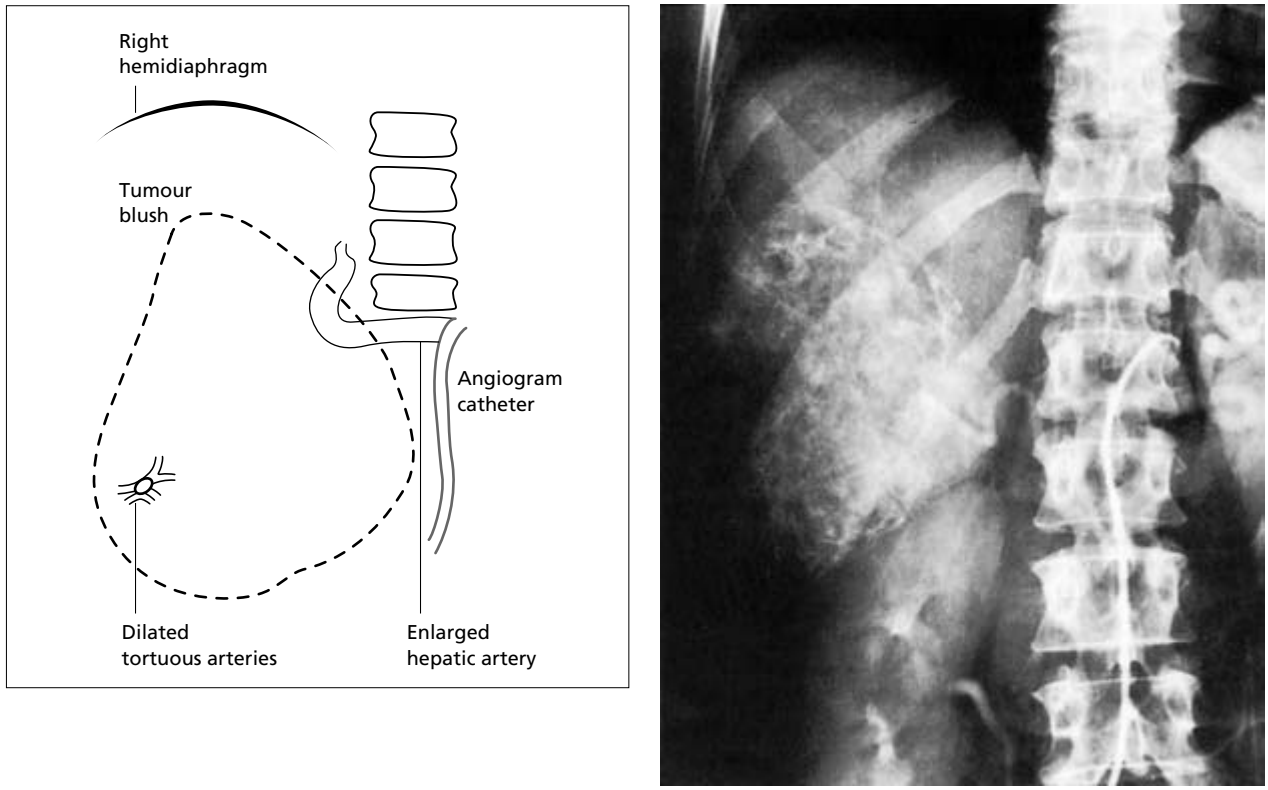


Fig. 30.14. Hepatic adenoma related to oral contraceptives. Late stage of coeliac angiogram shows abnormal vascularity in the tumour of the lower part of the right lobe of the liver.

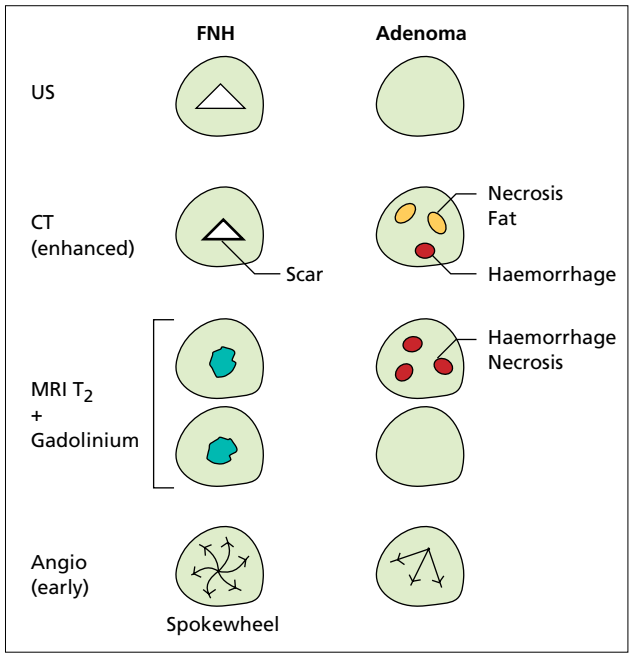


Fig. 30.15. The imaging of focal nodular hyperplasia (FNH) and adenoma contrasted.

Table 30.1. Focal nodular hyperplasia (FNH) and hepatic adenoma

	FNH	Adenoma
Sex	Female	Female
Hormone therapy	0	+++
Symptoms	Rare	Occasional
Multiple	About 30%	12–30%
Associations	Haemangiomas	Glycogenoses, androgens, peliosis
Central arterial scar	Yes	No
Growth	Static	If stimulated
Treatment	Conservative	Resection if symptomatic

Serological oncology markers such as carcino-embryonic antigen (CEA) and CA 19-9 should be performed and the imaging characteristics of metastases sought. If necessary, directed biopsy of the nodule may be done.

Other benign tumours

Cholangioma (bile duct adenoma)

This is a very rare tumour of bile duct origin. It has the structure of a cystadenoma and must be distinguished from a simple cyst. A mixed tumour contains both proliferating bile ducts and hepatic cells.

Biliary cystadenoma

The tumour is usually large and affects the right lobe. It may be pedunculated. The cysts contain clear yellow or mucinous brown material. It affects largely middle-aged women. Symptoms include abdominal mass and pain. Rarely the biliary tree is obstructed. The tumour must be distinguished from fibro-polycystic disease and simple cyst.

Resection may be possible.

Nodular regenerative hyperplasia

This is a common condition frequently found at autopsy [20]. Monoacinar nodules of cells resembling normal hepatocytes involve liver diffusely (fig. 30.16). They are not outlined by fibrous tissue. They are related to the obliteration of small portal veins at the level of the acinus. This causes atrophy of the involved acinus while adjacent acini, within the intact blood supply, undergo compensatory hyperplasia causing micronodularity (fig. 30.17) [20]. The nodular regenerative hyperplasia is a secondary and non-specific tissue adaptation to heterogeneous distribution of blood flow [20].

The commonest association is with rheumatoid arthritis and Felty's syndrome. Nodules are also seen with myeloproliferative syndromes, hyperviscosity syndromes, in the transplanted liver [6] and as a reaction to drugs, particularly anabolic steroids and cytotoxics.

Portal hypertension is marked and there is sometimes haemorrhage into the nodule. Ultrasound shows hypo-isoechoic masses with anechoic centres after bleeding. CT shows a hypodense pattern with no contrast

Fig. 30.16. Nodular regenerative hyperplasia. Surgical liver biopsy shows nodules of varying sizes resembling normal hepatocytes. (H & E, × 25.)

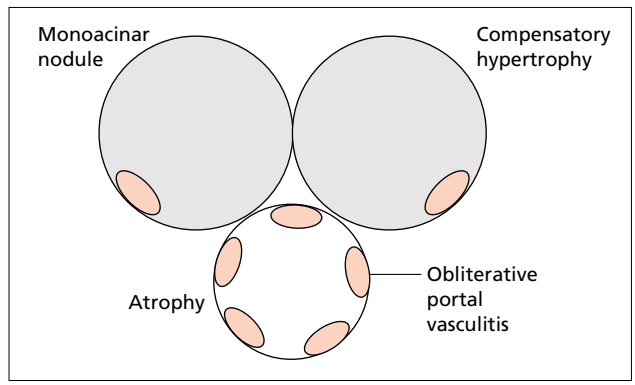


Fig. 30.17. Diagram of nodular regenerative hyperplasia shows obliteration of a small portal venule with compensatory hypertrophy of adjacent acini.

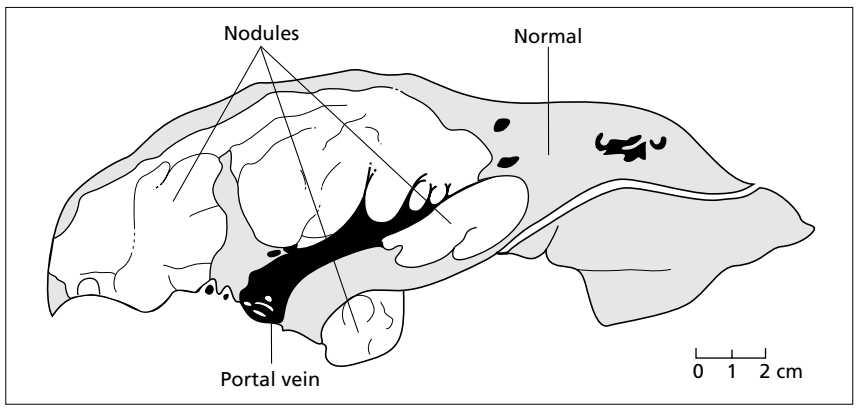


Fig. 30.18. Partial nodular transformation.

enhancement. Liver biopsy is not diagnostic, but shows two populations of hepatocytes differing in size. Portacaval shunting or TIPS for bleeding oesophageal varices is well tolerated.

Partial nodular transformation [16]

This is very rare. The peri-hilar region is replaced by nodules. The periphery of the liver is normal or atrophic (fig. 30.18). Portal hypertension is due to obstruction by the nodules. Liver cell function is good. Fibrosis is inconspicuous. Diagnosis is difficult and awaits autopsy. The cause is unknown.

References

1 Belli L, DeCarlis L, Beati C *et al*. Surgical treatment of symptomatic giant haemangiomas of the liver. *Surg. Gynecol. Obstet*. 1992; **174**: 474.

2 Carlson SK, Johnson CD, Bender CE *et al*. CT of focal nodular hyperlasia of the liver. *Am. J. Roentgenol*. 2000; **174**: 705.

3 Cherqui D, Rahmouni A, Charlotte F *et al*. Management of focal nodular hyperplasia and hepatocellular adenoma in young women: a series of 41 patients with clinical, radiological and pathological correlations. *Hepatology* 1995; **22**: 1674.

4 Fermand JP, Levy Y, Bousary D *et al*. Danazol-induced hepatocellular adenoma. *Am. J. Med*. 1996; **88**: 529.

5 Ferrell L, Wright T, Lake J *et al*. Incidence and diagnostic features of macroregenerative nodules vs. small hepatocellular carcinoma in cirrhotic livers. *Hepatology* 1992; **16**: 1372.

6 Gane E, Portmann B, Saxena R *et al*. Nodular regenerative hyperplasia of the liver graft after liver transplantation. *Hepatology* 1994; **20**: 88.

7 International Working Party. Terminology of nodular hepatocellular lesions. *Hepatology* 1995; **22**: 983.

8 Kawakastu M, Vilgrain V, Erlinger S *et al*. Disappearance of liver cell adenoma: CT and MRI imaging. *Abdominal Imaging* 1997; **22**: 274.

9 Labrune P, Trioche P, Duvaltier I *et al*. Hepatocellular adenomas in glycogen storage disease type I and III: a series of 43 patients and review of the literature. *J. Pediatr. Gastroenterol. Nutr*. 1997; **24**: 276.

10 Mathieu D, Kobeiter H, Malson P *et al*. Oral contraceptive use and focal nodular hyperplasia of the liver. *Gastroenterology* 2000; **118**: 560.

11 Mungovan JA, Cronan JJ, Vacarro J. Hepatic cavernous haemangiomas: lack of enlargement over time. *Radiology* 1994; **191**: 111.

12 Nagorney DM. Benign hepatic tumours: focal nodular hyperplasia and hepatocellular adenoma. *World J. Surg*. 1995; **19**: 13.

13 Paradis V, Laurent A, Flejou J-F *et al*. Evidence for the polyclonal nature of focal nodular hyperplasia of the liver by the study of X-chromosome inactivation. *Hepatology* 1997; **26**: 891.

14 Rodés J, Sherlock S. Focal nodular hyperplasia in a young female. *J. Hepatol*. 1998; **29**: 1005.

15 Schotman SN, DeMan RA, Stoker J *et al*. Subcutaneous seeding of hepatocellular carcinoma after percutaneous needle biopsy. *Gut* 1999; **45**: 626.

16 Sherlock S, Feldman CA, Moran B *et al*. Partial nodular transformation of the liver with portal hypertension. *Am. J. Med*. 1966; **40**: 195.

17 Sinanan MN, Marchioro T. Management of cavernous haemangioma of the liver. *Am. J. Surg*. 1989; **157**: 519.

18 Terasaki S, Kaneko S, Kobayashi K *et al*. Histological features predicting malignant transformation of non-malignant hepatocellular nodules: a prospective study. *Gastroenterology* 1998; **115**: 1216.

19 Theise ND, Schwartz M, Miller C *et al*. Macroregenerative nodules and hepatocellular carcinoma in 44 sequential adult liver explants with cirrhosis. *Hepatology* 1992; **16**: 949.

20 Wanless IR, Peterson P, Das A *et al*. Hepatic vascular disease and portal hypertension in polycythemia vera and agnogenic myeloid metaplasia: a clinicopathological study of 145 patients examined at autopsy. *Hepatology* 1990; **12**: 1166.

21 Wiemann A, Mossinger M, Fronhoff K *et al*. Pregnancy in women with observed focal nodular hyperplasia of the liver. *Lancet* 1998; **351**: 1251.

Chapter 31
Malignant Liver Tumours

Benign liver tumours are usually anatomical curiosities of no importance (table 31.1). Malignant disease of the liver, however, is common, secondary deposits being at least 30 times commoner than primary cancers.

Hepato-cellular cancer

This tumour is increasingly associated worldwide with estimates of hepatitis B and hepatitis C prevalence. Marked increase has been shown in the USA over the last two decades (fig. 31.1) [22]; it has also increased in France and the UK. Hepato-cellular cancer (HCC) ranks as the fifth most common cancer in the world with an estimated 437000 new cases in 1990 [77]. It accounts for 7.4% of all cancers in males and 3.2% of all cancers in females. The highest prevalence areas are eastern Asia (including Japan and China) and sub-Saharan Africa. Geographic areas of lowest incidence are northern Europe, Australia and New Zealand and the Caucasian populations in North and Latin America. In America, the highest incidence is in migrants from high-risk countries and their descendants.

Experimental liver cancer

A bewildering number of carcinogens can initiate tumours in animals, but their relevance to man is uncertain. They include *p*-dimethyl-amino-azobenzene (butter yellow), nitrosamines, aflatoxin and *Senecio* alkaloids.

There are multiple steps from initiation to progression and finally to expression of the cancer. The carcinogen binds covalently to DNA. The development of cancer depends on the ability of the host to repair the DNA or on its tolerance to the carcinogen.

Work with transgenic and 'knock-out' mice indicate that hepatocyte proliferation accompanied by liver cell damage is essential for liver tumour development [25].

The cancer is associated with multiple genetic mutations in the chromosomes of affected hepatocytes. These aberrations can be detected by comparative hybridization. Many are basically common to hepatitis C virus (HCV) and hepatitis B virus (HBV) positive tumours, but there are differences between the two suggesting different processes of carcinogenesis [49].

Cellular pathways are regulated by the p53 tumour-suppressor gene which initiates apoptosis. p53 is activated in response to DNA damage and is frequently mutated in HCC. This is linked with progression of the tumour [65].

CD40, a member of the TNF receptor (TNFR) family is expressed in human HCC tissue [92]. TNFR mediates apoptosis and plays an important role in the host's defences against tumour cells by T-lymphocytes and macrophages.

Telomerase is a ribosomal protein complex which adds telomere repeater units at the end of the chromosomes. It is thought to be a key determinant for cell senescence [4]. Telomerase activity is increased in small liver tumours [23, 47].

Aetiological factors

Relation to cirrhosis

Cirrhosis may be premalignant irrespective of aetiology. The nodular hyperplasia progresses to carcinoma. Liver cell *dysplasia* may be an intermediate step (see fig. 30.5) [2]. This is found in 60% of cirrhotic livers containing HCC and in only 10% of non-cirrhotic livers. Patients with cirrhosis and high cell proliferation rates are at increased risk of developing cancer. Alternatively, carcinogenesis may be monoclonal with genetic alteration.

In one series of 1073 HCCs, 658 (61.3%) also showed cirrhosis. However, in 30% of African patients with hepatitis B-related hepato-cellular cancer, cirrhosis was not present. In the UK, about 30% of patients with HCC have no cirrhosis and survival is significantly better.

There are pronounced geographical differences in the frequency of cancer in cirrhotic livers. There is a particularly high association in South Africa and Indonesia, where cancer is reported in more than 30% of cirrhotic livers, whereas frequencies of 10–20% are reported from India, Britain and North America.

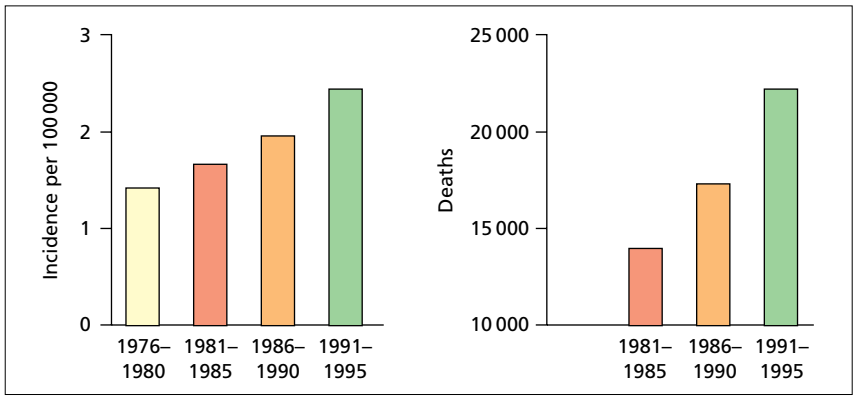


Fig. 31.1. Data showing a significant rise in the incidence of HCC in the USA over the 1980s and 1990s [22].

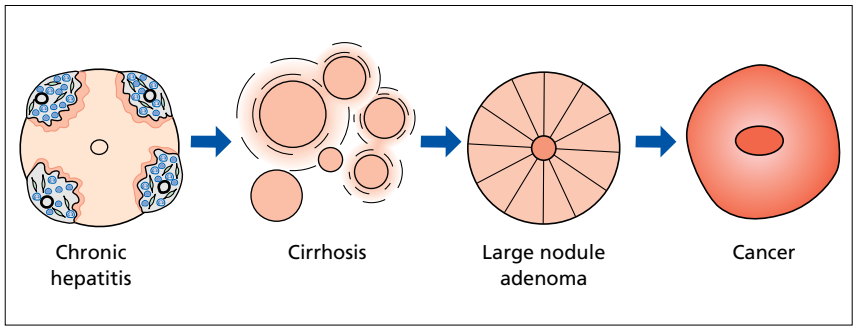


Fig. 31.2. Stages in the evolution of HCC from chronic hepatitis through cirrhosis and large nodules [88].

Table 31.1. Primary tumours of the liver

	Benign	Malignant
Hepato-cellular	Adenoma	HCC Fibro-lamellar Hepatoblastoma
Biliary	Adenoma Cystadenoma Papillomatosis	Cholangiocarcinoma Combined hepato-cellular–cholangiocarcinoma Cystadenocarcinoma
Mesodermal	Haemangioma	Angiosarcoma (haemangio-endothelioma) Epithelioid haemangio-endothelioma Sarcoma
Other	Mesenchymal hamartoma Lipoma Fibroma	

Relation to viruses

The relation of the virus to the development of HCC is through chronic hepatitis and cirrhosis (fig. 31.2). Almost all patients with virus-related HCC have an underlying cirrhosis. The hepatocyte necrosis and mitosis of chronic hepatitis favour nodular regeneration which, in appropriate circumstances, is followed by hepatocyte dysplasia and carcinoma. Although nodular regeneration and cirrhosis remain the most important antecedents, the tumour can develop in the absence of cirrhosis. In this case, and by analogy with the hepatitis B-like woodchuck chronic hepatitis, necro-inflammatory activity may be an important requisite.

Relation to HBV

Worldwide, HBV carriage correlates with the frequency of HCC. The geographical distribution of those affected is related to the prevalence of the HBV carrier state in that area. Chronic carriers of HBV are at greater risk of HCC than the general population. Hepadnaviruses, such as the woodchuck hepatitis virus, are also associated with HCC [80]. HBV DNA has been found in HCC tissue.

During the course of HBV, the virus becomes integrated with host chromosomal DNA but the method by which this leads to cancer is uncertain. Integration is accompanied by chromosomal deletions and translocations, which affect cell growth and differentiation (*insertional mutagenesis*) (fig. 31.3). The deletions are not related to the sites of integration.

Inconsistent patterns of integration have emerged and the viral genome may integrate in different sites in tumours from different subjects.

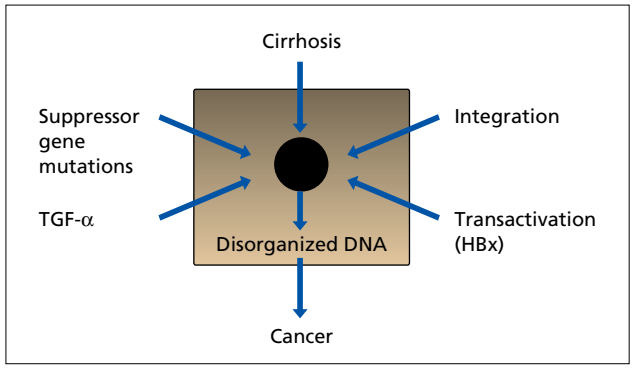


Fig. 31.3. Factors in the production of hepato-cellular cancer [100].

The hepatitis B X protein (HBx) has transactivating activity. It affects other genes and binds to p53, an important oncogene related to hepato-cellular cancer.

In transgenic mice, overproduction of HBV pre-S results in severe hepatic inflammation and regeneration which is followed by neoplasia. Dysregulation of HBV envelope expression might be a consequence of integration.

Translocation of tumour-suppressor genes located on chromosome 17 have been associated with HBV DNA integration. Thus tumour-suppressor genes, such as the p53 oncogene on chromosome 17, may be crucial in HBV-related hepato-carcinogenesis [36, 64]. TGF-α is expressed at a high value in 80% of human HCC [35] and may be a co-factor. Histochemistry shows that it is localized with HBsAg to the same hepatocyte but not in the cancer cell.

Chronic hepatitis, progressing to cirrhosis, remains the most important precancerous factor. HBV induces the cancer through integration, transactivation, mutations in tumour-suppressor genes and increases in TGF-α (fig. 31.3).

HBsAg-positive patients infected with the delta agent have a reduced incidence of hepato-cellular cancer, perhaps because the delta virus suppresses HBV.

Relation to HCV

Worldwide there is a strong association between chronic HCV infection and HCC. HCV may be more important than HBV in the aetiology of HCC. There is a four times higher incidence of liver cancer among anti-HCV positive patients than among HBsAg carriers.

The low prevalence of HCV-related HCC in the USA compared with Japan might be related to the age of infected patients. HCC only develops some 10–29 years after infection. The Japanese probably acquired HCV infection in early childhood through unsterile syringes and injections. The Americans largely contracted it in adult life from drug abuse or infected blood transfusions.

In contrast to HBV, HCV is an RNA virus that lacks a reverse transcriptase enzyme and does not integrate into the host genome. The mode of carcinogenesis is uncertain, but is presumably through cirrhosis. HCV genomes, however, can be detected in the tumour and surrounding liver tissue [29]. HCV reacts with cellular genes regulating cell growth and differentiation. p53 is downregulated, thus weakening tumour-suppresser functions. HCV core proteins are possibly oncogenic [68].

There may be an interaction between hepatitis B and C infections as patients who are anti-HCV positive have HCC more often if they are HBsAg positive.

Relation to alcohol

In Northern Europe and North America there is a four-fold risk of primary hepato-cellular cancer in alcoholics, particularly in older patients. Cirrhosis is always present.

It has been questioned whether alcohol is truly carcinogenic. Cirrhosis and HCC may follow episodes of hepato-cellular injury and regeneration [70]. Alcohol-mediated enzyme induction increases the conversion of co-carcinogens to carcinogens. Alcohol may also promote carcinogenesis through depression of immune responses. Carcinogen-mediated DNA alkylation is impaired by alcohol.

Hepato-cellular cancer in alcoholic cirrhotics is sometimes accompanied by the finding of integrated HBV DNA in malignantly transformed hepatocytes.

Mycotoxins

Aflatoxin is produced by a contaminating mould, *Aspergillus flavus*. It is highly carcinogenic to the rainbow trout, mouse, guinea-pig and monkey. There is species variation in susceptibility. Aflatoxin and similar toxic moulds can readily contaminate food such as ground nuts or grain, especially when stored in tropical conditions.

Estimated aflatoxin intake from foods in various areas of Africa correlates with the frequency of HCC. Aflatoxin may act as a co-carcinogen with hepatitis B.

Mutations in p53 have been found in human cancers from Mozambique, South Africa and China, and have been linked to increased intake of aflatoxin [14]. Such mutations are a rare event in hepato-carcinogenesis in the UK, an area of low aflatoxin exposure.

Race and sex

There is no clear evidence of genetic predisposition.

Worldwide, hepato-cellular cancer is three times more

frequent in males than females. This may partly be due to the higher carriage rate of hepatitis B in males.

Sex hormone therapy

See Chapter 20.

Miscellaneous factors

Hepato-cellular cancer is a rare complication of autoimmune chronic hepatitis and cirrhosis.

It is also rare in patients with Wilson's disease or primary biliary cirrhosis.

Hepato-cellular cancer is a frequent cause of death in haemochromatosis. It is increased in α_1-antitrypsin deficiency, type 1 glycogen storage disease, tyrosinosis and porphyria cutanea tarda.

Hepato-cellular cancer can complicate massive immunosuppressive therapy in patients having renal transplants.

Clonorchiasis may be followed by HCC and cholangiocarcinoma.

The relationship between schistosomiasis and liver cancer has not been established.

Conclusions

Worldwide, hepatitis B and C are the most important factors for the development of hepato-cellular cancer. Co-factors contribute. However, in low prevalence areas, other factors are concerned. The mechanisms in such cases and in particular the role of cirrhosis *per se* remain obscure.

Pathology

The tumour is usually white, sometimes necrotic, bile stained or haemorrhagic. Large hepatic or portal veins within the liver are often thrombosed and contain tumour. The morphological division is into three types: *expanding* with discrete margins, *spreading* (infiltrative) and *multifocal*. The expanding type tends to affect the non-cirrhotic liver and in Japan may be encapsulated. In the West and Africa, most tumours are either spreading or multifocal.

Hepato-cellular carcinoma (fig. 31.4)

The cells resemble normal liver, with compact finger-like processes or solid trabeculae. The tumour simulates normal liver with varying degrees of success. The cells sometimes secrete bile and contain glycogen. There is no intercellular stroma and the tumour cells line the blood spaces.

The tumour cell is usually smaller than the normal liver cell; it is polygonal, with granular cytoplasm. Occasionally, atypical giant cells are found. The cytoplasm is eosinophilic, becoming basophilic with increasing malignancy. The nuclei are hyperchromatic and vary in size. Predominantly eosinophilic tumours may sometimes be seen. The centres of the tumours are often necrotic. Peri-portal lymphatic involvement with malignant cells is an early feature. PAS-positive, diastase-resistant globular inclusions are found in about 15%, usually in those with high α-fetoprotein (AFP) levels. They may represent hepatocyte-produced glycoproteins. α_1-antitrypsin and AFP have also been shown.

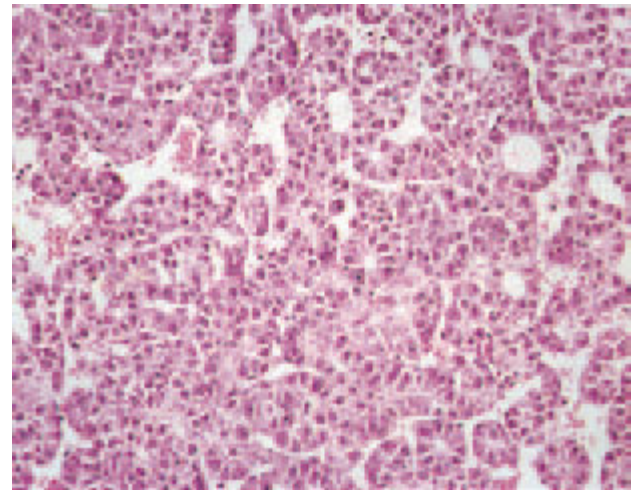


Fig. 31.4. HCC. The tumour cells are smaller than normal with granular cytoplasm and large hyperchromatic nuclei. Mitoses are conspicuous. Atypical giant cell may be seen. Stroma is scanty and the tumour cells have blood spaces between them. (H & E, ×90.)

All gradations exist from benign regenerative nodules to malignant tumours. Dysplasia is an intermediate appearance. The small dysplastic cell may be particularly precancerous. Nuclear density more than 1.3 times that of controls suggests well-differentiated HCC [69].

Electron microscopy. 'Cytoplasmic' hyaline is described in human HCC cells [42]. The cytoplasmic inclusions are filamentous bodies and also autophagic vacuoles.

Clear cell HCC

Tumour cells have clear non-staining cytoplasm, often foamy. Lipids and sometimes glycogen are present in excess abundant cytoplasm. The condition is often associated with hypoglycaemia and hypercholesterolaemia and has a variable prognosis [81].

HCC with giant cells

This rare entity shows osteoclast-like giant cells in sheets with a background of mononuclear cells [34]. Other areas show typical features of HCC.

Spread

Intra-hepatic. Metastases in the liver may be multiple or in one lobe. Spread is by the blood vessels, for the tumour cells abut on vascular spaces. Lymphatic permeation and direct infiltration also occur.

Extra-hepatic. Involvement of small or large hepatic or portal veins or the vena cava may be seen. Metastases have also been found in oesophageal varices even if sclerosed. Lung metastases, usually small, may develop by this route. Tumour emboli result in pulmonary thrombosis. Systemic spread results in deposits anywhere, but especially in bone. Regional lymph nodes at the porta hepatis are frequently involved and the mediastinal and cervical chains can also be infiltrated.

The tumour may involve the peritoneum with resulting haemorrhagic ascites; this may be terminal.

The histology of metastases. The secondary tumour may faithfully reproduce the structure of the primary, even forming bile. Sometimes, however, the cell type diverges widely. Bile or glycogen in cells of a metastasis suggests a hepatic primary.

Clinical features

The clinical picture is very variable (fig. 31.5). The patient may be completely asymptomatic with no physical signs other than those of cirrhosis. The tumour may have been diagnosed incidentally (see section on screening below). Alternatively, the presentation may be so florid and liver failure so great that the picture resembles a liver abscess. These are all intervening stages.

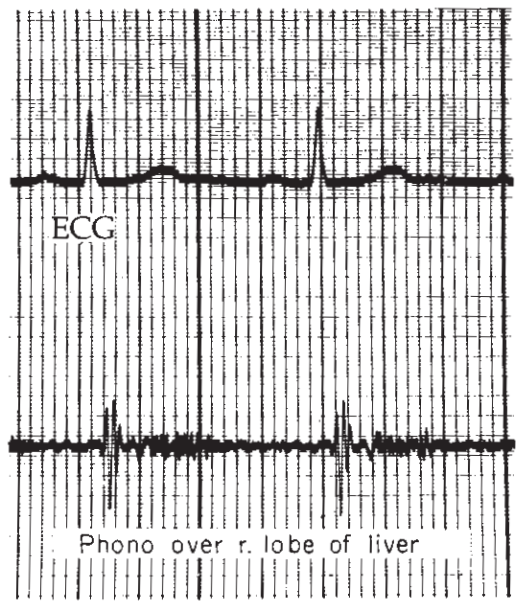


Fig. 31.5. HCC in the right lobe. Phonogram of the right lobe of the liver showing a systolic murmur [11].

Age. All ages are affected. In races such as the Chinese and the Bantu the sufferers are often below 40 years. In temperate climates the patients are usually over 40.

Sex. Males exceed females in a ratio of 4–6:1.

Associated cirrhosis must be established. Primary carcinoma of the liver should be suspected if a patient with cirrhosis deteriorates or develops right upper quadrant pain, or if a local lump can be palpated in the liver. It should be considered if there is no improvement when ascites, bleeding varices or pre-coma is adequately treated.

Rapid decline in a patient with haemochromatosis or with chronic liver disease and a positive HBsAg or anti-HCV suggests a complicating carcinoma.

The patient complains of malaise and abdominal fullness. He loses weight. The temperature is rarely higher than 38°C.

Pain is frequent but rarely severe and is felt as a non-specific, continuous dull ache in the epigastrium, right upper quadrant or back. Severe pain is due to peri-hepatitis or involvement of the diaphragm.

Gastrointestinal symptoms such as anorexia, flatulence and constipation are common. Diarrhoea may be a presenting symptom. This is due to cholestasis or production of active substances, such as prostaglandins, by the tumour.

Dyspnoea is late and due to the large size of the tumour compressing or directly involving the diaphragm, or to pulmonary metastases.

Jaundice is rarely deep and has little relation to the extent of hepatic involvement. Rarely, the tumour presents as an intra-biliary, pedunculated polyp causing obstructive jaundice [93]. The tumour may rupture into the common bile duct [7]. Haemobilia may be the immediate cause of death.

Occasionally the tumour presents with pyrexia and leucocytosis and with a necrotic centre. The picture resembles pyogenic liver abscess [74].

The liver is enlarged, not only downwards into the abdomen but also into the thorax. A hard irregular lump may be felt in the right upper quadrant, continuous with the liver. If the left lobe is involved, the mass is epigastric. Sometimes multiple masses are palpable. Tenderness may be so severe that the patient cannot tolerate palpation.

A friction rub, due to peri-hepatitis, is occasionally heard over the tumour. An *arterial murmur* (fig. 31.5) is due to increased arterial vascularity. In the absence of acute alcoholic hepatitis this is diagnostic of HCC.

Ascites is found in about half the patients. The protein content is high. Malignant cells may be found but interpretation of these in peritoneal fluid is difficult. LDH and carcinoembryonic antigen (CEA) may be increased. The fluid may be blood stained. Rupture causes *haemo-peritoneum*. This may present insidiously or as an

acute abdomen with severe pain [66]. Prognosis is very poor.

Portal vein thrombosis adds to ascites. *Hepatic vein block* may occur. Tumour may grow into the right atrium or oesophageal varices.

Haemorrhage from oesophageal varices is frequent and usually terminal. Failure to control variceal bleeding in a cirrhotic patient is often due to a complicating HCC with portal vein invasion.

Clinical features of metastases

Lymph glands may be felt, especially in the right supraclavicular region [45]. *Pulmonary metastases* may result in a pleural effusion. Massive pulmonary emboli may lead to dyspnoea and to pulmonary hypertension. Massive arterio-portal fistulae can develop. *Osseous metastases* may appear in ribs and vertebrae. *Brain secondaries* give the features of a brain tumour (see fig. 31.16).

Systemic effects

Florid endocrine changes are associated more often with the hepatoblastoma of childhood than with adult carcinoma.

Painful *gynaecomastia* with increased secretion of oestrogen may be seen.

Hypercalcaemia is sometimes due to pseudo-hyperparathyroidism. The tumour may contain a parathormone-like material and serum parathormone levels are raised. Hepatic arterial embolization may be useful therapeutically.

Hypoglycaemia can be found in up to 30% of patients. This may be due to demand for glucose by an enormous tumour mass and so is often associated with an undifferentiated, rapidly progressing tumour. Rarely the hypoglycaemia is seen with a slowly progressive cancer. In this type glucose-6-phosphatase and phosphorylase are reduced or absent in the tumour while the glycogen content in tumour and adjacent tissues is increased. This suggests an acquired glycogen storage disease as the mechanism of the hypoglycaemia. In this group, control is difficult even with an enormous carbohydrate intake.

In patients with severe recurrent hypoglycaemia, the tumour tissue contains 10–20-fold more high molecular weight insulin-like growth factor II (IGF-II) than normal liver [86]. This might mediate the hypoglycaemia.

Hyperlipidaemia is rare, but about a third have increased serum cholesterol levels when maintained on a low cholesterol diet.

Hyperthyroidism may be due to inappropriate thyroid-stimulating hormone production.

Pseudo-porphyria with markedly elevated levels of

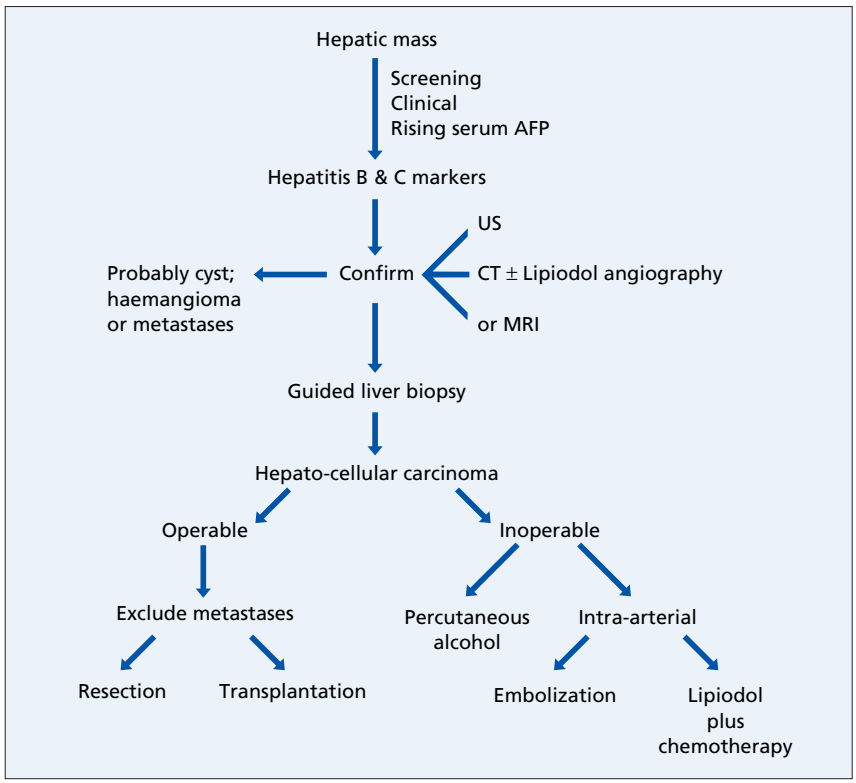


Fig. 31.6. Management of a patient with cirrhosis with positive screening for HCC.

porphobilinogen in urine and serum may be related to porphyrin production by the carcinoma.

Biochemical changes

Biochemical changes may be only those of cirrhosis. The serum alkaline phosphatase is markedly elevated and serum transaminase levels increase.

Electrophoresis of serum proteins may show a γ and an α_2 component. A serum macroglobulin of myeloma type is a rare finding.

Serological markers

Serum α-fetoprotein (AFP). AFP is a normal fetal serum protein. The adult value of up to 20 ng/ml is reached 10 weeks after birth. Progressive increases are found in some patients with HCC (fig. 31.6) although values can be normal. Raised levels at presentation in a cirrhotic patient predict development of HCC at follow-up. Patients with levels greater than 20 ng/ml or who have transient increases over 100 ng/ml, particularly with hepatitis B- or C-related cirrhosis, are in a super high-risk group for HCC [72]. Those with repeated values greater than 100 ng/ml show a 36% incidence of HCC during a 5-year follow-up [72].

Slight increases are usual in acute hepatitis, chronic hepatitis and cirrhosis and overlaps can cause diagnostic difficulties.

The level usually correlates with tumour size but there are exceptions. However, AFP doubling time is closely related to tumour doubling time. Resection of the primary tumour, or hepatic transplantation, results in a fall in serum AFP. Persisting low levels indicate residual tumour and increases indicate rapid tumour growth. Serial values are useful in assessing therapy.

The structure of circulating AFP differs in patients with HCC from those with cirrhosis. Measurement of the AFP fractions may be useful in diagnosing HCC from cirrhosis and be predictive of HCC developing during follow-up [83].

Fibrolamellar tumours and cholangiocarcinomas usually give normal AFP results. Values can be very high with hepatoblastoma.

CEA values are particularly high with hepatic metastases. Because of lack of specificity it is of little value in the diagnosis of HCC.

Serum ferritin increase is due to production of ferritin by the tumour rather than to liver necrosis. Ferritin is increased in active hepato-cellular disease and does not necessarily mean hepato-cellular cancer.

Des-γ-carboxyprothrombin or the protein induced by vitamin K absence or antagonist II (PIVKA-II) increases in HCC. These are normal in chronic hepatitis and metastases. Specificity is superior to AFP [73].

AFP molecules from HCC patients show altered fucosylation of the sugar chain. This has led to the *fucosylation index* test which is highly specific for HCC but relatively insensitive.

Haematological changes

The leucocyte count is usually raised to about $10\,000/mm^3$ with 80% polymorphs. Eosinophilia is an occasional finding. The platelet count may be high—an unusual feature of uncomplicated cirrhosis.

The erythrocyte count is usually normal and anaemia is mild. Erythrocytosis is seen in 1%. It is probably due to increased erythropoietin production by the tumour.

Increased serum erythropoietin levels may even be found with a normal haemoglobin and packed cell volume.

Blood coagulation may be disturbed. Fibrinolytic activity tends to be decreased. This may be due to liberation by the tumour of an inhibitory substance. Increase in plasma fibrinogen levels may be secondary to this effect.

Dysfibrinogenaemia may represent reversion to a fetal form of fibrinogen. Ground glass cells in HCC may contain fibrinogen and be producing it.

Hepatitis markers

Tests for HBV and HCV should be done (fig. 31.6).

Tumour localization

Plain X-ray may show calcification (sunburst lesion) (fig. 31.7).

Hepatic scanning [26]

Ultrasound. Sonographic appearances are variable. The lesion is usually hypoechoic. In larger HCC a typical hyperechoic or heterogeneous appearance is due to necrosis, haemorrhage, fatty change or sinusoidal dilatation. Small HCC have a hypoechoic halo which represents a fine fibrous capsule. Lesions less than 2 cm in diameter can usually be detected (fig. 31.8). However, sensitivity for detection of HCC in an end-stage cirrhotic liver is only 50%.

Duplex and colour Doppler sonography are useful in detecting vascular invasion of the portal vein, hepatic vein or inferior vena cava. The pattern of flow in the tumour may be helpful in diagnosing HCC from other tumours.

CT scan can show a hypodense lesion (fig. 31.9). It frequently fails to depict the size and number of the tumours, especially when cirrhosis is present. Contrast enhancement is essential. The picture is of a mosaic

pattern with multiple nodules of differing attenuation with enhancing septa within the masses. The tumour may or may not be encapsulated. Fatty change is frequent. There may be invasion of the portal vein and arterio-portal shunting.

Helical (*spiral*) *CT* is a rapid technique allowing both hepatic arterial and portal venous phases to be shown. It detects 17% of lesions less than 1 cm, 29% of 1–2 cm and 63% of those more than 2 cm in diameter.

CT arterioportography is performed by taking serial CT scans after injecting contrast into the superior mesenteric artery. It is very sensitive in detecting small HCC and, in particular showing up colorectal metastases.

MRI. This is better than CT in showing local lesions (fig. 31.10). The tumour is hypo-intense on T_1-weighted and hyper-intense on T_2-weighted images. T_2-weighted images show good tumour–liver contrast and can detect vascular invasion and satellite nodules.

Dynamic, multiphase gadolinium-enhanced MRI

Fig. 31.7. Primary liver cancer. A plain X-ray of the abdomen shows calcification (sunburst lesion).

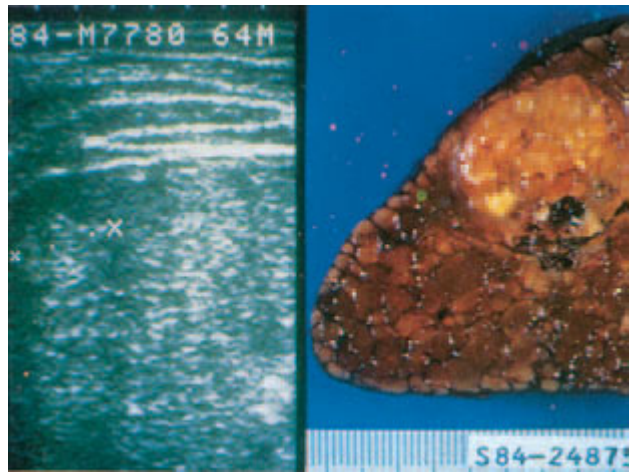


Fig. 31.8. Ultrasound shows a small HCC (marked xX). This was surgically resected and the specimen is shown. (Courtesy of J.F. Liaw.)

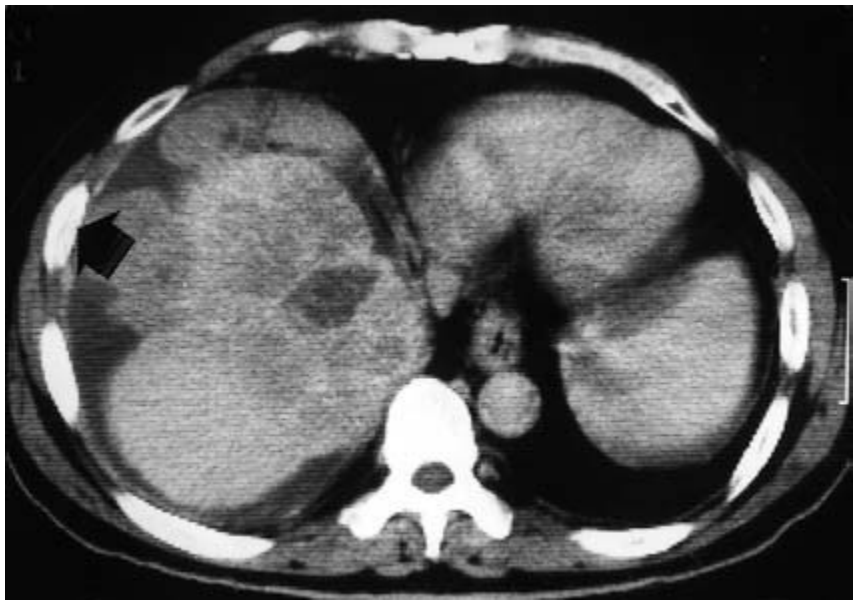


Fig. 31.9. CT scan in hepato-cellular cancer shows tumour bursting through capsule (arrow). Ascites is also present.

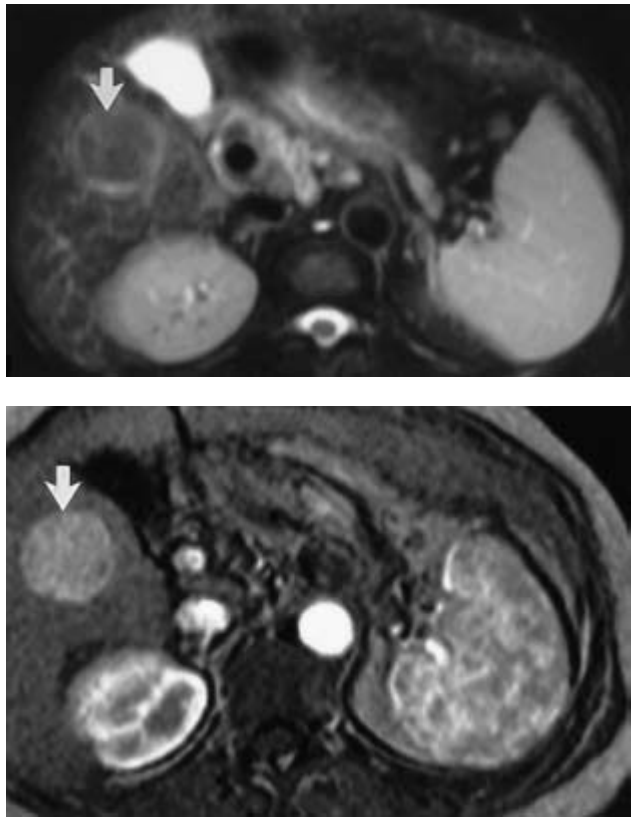


Fig. 31.10. MRI of small hepato-cellular carcinoma in segment 4 (arrows). (a) T_1W pre-contrast. (b) Gadolinium contrast enhanced—arterial phase.

improves tumour detection and may be superior to helical CT [97].

Hepatic angiography. HCC is supplied by the hepatic artery and selective coeliac and superior mesenteric arteriography may demonstrate the lesion (figs 31.11, 31.12, 31.13). Super-selective contrast infusion angiography is of value in identifying small tumours. However, hepatic angiography is invasive. Its diagnostic use has largely been replaced by helical CT and MRI. It continues to be used for chemo-embolization therapy.

The arterial pattern is bizarre with pooling, stretching and displacement of vessels. The vessels may be sclerosed, have an irregular lumen and be fragmented. Arteriovenous shunts can be shown, often with retrograde filling of the portal trunk. The portal vein may be distorted if there is tumour invasion.

Lipiodol angiography. Lipiodol introduced into the hepatic artery is cleared from non-cancerous tissue, but remains in a tumour almost permanently so that lesions as small as 3 mm may be detected by a CT performed some 2 weeks later (fig. 31.13). This technique is used only as a means of identifying multiple tumours and of deliverying isotope therapy, for instance I^{131}, to them.

Even with the most sophisticated imaging, the distinction of small HCC from pre-neoplastic (dysplastic) or early transformed nodules can be impossible (Chapter 30).

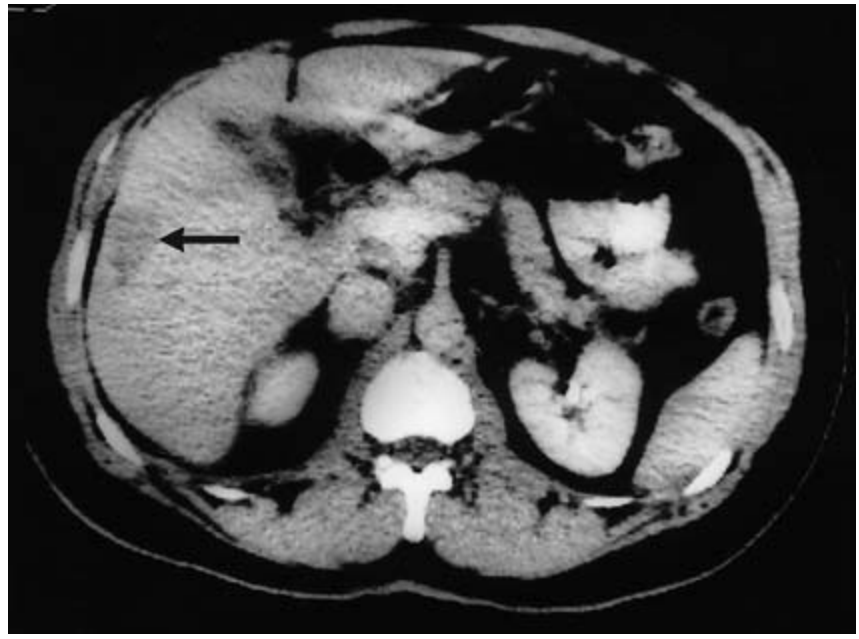


Fig. 31.11. Contrast-enhanced CT scan shows hypodense lesion in the right lobe of the liver (arrow).

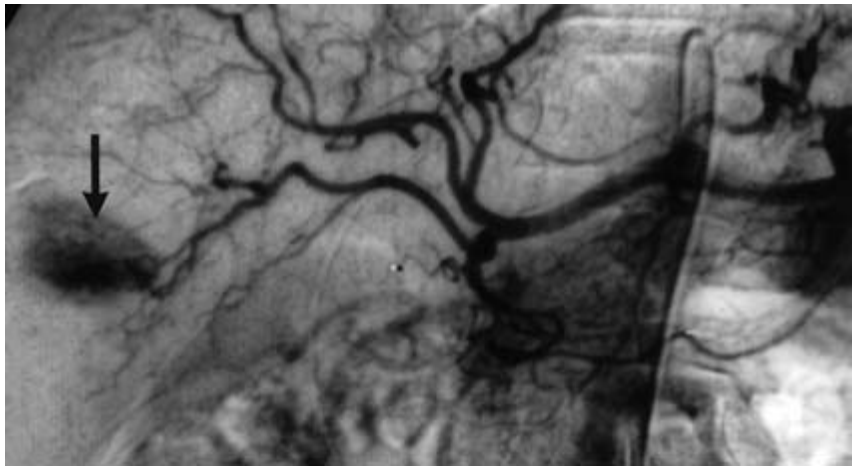


Fig. 31.12. Same patient as in fig. 31.11. Selective hepatic arterial angiography confirms tumour in right lobe (arrow).

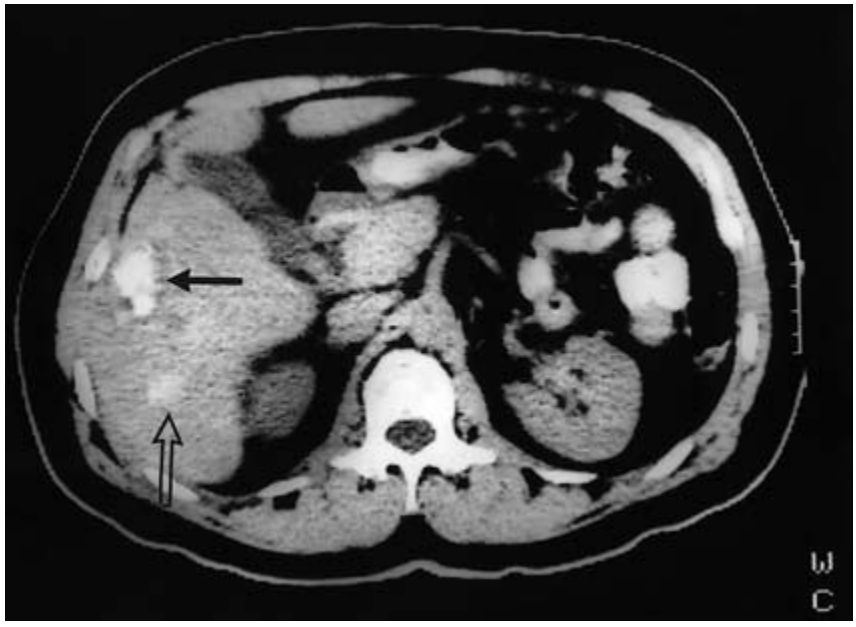


Fig. 31.13. Same patient as in figs 31.11 and 31.12. Oral contrast CT scan 9 days after intra-hepatic arterial lipiodol shows uptake into the right lobe tumour (arrow) with another possible lesion more posteriorly (open arrow).

Needle liver biopsy

Histological confirmation is important if small space-occupying lesions have been detected by ultrasound or CT (fig. 31.6). The biopsy should be done under imaging control. The possibility that biopsy will facilitate spread along the needle tract exists.

Fine-needle aspiration, using a 22-gauge needle, yields cytological specimens which will diagnose moderately and poorly differentiated tumours (fig. 31.14), but the cytological diagnosis of well-differentiated tumours is difficult.

Screening

Small, asymptomatic HCC in a cirrhotic liver may be diagnosed during screening of high-risk patients, by chance during imaging or found in a liver removed at the time of transplantation. Early recognition is important. The 1-year survival of untreated patients with well-compensated liver disease (Child's grade A) and having asymptomatic HCC is 90% at 1 year, whereas the 1-year survival of symptomatic patients is only 40%

Screening is indicated for high-risk patients. These are men, HBsAg or anti-HCV positive, more than 40 years old, and with chronic liver disease especially with cirrhosis and large macro-regenerative nodules. Ultrasound is more sensitive than CT. This is usually followed by directed fine-needle biopsy. Specimens must also be taken from non-tumorous tissue to determine the presence or absence of a concomitant cirrhosis and its activity.

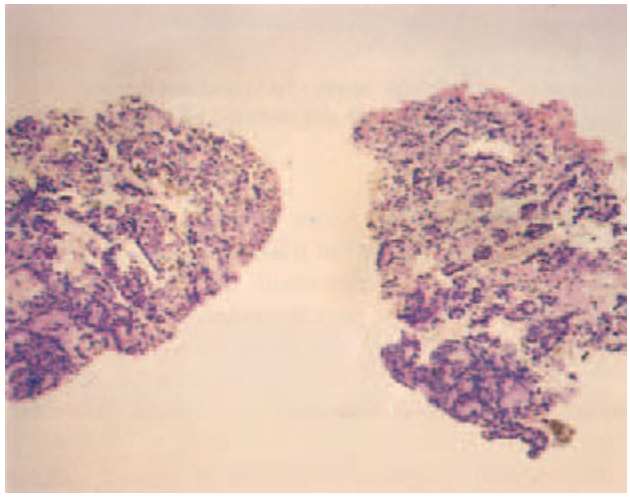


Fig. 31.14. Fine-needle aspiration under ultrasound guidance yielded a clump of HCC cells.

Serum AFP estimation should be performed at 4–6-monthly intervals, particularly in those who have an initially increased concentration or where macro-regenerative nodules have been detected. Normal serum AFP does not exclude a tumour.

The reported value of screening is high in areas such as Japan where tumours are small and often encapsulated. In South Africa, tumours are rapidly growing and aggressive and screening is of little value. Europe seems to be in an intermediate position. Economics play a part. In Japan, such procedures as ultrasound and AFP estimations are routinely available at no cost to the patient. This is clearly not so in most other parts of the world. The prognosis of HCC is so poor that where cost is an important consideration there is probably a reluctance to screen especially as there is no firm consensus that the death rate will be reduced [15, 18].

Prognosis and risk factors

The outlook is usually hopeless. The time between exposure to hepatitis B or C and tumour development can vary from a few years to many decades [16].

The growth rate of the tumour varies greatly and correlates with survival. Asymptomatic Italian patients had a tumour volume doubling time varying from 1 to 19 months with a mean of 6 months. HCC in Africans is much more rapidly growing. Reasons are speculative, perhaps genetic, perhaps related to malnutrition, to co-factors such as aflatoxin or perhaps to late diagnosis in an itinerant African mine worker.

Small tumours (less than 3 cm in diameter) are associated with a 1-year survival of 90.7%, a 2-year survival of 55% and a 3-year survival of 12.8%. Infiltrating tumours have a worse prognosis than expanding ones. The presence of an intact capsule is a good sign. Although cirrhosis is the main risk factor, macro-regenerative nodules (at least 1 cm in diameter) and hypoechoic ones are particularly precancerous [27, 94].

Table 31.2. Okuda staging system [75]

Criterion	*Cut-off*
Tumour size*	>50% = +; <50% = –
Ascites	Detectable = +; absent = –
Albumin	<3 g/dl = +; >3 g/dl = –
Bilirubin	>3 mg/dl = +; <3 mg/dl = –
Stage	***Survival (months)***†
I: no positives	8.3
II: one or two positives	2.0
III: three or four positives	0.7

*Largest cross-sectional area of tumour to largest cross-sectional area of liver.
†Without treatment.

Severity of liver disease correlates with the chances of developing HCC. Patients less than 45 years old survive longer than older ones. A tumour size exceeding 50% of the liver, a serum albumin less than 3 g/dl and a raised serum bilirubin level are ominous features.

The risk increases if the patient is HBsAg or anti-HCV positive.

In high endemic areas, progression to chronic hepatitis and cirrhosis is increased by infection with hepatitis B and C. Pulmonary metastases adversely affect survival.

Prognostic indices are particularly valuable in clinical trials and in selecting those who would benefit from more aggressive therapy [8]. The Okuda staging system uses tumour size, presence or absence of ascites and the serum bilirubin level (table 31.2).

The Cancer of the Liver Italian Program (CLIP) score [13] is based on the Child's stage, tumour morphology and extension, AFP level and portal vein thrombosis. It may give more accurate prognostic information than the Okuda method.

Surgical treatment (fig. 31.6)

There are various therapeutic options, but the only procedures that offer possibility of cure are resection or transplantation.

Doppler imaging, and particularly enhanced MRI, has revealed more small tumours than those shown by CT or ultrasound. The number of candidates suitable for resection has therefore fallen. Laparoscopic ultrasonography before planned surgery can avoid unnecessary operation [60].

Resection

After partial resection, DNA synthesis increases and the remaining liver cells become larger (*hypertrophy*) and

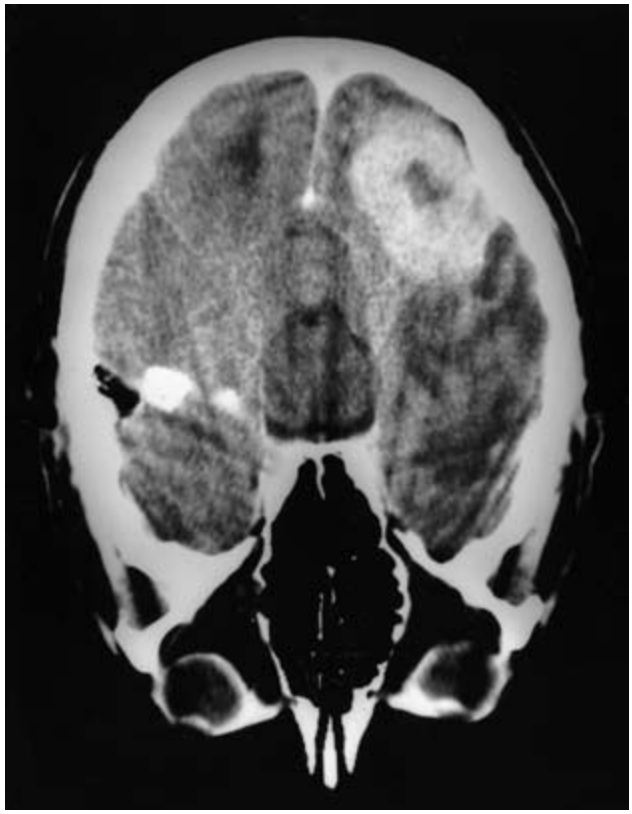


Fig. 31.15. Brain MRI shows large occipital metastasis in a patient with HCC.

undergo increased mitosis (*hyperplasia*). Up to 90% of a non-cirrhotic liver may be removed with eventual survival.

The resectability rate for HCC is only about 3–30%. Success depends on size (less than 5 cm in diameter), position, particularly in relation to large vessels, presence of vascular invasion, presence of a capsule, absence of satellite lesions and the number of lesions (table 31.3). Multiple lesions have a high recurrence rate and a low survival time.

Cirrhosis is not a definite contraindication but is associated with a higher intra-operative and peri-operative morbidity and mortality. The operative mortality in the non-cirrhotic is less than 3%, but 23% in the cirrhotic. The cirrhosis should be Child's grade A. Over-aggressive resection can lead to hepatic decompensation. The patient's age and general condition must be taken into account.

Metastases must be sought by chest X-ray, CT scan or MRI, and isotope bone scan. Symptoms or signs of metastasis elsewhere should be investigated (fig. 31.15).

Improved results for resection have followed better knowledge of the segmental anatomy of the liver. The left lobe is resected with relative ease. The right lobe is more difficult. Small tumours may be removed by segmentectomy; in others, lobectomy or trisegmentectomy may be necessary and this demands adequate liver function. The post-resection prognosis is related to the resection of a wide margin around the tumour, the absence of tumour thrombosis in hepatic vein or portal vein and no obvious intra-hepatic metastases.

Table 31.3. Factors in resection for HCC

Size <5 cm
One lobe
Capsule
Vascular invasion
Cirrhosis grade
Age and general condition

The chances of 3-year survival are 30–40%; 25% of patients per year will develop recurrence in the residual liver.

Hepatic transplantation

This is used in patients with advanced cirrhosis (Child's grade B and C) who could not survive tumour resection. However, results are particularly poor if the candidate has a large tumour and is considered unsuitable for resection. Tumours greater than 5 cm are unacceptable for transplantation because of the high recurrence rate. Liver transplant is effective for single small (5 cm or less) tumours and no more than three tumour nodules (3 cm or less).

Five-year survival rates are about 20%. The liver is the common site of recurrence, which develops in up to 65% of patients. Those who are HBsAg or HCV positive do considerably worse, as the virus infection recurs in the new liver (Chapter 38). Results are better when tumour is discovered at screening or when a transplant is performed for another indication.

The choice between resection and transplant for a patient with a tumour of less than 5 cm can be extremely difficult. Poor liver function would favour transplant. The decision also depends on the expertise of available physicians and surgeons and the availability of a donor liver.

When the waiting list for transplant is long, resection has been followed by salvage transplant when the tumour recurs or liver function deteriorates [62].

Non-surgical treatment (fig. 31.16)

Systemic therapy

Mitozantrone may be given intravenously in courses

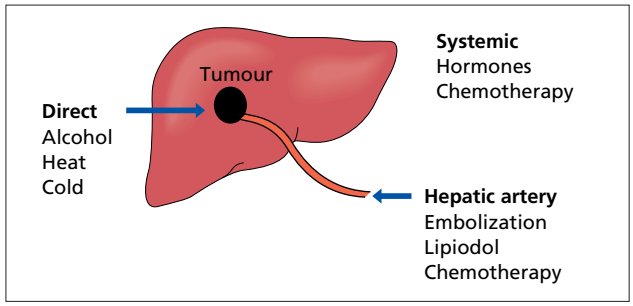


Fig. 31.16. Non-surgical therapeutic options in HCC.

every 21 days. Results are disappointing with a response rate of only 27.3% [21].

Tamoxifen treatment does not prolong survival [14].

Interferon therapy in HCV-positive patients may reduce the risk of later HCC, particularly if the patient has been a sustained responder [98]. Interferon treatment of advanced HCC is not beneficial in terms of tumour progression rate or survival [59].

Trans-arterial embolization

Catheterization of the hepatic artery via the femoral artery and coeliac axis allows embolization of the blood supply to the tumour. Chemotherapeutic agents may be delivered in high concentration. The procedures have limited success due to the development of arterial collaterals which ultimately supply the tumour.

Embolization is used for unresectable tumours. It may be used as an emergency to control intra-peritoneal haemorrhage from a ruptured HCC.

The procedure is performed under local or general anaesthesia and with antibiotic cover. The portal vein must be patent. The hepatic artery branch feeding the tumour is then embolized using gel foam, sometimes with an added agent such as doxorubicin or cysplatin (figs 31.17, 31.18). The tumour undergoes complete or partial necrosis.

Side-effects include pain, which can be severe, fever, nausea, encephalopathy, ascites and massive rises in transaminases. The AFP falls. Abscess formation and misplaced embolization are other complications.

HCCs are not sensitive to radiotherapy.

The results of embolization are variable from failure to prolongation of survival. Prognosis depends on the tumour type and extension, size, portal vein involvement, presence of ascites and jaundice. All lesions without a capsule are resistant to embolization. The technique is more useful in the treatment of *hepatic carcinoid tumours* where there is marked reduction in symptoms and tumour size (figs 31.19, 31.20).

Lipiodol, an iodized poppy seed oil, is retained in the

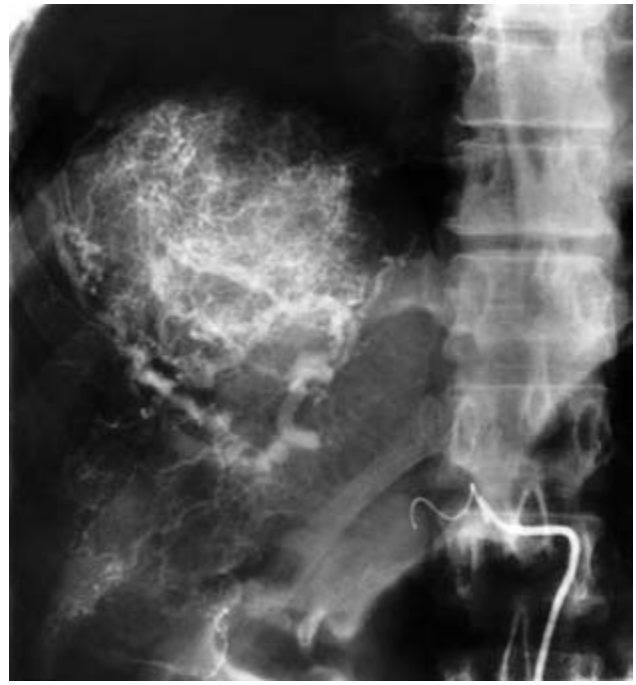


Fig. 31.17. Selective hepatic angiography shows a large HCC in the right lobe of the liver.

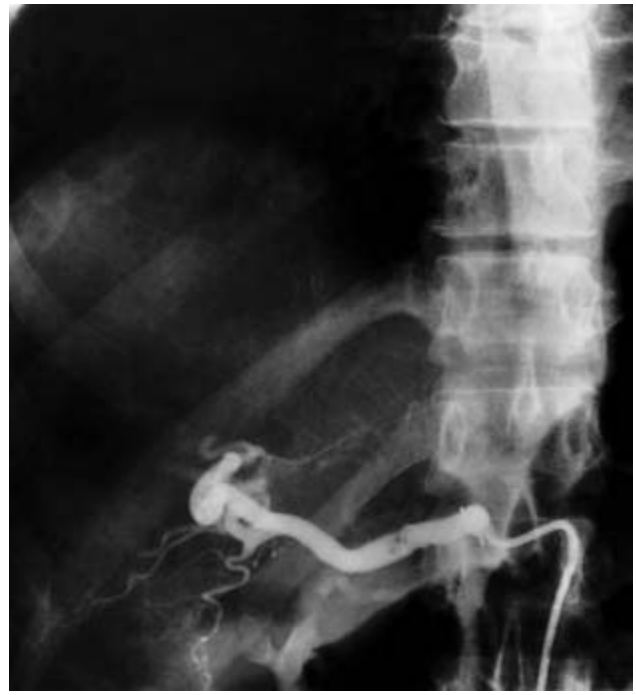


Fig. 31.18. Same patient as fig. 31.17. Hepatic arterial embolization with gel foam occlusion of blood supply to the tumour.

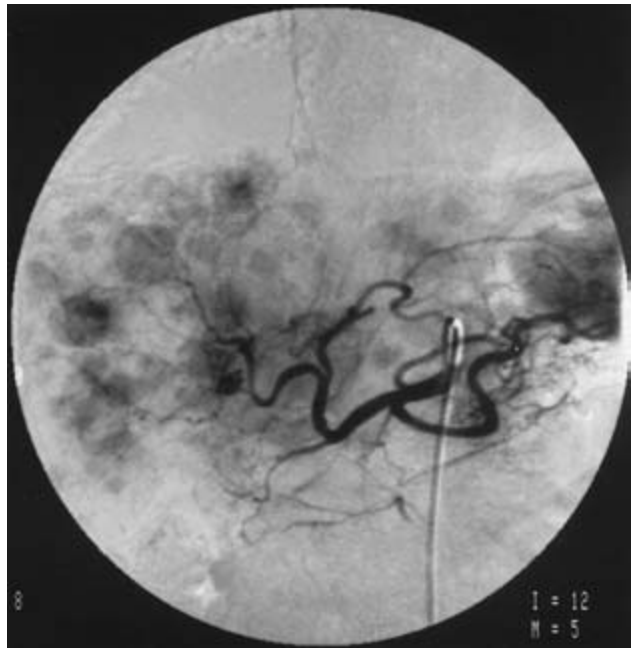


Fig. 31.19. Coeliac angiography in a patient with primary carcinoid tumour of the ileum and multiple, symptomatic liver metastases.

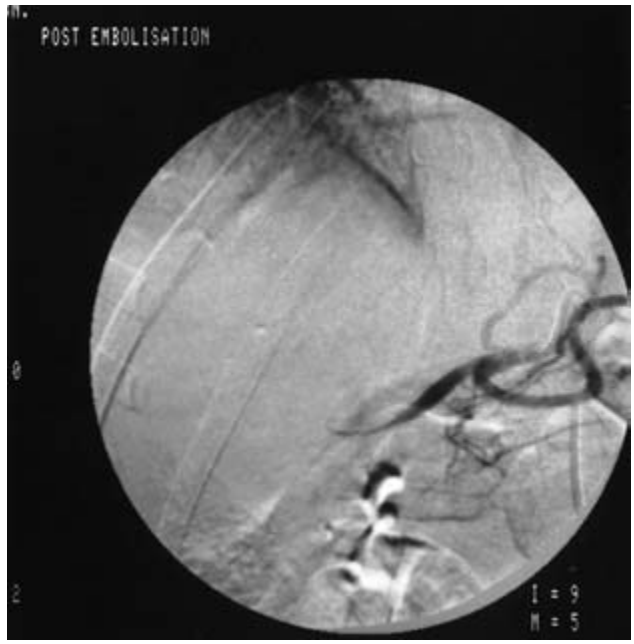


Fig. 31.20. Same patient as fig. 31.19 after selective hepatic arterial embolization to ablate tumour effects.

tumour for 7 or more days after hepatic arterial infusion but disappears from non-tumorous liver (see fig. 31.13). This is valuable in showing very small tumours. It is used to target lipophilic anticancer drugs such as epirubicin or lipiodol I^{131} to the tumour. These drugs all seem to prolong survival. The treatment can be repeated at 3–6-month intervals.

Pre-operative trans-arterial chemo-embolization using lipiodol reduces tumour size and may improve survival after resection or transplant [61]. After resection, adjuvant intra-arterial I^{131}-labelled lipiodol decreases the rate of recurrence and increases overall survival [51].

Unfortunately, viable tumour cells often remain in and around the tumour and a complete cure cannot be expected.

Table 31.4. Percutaneous alcohol injection for HCC

Less than 5 cm
Not more than three lesions
Local anaesthesia
Ultrasound or CT control
2–12 ml absolute alcohol
Side-effects

Percutaneous ethanol injection

This was originally used for advanced disease in patients who were excluded from any other therapy [57]. It is now used for small (less than 5 cm) tumours, usually not more than three in number. Absolute alcohol is injected percutaneously under ultrasound or CT guidance (table 31.4).

The patient can be treated as an outpatient twice a week with 2–12 ml absolute alcohol for 3–15 sessions. Alternatively, a single session under general anaesthesia using a larger volume may be used for larger lesions [57]. The treatment results in intra-tumoural arterial thrombosis and coagulative necrosis followed by ischaemia of the tumour. It is only used for encapsulated tumours. Necrosis of the tumour is rarely complete. MRI may be useful for showing the effectiveness of therapy.

The injection may be a preliminary to resection and can be repeated if the tumour recurs. Multiple tumours can be treated. Injection is used to control bleeding following rupture of the tumour. The side-effects are similar to those of embolization. Three-year survival for Child's grade A is 71%, and for Child's grade B is 41% [58].

Overall recurrence is related to tumour size and the peri-tumoral capsule. This is 15.6% at 12 months and 45.1% at 24 months [46]. Percutaneous acetic acid injection may be associated with less recurrence and longer survival than alcohol [71].

Percutaneous microwave coagulation may be useful in small, well-differentiated tumours [82].

Radiofrequency obliteration has also been used [31].

Targeted gene transfer

This is used to deliver therapeutic genes specifically to malignant cells without damaging normal tissue.

Viral vectors, such as adenovirus, are efficient, but may exert a host immune response limiting repetitive administration [78]. A tumour-reactive monoclonal antibody coupled with a DNA binding cationic amphiphile, cholesteryl-spermine, has been used for gene delivery to HCC cells [67].

Conclusions

Hepato-cellular cancer remains a fatal disease. In a large trial of 123 patients with stage I HCC, usually with cirrhosis, all treatments increased the probability of survival (fig. 31.21) [3]. Results, however, did not differ between resection, liver transplantation and transarterial oily embolization. The various procedures have rarely been subjected to prospective clinical trials. Results are compared with historical controls or no treatment. The management of the small encapsulated HCC in a patient with well-compensated cirrhosis has improved. However, more often the tumour is large and the patient has decompensated liver disease so that little can be offered.

Fibro-lamellar carcinoma of the liver

This tumour is found in young people (aged 5–35) of both sexes [17]. It presents as an abdominal mass, sometimes with pain. It is unrelated to sex hormones. The liver is non-cirrhotic.

Histologically, clumps of large, polygonal deeply eosinophilic tumour cells are interspersed with bands of mature fibrous tissue (fig. 31.22). The cells have cytoplasmic pale bodies representing intra-cellular fibrinogen storage. Occasionally the fibrous stroma is lacking.

Electron microscopy shows the cytoplasm packed with mitochondria and thick compact bands of collagen in parallel arrays. The tumour cells are believed to be oncocytes. The hepatocytes contain an excess of copper-associated protein, produced by the cancer cell.

Serum AFP is normal. Serum calcium levels may be raised with pseudo-hyperparathyroidism. Serum vitamin B_{12} binding protein [76] and neurotensin may also be increased.

CT shows a typical stellate scar with radial septa which show persistent enhancement on 10–20-min enhanced CT and MRI [38].

Prognosis is better than for other forms of liver cancer (survival 32–62 months), although the tumour may metastasize to regional lymph nodes.

Treatment is by surgical resection or transplantation [79].

Hepatoblastoma

This rare tumour affects children of both sexes less than 4 years old and very rarely older children and adults. It presents as progressive enlargement of the abdomen with anorexia, failure to thrive, fever and, rarely, jaundice. Associated features include sexual precocity due to secretion of an ectopic gonadotrophin by the tumour, cystathioninuria, hemihypertrophy and renal adenomas. Serum AFP levels are markedly increased. Imaging shows a space-occupying lesion in the liver with displacement of adjacent organs. There may be focal calcification. Angiography shows the features of primary liver cancer with a diffuse parenchymal blush persisting into the venous phase, encasement of vessels, pooling of contrast and an ill-defined margin.

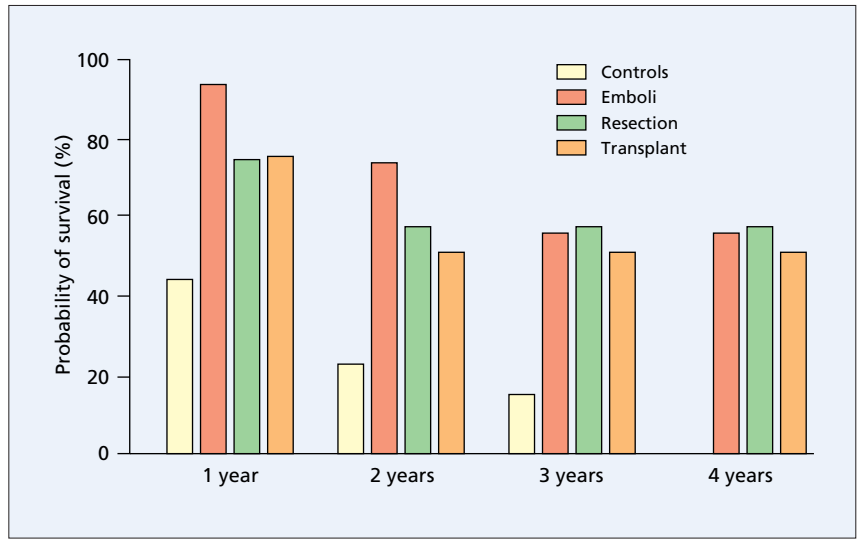


Fig. 31.21. Results of treating early (stage I) HCC on survival [3].

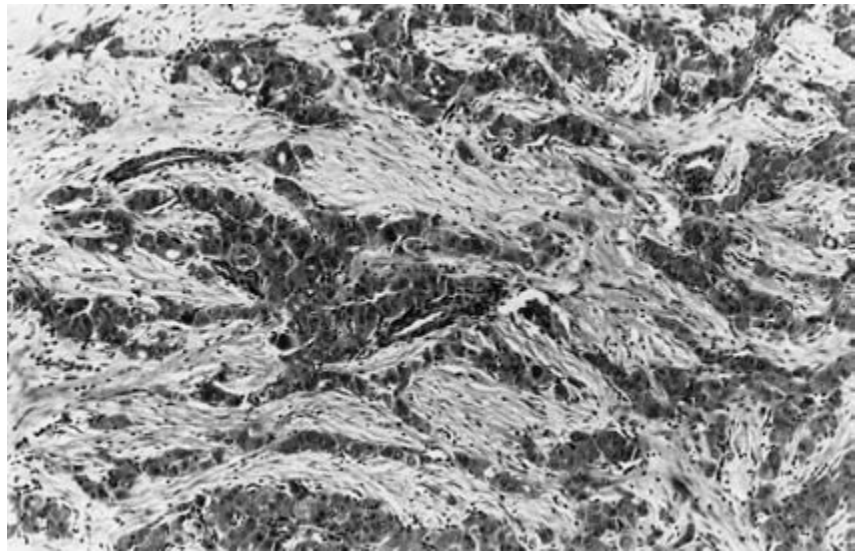


Fig. 31.22. Fibro-lamellar carcinoma: clumps of eosinophilic cells are interspersed with bands of mature connective tissue. (H & E,×275.)

Histological features recapitulate the developmental stages of the liver. Teratoid features may therefore be seen. The usual picture is fetal-like with embryonal cells in acini, pseudo-rosettes or papillary formations. Sinusoids contain haematopoietic cells. The mixed epithelial–mesenchymal type shows primitive mesenchyma, osteoid tissue and, rarely, cartilage, rhabdomyoblasts or squamous foci.

An association has been found between familial adenomatous polyposis coli and hepatoblastoma [19]. A gene on chromosome 11 may be important in hepatoblastoma as it is in other embryonal tumours.[19].

If a resection is possible, the prognosis is better than for primary HCC, with 36% of patients surviving 5 years.

Hepatic transplantation has been performed.

Pre-operative cisplatin and Adriamycin may reduce the tumour size allowing a less extensive hepatectomy [85].

Intra-hepatic cholangiocarcinoma

Aetiological factors include clonorchiasis, primary sclerosing cholangitis, the fibrocystic diseases, anabolic steroids and thorotrast (Chapter 37).

The tumour is firm to hard and of whitish colour. This is a glandular tumour arising from intra-hepatic bile ducts. The tumour cells resemble bile duct epithelium; sometimes they have a papillary arrangement. There is no bile secretion. The stroma differs from that of HCC as it consists of fibrous tissue with little or no capillary formation (fig. 31.23). Histological appearances do not allow distinction of intra-hepatic cholangiocarcinoma from metastatic adenocarcinoma.

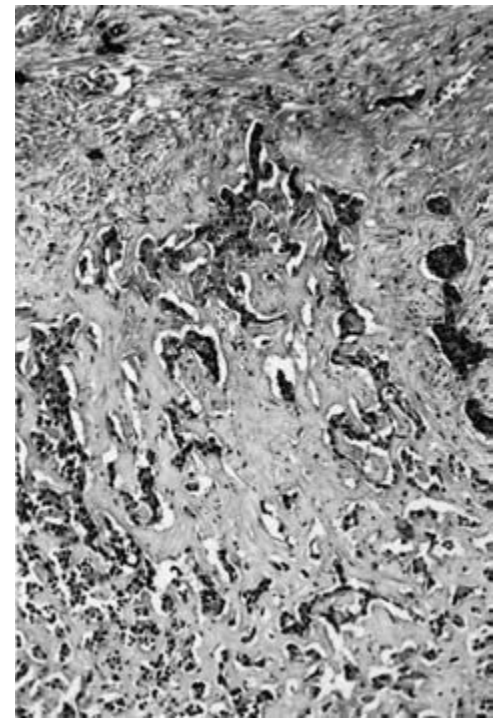


Fig. 31.23. Bile duct carcinoma. The tumour cells are arranged in tubular fashion simulating bile ducts. The cell type is columnar. Stroma is dense, fibrous and avascular. (H & E,×90.)

Keratin is a good marker of biliary epithelium and is found in 90% of cholangiocarcinomas.

The tumour affects older persons. The clinical features are those of hepatic malignancy with jaundice prominent. Serum AFP is not increased.

CT scan shows a space-occupying lesion of low

attenuation, sometimes with calcification. It is usually hypovascular. Angiography and MRI may show vascular encasement.

Treatment is unsatisfactory, and there is no response to chemotherapy.

Combined hepato-cellular–cholangiocarcinoma

This primary liver cancer shows the features of both hepato-cellular and biliary epithelial differentiation. Some represent coincidental occurrence of both hepato-cellular and cholangiocarcinoma in the same patient. Some contain transition elements between hepato-cellular and cholangiocarcinoma, and some are examples of fibro-lamellar tumours.

Within the tumour, intra-cellular AFP is found in 29% and keratin markers of bile duct epithelium in 52%.

The *clinical features* are those of HCC. Cirrhosis may or may not be present.

Other primary liver tumours

Cystadenocarcinoma

This rare tumour occurs in adults, more often female. It presents as abdominal fullness with pain and weight loss.

The large tumour, usually in the right lobe, is multicystic and contains bile-stained, mucinous material. Histologically, the cysts are lined by malignant epithelial cells with papillary enfoldings and dense fibrous stroma. The origin may be from a benign cystadenoma or even a congenital cyst.

Imaging shows a space-occupying lesion, usually large, with cystic features.

The prognosis is better than for cholangiocarcinoma with survival of up to 5 years after resection. Hepatic transplantation may also be possible.

Angiosarcoma (haemangio-endothelioma)

This very rare and highly malignant tumour is difficult to distinguish from primary hepato-cellular cancer. The liver is enlarged and full of knobbly cavernous growths. Angiosarcoma is part of a spectrum of diseases of the sinusoidal barrier including peliosis and sinusoidal dilatation. All three conditions can be related to vinyl chloride, arsenic, thorotrast and anabolic steroids [24]. It may complicate neurofibromatosis [53].

Histologically, blood-filled cavernous sinuses are lined with layers of highly malignant, anaplastic, endothelial cells which in parts may resemble the earliest stages of embryonic vascular development. Well-differentiated tumours resemble peliosis hepatis.

Giant cell formations, solid sarcomatous foci and intra-sinusoidal spread with invasion of portal venous and hepatic venous radicles are prominent. Adjacent liver shows cholangio-proliferation and hypertrophy of sinusoidal lining cells.

Factor VIII-related antigen, an endothelial cell marker, may be identified in tumour cells.

The disease affects older people. It presents as hepato-cellular liver disease, weight loss and fever. The course is rapidly downhill with cachexia, blood-stained ascites and death within 2 years.

A bruit may be heard over the liver. Platelets may be consumed in the tumour and disseminated intravascular coagulation has been reported. Occasionally the course is chronic with ascites and hepatomegaly over many years [10].

Scanning shows multiple defects in the liver (fig. 31.24). The right diaphragm is high.

The *prognosis* is very poor, and the tumour is only rarely radiosensitive.

Thorotrast

This consists of a colloidal solution of thorium dioxide with the isotope radiothorium which is mainly an α-ray emitter and has a half-life of 1.3×10^6 years. It was formerly used as a contrast medium in radiology. Primary hepatic tumours have developed years after intravascular administration. Hepato-cellular or bile duct carcinoma has a latent period of about 20 years and haemangio-endothelioma about 15 years. Plain X-ray of the abdomen shows continued presence of the isotope in liver and spleen and this is confirmed by autoradiographs of liver tissue. Total body counting may be used to quantify radioactivity in the patient's body. Cirrhosis can develop even without liver tumours.

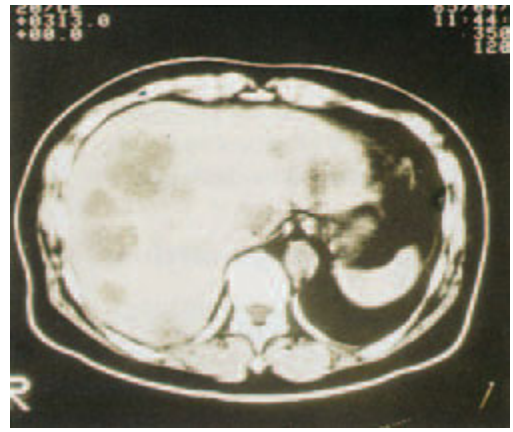


Fig. 31.24. Haemangio-endothelioma. CT showing multifocal nodules.

Epithelioid haemangio-endothelioma [39]

This rare tumour of adults, predominantly female, is usually slow growing with low-grade malignancy but can be rapidly progressive. It presents incidentally with abdominal fullness and pain, with jaundice or with haemoperitoneum.

Microscopically, tumour cells are dendritic and epithelioid and infiltrate sinusoids and intra-hepatic veins of all sizes. The matrix may show inflammation, sclerosis and calcification.

The histochemical demonstration of endothelial markers (factor VIII antigen and lectins: UEA-I) in the tumour cells is diagnostic.

Ultrasound, CT and MRI show coalescent peripheral hepatic masses with capsular retraction due to fibrosis. CT shows the tumours of low attenuation on enhancement, peripheral or alternating attenuations correlate with the hyperaemic rim. MRI shows low signal halos around many lesions which have a high T_2 signal.

The prognosis is more favourable than for angiosarcoma but the tumour can metastasize. Surgical excision and liver transplantation must be considered [43, 52].

Undifferentiated sarcoma of the liver

This is an extremely rare tumour differentiated from anaplastic HCC, angiosarcoma or epithelioid haemangio-endothelioma by hepatic histology. Spread of a sarcoma from a nearby structure such as the thoracic cage, diaphragm or retroperitoneum must be excluded.

The tumour usually affects children [56] but can affect the adult [28].

The histology is typical of sarcoma. Reticulin stains show the characteristic uniform distribution of fibres.

The prominent clinical features are pyrexia and an abdominal mass. Hypoglycaemia may develop. The course is rapidly downhill with a survival of about 2 months.

Imaging shows a solid and cystic lesion with multiple loculi. Calcification and invasion of the right atrium and inferior vena cava may be noted. Angiography shows variable vascularity depending on the degree of cystic transformation.

Chemotherapy is useless and hepatic transplantation is rarely possible.

Benign tumours of the liver

See Chapter 30.

Mesenchymal hamartoma [20]

This usually presents in the first 2 years of life as a massive cystic lesion of the right lobe of liver [50]. It can affect adults. It arises from tissues in the portal zones and histology shows an admixture of hepatocytes, biliary epithelium, mesenchymal elements and cysts. Extra-medullary haematopoiesis may be seen. The lesion probably has an anomalous solitary vascular supply evolving into stromal cysts due to early ischaemic change [55].

Treatment is by surgical resection, but aspiration and careful follow-up may be considered in some cases.

Paraneoplastic hepatopathy

Hepato-splenomegaly with cholestasis, fever, weight loss, increased serum globulins and alkaline phosphatase can complicate hypernephroma without hepatic metastases [91]. Liver biopsy shows non-specific cellular infiltration. It has also been reported with soft-tissue sarcomas not involving the liver [77]. The changes may regress if the tumour is resected. The mechanism of the hepatic changes is unknown.

Hepatic metastases

The liver is the most frequent site of blood-borne metastases, irrespective of whether the primary is drained by systemic or portal veins. It is involved in about a third of all cancers, including half of those of the stomach, breast and lung and those arising from the colon. Other frequent primary sites include oesophagus, pancreas and malignant melanoma. Prostatic and ovarian metastases in the liver are exceedingly rare.

Pathogenesis

Invasion from tumours in adjacent organs, retrograde lymphatic permeation and extension along the lumen of blood vessels are all unusual.

Portal emboli. Primary tumours in the uterus and ovaries, kidneys, prostate or bladder may involve contiguous tissue drained by the portal vein and hence give embolic metastases to the liver; these are extremely rare.

Microscopically, *hepatic arterial seeding* is difficult to identify, because the picture is confused by the succeeding intra-hepatic metastases. It must be frequent.

Pathology

There may be only one or two microscopic nodules or the whole liver may be enormous and full of metastases. Liver weights of 5000 g are not unusual and one liver is

said to have weighed 21.5kg. The deposits are usually white and well demarcated. The consistency depends on the ratio of cancer cells to fibrous stroma. Occasionally the centre may be soft, necrotic and haemorrhagic. On the surface of the liver they show characteristic umbilication; this results from necrosis of the centre, which has outgrown its blood supply. Peri-hepatitis may be seen over peripheral lesions. A zone of venous hyperaemia may surround the deposits. Portal vein invasion is usual, and arteries are rarely involved by tumour thrombus although they may be encased.

The tumour cells metastasize rapidly and widely through the liver, both by peri-vascular lymphatics and by direct invasion of the portal venous radicles.

Injection studies show that, in contrast to HCC, metastases may have a decreased rather than increased blood supply from the hepatic artery. This is particularly so in those of gastrointestinal origin.

Histology

The secondary deposits in the liver may reproduce the histology of the primary lesions. However, this is not necessarily so, and in many instances the primary tumour may be well differentiated, while the secondary deposits in the liver may be extremely anaplastic and give no hint of their origin (fig. 31.25).

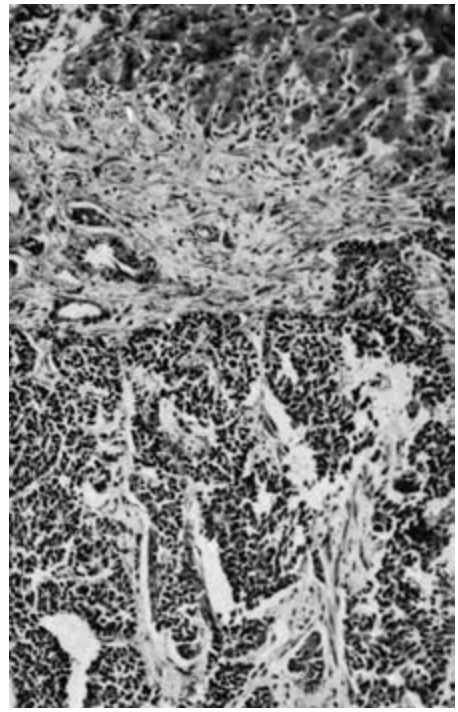


Fig. 31.25. Anaplastic secondary carcinoma of the liver. The tumour is composed of sheets of undifferentiated malignant cells. Normal liver cells are seen at the top. There was a small bronchial primary growth which was not revealed by chest X-ray. (H & E, ×110.)

Clinical features

These may be due to the hepatic metastases, to the distant primary growth or more usually to a combination of both.

The patients complain of malaise, lassitude and loss of weight. Abdominal distension and a dragging sensation are due to the enlarged liver. Occasionally the pain is sharp and intermittent, simulating biliary colic. Fever and sweats may occur.

Depending upon the weight loss, the patient may be emaciated, with an enlarged abdomen. The liver may be normal sized or so large that it protrudes visibly in the right upper abdomen. The tumour deposits are hard and may be umbilicated. Friction may be heard over them. The deposits are not vascular, so an arterial bruit is not heard. Splenomegaly is frequent, even in those with a patent portal vein. Jaundice is mild and may be absent. Deep jaundice implies invasion of major bile ducts.

Oedema of the legs with dilated veins coursing upwards over the abdominal wall suggests that the inferior vena cava is obstructed on the posterior aspect of the liver.

Glands in the right supra-clavicular region may be involved.

A pleural effusion may indicate pulmonary metastases.

Ascites reflects peritoneal involvement and occasionally a thrombosed portal vein. Bleeding may be secondary to portal hypertension. Rarely, obstructive jaundice may be seen due to metastases from breast, colon or small cell lung cancer [40].

Secondary malignant deposits are by far the commonest causes of a really large liver.

Hypoglycaemia is rare. The primary is usually a sarcoma. Rarely, extensive tumour infiltration and parenchymal infarction may lead to the picture of fulminant hepatic failure [32].

When *malignant carcinoid* is associated with vasomotor abnormalities and pulmonary stenosis, there are always many hepatic metastases.

Unless the bile ducts are completely obstructed, the faeces are well coloured, and if the primary lesion is in the alimentary tract they may give a positive reaction for blood.

Laboratory investigations

Biochemical tests

Even with an enormous liver, sufficient functioning tissue remains. The smaller intra-hepatic bile ducts may be compressed yet no jaundice develops. The area with

uninvolved ducts may excrete the bilirubin from the occluded areas. Serum total bilirubin values greater than 2 mg/dl (34 μmol/l) suggest involvement of major bile ducts at the hilum.

Biochemical tests suggesting hepatic metastases include a raised serum alkaline phosphatase or lactic dehydrogenase level. Transaminase levels may be increased. If serum bilirubin, alkaline phosphatase, lactic dehydrogenase and transaminase levels are all normal, there is a 98% probability that metastases are absent [41].

Serum albumin concentration is normal or slightly decreased. The *serum globulin* level may be normal, slightly raised or even, occasionally, very high. Electrophoresis may show a raised α_2- or γ-globulin.

Serum CEA may be raised.

The *ascitic fluid* shows increased protein, occasionally the presence of CEA and increases in lactic dehydrogenase three times over the serum value.

Haematology

A polymorph leucocytosis is fairly common: even values up to 40 000–50 000/mm^3 are sometimes recorded. There may be a mild anaemia.

Needle liver biopsy

The biopsy needle is directed into the lesion under ultrasound, CT or peritoneoscopic guidance. Tumour tissue is characteristically white and friable. If a cylinder of tissue is not obtained, any blood clot or debris should be examined for malignant cells. Proliferated and abnormal bile ducts and polymorphs in oedematous portal tracts and focal sinusoidal dilatation suggest an adjacent metastasis [30].

Histology will not always diagnose the site of the primary especially if the tumour is undifferentiated (see fig. 31.25). Cytological examination of aspirated fluid and touch preparations of the biopsy may slightly increase the yield of cancer cells.

Histochemical studies are particularly valuable for cytology if the sample is small. Monoclonal antibodies, which react with hepatocytes but not bile ducts and non-parenchymal liver cells, can be used to distinguish primary from metastatic carcinoma of the liver [96].

The chances of obtaining a positive needle biopsy increases with the extent of tumour, size of liver and the presence of a palpable nodule.

Radiology [95]

A *plain film* of the abdomen demonstrates the large liver. The diaphragm may be elevated and its contour irregular. *Calcification* in hepatic tumours is rare but is noted with primary cancer or haemangiomas and in secondaries, for instance from the colon, breast, thyroid or bronchus.

Chest radiograph may show associated pulmonary metastases.

Scanning

Scanning usually detects lesions of 2 cm in diameter. Imaging for number, size and location is important for diagnosis and for assessing possible resection [89].

Ultrasound usually shows echogenic lesions. The addition of intravenous liver-specific micro-bubbles to ultrasonography improves the detection of subcentimetre metastases [33].

CT shows metastases as low attenuation lesions (fig. 31.26). Those from the colon generally have a large avascular centre with a dense peripheral ring-like accumulation of contrast.

Spiral (*helical*) *CT* after an intravenous bolus of contrast shows three phases: arterial, portal and equilibrium. Metastases are best seen in the portal phase and lesions greater than 1 cm can be shown. Arterioportography is more sensitive (fig. 31.27a, see fig. 5.15).

MRI shows the metastases as low or normal intensity on T_1-weighted images and high intensity on T_2-weighted images (figs 31.27b, 31.28). The metastases are not enhanced after contrast.

MRI in the hepatic arterial dominant phase with gadolinium enhancement is probably superior to CT [96]. It is less expensive and has fewer artefacts.

MRI can provide important information about the vascular anatomy of the liver.

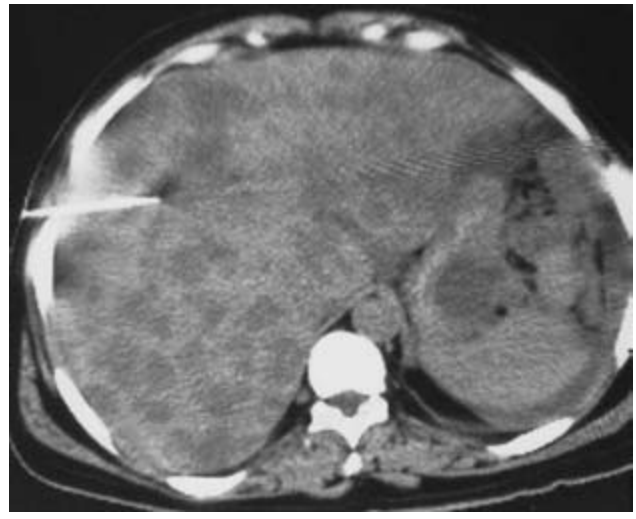


Fig. 31.26. CT scan of widespread hepatic metastases from a primary in the colon. A biopsy needle is directed into one of them.

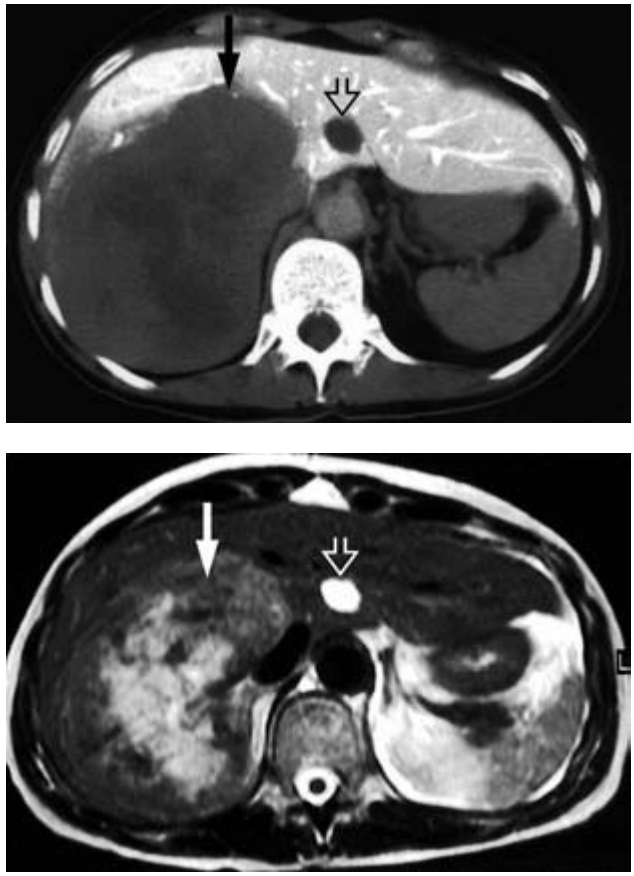


Fig. 31.27. (a) CT arterio-portogram. A large metastasis from a colo-rectal cancer is shown in the right lobe of the liver (arrow). There is a cyst in the left lobe (open arrow). (b) MRI fast spin echo T_2 in the same patient shows the right lobe metastasis (arrow). The simple cyst in the left lobe is shown again (open arrow). (Courtesy of Dr Jon Tibballs.)

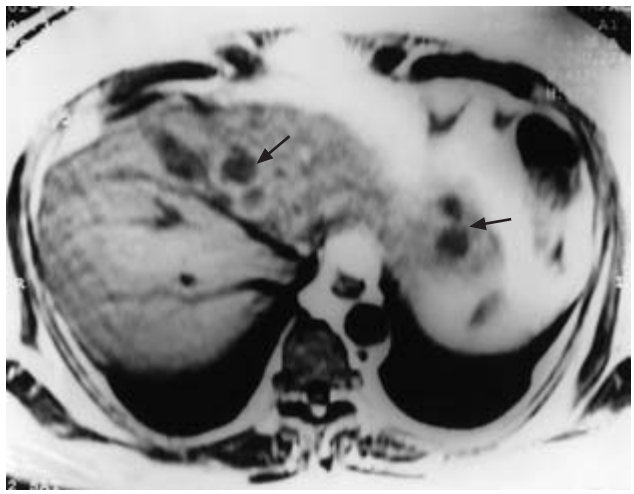


Fig. 31.28. MRI shows multiple hepatic metastases in both lobes but especially along the hepatic vein (arrows).

Special diagnostic problems

Suggestive evidence of liver metastases includes slightly increased serum bilirubin, transaminase and alkaline phosphatase levels. Aspiration needle biopsy, scanning and peritoneoscopy are useful.

Of more academic interest is obvious involvement of the liver when the primary is unknown. Breasts, thyroid and lungs must be considered as possible primaries. Positive stool blood suggests gastrointestinal cancer. Removal of skin tumours and the presence of melanomas suggest malignant melanoma. Suspected carcinoma of the body of the pancreas merits ERCP. Needle liver biopsy is usually positive and may indicate the site of the primary. However, even this may show only the presence of a squamous, scirrhous, columnar or anaplastic tumour, the site of the primary remaining unknown.

Prognosis

This depends on the site of the primary and the malignancy. In general, patients die within 1 year of diagnosis of hepatic metastases. Secondaries from tumours of the colon and rectum have the best outlook.

Treatment

This remains unsatisfactory. Those patients that have the best prognosis without therapy, for instance with metastases from the rectum, do best with treatment. Most of the published results are uncontrolled and are likely to remain so. The treatment should be the one having the greatest prospect of slowing tumour growth and with the least undesirable side-effects [9].

Systemic chemotherapy. The choice depends on the tumour type. Combined therapy uses 5-fluorouracil (5-FU) [54] or mitozantrone, methotrexate and methyl CCNU. Side-effects are great. The best results are associated with breast metastases.

For colorectal cancer metastases, 5-FU has been combined with leucovarin, a modulator of fluoropyrimidine metabolism. The response rate is increased but there is no effect on the median survival of approximately 12 months.

Hepatic arterial infusion chemotherapy

Cytotoxic drugs may be delivered directly to the tumour by hepatic artery catheterization. The catheter is usually introduced surgically into the hepatic artery via the gastroduodenal artery. The gallbladder is removed. The agent is usually 5-fluorodeoxy uridine (FUDR).

Side-effects include sepsis and catheter failure, peptic ulcer, chemical cholecystitis and hepatitis. 19–25% will

show a raised serum bilirbuin due to chemical sclerosing cholangitis.

Ablative treatment

Cryosurgery destroys tumour by freeze-thawing, using probes cooled by liquid nitrogen to sub-zero temperatures [1]. It is being evaluated in increased numbers of patients suitable for resection and also for unresectable tumours.

Other *local approaches* under investigation include microwave, radio-frequency, focused high intensity ultrasound and interstitial laser photocoagulation [9]. Their therapeutic role is not clearly defined yet.

Colorectal metastases

The liver is most commonly involved. Approximately 20% of patients will have liver metastases at the time of primary diagnosis. Of those without apparent metastases at surgery, 50% will develop metastatic liver disease. Of those treated, only about 20% will survive for about 2 years.

Resection may be possible as the metastases grow slowly, can be single and are mostly found in the subcapsular region. Resection may be possible in about 10% of patients. The peri-operative mortality is less than 5% in experienced hands. The overall 5-year survival is 25–46% [9]. Resection is possible if there are less than four metastases with no extra-hepatic recurrence or disease. Intra-operative ultrasound is essential to diagnose metastases and may alter the management. The surgeon must be prepared at the time of operation to modify the resection planned and to abandon a cure in 10–15% of patients. Lobectomy or a segmentectomy is usually performed.

In a multicentre report of 607 patients having metastases resected, 53% showed a recurrence in the liver and 53% in the lungs [37]. 66% recurred in the first year and 25% were alive and disease-free at 5 years. Patients with a CEA of less than 200 mg/ml with 1-cm surgical margins and less than 1000 g liver removed have a greater than 40% estimated 5-year disease-free survival [5]. In another series of 150 patients, curative resection (46% of patients) gave a median survival of 37 months, non-curative resection (12%), a survival 20.2 months and in the unresectable (52%), the survival was 16.5 months [90].

60% will develop recurrent disease after resection and a second operation must be considered, of similar type to that of the first resection.

Hepatic arterial (HA) infusion chemotherapy can be given continuously by an implantable pump for six 14-day courses, with 1 week rest in between. Starting 4 weeks post-resection, arterial and systemic chemotherapy improves the outlook at 2 years [44]. Survival is 86% for combined HA–5-FU and dexamethasone and 72% for monotherapy.

Metastatic carcinoid tumours

Small bowel carcinoids present with liver or lymph node metastases. Neuroendocrine tumours of the stomach and pancreas are also liable to metastasize to the liver.

Surgical resection has resulted in long-term relief of symptoms and prolonged survival [6, 48]. Surgery can be considered as the tumours shell out easily.

Hepatic artery occlusion and embolization can be palliative (see figs 31.19, 31.20). Transplantation in highly selected patients with metastatic carcinoid has resulted in a 69% 5-year survival.

Octeotride, a somastatin analogue, inhibits 5-HT release and reduces flushing and diarrhoea. Indium-labelled octreotide has been used for scintigraphy (see fig. 5.1) [6].

Indium-III labelled octeotride is under investigation for receptor-targeted therapy.

References

1 Adam R, Akpinar E, Johann M *et al*. Place of cryosurgery in the treatment of malignant liver tumours. *Ann. Surg*. 1997; **225**: 39.

2 Anthony PB. Liver cell dysplasia: what is its significance? *Hepatology* 1987; **7**: 394.

3 Bronowicki J-P, Nisand G, Altieri M *et al*. Compared results of resection (RX), orthotopic liver transplantation (OLT) and transcatheter oily chemoembolization (TOCE) in the treatment of Okuda's stage 1 hepatocellular carcinoma (HCC). *Gastroenterology* 1993; **104**: A881.

4 Buys CHCM. Telomeres, telomerase and cancer. *N. Engl. J. Med*. 2000; **342**: 1282.

5 Cady B, Stone MD, McDermott WV Jr *et al*. Technical and biological factors in disease-free survival after hepatic resection for colorectal cancer metastases. *Arch. Surg*. 1992; **127**: 561.

6 Caplin ME, Buscombe JR, Hilson AJ *et al*. Carcinoid tumour. *Lancet* 1998; **352**: 799.

7 Chen M-F, Jan Y-Y, Jeng L-B *et al*. Obstructive jaundice secondary to ruptured hepatocellular carcinoma into the common bile duct. *Cancer* 1994; **73**: 1335.

8 Chevret S, Trinchet J-C, Mathieu D *et al*. A new prognostic classification for predicting survival in patients with hepatocellular carcinoma. *J. Hepatol*. 1999; **31**: 133.

9 Choti MA, Bulkely GB. Management of hepatic metastases. *Liver Transplant Surg*. 1999; **5**: 65.

10 Chowdhury AR, Black M, Lorber SH *et al*. Hemangioendotheliomatosis of the liver: a 12 year follow-up. *Gastroenterology* 1977; **72**: 157.

11 Clain D, Wartnaby K, Sherlock S. Abdominal arterial murmurs in liver disease. *Lancet* 1966; **ii**: 516.

12 CLIP Group (Cancer of the Liver Italian Program). Tamoxifen in treatment of hepatocellular carcinoma: a randomized controlled trial. *Lancet* 1998; **352**: 17.

13 CLIP Investigators: Prospective validation of the CLIP score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. *Hepatology* 2000; **31**: 840.
14 Collier JD, Carpenter M, Burt AD *et al*. Expression of mutant p53 protein in hepatocellular carcinoma. *Gut* 1994; **35**: 98.
15 Collier J, Sherman M. Screening for hepatocellular carcinoma. *Hepatology* 1998; **27**: 273.
16 Colombo M. Hepatocellullar carcinoma. *J. Hepatol.* 1992; **15**: 225.
17 Craig JR, Peters RL, Edmondson HA *et al*. Fibrolamellar carcinoma of the liver: a tumour of adolescents and young adults with distinctive clinico-pathologic features. *Cancer* 1980; **46**: 372.
18 Di Bisceglie AM, Carithers L Jr, Gores GJ. Hepatocellular carcinoma. *Hepatology* 1998; **28**: 1161.
19 Ding S-F, Michail NE, Habib NA. Genetic changes in hepatoblastoma. *J. Hepatol*. 1994; **20**: 672.
20 Dooley JS, Li AKC, Scheuer PJ *et al*. A giant cystic mesenchymal hamartoma of the liver: diagnosis, management, and study of cyst fluid. *Gastroenterology* 1983; **85**: 958.
21 Dunk AA, Scott SC, Johnson PJ *et al.* Mitoxantrone as a single agent therapy in hepatocellular carcinoma. A phase II study. *J. Hepatol.* 1985; **1**: 395.
22 El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N. Engl. J. Med.* 1999; **340**: 745.
23 Erlitzki R, Minuk GY. Telomeres, telomerase and HCC; the long and the short of it. *J. Hepatol*. 1999; **31**: 939.
24 Falk H, Thomas LB, Popper H *et al*. Hepatic angiosarcoma associated with androgenic-anabolic steroids. *Lancet* 1979; **ii**: 1120.
25 Fausto N. Mouse liver tumorigenesis: models, mechanisms and relevance to human disease. *Sem. Liver Dis.* 1999; **19**: 243.
26 Fernandez M, Del P, Redvanly RD. Primary hepatic malignant neoplasms. *Radiol. Clin. North Am.* 1998; **36**: 333.
27 Ferrell L, Wright T, Lake J *et al*. Incidence and diagnostic features of macroregenerative nodules vs. small hepatocellular carcinoma in cirrhotic livers. *Hepatology* 1992; **16**: 1372.
28 Forbes A, Portmann B, Johnson P *et al*. Hepatic sarcomas in adults: a review of 25 cases. *Gut* 1987; **31**: 668.
29 Gerber MA, Shieh YSC, Shim K-S *et al*. Detection of replicative hepatitis C virus sequences in hepatocellular carcinoma. *Am. J. Pathol*. 1992; **141**: 1271.
30 Gerber MA, Thung SN, Bodenheimer HC Jr *et al*. Characteristic histological triad in liver adjacent to metastatic neoplasm. *Liver* 1986; **6**: 85.
31 Goldberg SN, Gazelle GS, Solbiati L *et al*. Ablation of liver tumours using percutaneous RF therapy. *Am. J. Roentgenol.* 1998; **170**: 1023.
32 Harrison HB, Middleton HM III, Crosby JH *et al*. Fulminant hepatic failure: an unusual presentation of metastatic liver disease. *Gastroenterology* 1981; **80**: 820.
33 Harvey CJ, Blomley MJK, Eckersley RJ *et al*. Pulse-inversion mode imaging of liver specific microbubbles: improved detection of subcentimetre metastases. *Lancet* 2000; **355**: 807.
34 Hood DL, Bauer TW, Leibel SA *et al*. Hepatic giant cell carcinoma: an ultrastructural and immunohistochemical study. *Am. J. Clin. Pathol*. 1990; **93**: 111.
35 Hsia CC, Axiotis CA, Di Bisceglie AM *et al*. Transforming growth factor alpha in human hepatocellular carcinoma and coexpression with hepatitis B surface antigen in adjacent liver. *Cancer* 1992; **70**: 1049.
36 Hsu H-C, Huang A-M, Lai P-L *et al*. Genetic alterations at the splice junction of p53 gene in human hepatocellular carcinoma. *Hepatology* 1994; **19**: 122.
37 Hughes KS, Simon R, Songhorabodi S *et al*. Resection of the liver for colorectal carcinoma metastases: a multiinstitutional study of patterns of recurrence. *Surgery* 1986; **100**: 278.
38 Ichikawa T, Federle MP, Grazioli L *et al*. Fibrolamellar hepatocellular carcinoma: imaging and pathologic findings in 31 recent cases. *Radiology* 1999; **213**: 352.
39 Ishak KG, Sesterhenn IA, Goodman MZD *et al*. Epithelioid haemangioendothelioma of the liver: a clinicopathologic and follow-up study of 32 cases. *Hum. Pathol.* 1984; **15**: 839.
40 Johnson DH, Hainsworth JD, Greco FA. Extrahepatic biliary obstruction caused by small-cell lung cancer. *Ann. Intern. Med*. 1985; **102**: 487.
41 Kamby C, Kirksen H, Vejborg I *et al*. Incidence and methodologic aspects of the occurrence of liver metastases in recurrent breast cancer. *Cancer* 1987; **59**: 1524.
42 Keeley AF, Iseri OA, Gottlieb LS. Ultrastructure of hyaline cytoplasmic inclusions in a human hepatoma: relationship to Mallory's alcoholic hyalin. *Gastroenterology* 1972; **62**: 280.
43 Kelleher MB, Iwatsuki S, Sheahan DG. Epithelioid hemangioendothelioma of the liver. Clinicopathological correlations in 10 cases treated by orthotopic liver transplantation. *Am. J. Surg. Pathol.* 1989; **13**: 999.
44 Kemeny N, Huang Y, Cohen AM *et al*. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N. Engl. J. Med.* 1999; **341**: 2039.
45 Kew MC. Virchow–Troisier's lymph node in hepatocellular carcinoma. *J. Clin. Gastroenterol*. 1991; **13**: 217.
46 Khan KN, Yatsuhashi H, Yamasaki K *et al*. Prospective analysis of risk factors for early intrahepatic recurrence of hepatocellular carcinoma following ethanol injection. *J. Hepatol.* 2000; **32**: 269.
47 Kojima H, Yokosuka O, Kato N *et al*. Quantitative evaluation of telomerase activity in small liver tumours: analysis of ultrasonography-guided liver biopsy specimens. *J. Hepatol.* 1999; **31**: 514.
48 Kulke MH, Mayer RJ. Carcinoid tumours. *N. Engl. J. Med.* 1999; **340**: 858.
49 Kusano N, Shiraishi K, Kubo K *et al*. Genetic aberrations detected by comparative genomic hybridization in hepatocellular carcinomas: their relationship to clinicopathological features. *Hepatology* 1999; **29**: 1858.
50 Lack EE. Mesenchymal hamartoma of the liver. A clinical and pathological study of nine cases. *Am. J. Pediatr. Hematol. Oncol.* 1986; **8**: 91.
51 Lau WY, Leung TFT, Ho SKW *et al*. Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomized trial. *Lancet* 1999; **353**: 797.
52 Lauffer JG, Zimmerman A, Krahenbuhl L *et al*. Epithelioid haemangioendothelioma of the liver. A rare hepatic tumour. *Cancer* 1996; **78**: 2318.
53 Lederman SM, Martin EC, Laffey KT *et al*. Hepatic neurofibromatosis, malignant shwannoma and angiosarcoma in von Recklinghausen's disease. *Gastroenterology* 1987; **92**: 234.

54 Leichman CC, Fleming TR, Muggia FM *et al*. Phase II study of fluorouracil and its modulation in advanced colorectal cancer. A South-west Oncology Group study. *J. Clin. Oncol*. 1995; **13**: 1303.

55 Lennington WJ, Gray GF Jr, Page DL. Mesenchymal haemartoma of liver. A regional ischemic lesion of a sequestered lobe. *Am. J. Dis. Child*. 1993; **147**: 193.

56 Leuschner I, Schmidt D, Harms D. Undifferentiated sarcoma of the liver in childhood. Morphology, flow cytometry and literature review. *Hum. Pathol*. 1990; **21**: 68.

57 Livraghi T, Benedini V, Lazzaroni S *et al*. Long-term results of single session percutaneous ethanol injection in patients with large hepatocellular carcinoma. *Cancer* 1998; **83**: 48.

58 Livraghi T, Bolondi L, Buscarini L *et al*. No treatment, resection and ethanol injection in hepatocellular carcinoma: a retrospective analysis of survival in 391 patients with cirrhosis. *J. Hepatol*. 1995; **22**: 522.

59 Llovet JM, Sala M, Castells L *et al*. Randomized controlled trial of interferon treatment for advanced hepatocellular carcinoma. *Hepatology* 2000; **31**: 54.

60 Lo CM, Lai ECS, Liu CH *et al*. Laparoscopy and laparoscopic ultrasonography avoid exploratory laparotomy in patients with hepatocellular carcinoma. *Ann. Surg*. 1998; **227**: 527.

61 Majno PE, Adam R, Bismuth H *et al*. Influence of preoperative transarterial lipiodol chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. *Am. Surg*. 1997; **226**: 688.

62 Majno PE, Sarasin FP, Mentha G *et al*. Primary liver resection and salvage transplantation or primary liver transplantation in patients with single small hepatocellular carcinoma and preserved liver function: an outcome-orientated decision analysis. *Hepatology* 2000; **31**: 899.

63 Mazzaferro V, Regalia E, Doci R *et al*. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N. Engl. J. Med*. 1996; **223**: 693.

64 Meyer M, Wiedorn KH, Hofschneider PH *et al*. A chromosome 17:7 translocation is associated with a hepatitis B virus DNA integration in human hepatocellular carcinoma DNA. *Hepatology* 1992; **15**: 665.

65 Mitry RR, Sarraf CE, Havlik R *et al*. Detection of adenovirus and initiation of apoptosis in hepatocellular carcinoma cells after Ad-p53 treatment. *Hepatology* 2000; **31**: 885.

66 Miyamoto M, Sudo T, Kuyama T. Spontaneous rupture of hepatocellular carcinoma: a review of 172 Japanese cases. *Am. J. Gastroenterol*. 1991; **86**: 67.

67 Mohr L, Schauer JI, Boutin RH *et al*. Targeted gene transfer to hepatocellular carcinoma cells *in vitro* using a novel monoclonal antibody based gene delivery system. *Hepatology* 1999; **29**: 82.

68 Moriya K, Fujie H, Shintani Y *et al*. The core protein of hepatitis C virus induces hepatocellular cancer in transgenic mice. *Nat. Med*. 1998; **4**: 1065.

69 Nagato Y, Kondo F, Kondo Y *et al*. Histological and morphometrical indicators for a biopsy diagnosis of well-differentiated hepatocellular carcinoma. *Hepatology* 1991; **14**: 473.

70 Nalpas B, Pol S, Thepor V *et al*. Relationship between excessive alcohol drinking and viral infections. *Alcohol Alcoholism* 1998; **33**: 202.

71 Ohnishi K, Youshioka H, Ito S *et al*. Prospective randomized controlled trial comparing percutaneous acetic acid injection and percutaneous ethanol injection for small hepatocellular carcinoma. *Hepatology* 1998; **27**: 67.

72 Oka H, Tamori A, Kuroki T *et al*. Prospective study of alpha-fetoprotein in cirrhotic patients monitored for development of hepatocellular carcinoma. *Hepatology* 1994; **19**: 61.

73 Okuda H, Nakanishi T, Takatsu K *et al*. Measurement of serum levels of des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma by a revised enzyme immuno-assay kit with increased sensitivity. *Cancer* 1999; **85**: 812.

74 Okuda K, Kondo Y, Nakano M *et al*. Hepatocellular carcinoma presenting with pyrexia and leukocytosis: report of five cases. *Hepatology* 1991; **13**: 695.

75 Okuda K, Ohtuki T, Obata H *et al*. Natural history of hepatocellular carcinoma and prognosis in relation to treatment: study of 850 patients. *Cancer* 1985; **56**: 918.

76 Paradinas RJ, Melia WM, Wilkinson ML *et al*. High serum vitamin B12 binding capacity as a marker of the fibrolamellar variant of hepatocellular carcinoma. *Br. Med. J*. 1982; **315**: 840.

77 Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. *Int. J. Cancer* 1999; **80**: 827.

78 Qian C, Drozdzik M, Caselmann WH *et al*. The potential of gene therapy in the treatment of hepatocellular carcinoma. *J. Hepatol*. 2000; **32**: 344.

79 Ringe B, Wittekind C, Weimann A *et al*. Results of hepatic resection and transplantation for fibrolamellar carcinoma. *Surg. Gyn. Obstet*. 1992; **175**: 299.

80 Robinson WS, Klote L, Aoki N. Hepadnaviruses in cirrhotic liver and hepatocellular carcinoma. *J. Med. Virol*. 1990; **31**: 18.

81 Ross JS, Kurian S. Clear cell hepatocarcinoma: sudden death from hypoglycemia. *Am. J. Gastroenterol*. 1985; **80**: 188.

82 Sato M, Watanabe Y, Neda S *et al*. Microwave coagulation therapy for hepatocellular carcinoma. *Gastroenterology* 1996; **110**: 1502.

83 Sato Y, Nakata K, Kato Y *et al*. Early recognition of hepatocellular carcinoma based on altered profiles of alpha-fetoprotein. *N. Engl. J. Med*. 1993; **331**: 1802.

84 Semelka RC, Cance WG, Marcos HB *et al*. Liver metastases: comparison of current MR techniques and spiral CT during arterial portography for detection in 20 surgically staged cases. *Radiology* 1999; **213**: 86.

85 Seo T, Ando H, Watanabe Y *et al*. Treatment of hepatoblastoma: less extensive hepatectomy after effective preoperative chemotherapy with cisplatin and adriamycin. *Surgery* 1998; **123**: 407.

86 Shapiro ET, Bell GI, Polonsky KS *et al*. Tumor hypoglycemia: relationship to high molecular weight insulin-like growth factor II. *J. Clin. Invest*. 1990; **85**: 1672.

87 Sharara AI, Panella TJ, Fitz JG. Paraneoplastic hepatopathology associated with soft tissue carcinoma. *Gastroenterology* 1992; **103**: 330.

88 Sherlock S. Viruses and hepatocellular carcinoma. *Gut* 1994; **35**: 828.

89 Sica GT, Ji H, Ros PR. CT and MR imaging of hepatic metastases. *Am. J. Roentgenol*. 2000; **174**: 691.

90 Steele G Jr, Bleday R, Mayer RJ *et al*. A prospective evaluation of hepatic resection for colorectal carcinoma metastases to the liver: gastrointestinal tumour study group protocol 6584. *J. Clin. Oncol*. 1991; **9**: 1105.

91 Strickland RC, Shenker S. The nephrogenic hepatic dysfunction syndrome: a review. *Am. J. Dig. Dis.* 1977; **22**: 49.
92 Sugimoto K, Shiraki K, Fusikawa K *et al*. Expression of functional CD-40 in human hepatocellular carcinoma. *Hepatology* 1999; **30**: 920.
93 Terada T, Nakanuma Y, Kawai K. Small hepatocellular carcinoma presenting as intrabiliary pedunculated polyp and obstructive jaundice. *J. Clin. Gastroenterol*. 1989; **11**: 578.
94 Theise ND, Schwartz M, Miller C *et al*. Macroregenerative nodules and hepatocellular carcinoma in 44 sequential adult liver explants with cirrhosis. *Hepatology* 1992; **16**: 949.
95 Vogl TJ, Muller PK, Mack MG *et al*. Liver metastases: interventional therapeutic techniques and results, state of the art. *Eur. Radiol*. 1999; **9**: 675.
96 Wennerberg AE, Nalasnik MA, Coleman WB. Hepatocyte paraffin I: a monoclonal antibody that reacts with hepatocytes and can be used for differential diagnosis of hepatic tumours. *Am. J. Pathol*. 1993; **143**: 1050.
97 Yamashita Y, Mitsuzaki K *et al*. Small hepatocellular carcinoma in patients with chronic liver damage. Prospective comparison of detection with dynamic MR imaging and helical CT of the whole liver. *Radiology* 1996; **200**: 79.
98 Yoshida H, Shiratori Y, Moriyama M *et al*. Interferon therapy reduces the risk for hepatocellular carcinoma: National Surveillance Program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. *Ann. Intern. Med.* 1999; **131**: 174.

Chapter 32
Imaging of the Biliary Tract: Interventional Radiology and Endoscopy

Imaging is central to the investigation and diagnosis of biliary tract disease. Upper abdominal pain is a common symptom and imaging of the gallbladder may be necessary to identify or rule out disease. The symptoms of cholestasis—jaundice and itching—are not specific, nor are the physical findings. Biochemical tests only confirm cholestasis. Common bile duct obstruction, for example from stones and tumour, must be distinguished from intra-hepatic cholestasis such as that caused by drugs. An algorithm helps (fig. 13.18). Non-invasive tests (ultrasound, CT, biliary scintigraphy, MRI scans) provide important data on which to choose more invasive and definitive techniques (ERCP, PTC, liver biopsy). Angiography is used to assess resectability of tumours. Interventional endoscopy and radiology provide an alternative therapeutic approach to surgery. Aspiration cytology or biopsy are done to give a tissue diagnosis.

Plain film of the abdomen

Diagnostic yield is low and this test is usually omitted. However, it may reveal gallstones, a calcified gallbladder, pancreatic calcification or, rarely, the outline of a distended gallbladder.

With obstruction to the cystic duct, calcium carbonate may be excreted with the bile (milk of calcium bile or 'limey bile'). The wall of the gallbladder may also calcify (porcelain gallbladder) or contain gas (emphysematous cholecystitis).

Gas in the biliary tree ('aerobilia') may be seen after endoscopic sphincterotomy or surgical bile duct/bowel anastomosis. In such a patient with cholestasis or fever, however, this finding should not be used as evidence of unobstructed bile drainage, since it may occur above a significant stricture, or stone (fig. 32.1). Rarely, biliary infection with gas-forming organisms produces aerobilia.

Ultrasound (US)

Bile ducts

Ultrasonography is the most important screening investigation in patients with cholestasis. The major intrahepatic bile ducts are normally 2 mm in diameter, the common hepatic duct < 4 mm and the common bile duct < 5–7 mm in diameter. The presence of dilated ducts characterizes large bile duct obstruction (fig. 32.2). US is 95% accurate if the serum bilirubin level exceeds 170 µmol/l (10 mg/dl). False negatives are seen if the obstruction is of short duration or intermittent. US diagnoses the correct level and cause of the obstruction in about 60% and less than 50% of cases, respectively, largely due to failure to visualize the complete biliary tract. The lower end particularly may not be seen because of overlying gas in the duodenum and bowel. Endoscopic US shows this area much better and very small lesions can be detected.

Gallbladder

The gallbladder is ideal for sonography which has a high accuracy in detecting disease. The examination should be performed after fasting which should result in a

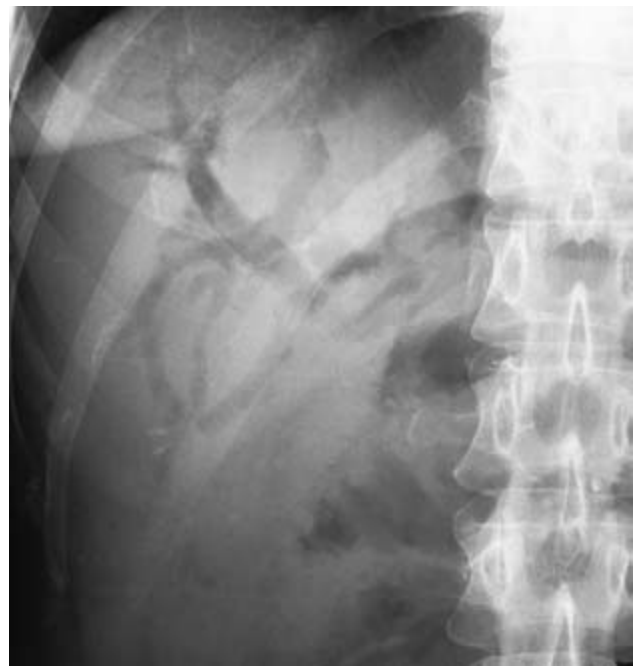


Fig. 32.1. Plain abdominal X-ray showing gas in the dilated intra-hepatic biliary tree.

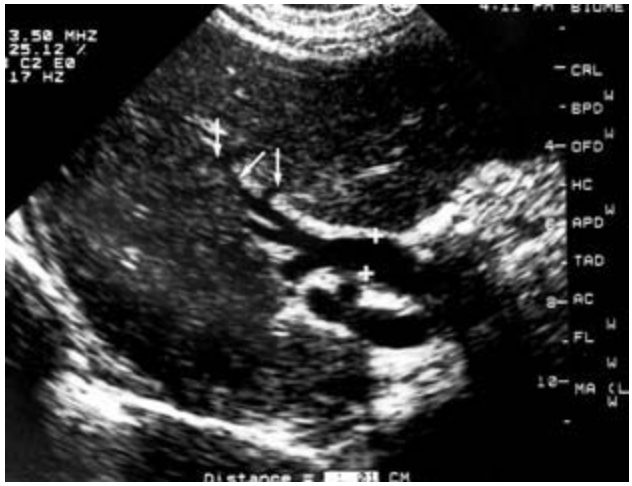


Fig. 32.2. Ultrasound scan showing dilated intra-hepatic ducts (arrowed) and common bile duct (marked ++).

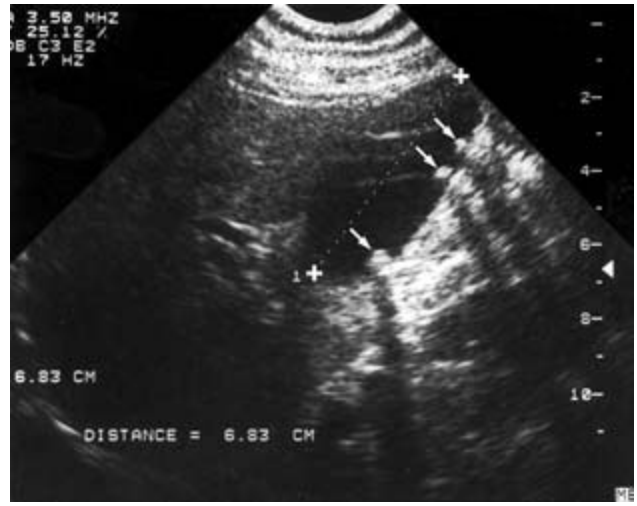


Fig. 32.3. Ultrasound scan of gallbladder showing three stones (arrowed) which cast acoustic shadows.

distended gallbladder full of bile. Failure to identify the gallbladder (no fluid-filled lumen and shadowing in the gallbladder bed) may be as important as finding an abnormality. Gallstones cast intense echoes with obvious posterior acoustic shadows (fig. 32.3). They change in position with turning of the patient. Stones 3 mm in size and upwards may be visualized. Diagnostic accuracy is said to be 96% but less experienced operators will not achieve this success and there are many diagnostic pitfalls [69].

Acute calculous cholecystitis is suggested by the finding of stones in the gallbladder together with other signs indicative of inflammation. These include a thickened wall of the gallbladder (>5 mm) (fig. 32.4) and a positive sonographic Murphy sign—the presence of maximum tenderness, elicited by direct pressure of the transducer, over a sonographically localized gallbladder. Distension, pericholecystic fluid, subserosal oedema (without ascites), intramural gas or a sloughed mucosal membrane are also important signs. The same features of gallbladder inflammation hold for the diagnosis of acute acalculous cholecystitis.

US examination of the gallbladder and liver may detect gallbladder polyps or carcinoma (Chapter 37), or congenital biliary anomalies such as Caroli's disease or choledochal cysts (Chapter 33).

Ultrasound allows guided percutaneous access to the gallbladder for drainage, antegrade cholangiography, and even gallstone dissolution or removal.

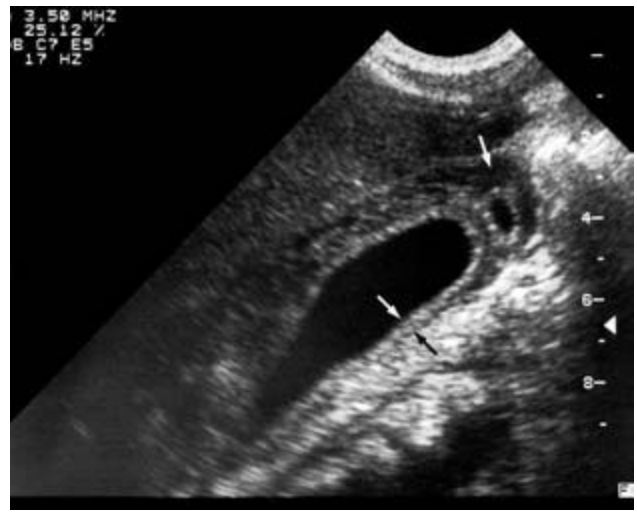


Fig. 32.4. Ultrasound scan in acute cholecystitis. Note the thickened wall of the gallbladder (between black and white arrows) with some pericholecystic fluid (single arrow).

Computed tomography (CT)

CT also shows dilated bile ducts distinguishing obstructive from non-obstructive jaundice in 90% of cases. But as a screening procedure it has no advantage over ultrasound. It is, however, more likely than ultrasound to show the level and cause of obstruction. The lower end of a dilated bile duct is usually seen; pancreatic lesions if large enough will be shown (fig. 32.5). Hilar cholangiocarcinoma is rarely demonstrated. Routine CT is not accurate in detecting duct and gallbladder stones. CT may be used, however, to distinguish cholesterol-rich gallbladder stones from calcium-containing stones (based on the attenuation value)—useful information if extracorporeal shock wave lithotripsy is being considered.

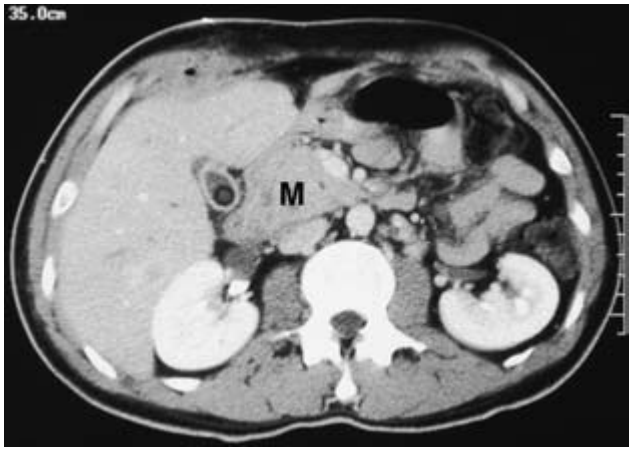


Fig. 32.5. Triple phase spiral CT scan showing mass (M) in head of pancreas due to carcinoma. There is involvement of the superior mesenteric vein medially, and the lesion was irresectable.

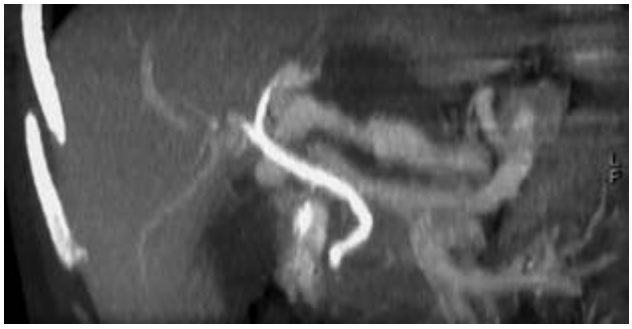


Fig. 32.6. Spiral CT after intravenous cholangiographic contrast. Three-dimensional reconstruction (maximum intensity projection, MIP) shows normal bile duct.

Spiral CT allows scanning to be done quickly (15–30 s) during a single breath hold. The major advantage is that the scan can be completed while there is a high concentration of contrast in the blood vessels of interest, and before significant contrast equilibration has occurred. Detail of small vessels is remarkable—particularly useful in the assessment of tumour resectability [11].

CT cholangiography (fig. 32.6) with or without contrast is possible. The disadvantages of cholangiography with contrast are the well-recognized risk of fatal anaphylaxis, and restriction of this technique to patients with normal or near normal liver function. However, three-dimensional reconstruction is possible [71]. Normal and abnormal intra- and extra-hepatic ducts are seen as well as the site of obstruction. In patients with bile duct obstruction three-dimensional spiral CT without contrast can be used. These techniques, however, await comparison with MR cholangiography, which at present is more widely used than this CT method.

Magnetic resonance cholangiopancreatography (MRCP) [7]

MRCP shows water containing bile and pancreatic juice within bile duct and pancreatic duct without the need for injection of contrast. Image acquisition has become more rapid with technical advances including the half-Fourier acquisition single-shot turbo (HASTE) spin–echo method, making this a more effective approach than with earlier technology. MRI with MRCP remains more expensive than US and CT, and is not available in all hospitals. However, where it is available it allows excellent non-invasive cholangiography.

Overall, MRCP has an accuracy of greater than 90% in showing common bile duct stones (fig. 32.7a) [59, 72]. The sensitivity is lower for stones less than 6 mm in diameter [76]. MRCP has high accuracy in showing bile duct strictures (fig. 32.7b) and is as sensitive as ERCP in detecting pancreatic carcinomas (84 vs. 70%, respectively). Specificity is around 95% for both techniques [1]. MRI gives additional staging information not given by ERCP alone [32]. MRCP shows the bile duct stricturing due to malignant *hilar* tumours (see fig. 37.3) and identifies patients in whom endoscopic drainage may not be the option of choice thus avoiding unnecessary ERCP [77].

In primary sclerosing cholangitis the classical features on MR scanning are dilatations and stricturing of bile ducts, seen particularly well peripherally in the liver (fig. 32.7c). Wedge-shaped areas of parenchyma with high T_2-signal intensity are also characteristic [60]. The choice in these patients between MRCP and ERCP depends upon the need for other information such as the presence of ascites, splenomegaly or lymphadenopathy and also whether cytology or a therapeutic intervention is likely to be needed [5].

MRCP is valuable in the evaluation of neonatal cholestasis [40].

Availability still limits MRCP primarily to major medical centres. Experience in the interpretation of the films is important. In centres which do not have access to MRCP, ERCP remains the primary approach to the patient with suspected biliary tract disease on US or CT. Where both MRI and ERCP are available, MRCP is indicated particularly in patients where there is a low suspicion of bile duct pathology on clinical grounds, for example in some patients before laparoscopic cholecystectomy. MRCP is also particularly useful in patients who are poor candidates for ERCP such as the elderly.

Its increasing role is to select patients for therapeutic ERCP. Patients with a low likelihood of biliary disease would avoid the risk of pancreatitis after a negative ERCP.

Routine screening for suspected biliary tract disease remains ultrasound or CT because of the higher cost of MRCP.

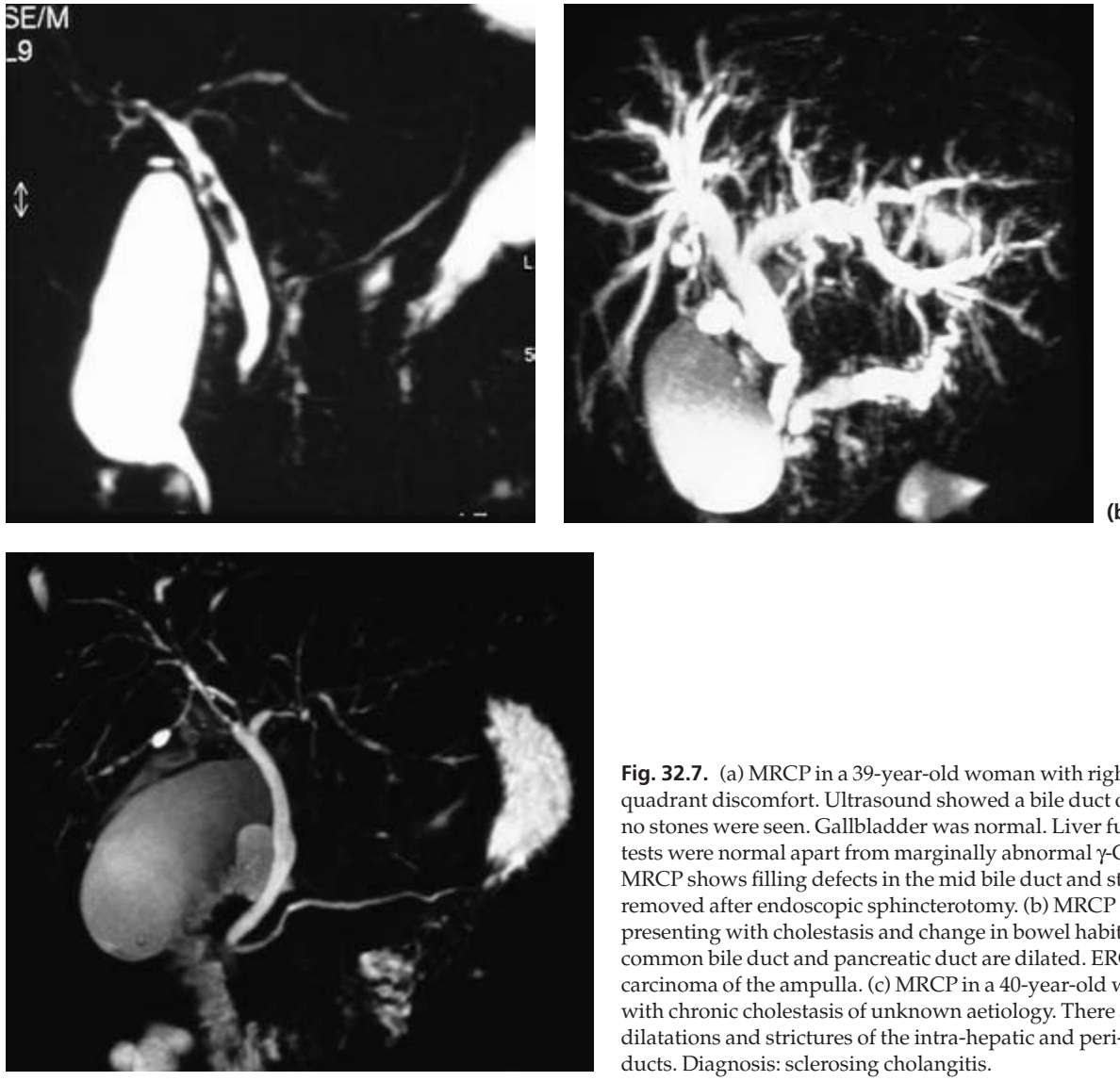


Fig. 32.7. (a) MRCP in a 39-year-old woman with right upper quadrant discomfort. Ultrasound showed a bile duct of 1 cm but no stones were seen. Gallbladder was normal. Liver function tests were normal apart from marginally abnormal γ-GT. The MRCP shows filling defects in the mid bile duct and stones were removed after endoscopic sphincterotomy. (b) MRCP in a patient presenting with cholestasis and change in bowel habit. Both the common bile duct and pancreatic duct are dilated. ERCP showed carcinoma of the ampulla. (c) MRCP in a 40-year-old woman with chronic cholestasis of unknown aetiology. There are dilatations and strictures of the intra-hepatic and peri-hilar bile ducts. Diagnosis: sclerosing cholangitis.

Endoscopic ultrasound (EUS)

This is done using an endoscope which has a miniature ultrasound transducer mounted on its tip. An endoscopic view is possible but is limited in comparison with normal diagnostic endoscopes.

Most endoscopes used for ultrasonography have a mechanical rotating scanner at the tip and are side or oblique viewing. The transducer rotates at approximately 10 cycles per second providing a 360-degree image. Because of the transducer the endoscope has a long rigid nose over several centimetres at the tip which makes introduction more difficult than a regular endoscope. Another design of endoscope uses a linear transducer which gives a 100-degree ultrasound image.

Recognizing the structures seen at endoscopic ultrasonography requires a sufficient period of training and this has limited its general availability to specialist centres.

EUS has a major application in the evaluation of oesophageal strictures but in the hepato-biliary system its prominent role is in the detection and evaluation of pancreatic tumours (fig. 32.8). It also detects common bile duct stones and can be used for image-directed biopsy.

EUS is at least as sensitive as ERCP in detecting stones and strictures [57]. The sensitivity and accuracy of endoscopic ultrasound for choledocholithiasis is greater than 90% [55] and it is more accurate than transabdominal ultrasound [15].

EUS has a greater sensitivity for detecting pancreatic

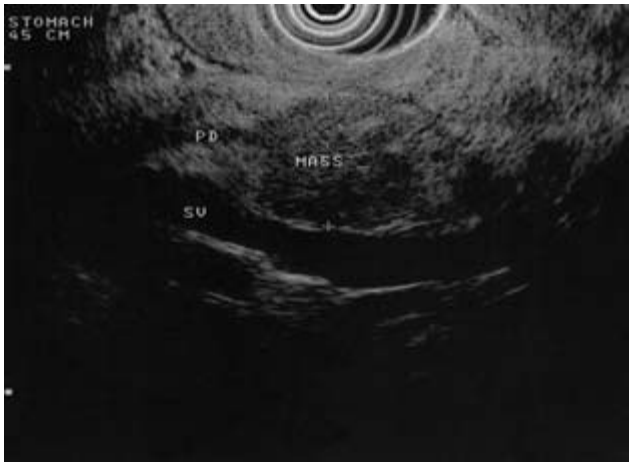


Fig. 32.8. Endoscopic ultrasound in a patient with suspected neuroendocrine tumour in whom CT scan had shown no abnormality. 2.5 cm diameter mass shown in head of pancreas PD, pancreatic duct; SV, superior mesenteric vein. (Courtesy of Dr Steve Pereira.)

tumour (93%) than CT (53%) [52]. Endoscopic ultrasound may also be used to stage pancreatic cancer but its accuracy needs further evaluation [2]. This technique is also highly accurate for localizing pancreatic neuroendocrine tumours which are often not well seen by other methods (fig. 32.8) [6].

Endoscopic ultrasound-guided fine-needle aspiration biopsy is possible from lymph nodes and pancreatic lesions and in experienced hands is safe [75].

With the increased availability of this technique it is being used more frequently for the evaluation of patients with pancreatic tumours, in particular for biopsy and assessing resectability. It may also be valuable for patients with problematic biliary tract pain where MRCP and other scanning has been negative and ERCP unhelpful. Endoscopic ultrasound to look for tiny bile duct stones and for pancreatic disease may be clinically indicated in combination with endoscopic biliary manometry.

Biliary scintigraphy

The technetium-labelled iminodiacetic acid derivative (IDA) is cleared from the plasma by hepato-cellular organic anion transport and excreted in the bile (fig. 32.9a). Biliary radiopharmaceuticals have so improved that one of the newest, Iodida, is easily prepared and is taken up by the liver and excreted into bile efficiently with only 5% of the injected dose excreted in the urine. Effective concentration in the bile duct is achieved in patients with total serum bilirubin levels exceeding 340 µmol/l (20 mg/dl). Resolution is much less than with other forms of bile duct visualization and the role of cholescintigraphy is therefore limited.

The method may be used to determine patency of the cystic duct in suspected *acute cholecystitis* (fig. 32.9b). The radio-activity is followed until it reaches the duodenum. If the gallbladder fails to visualize, despite common bile duct patency and intestinal visualization, the probability of acute cholecystitis is 99%.

The gallbladder ejection fraction can be calculated from the loss of isotope from the gallbladder after a standard infusion of sincalide (the C-terminal octapeptide of CCK) [78]. This technique can help to identify gallbladder disease in some patients who have gallbladder-like pain but a normal ultrasound.

Cholescintigraphy can show whether the bile duct is obstructed, but in most units US serves this role.

In the more complicated patient, analysis of the pattern of uptake and hepatic clearance of radio-activity, or the combination of scintigraphy with US, can differentiate intra-hepatic cholestasis from bile duct obstruction—useful, for example, in the patient with a biliary stricture, who remains cholestatic despite insertion of a biliary endoprosthesis. Scintigraphy is also useful in assessing the patency of biliary-enteric anastomoses, and may show biliary leaks after cholecystectomy (fig. 32.9c) or liver transplantation [44].

Choledochal cysts can be diagnosed although ultrasound CT and MRI scanning are just as satisfactory (see fig. 33.13).

In the *neonate*, IDA scanning is used to differentiate between biliary atresia and neonatal hepatitis (fig. 32.9d). It may be combined with ultrasound.

Functional obstruction of the sphincter of Oddi after cholecystectomy may be suggested by delayed and reduced excretion of activity with slower emptying of the biliary tree.

Oral cholecystography

Although oral cholecystography shows gallbladder stones with an accuracy of 85–90%, it is now rarely used because of the greater sensitivity and wide availability of transabdominal ultrasonography. In recent years it had a limited role in the evaluation of the gallbladder before oral bile acid therapy but this treatment has also become much less frequent with the development of laparoscopic cholecystectomy.

The contrast agents used were iodine containing, conjugated with glucuronic acid by the liver, and excreted in bile. In the fasting patient contrast enters the gallbladder if the cystic duct is patent. There is reabsorption of water by the lining mucosa, concentration of contrast and gallbladder opacification (fig. 32.10). Complications including hypersensitivity are extremely rare.

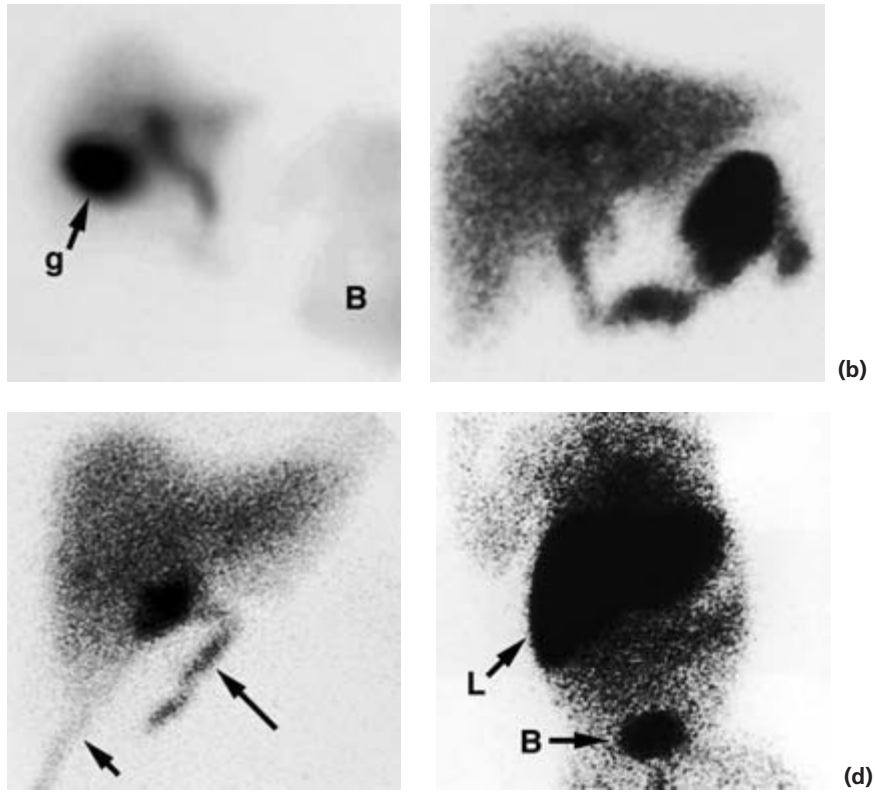


Fig. 32.9. Cholescintigraphy (^{99m}Tc Iodida). (a) Normal scan. At 30 min the gallbladder (g) has filled. Isotope has already entered the bowel (B). (b) Acute cholecystitis. Gallbladder has not filled by 60 min (c) Post-cholecystectomy bile leak. Isotope tracks laterally from gallbladder bed (short arrow) and T-tube track (long arrow). (d) Two-week-old infant with severe jaundice. Radio-activity is concentrated in the liver (L) and did not enter the bowel. Biliary atresia was confirmed. B, bladder.

When this method is used three X-ray films are necessary; control, fasting after oral contrast, and after gallbladder contraction by fat stimulation or CCK. The gallbladder is seen in 85% of patients. Films are taken erect and prone. Normal visualization without stones gives a 95% probability that the gallbladder is normal. The technique is not valuable if the bilirubin is greater than twice the upper limit of normal because of failure of efficient secretion of contrast by the liver.

Oral cholecystography is of value in showing lesions of the gallbladder wall, for example *adenomyomatosis* [47]. This is seen as small fundal outpouchings. *Rokitansky–Aschoff sinuses* are seen as a dotted second contour around the gallbladder lumen. Anomalies of the gallbladder may be visualized by oral cholecystography.

Intravenous cholangiography

The contrast (meglumine iotroxate; biliscopin) is concentrated by the liver so that hepatic and common bile ducts are demonstrated. Tomography is used.

However, intravenous cholangiography had become obsolete because of its poor diagnostic accuracy, its morbidity and the advent of MRCP.

Endoscopic retrograde cholangiopancreatography [18]

The ampulla of Vater is visualized endoscopically, the common bile duct or pancreatic duct is cannulated and contrast material injected (fig. 32.11).

Patients with suspected biliary obstruction, a history of cholangitis or a pancreatic pseudocyst are at risk of procedure-related sepsis, and require antibiotic premedication [66]. The elderly are also at greater risk. Micro-organisms responsible include colonic flora (*Escherichia coli*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Streptococcus faecalis*) and the antibiotic choice should reflect this and the hospital antimicrobial policy. Oral ciprofloxacin is as effective as intravenous cefuroxime, and more cost-effective [66].

The patient is starved for 6 h. The procedure is done under sedation with a benzodiazepine (diazepam, midazolam) with an opiate as necessary.

At ERCP, diseases of the oesophagus, stomach, duodenum, pancreas and biliary tract including duodenal diverticula and fistulae may be diagnosed. Manometry of the sphincter area is possible. Immediate treatment may be instituted, for example sphincterotomy for common duct stones. However, endoscopes are costly and the technique demands an experienced team. Usually the patient must be under observation for 24 h

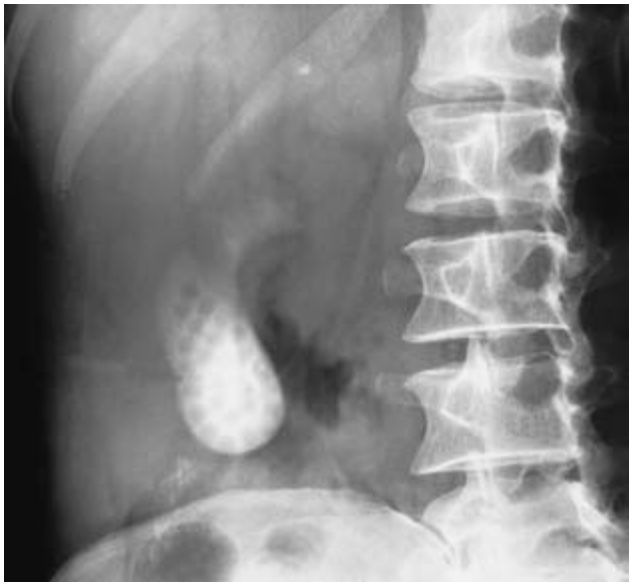


Fig. 32.10. Oral cholecystogram showing gallbladder packed with stones.

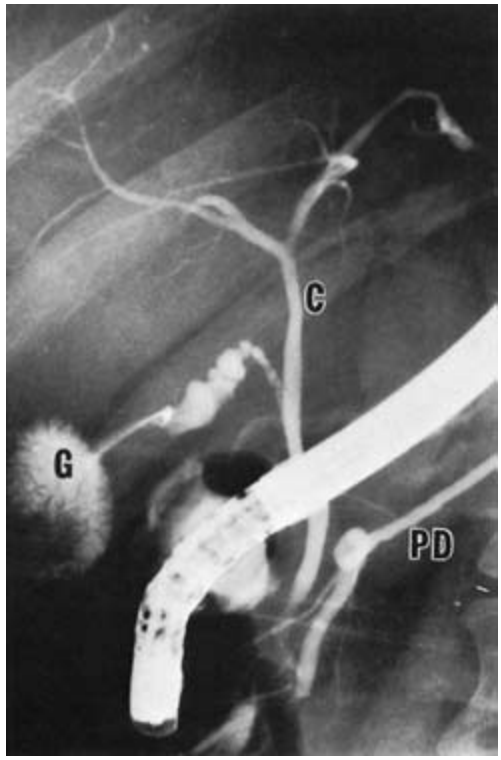


Fig. 32.11. ERCP, normal appearances. C, common bile duct; G, gallbladder; PD, pancreatic duct.

after the procedure. However, outpatient ERCP may be done for selected patients, although around 25% may need admission for complications or observation after a therapeutic procedure [36]. After sphincterotomy observation for 6 h or overnight may reduce the need for readmission [30].

The side-viewing duodenoscope is passed. The stomach and duodenum are inspected and biopsy and cytology specimens taken if indicated. The papilla is identified. Duodenal ileus is maintained by intermittent intravenous hyoscine *N*-butylbromide (Buscopan) or glucagon. The cannula is then introduced under direct vision into the papilla and contrast (e.g. iopromide) injected under fluoroscopic control. Preferential catheterization of bile duct and pancreatic duct is helped by directing the catheter towards 11 and 12 o'clock, respectively, with the ampullary area *en face* seen as a clock face. Use of a dual channel sphincterotome allows selective bile duct cannulation or cannulation after failure with a standard catheter.

The intra-hepatic biliary tree, cystic and common bile ducts and gallbladder are filled (fig. 32.11). Changes in the position of the patient and tilting of the screening table after injection encourage distribution of contrast material throughout the duct system. In difficult cases, such as after sphincterotomy, a balloon catheter in the duct may be used to prevent reflux of contrast into the duodenum and so obtain better bile duct filling. The pancreatic duct is similarly cannulated and X-ray films taken.

An aseptic technique is maintained throughout. Endoscopes are thoroughly cleansed with soap and water and disinfected with activated glutaraldehyde. The danger of introducing infection is shown by a single endoscope which, although cleaned in an automatic machine, remained contaminated with *Pseudomonas aeruginosa* so resulting in biliary infection in 10 patients, with one fatality [3].

A history of minor reactions to intravenous contrast is not important but those who have had a major allergic reaction to iodinated contrast should be premedicated with corticosteroids and antihistamines [25].

The success rate for ERCP is 80–90% but depends on experience. Anatomical causes of failure include a periampullary diverticulum or an ampullary tumour or stricture. Billroth II gastrectomy poses difficulties which may be overcome by an experienced endoscopist if necessary using a forward-viewing endoscope.

Interpretation of the cholangiogram is not always easy. Contrast may obscure small stones. Air bubbles may cause confusion. Failure to fully fill the biliary tree, particularly in non-dependent parts, may add to the difficulty.

Complications

The complication rate is 2–3% and mortality 0.1–0.2%. Complications are directly related to the skill and experience of the operator and to the presence of underlying pancreatic or biliary disease.

Serum amylase levels rise considerably after ERCP and acute pancreatitis is the commonest complication. It almost always follows successful pancreatic cannulation and injection. The volume of contrast injected should be kept to a minimum. Non-ionic lower osmolarity contrast media have not been proven to carry a lower risk of acute pancreatitis. In most cases pancreatitis is clinically mild with recovery over a few days. For this and other reasons (duration of infusion required, cost-effectiveness) somatostatin or gabexate, both shown in randomized studies to reduce post-ERCP pancreatic injury, are not routinely used [4]. Pancreatic pseudocyst is a relative contraindication to ERCP.

Cholangitis is the second most common complication but the commonest cause of death. Bacteraemia is reported in 0–14% [66]. Pre-existing biliary infection and obstruction are important risk factors. Prophylactic antibiotics are important in prevention, together with early decompression of any biliary obstruction.

In patients with primary sclerosing cholangitis and advanced disease, there may be deterioration after ERCP [10].

Indications

ERCP adds to the speed of diagnosis of the jaundiced patient as it can be performed irrespective of depth of jaundice or state of liver function. It outlines the site of any biliary obstruction and in many instances indicates the cause.

It can be used to show duct strictures, and gallbladder and common bile duct stones (figs 32.12, 32.13). It is of particular value in those with biliary disease and undilated intra-hepatic ducts. Diagnoses include primary sclerosing cholangitis, Caroli's disease and other congenital anomalies.

ERCP may be performed after biliary surgery in the investigation of benign post-cholecystectomy symptoms or to define and treat more serious sequelae such as residual calculi, leaks and biliary strictures [22].

ERCP may be used to diagnose pancreatic disease, particularly in those with coincident hepato-biliary problems such as carcinoma of the pancreas and alcoholic pancreatitis with biliary obstruction.

ERCP is occasionally used in the investigation of the patient with obscure epigastric pain. It allows visualization of stomach and duodenum as well as pancreatic and biliary ducts, all at one sitting.

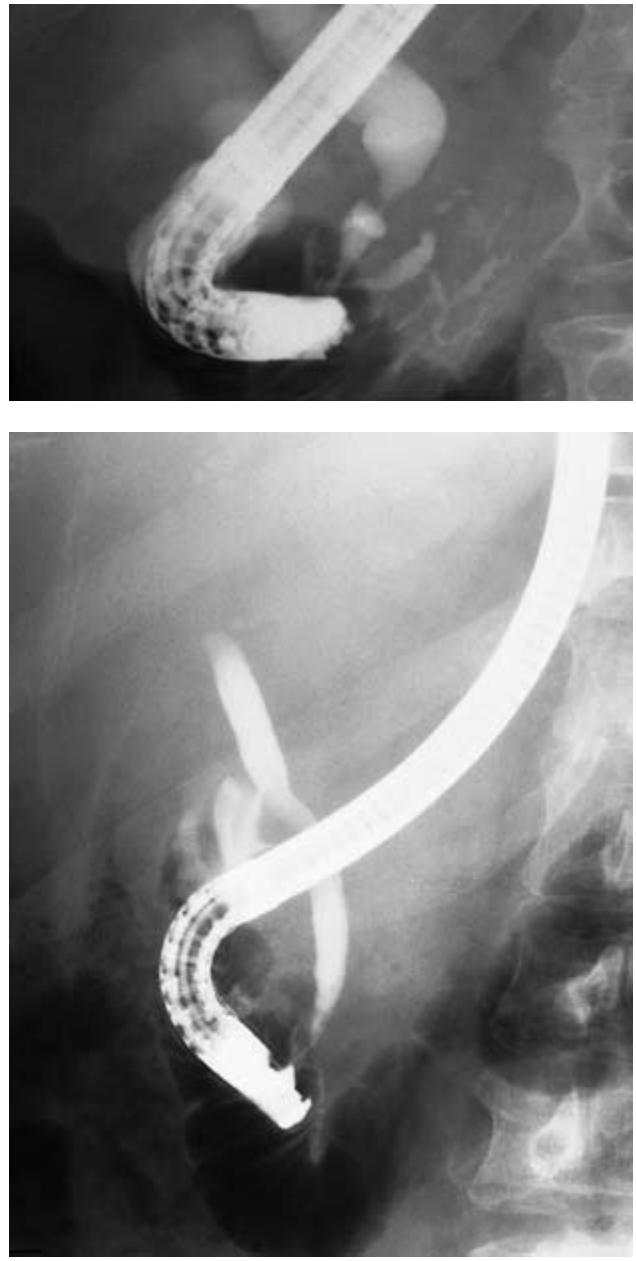


Fig. 32.12. ERCP showing: (a) dilated bile duct above a stricture. The pancreatic duct comes to an abrupt halt in the head of the pancreas. Appearances are characteristic of carcinoma of the pancreas; (b) common bile duct filling as far as a hilar stricture due to a cholangiocarcinoma.

Pure bile or pancreatic juice may be obtained for culture, aspiration cytology or chemical analysis.

Strictures may be brushed for cytology or biopsied [43].

Endoscopic sphincterotomy [18]

Normal coagulation is a prerequisite for endoscopic

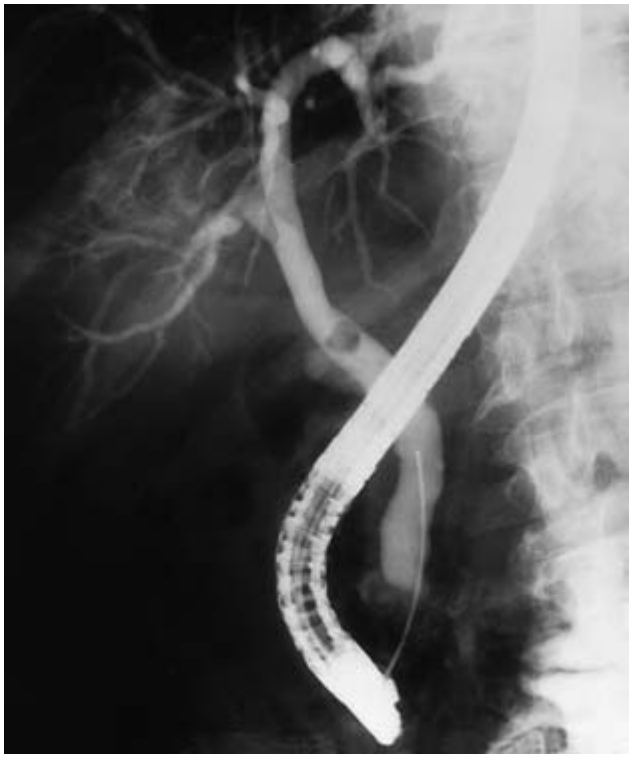


Fig. 32.13. ERCP showing common bile duct stone. A sphincterotome has been passed into the lower end of the bile duct.

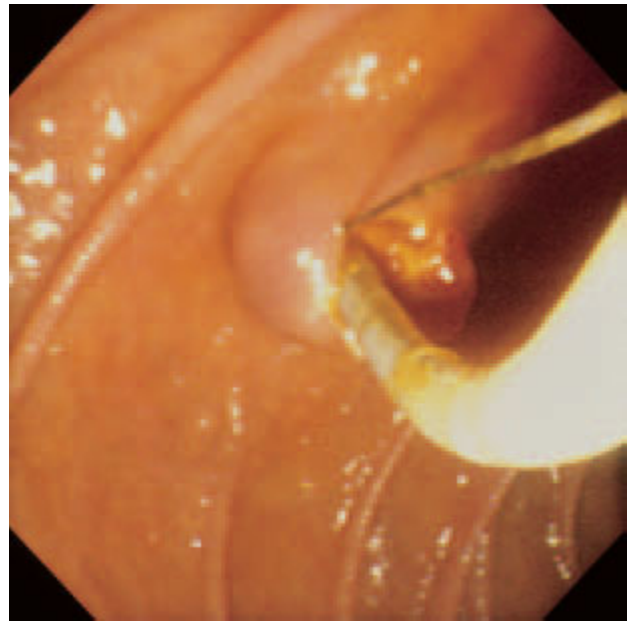


Fig. 32.14. Sphincterotome inserted into ampulla of Vater. The wire has been bowed and the sphincterotomy cut has begun.

sphincterotomy and the result of platelet count and prothrombin time as well as haemoglobin should be known. Serum is taken for blood group analysis and saved in case transfusion is necessary. Premedication with antibiotic is routine in most units. A skilled team is required with adequate equipment, in a hospital with facilities to treat any complication.

After the diagnostic ERCP has shown a stone, the ampulla is catheterized with a dual-channel sphincterotome appropriate in length and design to the anatomy found. Fluoroscopy is used to establish that this has entered the bile duct. A guide-wire is usually passed into the bile duct to stabilise the sphincterotome position during sphincterotomy. The sphincterotome is withdrawn leaving approximately 1 cm of the wire within the ampulla, the wire is bowed and, under direct vision, a cut is made using a blend or cutting current from the cautery unit (fig. 32.14). The length of cut depends upon the anatomy of the ampulla and the supra-ampullary area, and the size of the stone. If sphincterotomy is being done as a preliminary to endoprosthesis insertion only a small cut is needed. For stones, the aim is to make a cut of sufficient length to allow removal. It may be necessary to cut through the biliary sphincter, shown by the release of bile. Air refluxes up the bile duct. For larger stones it is necessary to decide when to use a mechanical lithotripter and a moderate cut, rather than risk a larger, possibly complicated sphincterotomy.

The success rate is above 90% [37], reaching 97% in an expert unit [70]. Causes of failure include a large periampullary diverticulum, a Billroth II partial gastrectomy and an impacted stone at the ampulla.

Related techniques which may be helpful include needle knife papillotomy [29], but this should only be used by experienced endoscopists.

Complications [20, 31]

These occur in about 10% and include haemorrhage, cholangitis, pancreatitis, duodenal perforation, Dormia basket impaction and Gram-negative shock. They are life threatening in 2–3%. Mortality is 0.4–0.6%.

Prospective studies show pancreatitis in 8–10% of patients having an endoscopic sphincterotomy. The rate will be influenced by the technique used including selective catheterization of the biliary system using a sphinctertome. Pure cut electrocautery may reduce the risk [27]. Post-sphincterotomy pancreatitis is usually mild.

Bleeding, usually from the retro-duodenal artery, is the most serious potential problem. It usually settles but, if not, surgery can be difficult. Treatment by arterial embolization may be successful. Bleeding is not always immediate and may be delayed several days after the procedure [30].

Cholangitis occurs if biliary decompression (stone removal) is unsuccessful. Prevention is by insertion of a naso-biliary tube or endoprosthesis.

Late results of sphincterotomy show that two-thirds of patients have air in the biliary tract and free reflux of duodenal juice. Bacterial colonization of the bile is present whether or not there are symptoms; the significance of this is unknown. Late complications (5–10% over 5 years) include sphincter stenosis [13] and recurrent stones. The long-term effects of loss of sphincter function are unresolved.

In cirrhotic patients with choledocholithiasis endoscopic sphincterotomy is effective and safe although coagulopathy must be corrected beforehand [58].

Indications

Choledocholithiasis is the commonest indication. Emergency ERCP with endoscopic sphincterotomy is the treatment of choice for patients with *acute suppurative obstructive cholangitis* [45] which is almost always caused by a stone. Where there is *acute cholangitis* of lesser severity elective ERCP is done after a period of antibiotic treatment. Whether or not the gallbladder is in place, sphincterotomy is the treatment of choice.

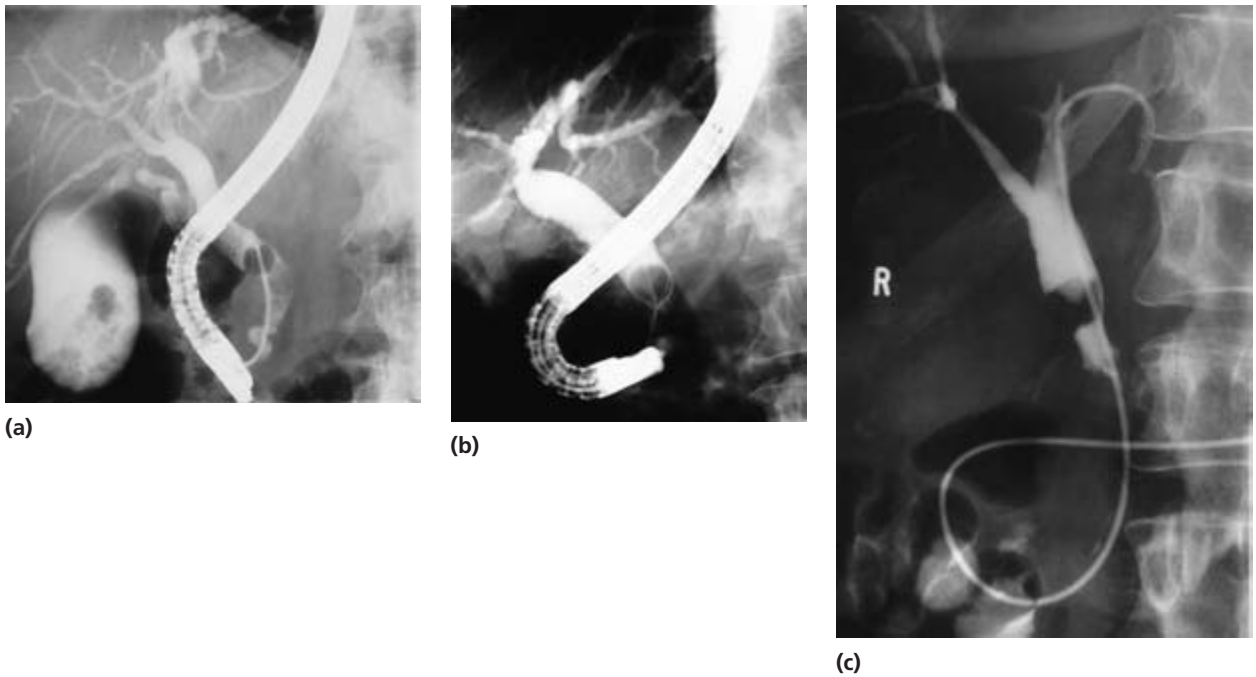
In patients with *common duct stones without cholangitis* the choice depends on the clinical situation. For *post-cholecystectomy retained bile duct stones* sphincterotomy is clearly the best treatment in elderly frail patients and those with other medical problems. In this group of patients it is also the accepted treatment even when the gallbladder is still *in situ*. After removal of the common duct stone(s), the decision whether to proceed to cholecystectomy depends upon clinical data, although when the patient is unfit for surgery conservative therapy without cholecystectomy is an option (Chapter 34).

In younger, fit patients with retained stones after cholecystectomy, sphincterotomy is preferred to surgical bile duct exploration. With the gallbladder in place, however, it is not clear whether cholecystectomy should be preceded by endoscopic sphincterotomy or accompanied by duct exploration and stone removal at the time of surgery.

The evolution of laparoscopic cholecystectomy and duct exploration adds to the therapeutic choice.

Acute gallstone pancreatitis, particularly if severe and unresolving, is an indication for emergency ERCP and sphincterotomy if a stone is found (Chapter 34).

Stone extraction is done with wire baskets or balloon catheters (fig. 32.15a,b). In 90% the common bile duct is successfully cleared of stones. If all the stones cannot be extracted from a patient with cholangitis a naso-biliary catheter or endoprosthesis must be left to drain the duct (fig. 32.15c). Stones larger than 15 mm may be difficult to



(a) **(b)** **(c)**

Fig. 32.15. (a) ERCP showing trawling of bile duct with balloon catheter to remove stones. (b) Removal of duct stone with basket. (c) Naso-biliary tube with stones in the common bile duct.

extract. Mechanical lithotripsy may be used to crush stones with success in 92% of patients [63]. Alternatively, an endoprosthesis may be inserted [50]. This prevents the stone obstructing the bile duct, and is a quicker procedure than lithotripsy. Endoprosthesis insertion may be temporary until another attempt at stone removal, or used for long-term drainage. Administration of oral ursodeoxycholic acid while the endoprosthesis is in place appears to make later clearance of stones from the duct more successful [41].

Extracorporeal shock wave lithotripsy of common bile duct stones fragments them and allows them to pass through the sphincterotomy [26]. Laser lithotripsy is available in some specialist centres.

Sphincterotomy is often done before *endoscopic endoprosthesis* insertion. This was originally recommended to reduce the risk of pancreatic duct obstruction and pancreatitis, but carries the risk of bleeding and is not essential unless the os is particularly small or tight.

Sphincterotomy at the main papilla may be used to treat the rare *sump syndrome* following choledochoduodenostomy [14]. *Papillary stenosis* (Chapter 34) can also be treated by sphincterotomy.

Stone removal without sphincterotomy

Small stones (<8 mm) may be removed through an intact ampulla, with or without balloon dilatation [51]. Larger stones have been removed using the combination of mechanical lithotripsy and balloon dilatation of the sphincter of Oddi. Pancreatitis is a complication in about 7%, but in a randomized trial was as frequent as with endoscopic sphincterotomy [9].

Naso-biliary drainage

A sphincterotomy is not usually necessary. After ERCP, the common bile duct is cannulated and a guide-wire passed deep into an intra-hepatic duct. The cannula is removed and a 300-cm 5 French (Fr) pigtail catheter with multiple side holes is threaded over the wire which is then removed (fig. 32.15c). The catheter is re-routed through the nose. This technique allows decompression of the biliary tree.

There are fewer complications than with percutaneous biliary drainage in terms of infection, bile leak and bleeding.

Naso-biliary drainage can be used as a preliminary to later sphincterotomy in poor risk patients with choledocholithiasis and acute suppurative cholangitis, especially if coagulation is abnormal.

A naso-biliary drain may be left in position when, after sphincterotomy, it has been impossible to clear all the stones from the common bile duct. Later cholangiography through the tube shows whether the stones have passed. Naso-biliary drainage may also be used to treat bile leaks after cholecystectomy or liver transplantation, although stent insertion is the first method of choice for both leaks and residual duct stones.

Endoscopic biliary endoprostheses

After catheterization of the ampulla and demonstration of the stricture by contrast, a guide-wire is passed through the catheter and an attempt is made to pass it through the stricture. At the first session this is possible in 60–70% of patients. Using a combination of an inner tube and pushing tube, an endoprosthesis is railroaded into position across the stricture. A 3.3-mm diameter (10Fr) tube requires an endoscope with a 4.2-mm channel and provides effective decompression (fig. 32.16). Barbs on the endoprosthesis prevent it passing all the way up into the bile duct or subsequently back into the duodenum. Two endoprostheses may be used if necessary, for example to left and right hepatic ducts when there is a hilar stricture. Overall success rate of endoprosthesis insertion is 85–90% in skilled hands.

Early complications include cholangitis and pancreatitis. Sphincterotomy is not necessary before 10Fr stent insertion and may cause haemorrhage [48]. Sphinc-

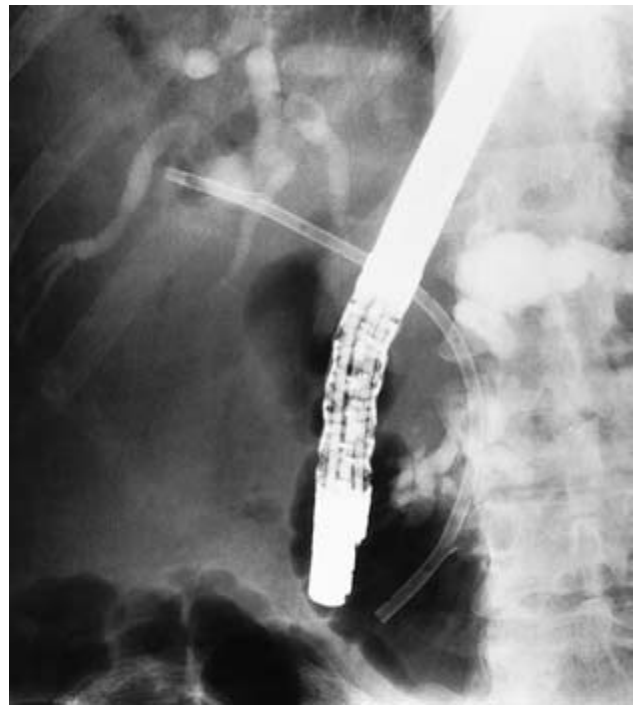


Fig. 32.16. ERCP: polyethylene stent inserted to relieve obstruction due to peri-ampullary tumour.

terotomy may be needed if the ampulla is too tight to admit the stent or if catherization of the biliary system has been difficult so as to allow easy access on a subsequent ERCP.

Late complications include cholangitis and recurrent jaundice due to blockage of the tube, which can easily be removed and replaced endoscopically. Mesh metal endoprostheses are now available which, after insertion in compressed form, expand when released to a diameter of up to 1 cm and remain patent for a longer period than conventional plastic stents (figs 32.17, 32.18). However, blockage still eventually occurs. Coated metal shunts may delay this [39].

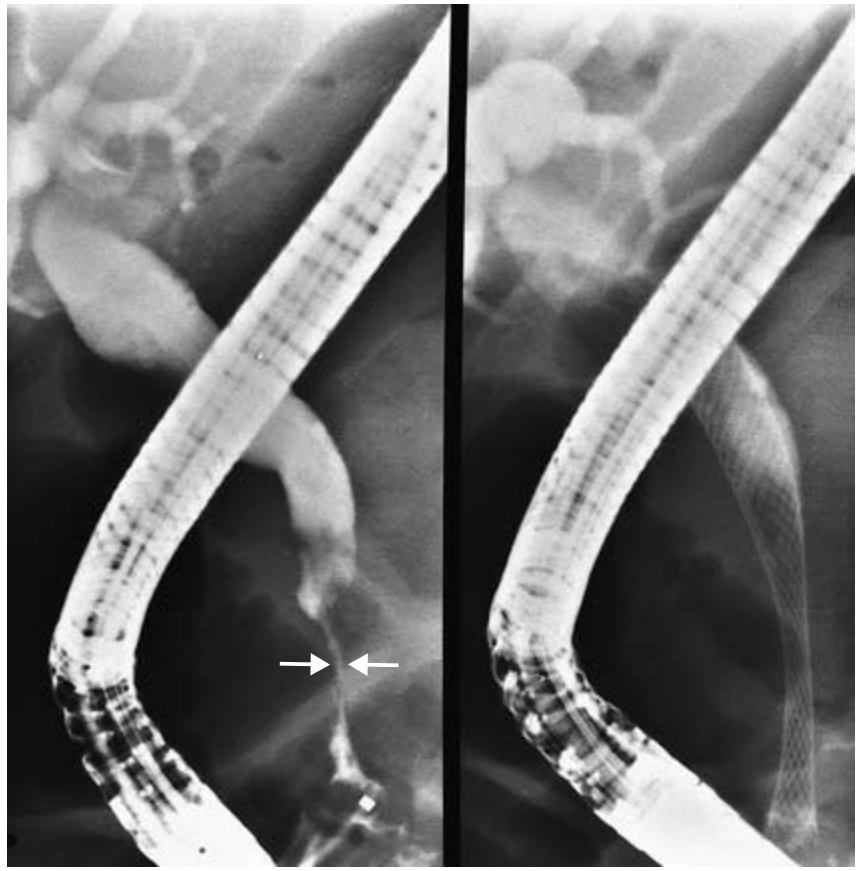
Results and indications

Endoscopic plastic endoprostheses successfully decompress the bile duct and relieve symptoms in about 70–80% of patients. The method carries fewer complications than the percutaneous route [65], and has a lower morbidity and mortality than surgical palliative bypass in patients with peri-ampullary carcinoma [64]. Blockage of polyethylene endoprostheses occurs in 25–30% at 3–6 months due to biliary sludge, containing bacteria. Antibiotic and ursodeoxycholic acid administration do not prevent this [33]. Tannenbaum stents made of Teflon do not have longer patency rates [28]. When expandable metal mesh endoprostheses block, obstruction is relieved by insertion of a plastic stent or another metal stent within the occluded endoprosthesis [67]. However, the patency of expandable metal mesh endoprostheses is significantly longer than plastic types (fig. 32.18) [19, 42], but the metal type is more expensive. Present experience suggests that a plastic type be placed first, and when it blocks, a metal endoprosthesis is inserted in those patients who are progressing more slowly and are expected to survive longer [53].

Inoperable malignant biliary obstruction from carcinoma of pancreas, ampulla and hilum can be relieved. For a malignant hilar obstruction, drainage of only one lobe provides good palliation. A second endoprosthesis is only needed if cholestasis is not relieved sufficiently or there is sepsis in the undrained side [56].

Benign strictures, whether due to primary sclerosing cholangitis or post-cholecystectomy, can be treated in this way, although balloon dilatation is an alternative.

Failed endoscopic removal of common duct stones. A stent may be introduced into the common bile duct where it



(a) (b)

Fig. 32.17. (a) ERCP showing malignant stricture (arrows) at lower end of bile duct. (b) Mesh metal stent (Wallstent) placed across the stricture. (Courtesy of Dr Kees Huibregtse.)

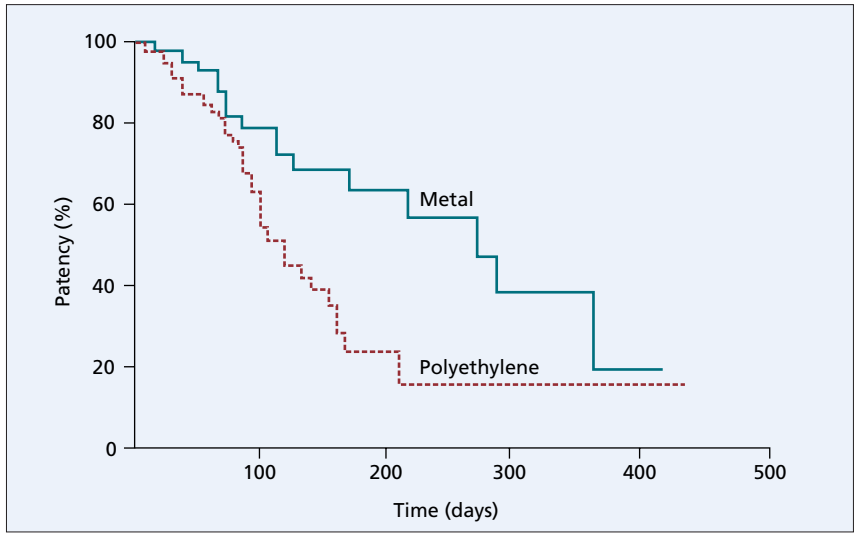


Fig. 32.18. Kaplan–Meier life table analysis of stent patency: randomized trial of metal vs. polyethylene stents. (From [19] with permission.)

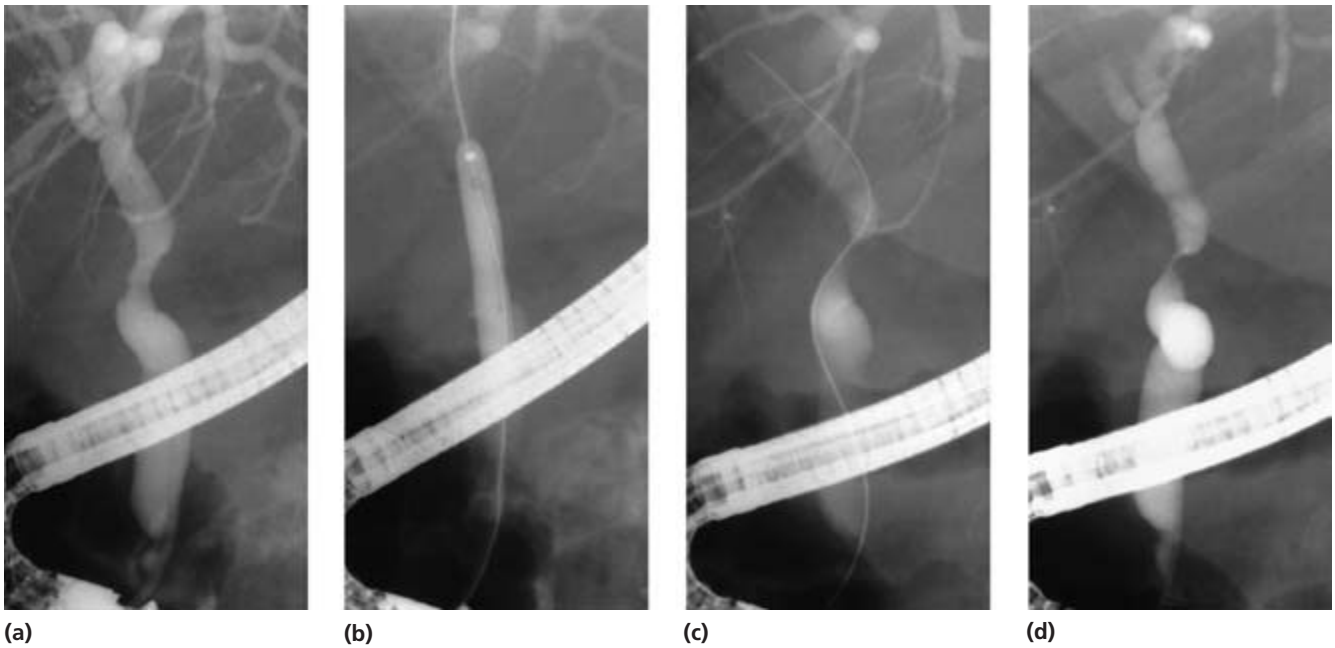


Fig. 32.19. Endoscopic balloon dilatation of bile duct stricture following liver transplantation. (a) Cholangiogram showing stricture. (b) Wire passed into intra-hepatic ducts. (c) Balloon dilatation to 8 mm diameter. (d) Final cholangiogram with good result.

has been impossible to remove all stones and when the patient is unfit for surgery.

External biliary fistulas. Post-operative leaks from the cystic duct or gallbladder bed may be treated by introduction of a biliary stent. The leak usually seals making re-operation unnecessary. The stent is removed after a few weeks.

Balloon dilatation

Following endoscopic cholangiography, a balloon catheter may be introduced into the common bile duct and inflated. This may be used to dilate a benign stricture (fig. 32.19), whether traumatic or secondary to primary sclerosing cholangitis. It may be a useful preliminary step before insertion of an endoprosthesis.

Per-oral cholangioscopy

The bile duct interior can be inspected using a 'baby' endoscope introduced via a large channel ('mother')

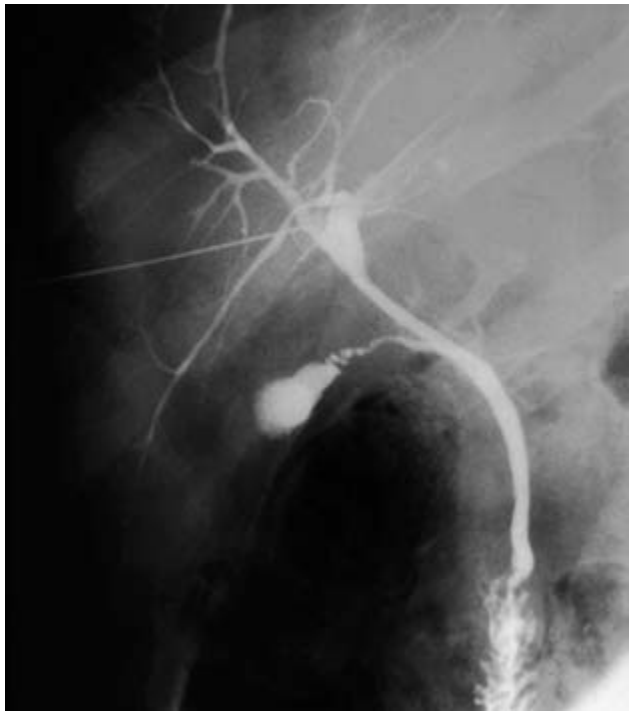


Fig. 32.20. Diagnostic percutaneous trans-hepatic cholangiogram showing normal right and left intra-hepatic ducts and common bile duct, and free flow of contrast into duodenum. The gallbladder is beginning to fill.

duodenoscope. This may provide additional information [61], but the thin scopes are fragile, the system expensive, and the technique requires two endoscopists.

Percutaneous trans-hepatic cholangiography [74]

Contrast is injected percutaneously into a bile duct within the liver (fig. 32.20). The procedure is done in the radiology department with intravenous sedation and under local anaesthesia. Antibiotic is given 0.5–1 h before the procedure. The 'skinny' Chiba needle is 0.7 mm (22 gauge) outside diameter. It is very flexible so that the patient is able to breathe normally with it *in situ*.

The needle is introduced in the 7th, 8th or 9th right intercostal space at the point of maximal dullness to percussion in the mid-axillary line. Ultrasound guidance adds to the success. It is advanced parallel to the table top to about 2.5 cm from the spine, bisecting a sagittal line between the dome of the diaphragm and the duodenal cap identified by its gas shadow. Contrast is injected continuously as the needle is withdrawn. Bile ducts are identified by the persistence of contrast in tube-like branching structures. Portal and hepatic veins are recognized by the peripheral direction of flow and rapid disappearance of contrast medium. Lymphatics can be filled and the contrast takes 5–10 min to be cleared. Up to six needle 'passes' are allowed before the procedure is abandoned.

After successful injection into obstructed and dilated ducts the patient may need to be tilted so that the common bile duct has an opportunity to fill. If hilar obstruction prevents communication between the right and left hepatic duct, a percutaneous cholangiogram from both sides should be done. The technique is relatively safe so that surgery need not inevitably follow immediately. If dilated ducts are encountered, they should be catheterized and external or internal biliary drainage established. Trans-hepatically aspirated bile should be cultured. The patient must be observed carefully in hospital.

The technique is easy and the success rate is 100% if intra-hepatic bile ducts are dilated. With undilated ducts, such as in primary sclerosing cholangitis or with some cases of choledocholithiasis, the success rate drops to 90% but can rise to 95% in specially skilled hands.

Complications

The complication rate is less than 5% and includes bleeding, bile peritonitis and septicaemia (usually Gram-negative) in those with cholangitis or unsuspected bacteria in the bile.

Indications

For the majority of patients needing direct cholangiography, the percutaneous approach is the *second choice* used only after ERCP has failed. This practice is based less on the relative complication rates of the two diagnostic procedures, and more on the greater therapeutic potential of ERCP, with a lower risk. Thus the endoscopic approach allows sphincterotomy for stones, and safer stent insertion. Percutaneous cholangiography comes into its own, however, when endoscopic access is difficult or impossible (*hepatico-enterostomy*, *Billroth II*). It is also important in the work-up of hilar cholangiocarcinoma, where detail of both right- and left-sided duct systems is needed. Brush cytology and biliary biopsy may be performed by the percutaneous as well as endoscopic route.

Percutaneous bile drainage

Bile duct catheterization

A sheathed needle is directed under antero-posterior and lateral fluoroscopy into a selected intra-hepatic duct already opacified by the 'skinny' needle cholangiogram. The needle is withdrawn and a guide-wire passed through the sheath into common bile duct or peripheral intra-hepatic duct.

External biliary drainage

A drainage catheter is exchanged for the sheath over the guide-wire, secured to skin and connected to a drainage bag. Theoretically, external bile drainage would be expected to bring the patient with biliary obstruction, particularly malignant, to surgery in better condition and so lessen the incidence of post-operative renal failure. There are, however, many complications including fluid and electrolyte loss, sepsis and dislodgement of the drainage tube [46]. Several randomized control trials have now shown that short-term (1–2 weeks) pre-operative external bile drainage does not reduce the post-operative mortality and morbidity in patients having surgery for malignant bile duct obstruction [35, 46, 54]. Long-term external drainage should be avoided, having both physical and psychological side-effects. It is now rarely necessary, since either endoscopic or percutaneous stenting, or surgical bypass is possible.

Internal/external biliary drainage

After bile duct catheterization, a guide-wire can usually be manipulated through the stricture and into low bile duct or bowel. A catheter (8–9Fr) can then be placed across the stricture with side holes above and below. Bile can then drain into bowel, or, if the external limb is not spigotted, into an external bag. This technique is usually used as the first stage before endoprosthesis insertion a few days later. It is occasionally used in its own right for long-term relief of obstruction but commits the patient to a permanent external tube even if closed off.

Percutaneous biliary endoprosthesis

Following percutaneous cholangiography, bile duct catheterization and manipulation of a guide-wire through the stricture, an endoprosthesis (10–14Fr) is inserted over the guide-wire across the stricture allowing free drainage of bile into bowel (fig. 32.21). Sometimes an external drain is left temporarily above the endoprosthesis for 24–48 h to guarantee biliary decompression and to allow check cholangiography. The external tube is then removed. Endoprostheses made of polyethylene and other plastics have been used for many years [21, 23]. As with endoscopic stents, these also block with time. Metal stents have been developed including the metal wire zigzag (Gianturco) and metal mesh (Wallstent) types [34, 38]. The longer patency of mesh metal stents is based on endoscopic trials (see above).

Results and complications

Success rate for endoprosthesis insertion is 85%. Failures are due to inability to find the lumen of the stricture with the guide-wire. Hilar strictures are more difficult than low common duct obstruction [23]. There is complete relief of bile duct obstruction in 65–70% of patients, a further 15% having partial decompression. Major complications (haemorrhage and bile leakage with peritonitis) occur in 3% of patients. Deaths due to the procedure are reported rarely. Other early complications include septicaemia and right-sided pleural effusion with atelectasis. Late complications are stent blockage with cholangitis and recurrent jaundice, and passage of the stent out of the bile duct.

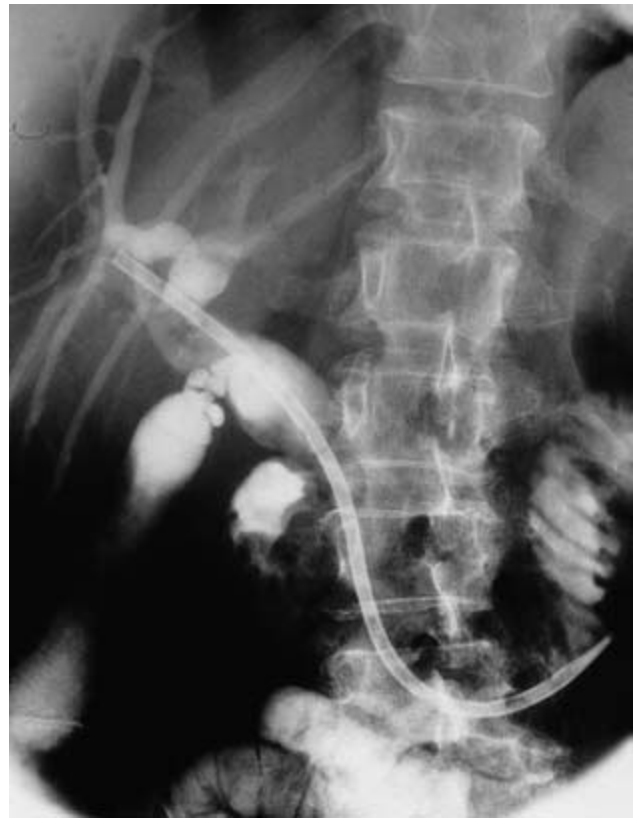


Fig. 32.21. Percutaneous trans-hepatic insertion of Carey–Coons stent.

Indications

When endoscopic access to the biliary tree is possible, ERCP and endoscopic stent insertion is the first choice to relieve irresectable malignant biliary obstruction. When this fails or endoscopic access is impossible, percutaneous insertion is indicated. An alternative is a *combined approach* with percutaneous catheterization of the stricture, placement of the guide-wire tip in the duodenum, and endoscopic retrograde insertion of the stent over the wire. This approach still carries an appreciable mortality and morbidity [24]. Since percutaneous metal mesh

stents can be inserted on a 7Fr catheter, this technique may replace the more complicated combined approach [49].

Re-stenosis of hepatico-enteric anastomoses may be treated by percutaneous stenting or balloon dilatation if surgical revision is not appropriate.

Percutaneous balloon dilatation

Benign strictures of the bile duct have been successfully treated by percutaneous trans-hepatic balloon dilatation (see fig. 35.4) [17].

Resectability of tumours

Pancreatic carcinomas and hilar cholangiocarcinomas are rarely resectable, but this possibility should be assessed particularly in the middle-aged and younger patient.

For pancreatic carcinoma, US and spiral CT are capable of predicting irresectability with a high degree of accuracy [11] based on hepatic metastases, local extension, vascular encasement or invasion, and lymphadenopathy (Chapter 36), but both depend on good technique and experience. Laparoscopy may show hepatic metastases or peritoneal seedlings. Each unit will have its preferred approach. Angiography is worthwhile but may not provide extra information on resectability. It gives a road map which some surgeons value greatly.

For cholangiocarcinoma, many imaging techniques have a place in the assessment of resectability, including US, CT, MRCP, direct cholangiography hepatic arteriography and portography (Chapter 37).

With ampullary carcinomas, the treatment is surgical resection if there is no medical contraindication.

Choice between surgical and non-surgical palliation of malignant obstruction

Randomized control trials have shown that percutaneous stenting has a similar outcome to bypass surgery [12]. Endoscopic insertion has a lower morbidity and mortality than either the percutaneous route [65] or palliative bypass surgery [64]. The disadvantage of plastic stents is that they block, but many patients die from their malignant disease before this problem occurs.

Clinical features influence the choice of treatment and in general it is the older, poorer risk patient who receives the non-surgical endoprosthesis and the younger, fitter patient who may still have surgery, especially if a tissue diagnosis has not been made. Exfoliative bile cytology, brush cytology and percutaneous aspiration cytology should be done in an attempt to establish a tissue diagnosis.

Table 32.1. Comparison of percutaneous trans-hepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP)

	PTC	ERCP
Technique	Easy	Difficult
Time taken (min)*	15–30	15–60
Anatomical difficulties	Few	Many
Cost	Low	High
Complications	5%	5%
	Biliary leak	Pancreatitis
	Cholangitis	Cholangitis
	Haemorrhage	
Success (%)		
Overall	95	80–90
Dilated ducts	100	85
Undilated ducts	90	85
Pancreatic duct	—	85
Endoprosthesis insertion (%)		
Overall	85	80
High stricture	70	80
Low stricture	90	80

* Radiation dose similar.

Choice between endoscopic and percutaneous approach (table 32.1)

Using ERCP or PTC the biliary tree can be visualized in virtually every patient in whom mechanical cholestasis has to be excluded. Any large hospital should have both techniques available and a surgeon should always have a cholangiogram to view when exploring the biliary tract. MRCP will be useful but ERCP is the first choice for direct cholangiography. PTC is used after failed ERCP or when the ampulla is inaccessible. Both techniques may be necessary, for example when ERCP has shown a hilar stricture but the intra-hepatic ducts have not filled. PTC is indicated, left and right sided if necessary, to show the detailed anatomy. The techniques are complementary rather than competitive. Intervention by both routes is now used widely. ERCP offers sphincterotomy and is the safer method for duct drainage.

Percutaneous cholecystostomy

The gallbladder is punctured percutaneously under real-time ultrasound or fluoroscopic control, and drained. This technique has been used successfully as an emergency for high-risk patients with acute calculous and acalculous cholecystitis [73]. Access is either direct

across the peritoneal cavity or trans-hepatic. The latter is generally safer since the point of gallbladder puncture is sealed by adjacent liver. The trans-peritoneal route is preferred if gallstones are to be removed [16]. The trans-hepatic approach is best for drainage of empyema (Chapter 34).

Operative and post-operative cholangiography

Routine operative cholangiography is not necessary at cholecystectomy unless there are indications suggesting that stones are present in the common bile duct [8]. These include a history of jaundice, dilated bile ducts, palpable gallstones or a raised serum bilirubin, alkaline phosphatase or γ-glutamyl transpeptidase (γ-GT) level. After exploration of the common bile duct, cholangiography should always be performed using high kilovolt peak technique and full strength contrast [68].

Debris may cause filling defects less sharply defined than those caused by gallstones. Air bubbles may simulate stones. Small stones may be obliterated by the contrast medium.

During laparoscopic cholecystectomy, laparoscopic ultrasound successfully detects duct stones [62] and may obviate the need for intra-operative cholangiography.

Post-operative cholangiography, using contrast injected gently, should be undertaken routinely before final removal of a T-tube draining the biliary tree. During the injection, bile duct contents, including bacteria, probably regurgitate into the blood. This is particularly marked in the presence of biliary obstruction.

A surprising number of operative and post-operative cholangiograms are technically unsatisfactory, through failure to visualize intra-hepatic bile ducts or the trans-duodenal or sphincteric segment of the ducts. It is essential not to use too dense contrast to fill the biliary tree and to ensure correct positioning and exposure.

T-tube extraction of gallstones

See Chapter 34.

References

1 Adamek HE, Albert J, Breer H *et al*. Pancreatic cancer detection with magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography: a prospective controlled study. *Lancet* 2000; **356**: 190.

2 Ahmad NA, Lewis JD, Ginsberg GG *et al*. EUS in preoperative staging of pancreatic cancer. *Gastrointest. Endosc*. 2000; **52**: 463.

3 Allen JI, Allen MO, Olson MM *et al*. Pseudomonas infection of the biliary system resulting from the use of a contaminated endoscope. *Gastroenterology* 1987; **92**: 759.

4 Andriulli A, Leandro G, Niro G *et al*. Pharmacologic treatment can prevent pancreatic injury after ERCP: a meta-analysis. *Gastrointest. Endosc*. 2000; **51**: 1.

5 Angulo P, Pearce DH, Johnson CD *et al*. Magnetic resonance cholangiography in patients with biliary disease: its role in primary sclerosing cholangitis. *J. Hepatol*. 2000; **33**: 520.

6 Bansal R, Tierney W, Carpenter S *et al*. Cost effectiveness of EUS for preoperative localization of pancreatic endocrine tumours. *Gastrointest. Endosc*. 1999; **49**: 19.

7 Barish MA, Yucel EK, Ferrucci JT. Magnetic resonance cholangiopancreatography. *N. Engl. J. Med*. 1999; **341**: 258.

8 Barkun AN, Barkun JS, Fried GM *et al*. Useful predictors of bile duct stones in patients undergoing laparoscopic cholecystectomy. *Ann. Surg*. 1994; **220**: 32.

9 Bergman JJGHM, Rauws EAJ, Fockens P *et al*. Randomised trial of endoscopic balloon dilation vs. endoscopic sphincterotomy for removal of bileduct stones. *Lancet* 1997; **349**: 1124.

10 Beuers U, Spengler U, Sackmann M *et al*. Deterioration of cholestasis after endoscopic retrograde cholangiography in advanced primary sclerosing cholangitis. *J. Hepatol*. 1992; **15**: 140.

11 Bluemke DA, Cameron JL, Hruban RH *et al*. Potentially resectable pancreatic adenocarcinoma: spiral CT assessment with surgical and pathologic correlation. *Radiology* 1995; **197**: 381.

12 Bornman PC, Tobias R, Harries-Jones EP *et al*. Prospective controlled trial of transhepatic biliary endoprosthesis vs. bypass surgery for incurable carcinoma of head of pancreas. *Lancet* 1986; **i**: 69.

13 Bourke MJ, Elfant AB, Alhalel R *et al*. Sphincterotomy-associated biliary strictures: features and endoscopic management. *Gastrointest. Endosc*. 2000; **52**: 494.

14 Caroli-Bosc FX, Demarquay JF, Peten EP *et al*. Endoscopic management of sump syndrome after choledochoduodenostomy: retrospective analysis of 30 cases. *Gastrointest. Endosc*. 2000; **51**: 180.

15 Chak A, Hawes RH, Cooper GS *et al*. Prospective assessment of the utility of EUS in the evaluation of gallstone pancreatitis. *Gastrointest. Endosc*. 1999; **49**: 599.

16 Chiverton SG, Inglis JA, Hudd C *et al*. Percutaneous cholecystolithotomy: the first 60 patients. *Br. Med. J*. 1990; **300**: 1310.

17 Citron SJ, Martin LG. Benign biliary strictures: treatment with percutaneous cholangioplasty. *Radiology* 1991; **178**: 339.

18 Cotton PB, Williams CB. 1999 *Practical Gastrointestinal Endoscopy*, 4th edn. Blackwell Science, Oxford.

19 Davids PHP, Groen AK, Rauws EAJ *et al*. Randomised trial of self-expanding metal stents vs. polyethylene stents for distal malignant biliary obstruction. *Lancet* 1992; **340**: 1488.

20 Deans GT, Sedman P, Martin DF *et al*. Are complications of endoscopic sphincterotomy age related? *Gut* 1997; **41**: 545.

21 Dick R, Platts A, Gilford J. The Carey–Coons percutaneous biliary endoprosthesis: a three centre experience in 87 patients. *Clin. Radiol*. 1987; **38**: 175.

22 Doctor N, Dick R, Dooley JS *et al*. A multidisciplinary approach to biliary complications of laparoscopic cholecystectomy. *Br. J. Surg*. 1998; **85**: 627.

23 Dooley JS, Dick R, George P *et al*. Percutaneous transhepatic endoprosthesis for bile duct obstruction: complications and results. *Gastroenterology* 1984; **86**: 905.

24 Dowsett JF, Vaira D, Hatfield ARW *et al*. Endoscopic biliary

therapy using the combined percutaneous and endoscopic technique. *Gastroenterology* 1989; **96**: 1180.
25 Draganov P, Cotton PB. Iodinated contrast sensitivity in ERCP. *Am. J. Gastroenterol*. 2000; **95**: 1398.
26 Ellis RD, Jenkins AP, Thompson RP *et al*. Clearance of refractory bile duct stones with extracorporeal shockwave lithotripsy. *Gut* 2000; **47**: 728.
27 Elta GH, Barnett JL, Wille RT *et al*. Pure cut electrocautery current for sphincterotomy causes less postprocedure pancreatis than blended current. *Gastrointest. Endosc.* 1998; **47**: 149.
28 England RE, Martin DF, Morris J *et al*. A prospective randomised multicentre trial comparing 10 Fr Teflon Tannenbaum stents with 10 Fr polyethylene Cotton-Leung stents in patients with malignant common duct strictures. *Gut* 2000; **46**: 395.
29 Foutch PG. A prospective assessment of results for needle-knife papillotomy and standard endoscopic sphincterotomy. *Gastrointest. Endosc.* 1995; **41**: 25.
30 Freeman ML, Nelson DB, Sherman S *et al*. Same-day discharge after endoscopic biliary sphincterotomy: observations from a prospective multicentre complication study. *Gastrointest. Endosc.* 1999; **49**: 580.
31 Freeman ML, Nelson DB, Sherman S *et al*. Complications of endoscopic biliary sphincterotomy. *N. Engl. J. Med*. 1996; **335**: 909.
32 Georgopoulos SK, Schwartz LH, Jarnagin WR *et al*. Comparison of magnetic resonance and endoscopic retrograde cholangiopancreatography in malignant pancreaticobiliary obstruction. *Arch. Surg.* 1999; **134**: 1002.
33 Ghosh S, Palmer KR. Prevention of biliary stent occlusion using cyclical antibiotics and ursodeoxycholic acid. *Gut* 1994; **35**: 1757.
34 Gillams A, Dick R, Dooley JS *et al*. Self-expandable stainless steel braided endoprosthesis for biliary strictures. *Radiology* 1990; **174**: 137.
35 Hatfield ARW, Terblanche J, Fataar S *et al*. Pre-operative external biliary drainage in obstructive jaundice: a prospective controlled clinical trial. *Lancet* 1982; **ii**: 896.
36 Ho KY, Montes H, Sossenheimer MJ *et al*. Features that may predict hospital admission following outpatient therapeutic ERCP. *Gastrointest. Endosc.* 1999; **49**: 587.
37 Horton RC, Lauri A, Dooley JS. Endoscopic removal of common duct stones: current indications and controversies. *Postgrad. Med. J.* 1991; **67**: 107.
38 Irving JD, Adam A, Dick R *et al*. Gianturco expandable metallic biliary stents: results of a European clinical trial. *Radiology* 1989; **172**: 321.
39 Isayama H, Komatsu Y, Tsujino T *et al*. A prospective randomized study of 'covered' vs. 'uncovered' metallic stent for distal malignant biliary obstruction [abstract]. *Gastrointest. Endosc*. 2000; **51**: 191.
40 Jaw T-S, Kuo Y-T, Liu G-C *et al*. MR cholangiography in the evaluation of neonatal cholestasis. *Radiology* 1999; **212**: 249.
41 Johnson GK, Geenen JE, Venu RP *et al*. Treatment of non-extractable common bile duct stones with combination ursodeoxycholic acid plus endoprostheses. *Gastrointest. Endosc.* 1993; **39**: 528.
42 Knyrim K, Wagner HJ, Pausch J *et al*. A prospective, randomized, controlled trial of metal stents for malignant obstruction of the common bile duct. *Endoscopy* 1993; **25**: 207.
43 Kurzawinski TR, Deery A, Dooley JS *et al*. A prospective study of biliary cytology in 100 patients with bile duct strictures. *Hepatology* 1993; **18**: 1399.
44 Kurzawinski TR, Selves L, Farouk M *et al*. Prospective study of hepatobiliary scintigraphy and endoscopic cholangiography for the detection of early biliary complications after orthotopic liver transplantation. *Br. J. Surg.* 1997; **84**: 620.
45 Lai ECS, Mok FPT, Tan ESY *et al*. Endoscopic biliary drainage for severe acute cholangitis. *N. Engl. J. Med.* 1992; **326**: 1582.
46 McPherson GAD, Benjamin IS, Hodgson HJF *et al*. Preoperative percutaneous transhepatic biliary drainage: the results of a controlled trial. *Br. J. Surg.* 1984; **71**: 371.
47 Maglinte DDT, Torres WE, Laufer I. Oral cholecystography in contemporary gallstone imaging: a review. *Radiology* 1991; **178**: 49.
48 Margulies C, Siqueira ES, Silverman WB *et al*. The effect of endoscopic sphincterotomy on acute and chronic complications of biliary endoprostheses. *Gastrointest. Endosc.* 1999; **49**: 716.
49 Martin DF. Combined percutaneous and endoscopic procedures for bile duct obstruction. *Gut* 1994; **35**: 1011.
50 Maxton DG, Tweedle DEF, Martin DF. Retained common bile duct stones after endoscopic sphincterotomy: temporary and long-term treatment with biliary stenting. *Gut* 1995; **36**: 446.
51 May GR, Cotton PB, Edmunds SEJ *et al*. Removal of stones from the bile duct at ERCP without sphincterotomy. *Gastrointest. Endosc.* 1993; **39**: 749.
52 Mertz HR, Sechopoulos P, Delbeke D *et al*. EUS, PET, and CT scanning for evaluation of pancreatic adenocarcinoma. *Gastrointest. Endosc.* 2000; **52**: 367.
53 O'Brien S, Hatfield ARW, Craig PI *et al*. A three-year follow-up of self-expanding metal stents in the endoscopic palliation of long-term survivors with malignant biliary obstruction. *Gut* 1995; **36**: 618.
54 Pitt HA, Gomes AS, Lois JF *et al*. Does preoperative percutaneous biliary drainage reduce operative risk or increase hospital cost? *Ann. Surg.* 1985; **201**: 545.
55 Polkowski M, Palucki J, Regula J *et al*. Helical computed tomographic cholangiography vs. endosonography for suspected bile duct stones: a prospective blinded study in non-jaundiced patients. *Gut* 1999; **45**: 744.
56 Polydorou AA, Cairns SR, Dowsett JF *et al*. Palliation of proximal malignant biliary obstruction by endoscopic endoprosthesis insertion. *Gut* 1991; **32**: 685.
57 Prat F, Amouyal G, Amouyal P *et al*. Prospective controlled study of endoscopic ultrasonography and endoscopic retrograde cholangiography in patients with suspected common-bile duct lithiasis. *Lancet* 1996; **347**: 75.
58 Prat F, Tennenbaum R, Ponsot P *et al*. Endoscopic sphincterotomy in patients with liver cirrhosis. *Gastrointest. Endosc.* 1996; **43**: 127.
59 Reinhold C, Taourel P, Bret PM *et al*. Choledocholithiasis: evaluation of MR cholangiography for diagnosis. *Radiology* 1998; **209**: 435.
60 Revelon G, Rashid A, Kawamoto S *et al*. Primary sclerosing cholangitis: MR imaging findings with pathologic correlation. *Am. J. Roentgenol.* 1999; **173**: 1037.
61 Riemann JF, Kohler B, Harloff M *et al*. Peroral cholangioscopy—an improved method in the diagnosis of common bile duct disease. *Gastrointest. Endosc.* 1989; **35**: 435.

62 Röthlin MA, Schlumpf R, Largiadèr F. Laparoscopic sonography. An alternative to routine intraoperative cholangiography? *Arch. Surg.* 1994; **132**: 694.
63 Shaw MJ, Mackie RD, Moore JP *et al*. Results of a multicentre trial using a mechanical lithotripter for the treatment of large bile duct stones. *Am. J. Gastroenterol.* 1993; **88**: 730.
64 Smith AC, Dowsett JF, Russell RCG *et al*. Randomised trial of endoscopic stenting vs. surgical bypass in malignant low bile duct obstruction. *Lancet* 1994; **344**: 1655.
65 Speer AG, Cotton PB, Russell RCG *et al*. Randomised trial of endoscopic vs. percutaneous stent insertion in malignant obstructive jaundice. *Lancet* 1987; **ii**: 57.
66 Subhani J, Kibbler C, Dooley JS. Antibiotic prophylaxis in ERCP. *Aliment. Pharmacol. Ther.* 1999; **13**: 103.
67 Tham TCK, Carr-Locke DL, Vandervoort J *et al*. Management of occluded biliary Wallstents. *Gut* 1998; **42**: 703.
68 Thompson WM, Halvorsen RA, Foster WL *et al*. Optimal cholangiographic technique for detecting bile duct stones. *Am. J. Roentgenol.* 1986; **146**: 537.
69 Turner MA. Diagnostic methods and pitfalls in the gallbladder. *Semin. Roentgenol.* 1991; **26**: 197.
70 Vaira D, Ainley C, Williams S *et al*. Endoscopic sphincterotomy in 1000 consecutive patients. *Lancet* 1989; **ii**: 431.
71 Van Beers BE, Lacrosse M, Trigaux M *et al*. Non-invasive imaging of the biliary tree before or after laparoscopic cholecystectomy: use of three-dimensional spiral CT cholangiography. *Am. J. Roentgenol.* 1994; **162**: 1331.
72 Varghese JC, Liddell RP, Farrell MA *et al*. The diagnostic accuracy of magnetic resonance cholangiopancreatography and ultrasound compared with direct cholangiography in the detection of choledocholithiasis. *Clin. Radiol.* 1999; **54**: 604.
73 Verbanck JJ, Demol JW, Ghillebert GL *et al*. Ultrasound-guided puncture of the gallbladder for acute cholecystitis. *Lancet* 1993; **341**: 1132.
74 Wilkinson M, Adam A. Hepatobiliary intervention. In: Watkinson A, Adam A, eds. *Interventional Radiology: a Practical Guide*. Radcliffe Medical Press, Oxford, 1996, p. 59.
75 Williams DB, Sahai AV, Aabakken L *et al*. Endoscopic ultrasound guided fine needle aspiration biopsy: a large single centre experience. *Gut* 1999; **44**: 720.
76 Zidi SH, Prat F, Le Guen O *et al*. Use of magnetic resonance cholangiography in the diagnosis of choledocholithiasis: prospective comparison with reference imaging method. *Gut* 1999; **44**: 118.
77 Zidi SH, Prat F, Le Guen O *et al*. Performance characteristics of magnetic resonance cholangiography in the staging of malignant hilar strictures. *Gut* 2000; **46**: 103.
78 Ziessman HA, Fahey FH, Hixson DJ. Calculation of a gallbladder ejection fraction: advantage of continuous sincalide infusion over the three-minute infusion method. *J. Nucl. Med.* 1992; **33**: 537.

Chapter 33
Cysts and Congenital Biliary Abnormalities

Fibropolycystic disease

Cystic lesions of the liver and bile ducts are increasingly being diagnosed. This can be related to the improved methods of imaging the liver and bile ducts, and of liver biopsy. Application of such methods makes it clear that the fibropolycystic diseases do not exist as single entities, but as members of a family [40].

The members are found in various combinations (fig. 33.1). They consist of polycystic liver disease, microhamartoma, congenital hepatic fibrosis, congenital intra-hepatic biliary dilatation (Caroli's disease) and choledochal cysts (fig. 33.2).

Clinically, fibropolycystic diseases have three effects, again present in different proportions: those of a space-occupying lesion, of portal hypertension and of cholangitis. They are usually inherited. Fibrocystic disease of the kidneys is associated to a variable extent. Malignant change may complicate congenital hepatic fibrosis, bile duct cysts and Caroli's syndrome.

Embryologically the hepato-biliary abnormalities are thought to stem from ductal plate maldevelopment in different parts of the biliary tree [11].

The ductal plate is a sleeve of epithelium, one and then two cells thick, that forms in the mesenchyme surrounding portal vein branches from bipotential liver progenitor cells—that is cells that may form either hepatocytes or bile duct epithelium. During hepato-biliary development ductal plates are remodelled into mature tubular ducts that eventually form (in descending size interhepatically from the hilum) hepatic ducts, segmental ducts, area ducts, interlobular ducts and the smallest bile duct branches.

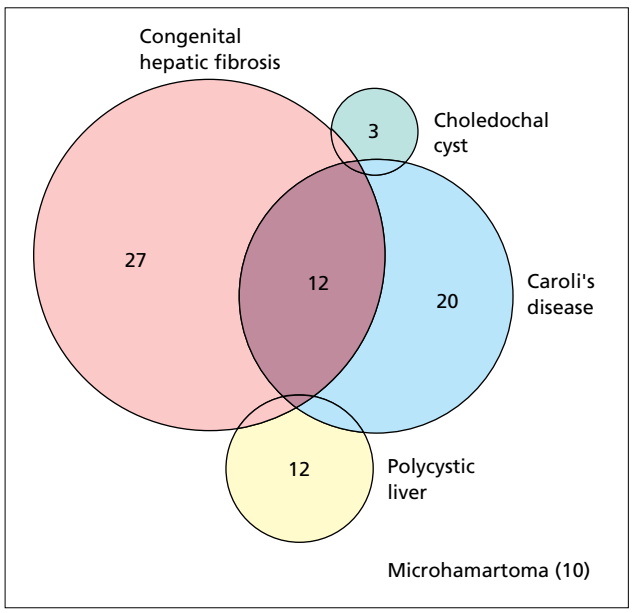


Fig. 33.1. Venn diagram showing one series of 51 patients in which many had more than one fibropolycystic disease. The combination of congenital hepatic fibrosis and Caroli's disease was most striking. Microhamartomas, although reported in only 10 patients in this series, are common [40].

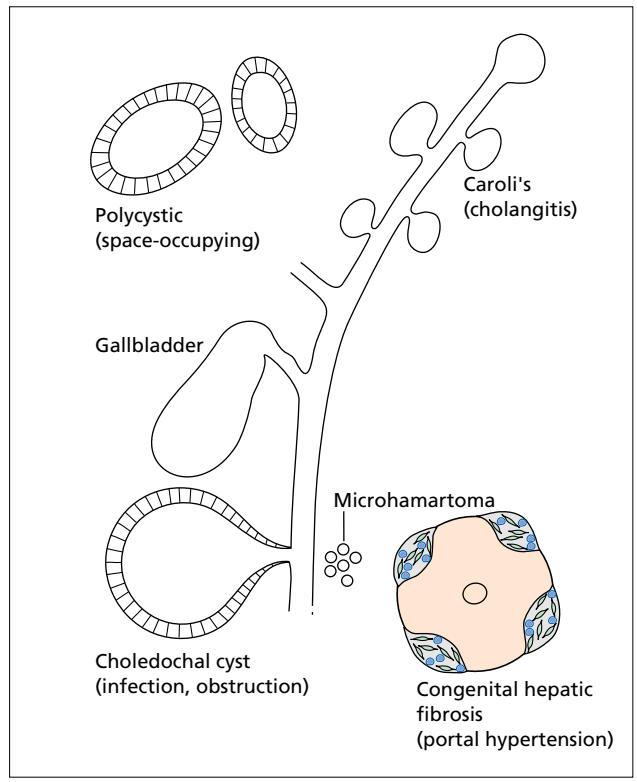


Fig. 33.2. Fibropolycystic disease: spectrum of pathology.

Ductal plate malformations include conditions where the intra-hepatic bile ducts are destroyed, as in biliary atresia, and conditions in which excess epithelial components do not disappear as normal but persist with some degree of dilatation and fibrosis (fibropolycystic diseases) [11]. The resulting disorder depends upon the level within the biliary tree of ductal plate malformation (table 33.1), and the degree of associated fibrosis.

Childhood fibropolycystic diseases

These are recessively inherited and may be perinatal, neonatal or infantile (table 33.2). Morphometry shows that the neonatal and infantile forms represent one disorder [26]. Prognosis depends on the extent of renal involvement. The association is with autosomal recessive polycystic kidney disease which usually presents shortly after birth and generally is more serious than the autosomal dominant form. The gene responsible has been mapped to chromosome 6p21. Patients may die in the perinatal period from renal failure. This recessive form of polycystic kidney disease is usually associated with congenital hepatic fibrosis. Choledochal cysts may coexist.

Table 33.1. The association of ductal plate malformations (DPM) with fibropolycystic disease

Level in bile duct of DPM	Disease
Small interlobular	Childhood fibropolycystic disease (association autosomal recessive polycystic disease) Congenital hepatic fibrosis (fibrotic element ++) Von Meyenberg complexes (dilatation = polycystic liver disease)
Large interlobular	Caroli's disease
Both	Caroli's syndrome

Adult polycystic disease

The liver cysts are probably developmental and frequently associated with autosomal dominant polycystic kidney disease. Understanding of polycystic kidney disease is more advanced than of the liver cysts. At least three different genes appear to be responsible. *PKD*-1 on chromosome 16p13.3 expresses polycystin 1 which is thought to have a role in epithelial cell differentiation and maturation, and in cell–cell interactions [19, 20]. Loss of function of this protein may be one prerequisite for cyst formation but a further somatic event is thought necessary.

A second gene implicated in autosomal dominant polycystic kidney disease is *PKD*-2 on chromosome 4q21–23 which expresses polycystin 2. Polycystin 1 and 2 interact through their C-terminal cytoplasmic tails suggesting that they function together through a common signal link pathway. Polycystic kidney disease type 2 is clinically milder than type 1.

Polycystic liver disease is most often associated with autosomal dominant polycystic kidney disease although polycystic liver may be an isolated finding and is genetically linked to chromosome 19p13.2–13.1 [34].

The molecular mechanism for the formation of cysts is not clear. They may arise from the failure of supernumerary intra-hepatic bile ducts within the hepatic embryonic anlage to involute when the biliary system forms. When the original segment of blind bile ducts is replaced by a second generation of highly active proliferating ducts, redundant ducts may become distorted and form cysts. The second-generation bile ducts are normal so there is no biliary dysfunction.

Pathology

Depending on the number and size of the cysts, the liver may be normal or greatly enlarged. Cysts may be scattered diffusely or restricted to one lobe, usually the left.

Table 33.2. Hepatic fibropolycystic disease

Subtype	Inheritance	Presentation	Hepatic	Portal hypertension	Renal*
Childhood fibropolycystic					
perinatal	Recessive	Birth	Fibrosis ± Ducts dilated +	—	90%
neonatal	Recessive	1 month	Fibrosis ++ Ducts dilated +	—	60%
infantile	Recessive	3–6 months	Fibrosis ++ Ducts dilated +	Common	25%
Congenital hepatic fibrosis	Recessive	Child or adult	Fibrosis +++ Ducts dilated +	Usual	0–10%
Adult polycystic	Dominant	Adult	Cysts	Rare	Cysts
Intra-hepatic biliary dilatation (Caroli's)	See text	Cholangitis any age	Dilated ducts only	—	—

* Percentage of tubules with cystic change.

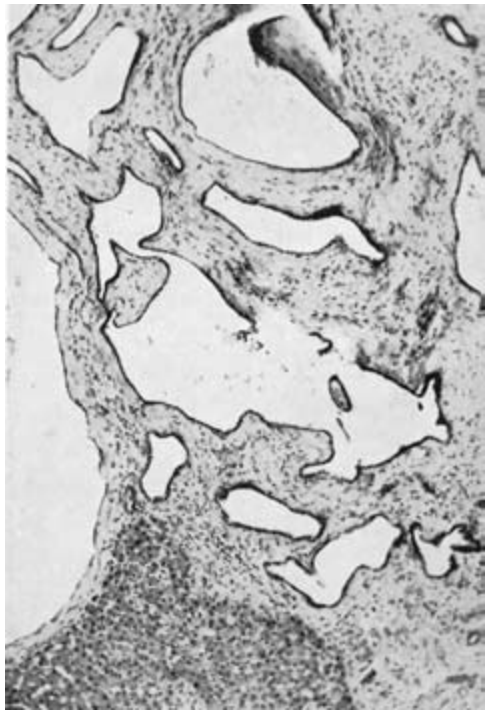


Fig. 33.3. Polycystic disease of the liver. The cysts vary in size and are lined by flattened epithelium. (H & E, × 63.)

The outer surface may be considerably deformed. A cyst may vary in size from a pin's head to a child's head, the largest having a capacity of over 1 litre. They are rarely greater than 10 cm in diameter. The larger ones are probably formed by rupture of septa between adjacent cysts, and the cut liver may display a honeycomb appearance. The cavities are thin walled and contain clear or brown fluid due to altered blood. They never contain bile because they are not in continuity with the biliary tract. They may be complicated by haemorrhage or infection.

Histologically (fig. 33.3) the lobular architecture is unchanged and the liver cells are normal. The cystic areas are related to the bile ducts and to biliary microhamartomas in the portal areas. They are surrounded by a fibrous tissue capsule and lined by columnar or cuboidal epithelium.

Frequently, there is cystic disease of other organs, including kidneys, spleen, pancreas, ovary and lungs. About half the patients with polycystic disease of the liver have polycystic kidneys. The majority (50–88%) of patients with polycystic kidneys have a polycystic liver [16]. The prevalance of hepatic cysts increases with age, being approximately 20% in the third decade rising to 75% in the seventh decade.

Cyst fluid

Fluid has been obtained using needle aspiration under ultrasound guidance [13]. The constituents and response to secretin support the concept that cyst fluid is formed by functioning bile duct epithelium lining the cysts.

Clinical features

In many patients the liver lesion is diagnosed incidentally during scanning or at autopsy. Sometimes the patient presents with some other disease or with polycystic kidneys.

Patients with symptoms and signs are usually in the fourth or fifth decade. The patient complains of abdominal distension and dull abdominal pain. Pressure on the stomach and duodenum causes epigastric discomfort, nausea, flatulence and occasional vomiting. Acute pain may be due to rupture of, or haemorrhage into, a cyst.

Cysts tend to be larger in women who have been pregnant [17]. Hormone replacement therapy is associated with an approximate 5% enlargement of the liver over a year [37]. There is no increase in symptoms. On the basis of these data hormone replacement therapy is not withheld when clinically indicated [37].

Ascites, obstructive jaundice and hepatic venous outflow obstruction [48] are rare.

On examination the liver may be impalpable or so large that it seems to fill the whole abdomen. The edge is firm and nodules can be palpated. There may be difficulty in distinguishing cysts from other types of liver nodule. The spleen is not enlarged.

Bilaterally enlarged irregular *kidneys* may suggest associated renal cysts which may be symptomatic.

Hepatic function is excellent because the liver cells are preserved. Serum alkaline phosphatase and γ-GT may be increased but bilirubin is normal.

Portal venous obstruction rarely may result in oesophageal varices which bleed [39].

Imaging

Ultrasound is the most satisfactory method of diagnosis (fig. 33.4). CT scanning (fig. 33.5) is also useful in symptomatic patients with multiple cysts to show how much normal liver remains. This helps with planning surgical options.

Differential diagnosis

Polycystic liver should be suspected in an apparently well person, often over 33 years of age, with nodular hepatomegaly, but no evidence of hepatic dysfunction, associated with polycystic kidney or a family history of this condition.

Polycystic liver may be confused with *hydatid disease* (Chapter 29).

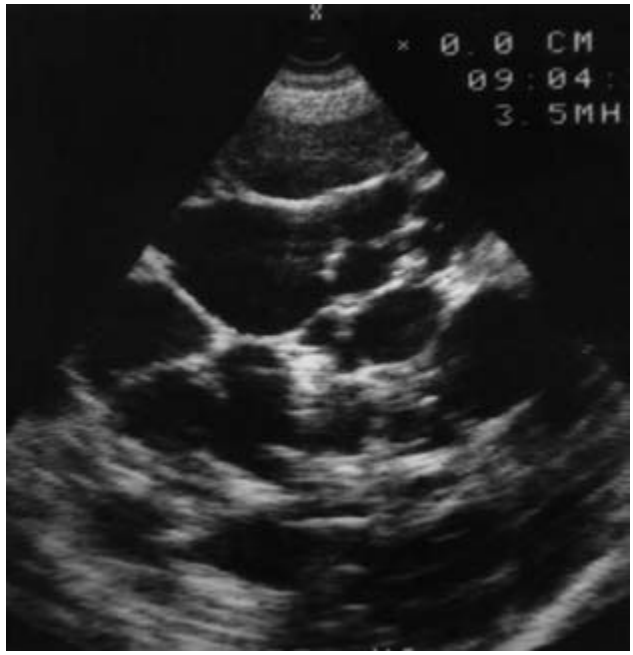


Fig. 33.4. Adult polycystic liver: ultrasound shows numerous echo-free space-occupying lesions.

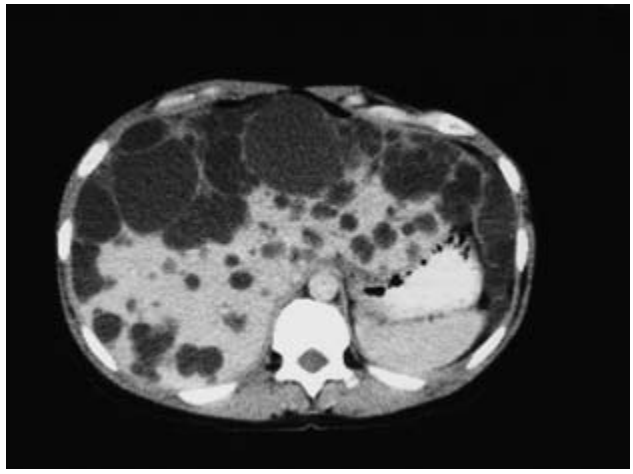


Fig. 33.5. CT scan (contrast enhanced) showing a polycystic liver.

Metastases are accompanied by malaise, weight loss, rapid increase in size of the liver, and, possibly, evidence of a primary neoplasm.

Cirrhosis may be accompanied by signs of hepatocellular disease and the spleen is usually enlarged.

Prognosis and treatment

Polycystic disease of the liver is compatible with long life.

The prognosis is determined by the extent of associated renal cystic disease. Carcinoma is very rare. Surgery is rarely necessary and aspiration under ultrasound control is easy and effective in controlling acute symptoms. However, the fluid returns.

There are several surgical techniques, the choice depending upon the extent of disease [18]. Patients with a limited number of large cysts may be treated by fenestration which can be performed laparoscopically [23]. Where there is localized involvement of the liver parenchyma by multiple medium-sized cysts but with adjacent large areas of normal parenchyma shown by CT, operative fenestration with or without hepatic resection produces symptomatic improvement in the majority [14, 33]. In patients with massive diffuse involvement of the majority of liver parenchyma by all sizes of liver cysts with only a small amount of normal parenchyma between them, fenestration may be useful but carries a high morbidity and mortality. In patients with severe limitation of daily activity and failed previous treatment, liver transplantation can be done (combined with kidney transplantation if necessary) and has a 1-year survival of 89% [41].

Successful liver transplantation has been reported using a donor liver with polycystic change [4].

Congenital hepatic fibrosis

This condition consists, histologically, of broad, densely collagenous fibrous bands surrounding otherwise normal hepatic lobules (fig. 33.6). The bands contain large numbers of microscopic, well-formed bile ducts (fig. 33.7), some containing bile. Arterial branches are normal or hypoplastic, while the veins appear reduced in size. Inflammatory infiltration is not seen. Caroli's syndrome may be associated, also choledochal cyst.

The disease appears both sporadically and in a familial form. It is inherited as autosomal recessive. A ductal plate malformation of interlobular bile ducts has been suggested as the pathogenetic mechanism [11].

Portal hypertension is common. Occasionally this may be due to defects in the main portal veins. More often it is caused by hypoplasia or fibrous compression of portal vein radicles in the fibrous bands surrounding the nodules.

Associated renal conditions include renal dysplasia, adult-type polycystic kidneys [6] and nephronophthisis (medullary cystic disease).

Clinical features

The condition is often misdiagnosed as cirrhosis. The patient is usually diagnosed between the ages of 3 and 10 years but recognition may be delayed until adult life. Sexes are equal. The patient presents with haemorrhage

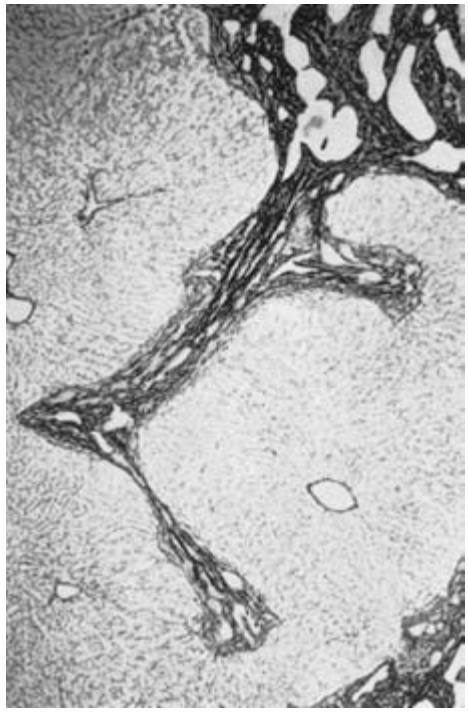


Fig. 33.6. Congenital hepatic fibrosis. Broad bands of fibrous tissue containing bile ducts separate and surround liver lobules. (Silver impregnation, × 36).

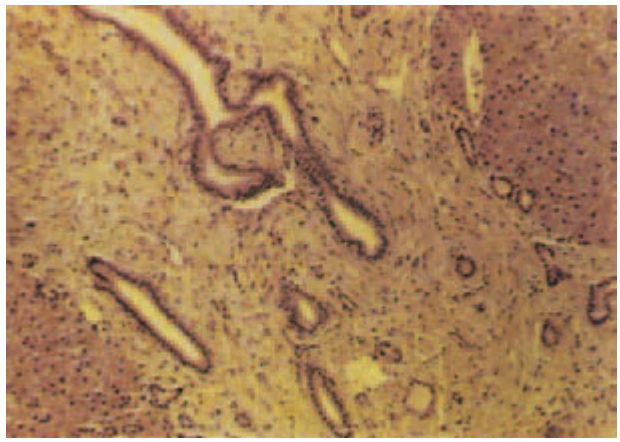


Fig. 33.7. Congenital hepatic fibrosis. Portal area shows dense mature fibrous tissue with a number of abnormal bile ducts. (H & E, × 40.)

from oesophageal varices, a symptomless, large, very hard liver or splenomegaly (fig. 33.8).

There may be other congenital anomalies, especially of the biliary system, with cholangitis [10].

Carcinoma, both hepato-cellular and cholangiocarcinoma, may be a complication [2, 49] as may adenomatous hyperplasia [3].

Congenital hepatic fibrosis is part of the rare disorder

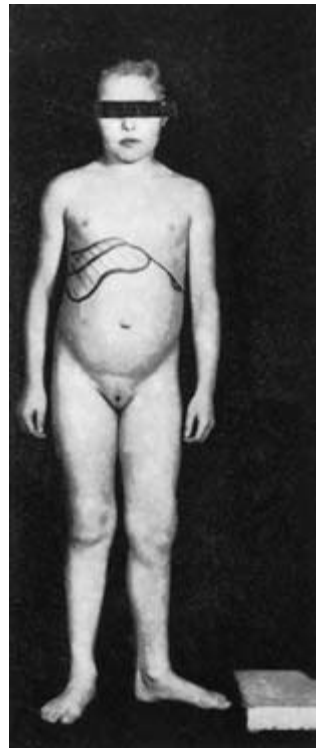


Fig. 33.8. Girl of 8 years with hepatosplenomegaly discovered at routine examination. Liver biopsy showed congenital hepatic fibrosis. Note normal development.

reported with phosphomannose isomerase deficiency [15].

Investigations

Serum protein, bilirubin and transaminase levels are usually normal, but serum alkaline phosphatase values are sometimes increased.

Liver biopsy is essential for diagnosis. Because of the tough consistency of the liver this may be difficult.

Ultrasound shows very bright areas of echogenicity due to the dense bands of fibrous tissue. Direct cholangiography in patients with congenital hepatic fibrosis alone shows tapered intra-hepatic radicals suggesting fibrosis. MR cholangiography shows duct abnormalities including biliary cysts in some patients and this association with congenital hepatic fibrosis has been termed Caroli's syndrome. Choledochal cysts may also be seen [12].

Portal venography reveals the collateral circulation and a normal or distorted intra-hepatic portal tree.

Ultrasound, *CT*, *MRI* and *intravenous pyelography* may show cystic renal changes or medullary sponge kidney.

Prognosis and treatment

Congenital hepatic fibrosis must be distinguished from

cirrhosis since hepato-cellular function is preserved and the prognosis is considerably better.

Following haemorrhage these patients are excellent candidates for porta-caval anastomosis.

Death can be due to renal failure, but renal transplantation has been successful.

Congenital intra-hepatic biliary dilatation (Caroli's disease) [42]

This rare disease is characterized by congenital, segmental, saccular dilatations of the intra-hepatic bile ducts without other hepatic histological abnormalities. The dilated ducts connect with the main duct system and are liable to become infected and contain stones (fig. 33.9).

The inheritance of Caroli's disease is uncertain [45]. Kidney lesions are usually absent, but renal tubular ectasia and larger cysts have been associated.

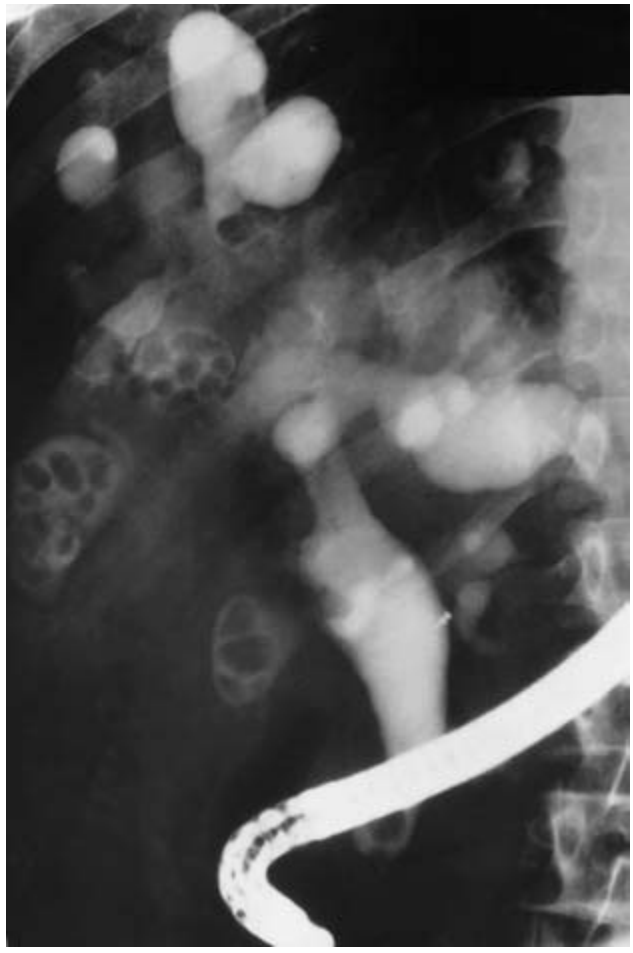


Fig. 33.9. Caroli's disease. Endoscopic cholangiography shows bulbous dilatations of the intra-hepatic bile ducts, some of which contain multiple gallstones.

Clinical features

The condition presents at any age, but usually in childhood or early adult life, as abdominal pain, hepatomegaly, and fever with Gram-negative septicaemia [8]. About 75% are male.

Jaundice is mild or absent but may increase during the episodes of cholangitis. Portal hypertension is absent.

If the cyst is drained bile volumes may be high, and flow increased by an infusion of secretin which stimulates ductular secretion. It is likely that the high resting flow arises from the cysts [46].

Imaging

Ultrasound may be helpful as may CT scanning (fig. 33.10) where portal vein radicles can be seen after enhancement within dilated intra-hepatic bile ducts (the 'central dot' sign) [5]. MR cholangiography is diagnostic [1] as is more invasive endoscopic or percutaneous cholangiography (fig. 33.9). The common bile duct is normal, but the intra-hepatic ducts are marked by bulbous dilatations with normal ducts between. The abnormality may be unilateral [30]. The appearances contrast with those of primary sclerosing cholangitis where the common bile duct is irregular with strictures and the intra-hepatic ducts show irregularities with dilatations.

Cholangiocarcinoma may be a complication, reported in about 7% of patients [9].

Prognosis

The prognosis is poor with survival varying between a mean survival of 9 months [45] in one report to a

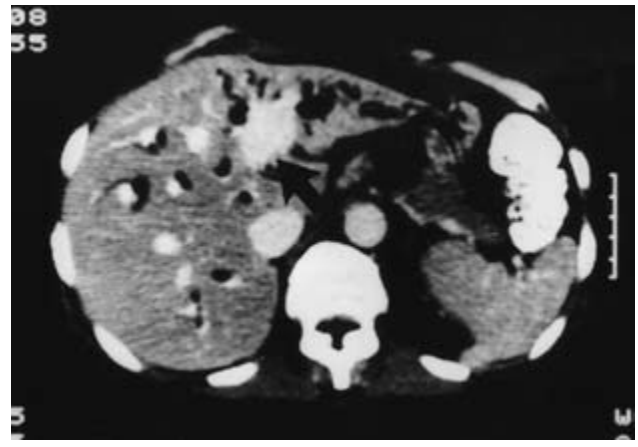


Fig. 33.10. Caroli's disease. CT scan after intravenous contrast shows dilated intra-hepatic bile ducts with adjacent enhanced radicles of the portal vein.

mortality over 5 years of 20% [8]. Death is related to septicaemia, liver abscess, liver failure and portal hypertension.

Treatment

Antibiotics are given to treat cholangitis. Drainage of the common bile duct, whether endoscopic or surgical, may be required to remove calculi. Intra-hepatic stones have been successfully treated with ursodeoxycholic acid [36].

Unilateral involvement may be treated by hepatic resection [30]. Hepatic transplantation must be considered, but infection is a relative contraindication.

The prognosis is poor but episodes of cholangitis can extend over many years.

Death from renal failure is very unusual.

Congenital hepatic fibrosis and Caroli's disease

Caroli's disease often coexists with congenital hepatic fibrosis [40] and is then designated *Caroli's syndrome*. Both result from malformations of the embryonic ductal plate at different levels of the biliary tree. Inheritance is autosomal recessive. Presentation may be as abdominal pain and cholangitis or as haemorrhage from oesophageal varices (fig. 33.11).

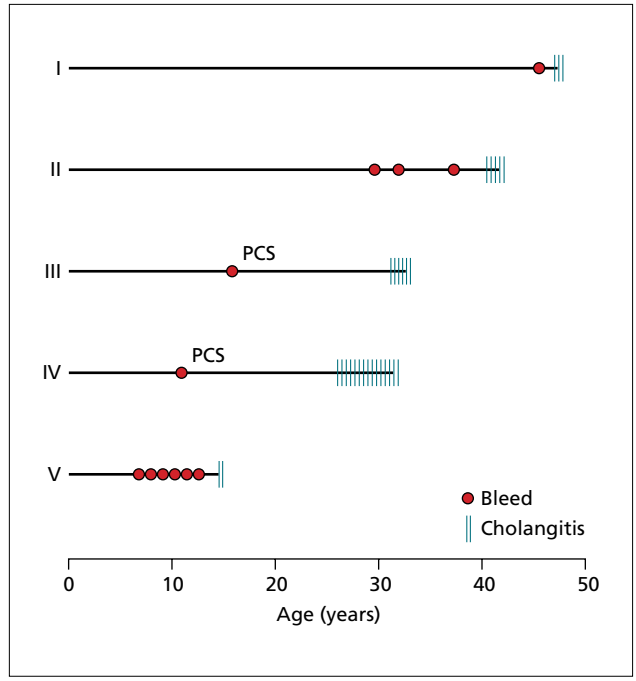


Fig. 33.11. The evolution of symptoms in five patients (I–V) with coexistent congenital hepatic fibrosis and Caroli's disease who had both variceal haemorrhages and cholangitis. Haemorrhage always occurred first, followed, a mean of 10 years later, by cholangitis. PCS, porta-caval shunt [40].

Choledochal cyst

This describes cystic dilatation of all or part of the extra-hepatic biliary tree with or without associated cystic change of intra-hepatic bile ducts. When the common duct itself is involved, the gallbladder, cystic duct and proximal hepatic ducts are not dilated, as distinct from the pattern of dilatation of the whole biliary tree above an obstructing lesion. Caroli's disease may coexist. Histologically the cyst wall consists of fibrotic tissue with acute and chronic inflammation.

No unifying pathological process explains all cysts. Some are associated with a long common channel between the pancreatic duct and the bile duct which predisposes to the reflux of pancreatic enzymes [24]. Many patients, however, do not have this anomaly. There may be infective and molecular genetic factors. Reovirus RNA was detected in tissue taken from eight out of nine infants and children with choledochal cysts [47]. Choledochal cysts may be found in patients with other fibropolycystic disease raising the possibility of a developmental anomaly.

Choledochal cysts are classified as follows (fig. 33.12) [27, 28].

Type I: cystic (Ia), segmental (Ib) or fusiform (Ic) dilatation of the extra-hepatic bile duct. A further group (Id) has been suggested with multiple extra-hepatic cysts. Differentiation between the fusiform type and dilatation of the bile duct secondary to obstruction is based on the absence of a previous history of gallstones or biliary surgery, a common bile duct diameter greater than 30 mm, and the presence of an anomalous bile duct junction shown on cholangiography [27].

Type II: the cyst forms a diverticulum from the extra-hepatic bile duct.

Type III: there is cystic dilatation (choledochocele) of the distal common bile duct lying mostly within the duodenal wall.

Type IV: this comprises type I anatomy together with intra-hepatic bile duct cysts. It has been proposed that IVa, IVb and IVc describe this picture with cystic, segmental or fusiform change of the extra-hepatic biliary tree [27].

When used, type V denotes Caroli's disease.

The commonest types are I and IV [27, 28]. Whether choledochocele (type III) should be classified as a choledochal cyst has been questioned [38].

Rarely a solitary cystic dilatation of an intra-hepatic bile duct is seen [43].

The type I lesion presents as a partially retroperi-

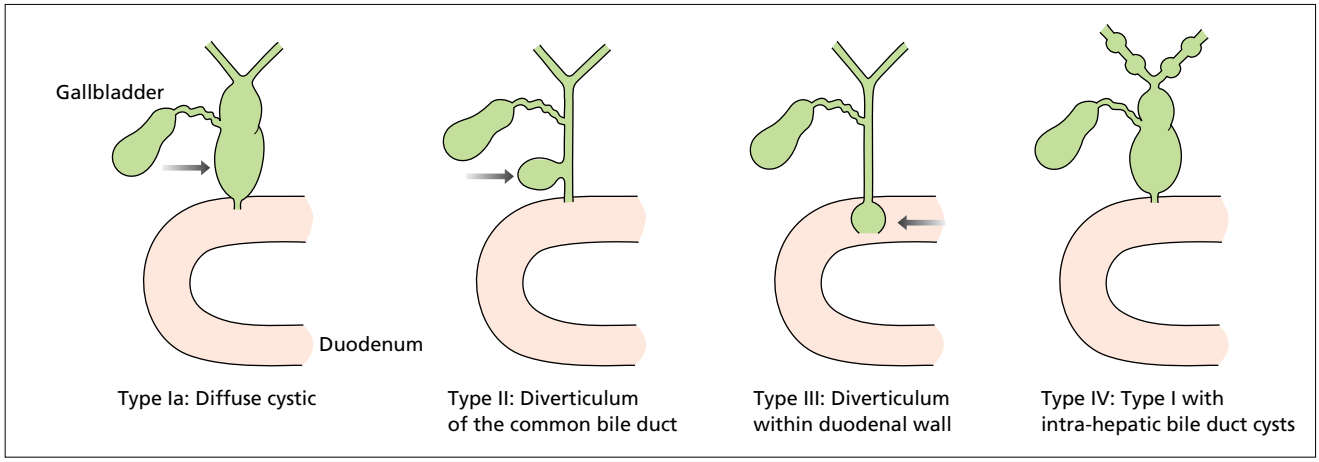


Fig. 33.12. Classification of congenital biliary dilatation (choledochal cyst) (IVb is type I plus III).

toneal, cystic tumour varying from 2 to 3 cm in size, to a capacity of 8 litre. The cyst contains thin, dark brown fluid. It is sterile but may become secondarily infected. The cyst can burst.

Biliary cirrhosis is a late complication. Choledochal cysts may obstruct the portal vein leading to portal hypertension. Malignant tumours in the cyst or bile ducts may develop [28].

Clinical features

The infantile form presents as prolonged cholestasis. In infancy the cyst may perforate causing bile peritonitis. Later the classical symptoms are intermittent jaundice, pain and an abdominal tumour. Children are more likely to have two or more of this 'classical' triad than adults (82 vs. 25%) [28]. Although formerly regarded as a childhood disease, the diagnosis is now more often made in adult life. One-quarter of individuals affected present with symptoms and signs of pancreatitis [28]. Choledochal cysts appear more frequently in the Japanese and other Oriental races.

The jaundice is intermittent, of cholestatic type, and associated with fever. The pain is colicky and mainly experienced in the right upper abdomen. The tumour is cystic and in the right upper quadrant of the abdomen. It characteristically varies in size and in tenseness.

Choledochal cysts may be associated with congenital hepatic fibrosis or Caroli's disease. Anomalous pancreatico-biliary drainage is important particularly if the duct junction is right-angular or acute [32].

Imaging

Plain X-ray of the abdomen may show a soft-tissue mass.

Fig. 33.13. MR cholangiogram in a 40-year-old woman with a type Ia choledochal cyst. The patient presented with acute pancreatitis.

HIDA scanning, ultrasound and CT can show the cystic lesion but magnetic resonance cholangiography (MRCP) is an effective approach and is the first choice imaging technique for examining these cysts (fig. 33.13) [21, 25]. It does not, however, remove the need for other approaches including endoscopic retrograde cholangiopancreatography (ERCP) in some patients [21].

Treatment

Because of the risk of subsequent adenocarcinoma or squamous cell carcinoma, excision is the method of

choice [22, 28]. Biliary tract continuity is maintained by choledocho-jejunostomy with Roux-en-Y anastomosis.

Anastomosis of the cyst to the intestinal tract without excision is simpler but post-operative cholangitis and subsequent biliary stricturing and stone formation are frequent. The risk of carcinoma remains, perhaps related to dysplasia and metaplasia of the epithelium [44].

Microhamartoma (von Meyenberg complexes)

These are usually asymptomatic, diagnosed incidentally or found at autopsy. Rarely, they may be associated with portal hypertension. Kidneys may show medullary sponge change. Microhamartomas can be associated with polycystic disease.

Histologically, microhamartomas consist of groups of rounded biliary channels, lined by cuboidal epithelium and often containing inspissated bile (fig. 33.14). These biliary structures are embedded in mature collagenous stroma. They are usually located in, or near, portal tracts. The appearances suggest congenital hepatic fibrosis, but in a localized form.

Imaging

In a hepatic arteriogram, multiple microhamartomas lead to stretching of the arteries and blushing in the venous phase.

Carcinoma secondary to fibropolycystic disease

Tumours may arise in association with microhamartomas, congenital hepatic fibrosis, Caroli's disease [9], and choledochal cyst [28]. Carcinoma is rare in association with non-parasitic cysts [31] or polycystic liver disease. Malignant change is more likely where epithelium is exposed to bile.

Solitary non-parasitic liver cyst

This is being increasingly diagnosed due to the increase in various scanning techniques. It is probably a variant of polycystic disease.

The lining wall has partitions, which suggest an origin from conglomerate polycystic disease. The fibrous capsule contains aberrant bile ducts and blood vessels. The contents vary from colourless to brown altered blood. The tension is low in contrast to the high pressure of hydatid cysts.

Symptoms are rare and related to abdominal distension, or pressure effects on adjacent organs including the bile ducts, causing intermittent jaundice. The patient should be reassured.

Symptoms follow rupture or haemorrhage into the cyst. These events are extremely rare. Surgical excision is indicated only for complications.

Other cysts

These are all very rare, small and superficial. Their contents vary with the cause. Bile cysts may follow prolonged extra-hepatic biliary obstruction of all types.

Blood cysts follow haemorrhage into a simple cyst. They can also follow trauma to the liver. Small cystic spaces containing blood may follow needle biopsy.

Lymphatic cysts are due to obstruction or congenital dilatation of liver lymphatics. They are usually on the surface of the liver.

Biliary cystadenoma and cystadenocarcinoma are rare (Chapter 31). Malignant pseudocysts from degeneration

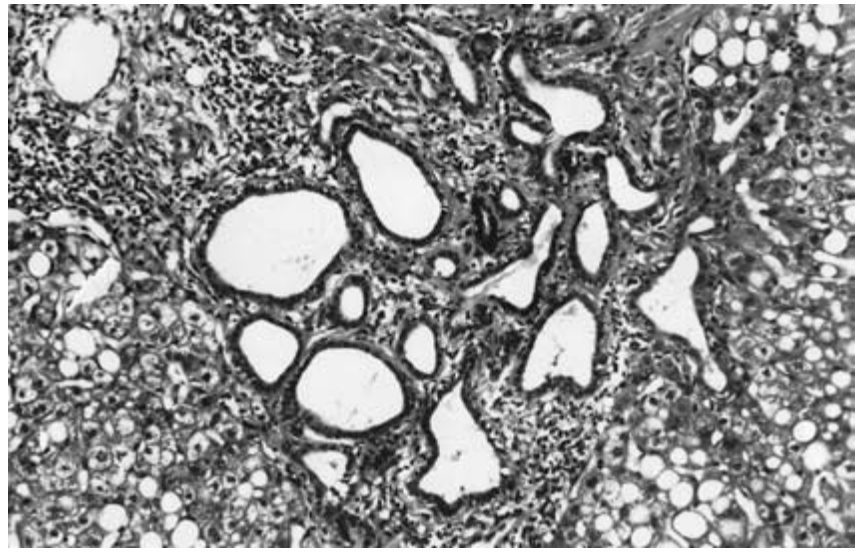


Fig. 33.14. Microhamartoma of the liver. Groups of biliary channels are lined by cuboidal epithelium and are embedded in mature fibrous tissue [40]. (H & E, × 180.)

and softening of secondary malignant growths also occur.

Congenital anomalies of the biliary tract

The liver and biliary tract develop from a bud-like outpouching of the ventral wall of the primitive foregut just cranial to the yolk sac. Two solid buds of cells form the right and left lobes of the liver while the original elongated diverticulum forms the hepatic and common bile duct. The gallbladder arises as a smaller bud of cells from this same diverticulum. The biliary tract is patent in early intra-uterine life but becomes solid later by epithelial proliferation within the lumen. Eventually revacuolization takes place, starting simultaneously in different parts of the solid gallbladder bud and spreading until the whole system is recanalized. At 5 weeks the ductal communications of gallbladder, cystic duct and hepatic ducts are completed and at 3 months the fetal liver begins to secrete bile.

The majority of the congenital anomalies can be related to alterations in the original budding from the foregut or to failure of vacuolization of the solid gallbladder and bile diverticulum (table 33.3).

These congenital defects are usually of no importance and cannot be related to symptoms. Occasionally bile duct anomalies lead to bile stasis, inflammation and gallstones [7]. They are of importance to the radiologist and to the biliary and hepatic transplant surgeon.

Anomalies of the biliary tree and liver may be associated with congenital lesions elsewhere, including cardiac defects, polydactyly and polycystic kidneys. They can also be related to maternal virus infections, such as rubella.

Table 33.3. Classification of congenital anomalies of the biliary tract

Anomalies of the primitive foregut bud
Failure of bud
absent bile ducts
absent gallbladder
Accessory buds or splitting of bud
accessory gallbladder
bilobed gallbladder
accessory bile ducts
Bud migrates to left instead of right
left-sided gallbladder
Anomalies of vacuolization of the solid biliary bud
Defective bile duct vacuolization
Congenital obliteration of bile ducts
Congenital obliteration of cystic duct
Choledochal cyst
Defective gallbladder vacuolization
rudimentary gallbladder
Fundal diverticulum
Serosal type of Phrygian cap
Hour-glass gallbladder
Persistent cysto-hepatic duct
Diverticulum of body or neck of gallbladder
Persistence of intra-hepatic gallbladder
Aberrant folding of gallbladder anlage
Retroserosal type of Phrygian cap
Accessory peritoneal folds
Congenital adhesions
Floating gallbladder
Anomalies of hepatic and cystic arteries
Accessory arteries
Abnormal relation of hepatic artery to cystic duct

Absence of the gallbladder [35]

This is a rare congenital anomaly. Two types can be recognized.

Type I is the failure of the gallbladder and cystic duct to develop as an outgrowth from the hepatic diverticulum of the foregut. This type is often found with other anomalies of the biliary passages.

Type II is the failure of the gallbladder to vacuolize from its solid state. This is usually associated with atresia of the extra-hepatic ducts. The gallbladder is not absent but *rudimentary*. This type is therefore found in infants who present the picture of congenital biliary atresia.

Most cases occur in infants with other major congenital anomalies. Adults are usually healthy and without other anomalies. Some have right upper quadrant pain or jaundice. The inability to show the gallbladder on ultrasound may be interpreted as gallbladder disease and lead to surgery. The possibility of agenesis or an ectopic location must be considered. Cholangiography should be diagnostic. Failure to identify the gallbladder at operation is not proof of its absence. The gallbladder may be intra-hepatic, buried in extensive adhesions, or atrophied following previous cholecystitis.

An intraoperative cholangiogram should be done.

Double gallbladder

Double gallbladder is very rare. In embryonic life, little pockets often arise from the hepatic or common bile ducts. Occasionally these persist and form a second gallbladder having its own cystic duct (fig. 33.15). This may enter the hepatic substance directly. If the pouch forms from the cystic duct the two gallbladders share a Y-shaped cystic duct.

Double gallbladder can be recognized by imaging. The accessory organ is frequently diseased.

Bilobed gallbladder is an extremely rare congenital anomaly. Embryologically, the single bud forming the

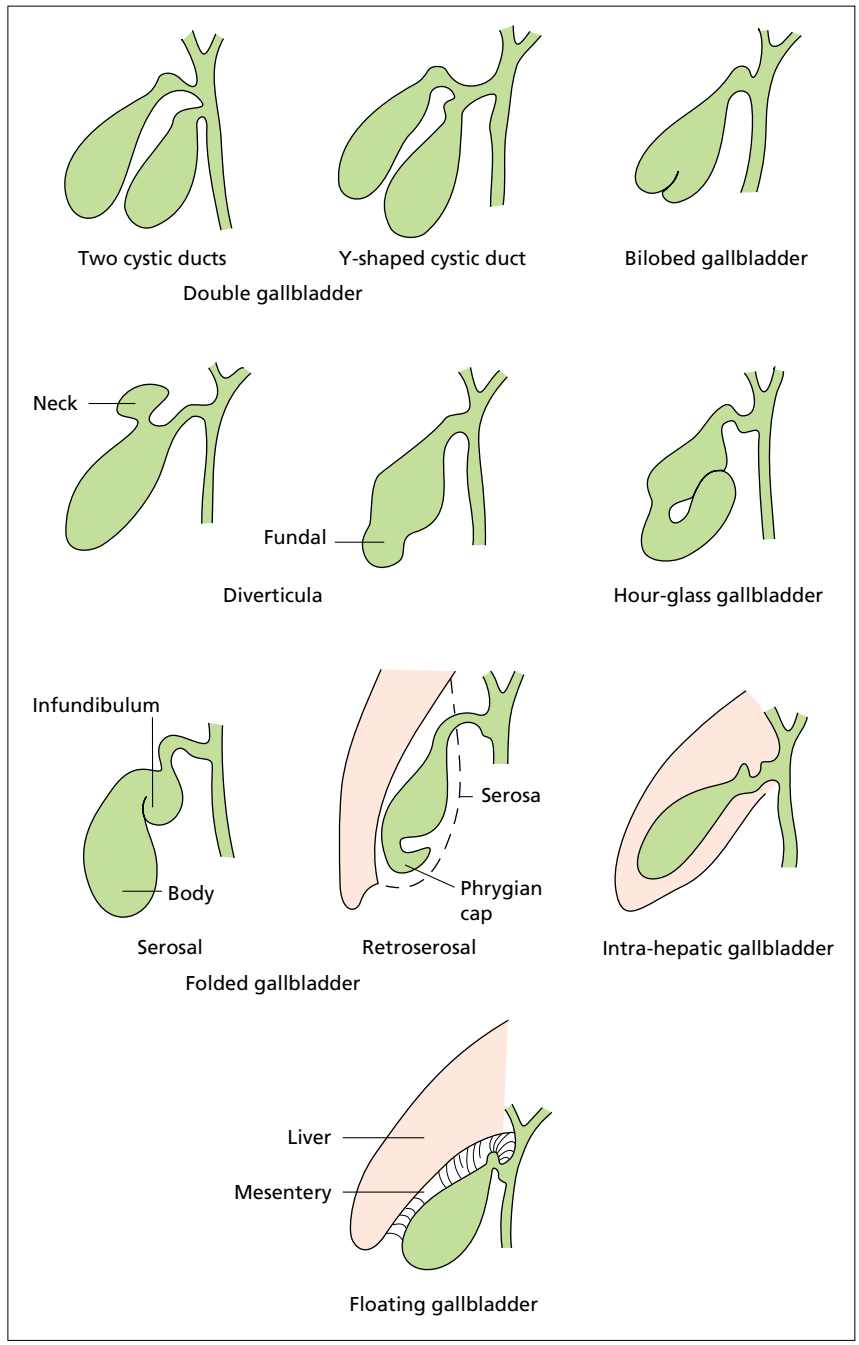


Fig. 33.15. Congenital anomalies of the gallbladder.

gallbladder becomes paired but primary connection is maintained, thus forming two separate and distinct fundi with a single cystic duct.

The anomaly is of no clinical significance.

Accessory bile ducts

These are rare. The extra duct is usually a subdivision of the right hepatic system and joins the common hepatic duct somewhere between the junction of the main right and left hepatic ducts and the entry of the cystic duct (fig. 35.1c). It may, however, join the cystic duct, the gallbladder or the common bile duct.

Cholecysto-hepatic ducts are due to persistence of fetal connections between the gallbladder and the liver parenchyma with failure of re-canalization of the right and left hepatic ducts. Continuity is maintained by the cystic duct entering a remaining hepatic duct or common hepatic duct or the duodenum directly.

Accessory ducts are of importance to the biliary and transplant surgeon as they may be inadvertently ligated or cut with resultant biliary stricture or fistula.

Left-sided gallbladder

In this rare anomaly the gallbladder lies under the left lobe of the liver, to the left of the falciform ligament.

This may be caused by the gallbladder migrating to a position under the left lobe of the liver (to the left of the round ligament). The path of the cystic duct is normal. Alternatively a second gallbladder may develop directly from the left hepatic duct with failure of development or regression of the normal structure on the right side. A left-sided gallbladder formed in this way is of little clinical significance.

In some cases however, a left-sided gallbladder may be described as such because of its relationship to the round ligament ('a right-sided round ligament'). In these cases the gallbladder is in its normal site. The right-sided round ligament anomaly is important because it is associated with abnormal intra-hepatic portal venous branching. This is important to recognize when performing hepatectomy [29].

Rokitansky–Aschoff sinuses of the gallbladder

These consist of hernia-like protrusions of the gallbladder mucosa through the muscular layer (intramural diverticulosis). Although potentially congenital they are particularly prominent with chronic cholecystitis when intraluminal pressure rises. They may be seen in an oral cholecystogram as a halo-like stippling surrounding the gallbladder.

Folded gallbladder

The gallbladder is deformed so that the fundus appears folded 'bent down to the breaking point after the manner of a *Phrygian cap*'. A Phrygian cap is a conical cap or bonnet, with the peak bent or turned over in front, worn by the ancient Phrygians, and identified with the Cap of Liberty (*Oxford English Dictionary*).

Two varieties are recognized:

1 *Kinking between body and fundus* (*retroserosal Phrygian cap*) (fig. 33.15). This is due to aberrant folding of the gallbladder within the embryonic fossa.

2 *Kinking between body and infundibulum* (*serosal Phrygian cap*) (fig. 33.15). This is due to aberrant folding of the fossa itself in the early stages of development. The bend in the gallbladder is fixed by development of fetal ligaments, vestigial septa or constrictions of the lumen following delayed vacuolization of the solid epithelial anlage.

These kinked gallbladders empty at a normal rate and are of no clinical significance. The importance lies in the correct interpretation of the cholecystograms.

Hour-glass gallbladder (fig. 33.15). This probably represents an exaggerated form of Phrygian cap, presumably of the serosal type. The constancy of position of the fundus during contraction and the small size of the opening between the two parts indicate that this is probably a fixed, congenital malformation.

Diverticula of the gallbladder and ducts

Diverticula of the body and neck may arise from persistent cysto-hepatic ducts which run in embryonic life between the gallbladder and the liver.

The fundal variety arises from incomplete vacuolization of the solid gallbladder of embryonic life. An incomplete septum pinches off a small cavity at the tip of the gallbladder (fig. 33.15).

These diverticula are rare and of no clinical significance. The congenital variety should be distinguished from *pseudo-diverticula* developing in the diseased gallbladder as a result of partial perforation. The pseudo-diverticulum in these cases usually contains a large gallstone.

Intra-hepatic gallbladder

The gallbladder is included and buried in hepatic tissue up to the second month of intra-uterine life, thereafter assuming an extra-hepatic position. In some instances the intra-hepatic condition may persist (fig. 33.15). The gallbladder is higher than normal and more or less buried but never entirely covered by liver tissue. It is frequently diseased, for the embedded organ has difficulty in contracting and so becomes infected, with subsequent gallstone formation.

Congenital adhesions to the gallbladder

These are very frequent. Developmentally these peritoneal sheets are due to an extension of the anterior mesentery, which forms the lesser omentum. The sheet may run from the common bile duct laterally over the gallbladder down to the duodenum, to the hepatic flexure of the colon and even to the right lobe of the liver, perhaps closing the foramen of Winslow. In a milder form, a band of tissue runs from the lesser omentum across to the cystic duct and anterior to the gallbladder; or a loose veil forms a mesentery to the gallbladder ('floating gallbladder') (fig. 33.15).

These adhesions are of no clinical importance. Surgically, their presence should be remembered, so that they are not mistaken for inflammatory adhesions.

Floating gallbladder and torsion of the gallbladder

The gallbladder possesses a supporting membrane in 4–5% of specimens. The peritoneal coat surrounding the gallbladder continues as two approximated leaves to

form a fold or mesentery to support the gallbladder from under the surface of the liver. This fold may allow the gallbladder to hang as much as 2–3 cm below the inferior hepatic surface.

The mobile gallbladder is apt to twist, and *torsion* results. The blood supply is impaired in the small pedicle and infarction follows.

The condition usually occurs in thin, elderly women. With ageing, omental fat lessens and there is a great caudal displacement of abdominal viscera due to loss of tone in the abdominal and pelvic muscles. The gallbladder with mesentery becomes more pendulous and can twist. It can affect all ages, including children.

Torsion is followed by sudden, severe, constant epigastric and right costal margin pain passing through to the back with vomiting and collapse. Characteristically a palpable tumour appears, having the features of an enlarged gallbladder. Within a few hours it may disappear. The treatment is cholecystectomy.

Recurrent partial torsion leads to acute episodes. Ultrasound or CT shows a gallbladder situated low in the abdomen and even in the pelvis. It is suspended by a very long, down-curved cystic duct. Early cholecystectomy is indicated.

Anomalies of the cystic duct and cystic artery

In 20% of subjects the *cystic duct* does not join the common hepatic duct directly but first runs parallel to it, lying in the same sheath of connective tissue. Occasionally it makes a spiral turn around the duct.

These variations are extremely important to the surgeon. Unless the cystic duct is carefully dissected and its union with the common hepatic duct identified, the common hepatic duct may be ligated, with disastrous consequences.

The *cystic artery* can arise not, as normally, from the right hepatic artery but from the left hepatic artery or even from the gastroduodenal artery. Accessory cystic arteries usually arise from the right hepatic artery. Again, the surgeon must be careful to identify the cystic artery precisely.

References

1 Asselah T, Ernst O, Sergent G *et al*. Caroli's disease: a magnetic resonance cholangiopancreatography diagnosis. *Am. J. Gastroenterol*. 1998; **93**: 109.

2 Bauman ME, Pound DC, Ulbright TM. Hepatocellular carcinoma arising in congenital hepatic fibrosis. *Am. J. Gastroenterol*. 1994; **89**: 450.

3 Bertheau P, Degott C, Belghiti J *et al*. Adenomatous hyperplasia of the liver in a patient with congenital hepatic fibrosis. *J. Hepatol*. 1994; **20**: 213.

4 Caballero F, Domingo P, Lopéz-Navidad A. Successful liver transplant using a polycystic donor liver. *J. Hepatol*. 1997; **26**: 1428.

5 Choi BI, Yeon KM, Kim SH *et al*. Caroli disease: central dot sign in CT. *Radiology* 1990: **174**: 161.

6 Cobben JM, Breuning H, Schoots C *et al*. Congenital hepatic fibrosis in autosomal-dominant polycystic kidney disease. *Kidney Int*. 1990; **38**: 880.

7 Cullingford G, Davidson B, Dooley J *et al*. Case report: hepatolithiasis associated with anomalous biliary anatomy and a vascular compression. *H P B Surg*. 1991; **3**: 129.

8 Dagli Ü, Atalay F, Sasmaz N *et al*. Caroli's disease: 1977–95 experiences. *Eur. J. Gastroenterol. Hepatol*. 1998: **10**: 109.

9 Dayton MT, Longmire WP Jr, Tompkins PK. Caroli's disease: a premalignant condition? *Am. J. Surg*. 1983; **145**: 41.

10 De Vos M, Barbier F, Cuvelier C. Congenital hepatic fibrosis. *J. Hepatol*. 1988; **6**: 222.

11 Desmet VJ. Ludwig symposium on biliary disorders—part 1. Pathogenesis of ductal plate abnormalities. *Mayo Clin. Proc*. 1998; **73**: 80.

12 Ernst O, Gottrand F, Calvo M *et al*. Congenital hepatic fibrosis: findings at MR cholangiopancreatopraphy. *Am. J. Roentgenol*. 1998; **170**: 409.

13 Everson GT, Emmett M, Brown WR *et al*. Functional similarities of hepatic cystic and biliary epithelium: studies of fluid constituents and *in vivo* secretion in response to secretin. *Hepatology* 1990; **11**: 557.

14 Farges O, Bismuth H. Fenestration in the management of polycystic liver disease. *World J. Surg*. 1995; **19**: 25.

15 Freeze HH. New diagnosis and treatment of congenital hepatic fibrosis. *J. Pediatr. Gastroenterol. Nutr.* 1999; **29**: 104.

16 Gabow PA. Autosomal dominant polycystic kidney disease. *N. Engl. J. Med*. 1993; **329**: 332.

17 Gabow PA, Johnson AM, Kaehny WD *et al*. Risk factors for the development of hepatic cysts in autosomal dominant polycystic kidney disease. *Hepatology* 1990; **11**: 1033.

18 Gigot J-F, Jadoul P, Que F *et al*. Adult polycystic liver disease: is fenestration the most adequate operation for long-term management? *Ann. Surg*. 1997; **225**: 286.

19 Hateboer N, v Dijk MA, Bogdanova N *et al*. Comparison of phenotypes of polycystic kidney disease types 1 and 2. *Lancet* 1999; **353**: 103.

20 Ibraghimov-Beskrovnaya O, Dackowski WR, Foggensteiner L *et al*. Polycystin: *in vitro* synthesis, *in vivo* tissue expression and subcellular localization identifies a large membrane-associated protein. *Proc. Natl. Acad. Sci. USA* 1997; **94**: 6397.

21 Irie H, Honda H, Jimi M *et al*. Value of MR cholangiopancreatography in evaluating choledochal cysts. *Am. J. Roentgenol*. 1998; **171**: 1381.

22 Ishibashi T, Kasahara K, Yasuda Y *et al*. Malignant change in the biliary tract after excision of choledochal cyst. *Br. J. Surg*. 1997; **84**: 1687.

23 Kabbej M, Sauvanet A, Chauveau D *et al*. Laparoscopic fenestration in polycystic liver disease. *Br. J. Surg*. 1996; **83**: 1697.

24 Komi N, Takehara H, Kunitomo K. Choledochal cyst: anomalous arrangement of the pancreatico-biliary ductal system and biliary malignancy. *J. Gastroenterol. Hepatol*. 1989; **4**: 63.

25 Lam WWM, Lam TPW, Saing H *et al*. MR cholangiography and CT cholangiography of paediatric patients with choledochal cysts. *Am. J. Roentgenol*. 1999; **173**: 401.

26 Landing BH, Wells TR, Claireaux AE. Morphometric analysis of liver lesions in cystic diseases of childhood. *Hum. Pathol*. 1980; **11**: 549.

27 Lenriot JP, Gigot JF, Ségol P *et al*. Bile duct cysts in adults: a multi-institutional retrospective study. *Ann. Surg.* 1998; **228**: 159.
28 Lipsett PA, Pitt HA, Colombani PM *et al*. Choledochal cyst disease: a changing pattern of presentation. *Ann. Surg.* 1994; **220**: 644.
29 Nagai M, Kubota K, Kawasaki S *et al*. Are left-sided gallbladders really located on the left side? *Ann. Surg.* 1997; **225**: 274.
30 Nagasue N. Successful treatment of Caroli's disease by hepatic resection: report of six patients. *Ann. Surg.* 1984; **200**: 718.
31 Nieweg O, Sloof MJH, Grond J. A case of primary squamous cell carcinoma of the liver arizing in a solitary cyst. *H P B Surg.* 1992; **5**: 203.
32 Oguchi Y, Okada A, Nakamura T *et al*. Histopathologic studies of congenital dilatation of the bile duct as related to an anomalous junction of the pancreatico-biliary ductal system: clinical and experimental studies. *Surgery* 1988; **103**: 168.
33 Que F, Nagorney DM, Gross JB *et al*. Liver resection and cyst fenestration in the treatment of severe polycystic liver disease. *Gastroenterology* 1995; **108**: 487.
34 Reynolds DM, Falk CT, Li A *et al*. Identification of a locus for autosomal dominant polycystic liver disease, on chromosome 19p13.2–13.1. *Am. J. Hum. Genet.* 2000; **67**: 1598.
35 Richards RJ, Raubin H, Wasson D. Agenesis of the gallbladder in symptomatic adults: a case and review of the literature. *J. Clin. Gastroenterol.* 1993; **16**: 231.
36 Ros E, Navarro S, Bru C *et al*. Ursodeoxycholic acid treatment of primary hepatolithiasis in Caroli's syndrome. *Lancet* 1993; **342**: 404.
37 Sherstha R, McKinley C, Russ P *et al*. Postmenopausal oestrogen therapy selectively stimulates hepatic enlargement in women with autosomal dominant polycystic kidney disease. *Hepatology* 1997; **26**: 1282.
38 Spier LN, Crystal K, Kase DJ *et al*. Choledochocele: newer concepts of origin and diagnosis. *Surgery* 1995; **117**: 476.
39 Srinivasan R. Polycystic liver disease: an unusual cause of bleeding varices. *Dig. Dis. Sci.* 1999; **44**: 389.
40 Summerfield JA, Nagafuchi Y, Sherlock S *et al*. Hepatobiliary fibropolycystic disease: a clinical and histological review of 51 patients. *J. Hepatol.* 1986; **2**: 141.
41 Swenson K, Seu P, Kinkhabwala M *et al*. Liver transplantation for adult polycystic liver disease. *Hepatology* 1998; **28**: 412.
42 Taylor ACF, Palmer KR. Caroli's disease. *Eur. J. Gastroenterol. Hepatol.* 1998; **10**: 105.
43 Terada T, Nakanuma Y. Solitary cystic dilation of the intrahepatic bile duct: morphology of two autopsy cases and a review of the literature. *Am. J. Gastroenterol.* 1987; **82**: 1331.
44 Todani T, Watanabe Y, Toki A *et al*. Carcinoma related to choledochal cysts with internal drainage operations. *Surg. Gynecol. Obstet.* 1987; **164**: 61.
45 Tsuchida Y, Sato T, Sanjo K *et al*. Evaluation of long-term results of Caroli's disease: 21 years' observation of a family with autosomal 'dominant' inheritance, and review of the literature. *Hepatogastroenterology* 1995; **42**: 175.
46 Turnberg LA, Jones EA, Sherlock S. Biliary secretion in a patient with cystic dilation of the intrahepatic biliary tree. *Gastroenterology* 1968; **54**: 1155.
47 Tyler KL, Sokol RJ, Oberhaus SM *et al*. Detection of reovirus RNA in hepatobiliary tissues from patients with extrahepatic biliary atresia and choledochal cysts. *Hepatology* 1998; **27**: 1475.
48 Uddin W, Ramage JK, Portmann B *et al*. Hepatic venous outflow obstruction in patients with polycystic liver disease: pathogenesis and treatment. *Gut* 1995; **36**: 142.
49 Yamato T, Sasaki M, Hoso M *et al*. Intrahepatic cholangiocarcinoma arising in congenital hepatic fibrosis: report of an autopsy case. *J. Hepatol.* 1998; **28**: 717.

Chapter 34
Gallstones and Inflammatory Gallbladder Diseases

Composition of gallstones

There are three major types of gallstone: cholesterol, black pigment and brown pigment (fig. 34.1, table 34.1). In the Western world most are cholesterol stones. Although these consist predominantly of cholesterol (51–99%) they, along with all types, have a complex content and contain a variable proportion of other components including calcium carbonate, phosphate, bilirubinate and palmitate, phospholipids, glycoproteins and mucopolysaccharides. Crystallography confirms that the cholesterol is in monohydrate and anhydrous forms. The nature of the nucleus of the stone is uncertain—pigment, glycoprotein and amorphous material have all been suggested.

The problem is to explain how in normal individuals insoluble cholesterol is kept in solution in bile, and what in other people leads to its precipitation to form gallstones.

Composition of bile

Biliary cholesterol is in the free unesterified form. Concentration is unrelated to serum cholesterol level and depends only to a limited extent on the bile acid pool size and bile acid secretory rate.

Biliary phospholipids. These are insoluble in water and include lecithin (90%) with small quantities of lysolecithin (3%) and phosphatidyl ethanolamine (1%). Entry of phospholipid into bile depends upon a canalicular protein that acts as a 'flippase' which is encoded by the *MDR3* gene (Chapter 13). Transgenic knockout mice in which the analogous gene has been deleted are incapable of secreting phospholipid (and cholesterol) into bile [173]. Bile acid secretion remains normal.

Phospholipids are hydrolysed in the gut and there is no entero-hepatic circulation. Bile acids determine excretion and enhance synthesis.

Bile acids. The primary bile acids are the trihydroxy, cholic acid and the dihydroxy, chenodeoxycholic acid. These are conjugated with glycine and taurine. They are converted by bacterial action, usually in the colon, to the secondary bile acids, deoxycholic acid and lithocholic acid. Cholic, cheno- and deoxycholic acids are absorbed and undergo an entero-hepatic circulation which takes place 6–10 times daily [48]. Lithocholic acid is poorly absorbed and there is little to be found in the bile. The total bile acid pool is normally 2.5 g and the average daily production of cholic acid is about 330 mg and chenodeoxycholic acid 280 mg.

The control of bile acid synthesis is complex; it is probably a negative feedback mechanism through the amount of bile salts and cholesterol reaching the liver from the gut. Bile acid synthesis is decreased by administration of bile salts and increased by interruption of the entero-hepatic circulation.

Table 34.1. Classification of gallstones

	Cholesterol	Black pigment	Brown pigment
Location	Gallbladder, ducts	Gallbladder, ducts	Ducts
Major constituents	Cholesterol	Bilirubin pigment polymer	Calcium bilirubinate
Consistency	Crystalline with nucleus	Hard	Soft, friable
% Radio-opaque	15%	60%	0%
Associations			
Infection	Rare	Rare	Usual
Other diseases	See fig. 34.2	Haemolysis, cirrhosis	Chronic partial biliary obstruction

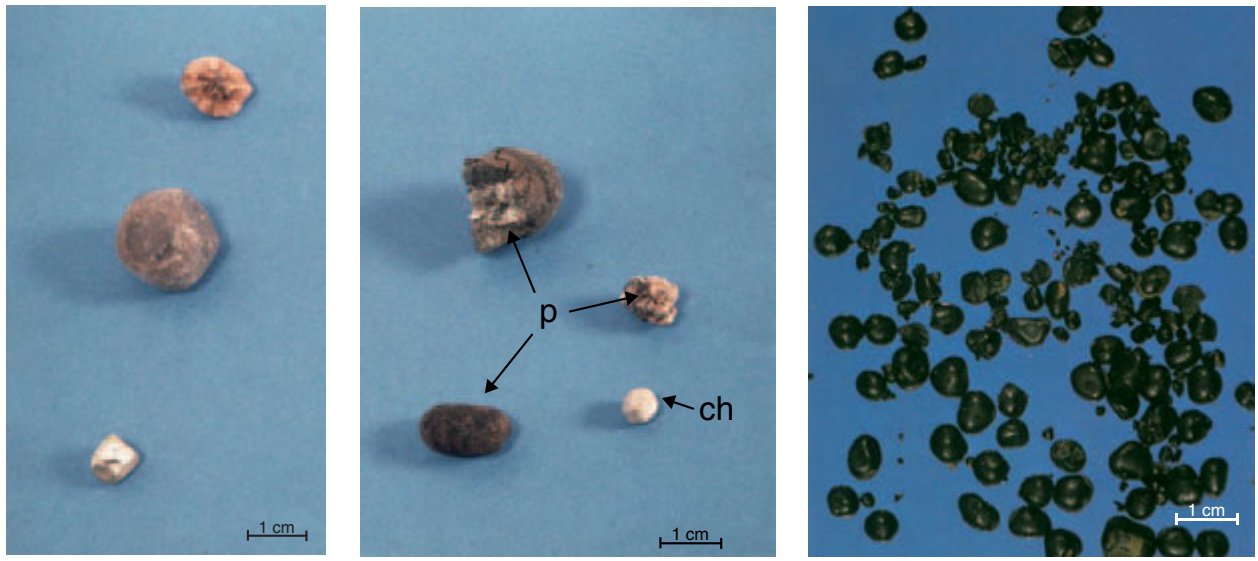


Fig. 34.1. (a) Two faceted cholesterol gallstones. The fragment above shows the concentric structure formed as layer upon layer of cholesterol crystals aggregate. (b) Stones removed from the common bile duct (ch, cholesterol gallstone; p, brown pigment stone). (c) Black pigment gallstones.

Factors in cholesterol gallstone formation [47, 49]

Three major factors determine the formation of cholesterol gallstones. These are: altered composition of hepatic bile, nucleation of cholesterol crystals and impaired gallbladder function (fig. 34.2). Hepatic bile supersaturated with cholesterol and with an increased proportion of deoxycholic acid favours stone formation.

Altered hepatic bile composition

Bile is 85–95% water. Cholesterol, which is insoluble in water and must be maintained in solution, is secreted from the canalicular membrane in unilamellar phospholipid *vesicles* (fig. 34.3). Whether cholesterol remains in solution depends upon the concentration of phospholipids and bile acids in bile, and also the type of phospholipid and bile acid present.

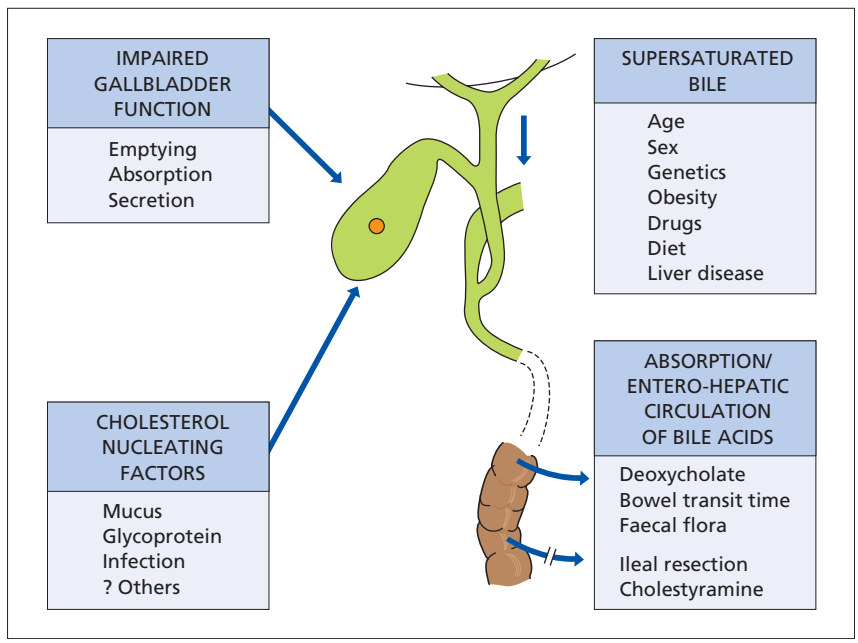


Fig. 34.2. Major factors in cholesterol gallstone formation are supersaturation of the bile with cholesterol, increased deoxycholate formation and absorption, cholesterol crystal nucleation and impaired gallbladder function.

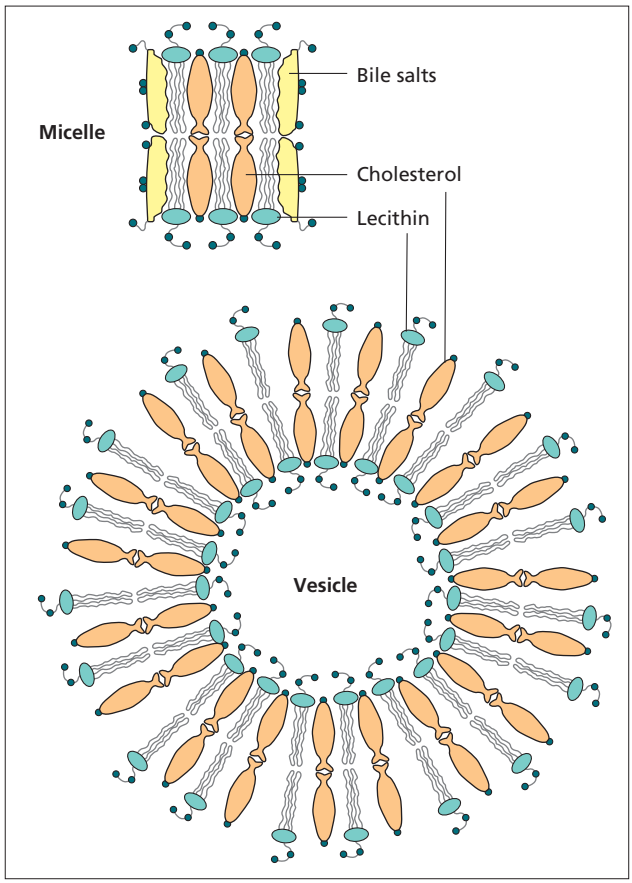


Fig. 34.3. Structure of mixed micelles and cholesterol/phospholipid vesicles.

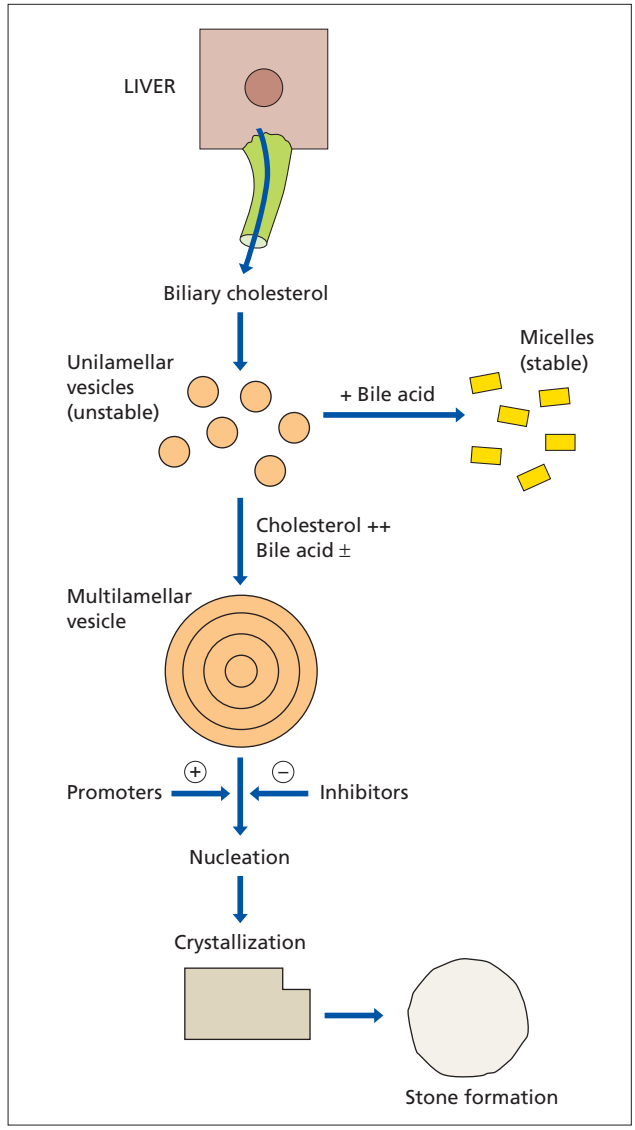


Fig. 34.4. Pathway for cholesterol crystallization in bile.

In hepatic bile unsaturated with cholesterol and containing sufficient bile acid, the vesicles are solubilized into mixed lipid *micelles*. These have a hydrophilic external surface and a hydrophobic interior. Cholesterol is incorporated into the hydrophobic interior. Phospholipids are inserted into the walls of the micelles so that they grow. These 'mixed micelles' are thus able to hold cholesterol in a stable thermodynamic state. This is the situation with a low cholesterol saturation index (derived from the molar ratio of cholesterol, bile acid and phospholipids).

When bile is supersaturated with cholesterol, or bile acid concentrations are low (a high cholesterol saturation index), the excess cholesterol cannot be transported in mixed micelles and unilamellar phospholipid vesicles remain (fig. 34.4). These are not stable and can aggregate. Large multilamellar vesicles form from which cholesterol crystals may *nucleate*. This process involves a sequence of complex events involving several different types of vesicle, micelle and disc [96]. Cholesterol precipitates in many forms including filaments, helices and tubules of non-hydrated cholesterol as well as characteristic plates of monohydrate cholesterol [145].

The type of bile acid present in bile influences gallstone formation. A higher proportion of deoxycholate is found in gallstone patients. This is a more hydrophobic bile salt and when secreted into bile extracts more cholesterol from the canalicular membrane increasing cholesterol saturation. It also accelerates cholesterol crystallization.

Deoxycholate is derived from dehydroxylation of cholic acid in the colon by faecal bacteria. There is an entero-hepatic circulation. The amount of deoxycholate present in the bile acid pool depends upon the large bowel transit time, which when increased (as in patients with acromegaly treated with octreotide) correlates with increased serum deoxycholic acid [196]. Other factors affect the amount of deoxycholate formed. Gallstone patients have significantly prolonged small bowel transit times [6] and increased bacterial dehydroxylating activity in faeces [203].

Thus many factors affect the concentration and type of bile acid and phospholipid in bile, and the amount of cholesterol. The process of gallstone formation is complex and many areas remain unclear [137]. The complexity is demonstrated by the finding that although cholesterol supersaturation is a prerequisite for gallstone formation, it does not alone explain the pathogenesis. Other factors must be important since bile supersaturated with cholesterol is frequently found in individuals *without* cholesterol gallstones [76].

Nevertheless, in most gallstone sufferers in the Western world, gallstone formation can be related to supersaturation of bile with cholesterol. There is hypersecretion of biliary cholesterol. Bile acid output is normal despite a reduced total body pool of bile acids, presumably because of a more rapid intra-hepatic cycling than normal. Increased biliary cholesterol leads to gallbladder hypomotility with increased mucin secretion by the epithelial lining. To what extent cholesterol hypersecretion influences other factors in gallstone formation is conjectural [3].

Cholesterol nucleation

Nucleation of cholesterol monohydrate crystals from multilamellar vesicles is a crucial step in the process leading to gallstone formation. The distinguishing feature between those who form gallstones and those who do not, is the ability of the bile to promote or inhibit nucleation rather than the degree of cholesterol supersaturation. The time taken for this process ('nucleation time') is significantly shorter in those with gallstones than in those without and in those with multiple as opposed to solitary stones [87]. The interactions resulting in nucleation are complex. Biliary protein concentration is increased in lithogenic bile [91, 178]. Proteins which accelerate nucleation (pro-nucleators) are gallbladder mucin [201], amino-peptidase-*N* [134], an α_1 acid glycoprotein [1], immunoglobulin and phospholipase C [137]. Some studies suggest that mucin gel rather than soluble biliary glycoproteins promote cholesterol crystallization [201]. Aspirin reduces mucus biosynthesis by gallbladder mucosa [152] which explains why this drug and other non-steroidal anti-inflammatory drugs inhibit gallstone formation [77].

Factors that slow nucleation (inhibitors) include apolipoprotein A1 and A2 [92] and a 120-kDa glycoprotein [136]. The interplay of pH and calcium iron concentration in stone formation *in vivo* remains to be established [142].

Ursodeoxycholic acid, as well as decreasing cholesterol saturation, also prolongs the nucleating time, which may have implications in the prevention of gallstone recurrence [145].

Fatty acid/bile acid conjugates inhibit cholesterol crystallization in bile experimentally [66] because of the cholesterol solubilizing activity of long-chain-free fatty acids. Conjugation with bile acid subserves hepatic uptake and biliary secretion.

Cholesterol gallstones have bilirubin at their centre, and a protein pigment complex might provide the surface for nucleation of cholesterol crystals from gallbladder bile.

Gallbladder function

The gallbladder fills with hepatic bile during fasting, concentrates the bile and injects the concentrated bile into the duodenum during a meal. It must be capable of emptying so as to clear itself of sludge and debris that might initiate stone formation, particularly in the patient with bile supersaturated with cholesterol and a short nucleation time.

Hepatic bile is stored in the gallbladder and concentrated by the absorption of Na^+, Cl^- and HCO_3^- with a nearly isotonic amount of water. Active transport of sodium and chloride by the mucosa is coupled to osmotic water absorption via intercellular and paracellular routes. The concentration of bile salts, bilirubin and cholesterol, for which the gallbladder wall is essentially impermeable, may rise 10-fold or more. The concentration of these constituents does not, however, rise in parallel and the cholesterol saturation index may decrease with concentration of bile because of the absorption of some cholesterol. The calcium carbonate saturation index also falls because of acidification [170].

Gallbladder contraction is under cholinergic and hormonal control. *Cholecystokinin* (CCK), derived from the intestine, contracts and empties the gallbladder and increases mucosal fluid secretion with dilution of gallbladder contents. *Atropine* reduces the contractile response of the gallbladder to CCK [79]. *Loxiglumide*, a selective CCK antagonist, inhibits both post-prandial gallbladder emptying and gallbladder contraction induced by the CCK analogue ceruletide. Other hormones found to have an influence on the gallbladder include *motilin* (stimulatory) and *somatostatin* (inhibitory).

The relationship between impaired gallbladder emptying and the increased incidence of gallstones in patients on long-term parenteral nutrition and in pregnant women has suggested that gallbladder stasis has a role in the formation of gallstones [191]. Studies of gallbladder motor function in patients with cholesterol stones have been conflicting. This probably relates to the technique used (ultrasound vs. scintigraphy) and patient variation. In general, patients with gallbladder stones have increased fasting and post-prandial gallbladder volumes [143]. Detailed analysis using simultaneous ultrasound and scintigraphy has challenged the conventional view of gallbladder function and shown a difference between normal and gallstone patients [85].

The concept of the gallbladder emptying after eating and then subsequently refilling to await the next meal appears oversimplified. Calculations from ultrasound and scintigraphic studies suggest continuous turnover of bile due to concurrent filling and emptying of the gallbladder. This turnover of gallbladder bile is reduced in patients with gallbladder disease [85] encouraging bile stasis and an environment in which nucleation and crystallization of cholesterol is likely to occur. Whether these changes are due to an alteration in gallbladder wall contractility and tone, or cystic duct resistance, is not clear.

Gallbladder muscle strips exposed to bile containing excess cholesterol have a reduced contractile response to CCK [12]. Reduced contraction may relate to a reduction in the number of receptors for CCK in the muscle of the gallbladder wall [204].

Cholesterol crystallization and the formation of biliary sludge predate gallstone formation and therefore whatever the mechanism may be, impaired gallbladder emptying will encourage stone formation.

Biliary sludge

Biliary sludge is a viscous suspension of a precipitate which includes cholesterol monohydrate crystals, calcium bilirubinate granules and other calcium salts/sludge [95]. It usually forms as a result of reduced gallbladder motility related to decreased food intake or parenteral nutrition. It may also occur when the sympathetic nerve supply is interrupted [182]. After formation, sludge disappears in 70% of patients [84]. Twenty per cent of patients develop complications of gallstones or acute cholecystitis. Whether treatment of sludge would reduce the incidence of complications is not known.

Role of infection

Although infection is thought to be of little importance in cholesterol stone formation, bacterial DNA is found in these stones [181]. Conceivably, bacteria might deconjugate bile salts, allowing their absorption and reducing cholesterol solubility.

Biliary infection plays a role in brown pigment stone formation, the majority containing bacteria on electron microscopy [105].

Age

There is a steady increase in gallstone prevalence with advancing years, probably due to the increased cholesterol content in bile. By age 75, 20% of men and 35% of women have gallstones. Clinical problems present most frequently between the age of 50 and 70.

Gallstones of both pigment and cholesterol type are reported in childhood.

Genetics

Relatives of patients with gallstones have an increased frequency of gallstones, irrespective of their age, weight or diet [162]. The increase is 2–4 times that expected.

The apoE4 allele of apolipoprotein E predisposes to cholesterol gallstones. The frequency of apoE4 is higher in patients undergoing cholecystectomy than those without gallstones [18]. The presence of apoE4 predicts rapid stone recurrence after extracorporeal shock-wave lithotripsy [144]. The mechanism is unclear although apolipoprotein E may play a role in dietary lipid absorption, transport and tissue distribution. ApoE4 is not related to the development of new gallstones during pregnancy [94].

In animals genes conferring susceptibility to gallstones are known and studies of human homologues are awaited [100].

Sex and oestrogens

Gallstones are twice as common in women as in men, and this is particularly so before the age of 50.

The incidence is higher in multiparous than in nulliparous women. Incomplete emptying of the gallbladder in late pregnancy leaves a large residual volume and thus retention of cholesterol crystals. Biliary sludge occurs frequently in pregnancy but is generally asymptomatic and disappears spontaneously after delivery in two-thirds [119]. In the post-partum period gallstones are present in 8–12% of women (nine times that in a matched group) [190]. One-third of those with a functional gallbladder are symptomatic. Small stones disappear spontaneously in 30%.

The bile becomes more lithogenic when women are placed on birth control pills [13]. Women on long-term oral contraceptives have a two-fold increased incidence of gallbladder disease over controls [20]. Postmenopausal women taking oestrogen-containing drugs have a highly significant (2.5 times) increase in gallbladder disease [21]. In men given oestrogen for prostatic carcinoma the bile becomes saturated with cholesterol and gallstones may form [73].

Obesity

This seems to be more common among gallstone sufferers than in the general population [111] and is a particular risk factor in women less than 50 years old. Obesity is associated with increased cholesterol synthesis [175]. There are no consistent changes in post-prandial gallbladder volume. 50% of markedly obese patients have gallstones at surgery.

Dieting (2100 kJ/day) can result in biliary sludge and the formation of symptomatic gallstones in obese individuals [107]. The addition of a small amount of fat in the

diet to maintain gallbladder emptying may reduce the risk of gallstone formation [63].

Gallstone formation during weight loss following gastric bypass surgery for obesity is prevented by giving ursodeoxycholic acid [180].

Dietary factors

In Western countries, gallstones have been linked to dietary fibre deficiency and a longer intestinal transit time [71]. This increases deoxycholic acid in bile, and renders it more lithogenic [196]. A diet low in carbohydrate and a shorter overnight fasting period protects against gallstones, as does a moderate alcohol intake in males [5]. Vegetarians get fewer gallstones irrespective of their tendency to be slim [141].

Increasing dietary cholesterol increases biliary cholesterol but there is no epidemiological or dietary data to link cholesterol intake with gallstones. Indeed, newly synthesized cholesterol is probably a more important source of biliary cholesterol.

Serum factors

The highest risk of gallstones (both cholesterol and pigment) is associated with low HDL levels and high triglyceride levels which may be more important than body mass [4, 185]. High serum cholesterol is not a determinant of gallstone risk.

Epidemiology (table 34.2)

In the Western world the prevalence of gallbladder stones is about 10%. In the United States more than 20 million people are estimated to have gallbladder disease. The prevalence in non-Hispanic white men is greater than in non-Hispanic black men (8.6 vs. 5.3%) [56]. The prevalence in women is twice that in men. Black Africans and the Eastern world are largely free of stones. The prevalence, however, is rising as lifestyles change. In Japan, the change from traditional to Western diets has been associated with a change from bilirubin to cholesterol gallstones.

American Indians have the highest known prevalence. This is related to supersaturation of the bile with cholesterol [199]. In Chile, the prevalence of gallstones is greatest (35%) in Mapuches. This relates to their strong Amerindian ancestry [126].

Cirrhosis of the liver

About 30% of patients with cirrhosis have gallstones. The risk of developing stones is most strongly associated with Child's grade C and alcoholic cirrhosis with a yearly incidence of about 5% [58]. The mechanisms are uncertain. All patients with hepato-cellular disease show a variable degree of haemolysis. Although bile acid secretion is reduced, the stones are usually of the black pigment type. Phospholipid and cholesterol secretion are also lowered so that the bile is not supersaturated.

Cholecystectomy and bile duct exploration are poorly tolerated, liver failure being frequently precipitated. Such operations should be done only for life-threatening complications of biliary tract disease, such as empyema or perforation. Endoscopic sphincterotomy is indicated for bile duct stones.

Table 34.2. Comparison of gallstone prevalence between countries and races [10]

Very high	High	Moderate	Low
North American Indians	USA whites	USA blacks	Greece
Chile	Great Britain	Japan	Egypt
Sweden	Norway		Zambia
Czechoslovakia	Australia		
	Italy		

Other factors

Diabetes mellitus is more frequent in individuals with gallstone disease [41]. Diabetics have a higher prevalence of gallstones (or a history of cholecystectomy) than non-diabetics [27]. Hyperinsulinaemia may play a role in gallstone formation [127, 157].

Ileal resection breaks the entero-hepatic circulation of bile salts, reduces the total bile salt pool and is followed by gallstone formation. The same is found in subtotal or total colectomy [117].

Gastrectomy increases the incidence of gallstones [82].

Long-term cholestyramine therapy increases bile salt loss with a reduced bile acid pool size and gallstone formation.

Cholesterol-lowering diets high in unsaturated fat and plant sterols but low in saturated fats and cholesterol result in increased gallstone formation.

Clofibrate enhances biliary cholesterol excretion and makes the bile more lithogenic.

Parenteral nutrition leads to a dilated, sluggish gallbladder containing stones.

Long-term *octreotide* treatment induces cholesterol-rich gallbladder stones in 13–60% of acromegalic patients. The bile is supersaturated with cholesterol, the nucleation time is abnormally rapid and gallbladder emptying is impaired. Serum deoxycholic acid is increased, due to a prolonged large bowel transit time [196].

Endoscopic sphincterotomy improves gallbladder emptying and decreases the lithogenicity of bile in

patients with gallstone disease [43]. Patients with gallbladder stones have significantly higher sphincter of Oddi tone [31]. Physical activity is associated with a decreased risk of cholecystectomy [102]. The mechanism is unclear.

Summary

The formation of cholesterol gallstones depends on the production of bile in which cholesterol cannot be maintained in solution. This is due to increased biliary secretion of cholesterol. Increased biliary deoxycholate, in part due to changes in intestinal transit, favours cholesterol crystallization. There are nucleation promoting and inhibiting factors in bile. Imbalance between these generates an environment favouring cholesterol crystallization and stone formation. The gallbladder acts as a reservoir allowing growth of the stone. Changes in motor and other functions of the gallbladder increase the risk of stone formation.

Pigment gallstones

This term is used for stones containing less than 30% cholesterol. There are two types: black and brown (table 34.1) [106].

Black pigment stones are largely composed of an insoluble bilirubin pigment polymer mixed with calcium phosphate and carbonate. There is no cholesterol. The mechanism of formation is not well understood, but supersaturation of bile with unconjugated bilirubin, changes in pH and calcium, and overproduction of an organic matrix (glycoprotein) play a role [106]. Overall, 20–30% of gallbladder stones are black. The incidence rises with age. They may pass into the bile duct. Black stones accompany chronic haemolysis, usually hereditary spherocytosis or sickle cell disease, and mechanical prostheses, for example heart valves, in the circulation. They show an increased prevalence with all forms of cirrhosis, particularly alcoholic [58]. Chemical dissolution therapy of pigment stones remains experimental [106]. Patients with ileal Crohn's disease may form pigment stones because of increased colonic absorption of bilirubin due to failure of ileal absorption of bile acid [23].

Brown pigment stones contain calcium bilirubinate, calcium palmitate, and stearate, as well as cholesterol. The bilirubinate is polymerized to a lesser extent than in black stones.

Brown stones are rare in the gallbladder. They form in the bile duct and are related to bile stasis and infected bile. They are usually radiolucent. Bacteria are present in more than 90%. Stone formation is related to the deconjugation of bilirubin diglucuronide by bacterial β-glucuronidase [106]. Insoluble unconjugated bilirubinate precipitates.

Brown pigment stones form above biliary strictures in sclerosing cholangitis and in the dilated segments of Caroli's disease. There is an association with juxtapapillary duodenal diverticula [161]. In Oriental countries, these stones are associated with parasitic infestations of the biliary tract such as *Clonorchis sinensis* and *Ascaris lumbricoides*. These stones are frequently intrahepatic. Removal from the common bile duct is by endoscopy sphincterotomy and from intra-hepatic ducts by lithotripsy techniques, percutaneous extraction or surgery.

Experimentally, stone and sludge formation is prevented by melatonin, a free radical scavenger [169]. Oxidative stress may lead to stones through promoting mucin–glycoprotein formation.

Radiology of gallstones (Chapter 32)

Only about 10% of gallstones are radio-opaque, compared with 90% of renal calculi (fig. 34.5). Visualization is due to the calcium content of the stone. Mixed stones may or may not have sufficient calcium to be rendered visible.

Gallstones are usually multiple and faceted, although a single, round stone may fill the whole gallbladder.

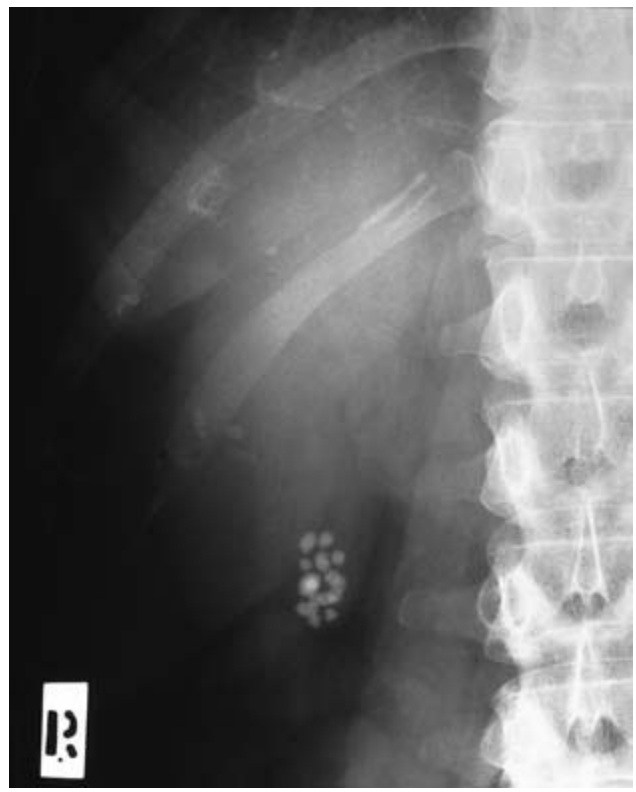


Fig. 34.5. Plain abdominal X-ray showing radio-opaque gallstones. Oral bile acid therapy is contraindicated.

They usually have a peripheral rim of calcium and a clear centre. Occasionally the structure is laminated due to alternate deposition of cholesterol and calcium bilirubinate. Rarely, gallstones contain gas which shows stellate, translucent areas (*Mercedes–Benz sign*).

Ultrasound is the technique of choice to detect gallbladder stones, having a diagnostic accuracy of 90–95%. They are seen as echogenic foci within the gallbladder and cast acoustic shadows (see fig. 32.3). Ultrasound may also show a thickened gallbladder wall (>5 mm) as well as other features of gallbladder disease such as a tender gallbladder (sonographic Murphy sign) and pericholecystic fluid. Non-visualization of the gallbladder also suggests disease.

With the availability of ultrasound, *oral cholecystography* is no longer used to look for gallbladder stones (Chapter 32). Because it is more successful than ultrasound in assessing the size and number of stones and the patency of the cystic duct, it does have a role in assessing patients for oral dissolution therapy and lithotripsy.

CT may show gallstones but is not the best test to assess their presence or absence. It has a role, however, in demonstrating the degree of calcification of cholesterol stones in patients who are being considered for non-surgical therapy with oral bile acid or shock-wave lithotripsy.

Imaging is basic to the diagnosis of gallstones and acute cholecystitis since there is not a good relationship between the 'characteristic' upper abdominal pain and the presence of gallbladder stones.

Natural history of gallstones (fig. 34.6)

Disease of the gallbladder is rare unless it complicates gallstones.

Gallstones can be dated from the atmospheric radiocarbon produced by nuclear bomb explosions. This suggests a time lag of about 12 years between initial stone formation and symptoms culminating in cholecystectomy [128].

Stones in the gallbladder are symptomless (*silent gallstones*) unless they migrate into the neck of the gallbladder or into the common bile duct.

Migration of a stone to the neck of the gallbladder causes *obstruction of the cystic duct* and a rise in gallbladder pressure. There is chemical irritation of the gallbladder mucosa by the retained bile, followed by bacterial invasion. According to the severity of the changes, *acute* or *chronic cholecystitis* results. Right upper quadrant pain radiating to the right shoulder is a suggestive feature [57]. However, the diagnosis of gallbladder disease related to stones depends upon the pattern of symptoms and signs together with ultrasound because of the overall lack of power of any specific symptom [14].

Acute cholecystitis may gradually subside or progress to acute gangrene and perforation of the gallbladder or to empyema. Death is, however, rare at the first presentation].

If the acute attack subsides spontaneously, chronic inflammatory changes persist with subsequent acute exacerbations.

Chronic cholecystitis can be silent. Usually, however, there are dyspeptic symptoms, and the patient may eventually come to cholecystectomy. This is usually curative, but may be followed by further episodes of pain, the *post-cholecystectomy syndrome*, or the unfortunate complication of *traumatic stricture of the bile duct*.

An internal biliary fistula follows the migration of a gallstone from the acutely, or more usually chronically, inflamed gallbladder into an adjacent viscus. The stone may be passed in the faeces, or impact in the intestine, causing *gallstone ileus*.

Gallstones entering the common bile duct may pass uneventfully into the duodenum, cause acute pancreatitis, or remain clinically silent in the duct. They may result in partial *obstruction to the common bile duct* with intermittent obstructive jaundice. Infection behind the obstruction is common with consequent *cholangitis*, and this may ascend to the liver, giving rise to abscesses.

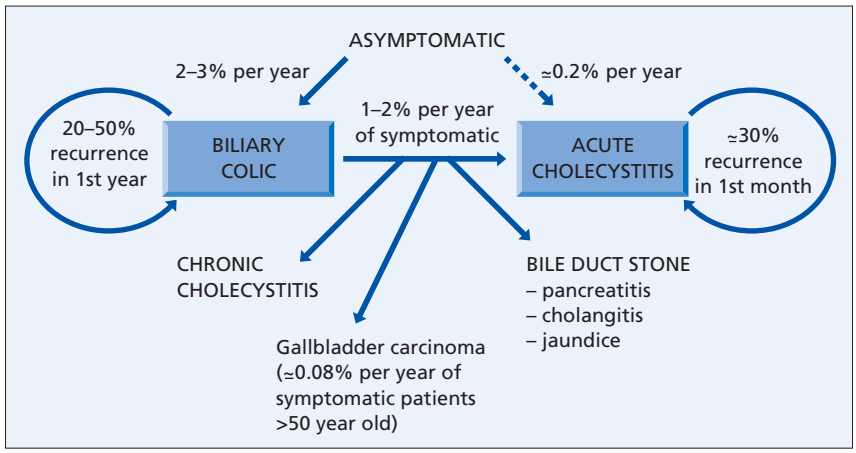


Fig. 34.6. The natural history of gallstones.

Silent gallstones

Gallbladder stones may be symptomless and diagnosed by chance by imaging or during investigation for some other condition. Physicians usually believe in leaving such stones well alone. The surgeon is more likely to intervene. Follow-up studies, however, show that only a small proportion develop symptoms. In one study only about 10% of patients with asymptomatic gallstones developed symptoms within 5 years and only 5% required surgery [115]. Only about half the patients with symptomatic gallstones come to cholecystectomy within 6 years of diagnosis. Patients with gallstones seem to tolerate their symptoms for long periods of time, preferring this to cholecystectomy. If symptoms develop, they are unlikely to present as an emergency.

Prophylactic cholecystectomy should not be performed [149]. It should not be done to prevent gallbladder cancer, a tumour associated with gallstones, as the risk is small and less than that of cholecystectomy [44].

Treatment of gallstones in the gallbladder

Cholecystectomy

This removes the gallstones and the factory making them. About 500 000 cholecystectomies are performed yearly in the USA and this operation is a billion dollar industry.

Laparoscopic cholecystectomy, introduced in the late 1980s, has replaced open cholecystectomy in the majority of patients [130]. *Open cholecystectomy* is still required where the laparoscopic approach fails, or is not possible. Thus expertise is still needed for the open operation.

The mortality rate of elective open cholecystectomy is 0.03% in patients under 65 years and 0.5% in those over 65 [155]. It is a safe and effective treatment for gallstones. There is a higher risk in those needing common duct exploration and in elderly patients (over 75 years old) having emergency surgery, often with gallbladder perforation and biliary peritonitis. To prevent this, early elective surgery is recommended in patients with *symptomatic* gallstones, especially if elderly.

The operation demands adequate assistance, exposure, illumination and the facilities for operative cholangiography if necessary. This is performed only if clinical, radiological and operative findings predict that stones will be found in the common bile duct. If pre-operative features, for example abnormal liver function tests, suggest duct stones, MRCP or ERCP will already have been done, and a stone if present removed by sphincterotomy. When the common duct is explored at operation, choledochoscopy is useful and reduces the chance of overlooking common duct calculi.

Laparoscopic cholecystectomy [62]

Under general anaesthesia the abdominal cavity is insufflated with CO_2 and the laparoscope and operating channels inserted (fig. 34.7). Cystic duct and vessels to the gallbladder are carefully identified and clipped. Haemostasis is achieved by electrocautery or laser. The gallbladder is dissected from the gallbladder bed on the liver and removed whole. When necessary large stones are fragmented while they are still within the gallbladder to allow its delivery through the anterior abdominal wall.

Outcomes

Laparoscopic cholecystectomy is successful in about 95% of patients. In the remainder, the operation has to be

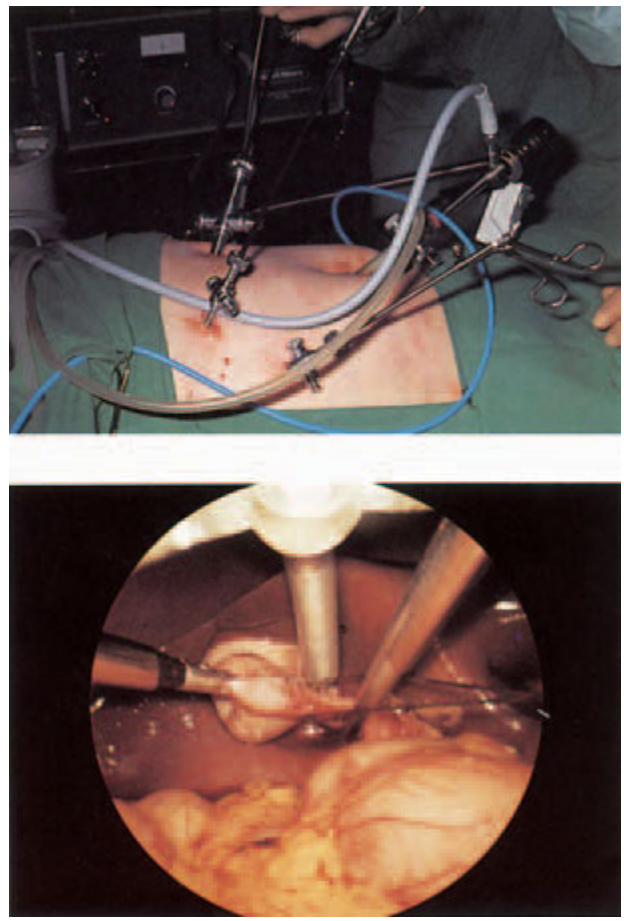


Fig. 34.7. Laparoscopic cholecystectomy. (a) Cannulae and endoscope in position. (b) Ligation of the cystic duct while the gallbladder is held [37].

converted to open cholecystectomy. This is more likely if there is acute cholecystitis particularly with empyema [35]. In these cases initial laparoscopic assessment is appropriate, and conversion to open operation made if indicated. In experienced hands laparoscopic cholecystectomy for acute and gangrenous cholecystitis is as safe and effective as open cholecystectomy although there is a moderately high conversion rate (16%) to the open procedure [93].

Most trials between laparoscopic and mini-cholecystectomy show that the laparoscopic approach has a significantly shorter hospital stay [112], duration of convalescence and delay before the patient returns to normal activities [7, 114] (fig. 34.8). Patients stay in hospital for 2–3 days and need about 2 weeks of convalescence, which compares with 7–14 days and up to 2 months, respectively, for conventional open cholecystectomy. However, similar results have been reported for laparoscopic and 'small incision cholecystectomy' [116]. Hospital costs are greater for the laparoscopic approach but despite this the advantages have led to it becoming the method of choice. Symptomatic improvement is similar for the two approaches [194].

Complications

The complication rate is 1.6–8%, including wound infection, bile duct injury (0.1–0.9%; mean 0.5%) [50, 113] and retained duct stones. The rate of bile duct damage falls with increasing operator experience, although duct injury may occur even with an experienced surgeon. The mortality rate is less than 0.1% and this compares favourably with open cholecystectomy. The post-operative mortality has been found to be higher during the first 10 laparoscopic cholecystectomies done by a surgeon [112]. Gallstones spilled into the peritoneal cavity may produce abscess [29, 150] and should be retrieved if possible.

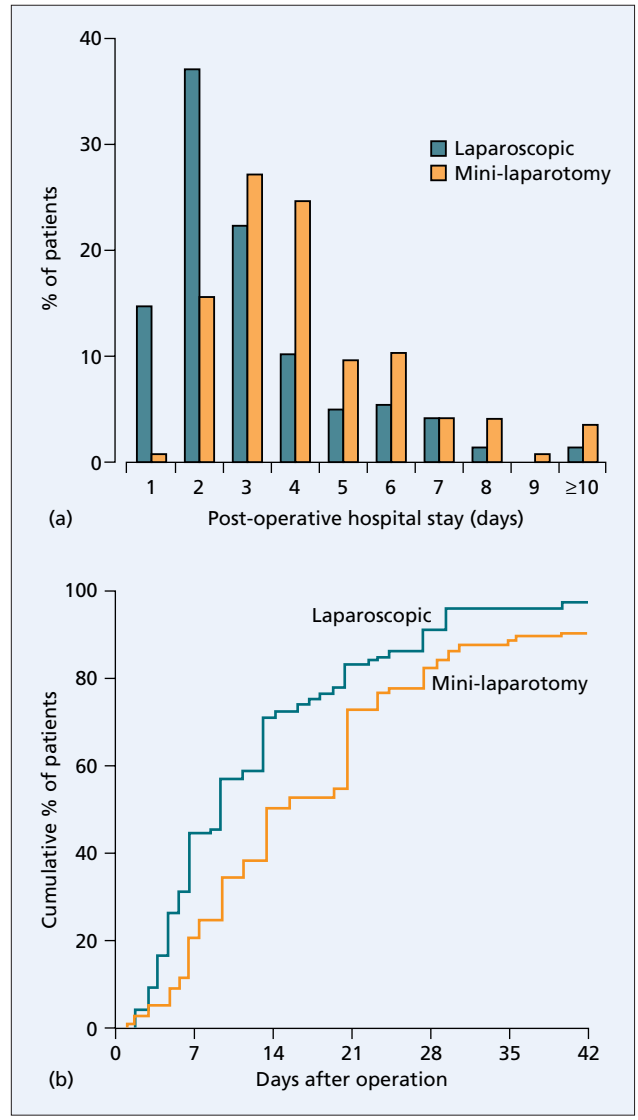


Fig. 34.8. Laparoscopic vs. mini-cholecystectomy. (a) Post-operative hospital stay. (b) Return to work in the home. (From [114] with permission.)

Cholangiography

10–15% of patients having cholecystectomy have common duct stones. Pre-operative ERCP is appropriate for patients with criteria suggestive of a duct stone—recent jaundice, cholangitis, pancreatitis, abnormal liver function tests, or duct dilatation on ultrasound. The duct stone is removed after sphincterotomy. If clinical features suggesting a duct stone are equivocal, MRCP is appropriate. This approach should reduce the number of normal ERCPs done and ERCP-related complications.

The strategy used to define or exclude duct stones depends on local endoscopic expertise, which will change with time. Greater expertise allows reliance on laparoscopic surgery with post-operative ERCP as necessary (the present trend); lesser expertise favours preoperative ERCP followed by laparoscopic or open operation [177].

Intra-operative cholangiography at laparoscopic cholecystectomy needs experience. Some advocate its routine use to define bile duct anatomy, anomalies and stones, but this prevents only the minority of bile duct injuries [8].

Laparoscopic common bile duct exploration

In experienced hands duct stones can be removed in 90% of patients [125]. However, this technique is not widespread because of lack of expertise and the need for special equipment. Laparoscopic removal of common duct stones is as effective and safe as post-operative endoscopic sphincterotomy [153].

Treatment of bile duct injury

Injuries include bile leak from cystic duct or gallbladder bed, complete transection of the duct, and complete or partial stricture due to clips or damage during dissection. They carry a high personal, medical and financial cost [164]. Recognition at the time of initial surgery reduces subsequent hospitalization, outpatient care and costs. Optimal investigation and treatment depends upon a multidisciplinary approach between endoscopist, interventional radiologist and biliary surgeon [45]. Leaks can be successfully treated by endoscopic stenting [9, 16, 124]. Complete transection and complete stricture are best treated surgically [176]. Results are significantly better if patients are referred to and managed in a specialist biliary unit. Whether incomplete strictures are better managed endoscopically by stenting or by surgical operation [176] awaits study with longer follow-up.

Conclusions

The major advantage of laparoscopic cholecystectomy is that there is a reduction in post-operative pain, hospital stay and recovery time, allowing earlier return to work than after open cholecystectomy. The latter, however, is still needed in some patients so that the laparoscopic surgeon must be 'fully trained' in general biliary surgery—a problem if laparoscopic cholecystectomy becomes the standard approach in the future.

Non-surgical treatment of gallstones in the gallbladder

Dissolution therapy

The widespread availability and acceptance of laparoscopic cholecystectomy has markedly reduced the use of non-surgical treatments for gallbladder stones. However, a small group of patients remain where these approaches need to be considered.

Oral bile salts [80]

The total bile salt pool is reduced in gallstone patients. This finding led to successful studies of oral bile acid therapy to treat gallbladder stones. The mechanism, however, is not an increase in biliary bile acid but rather a reduction in biliary cholesterol. After chenodeoxycholic acid, intestinal absorption of cholesterol falls and hepatic cholesterol synthesis is suppressed. Ursodeoxycholic acid also decreases cholesterol absorption but in contrast only inhibits the normal compensatory increase in cholesterol biosynthesis. During treatment with these agents bile acid secretion into bile remains relatively unchanged, but because of the reduced cholesterol secretion bile is desaturated. Also, ursodeoxycholic acid prolongs nucleation time.

Indications

Oral bile acid therapy is usually reserved for patients unfit for or unwilling to undergo surgery. The patient must be compliant and prepared for at least 2 years of treatment. Symptoms must be mild to moderate and silent stones should not be treated. On cholecystography the stones must be radiolucent, preferably floating, and the cystic duct patent. Stones should be less than 15 mm in diameter. Best results are for stones less than 5 mm diameter.

Unfortunately no imaging technique accurately determines the composition of gallstones. Ultrasound is of little value in assessing stone solubility. CT is useful and, because of the expense of bile acid therapy, cost-effective in assessing stones. Stones with an attenuation value of less than 100 Hounsfield units (reflecting low calcium content) are more likely to dissolve [200].

Chenodeoxycholic acid

The dose is 12–15 mg/kg per day in the non-obese. The markedly obese have increased biliary cholesterol and so require 18–20 mg/kg per day. Diarrhoea is a side-effect and the dose should be increased gradually starting with 500 mg daily. A bedtime dose gives the maximum effect. Other side-effects include a dose-dependent rise in serum aspartate transaminase levels which usually subside. Values must be monitored monthly for 3 months, then at 6, 12, 18 and 24 months.

Ursodeoxycholic acid

This is derived from the Japanese white-collared bear. It is the the 7β epimer of chenodeoxycholic acid. The dose is 8–10 mg/kg per day with more being needed if the patient is markedly obese. It dissolves about 20–30% of radiolucent gallstones completely [67] and does so more rapidly than chenodeoxycholic acid [55]. Side-effects are absent.

During treatment the stones may undergo surface calcification [11], but this is probably of little significance.

Combination therapy

A combination of chenodeoxycholic acid (6–8 mg/kg per day) and ursodeoxycholic acid (6–8 mg/kg per day) is more effective than ursodeoxycholic acid alone [122] and avoids the side-effects of the higher dose of chenodeoxycholic acid.

Results

The overall success rate for oral bile acid therapy is approximately 40%, rising to 60% with careful patient selection. Stones of 5 mm or less in diameter that float dissolve more quickly (80–90% complete dissolution by 12 months). Larger non-floating stones take longer or never disappear. Careful evaluation with CT to show the degree of calcification of the stone may avoid inappropriate bile acid therapy.

The effect of bile acid therapy on symptoms is variable. Biliary pain is less frequent in those patients on long-term ursodeoxycholic acid therapy [188]. Stone recurrence develops in 25–50% of patients at a rate of 10% per year. They are most likely in the first 2 years and unlikely after the first 3 years. Recurrence is higher in those with multiple rather than solitary stones.

Low-dose ursodeoxycholic acid (200–300 mg/day) may be effective in reducing the frequency of gallstone recurrence [78].

Conclusions

The disadvantages of oral bile acid therapy for gallbladder stones include restriction to non-calcified and, if possible, pure cholesterol stones. Dissolution is slow. Combined cheno- and ursodeoxycholic acid therapy appears to be the first choice. Therapy should be reserved for those who are symptomatic and will co-operate. They should have small, lucent gallstones in a functioning gallbladder and poor general health, including obesity, age or associated conditions preventing surgery.

Direct solvent dissolution

A percutaneous trans-hepatic catheter (7 French diameter) is inserted under real-time ultrasound guidance into the gallbladder and solvent is pumped in and out (fig. 34.9) [187]. The solvent used is *methyl tert-butyl ether* (MTBE), a gasoline additive of low viscosity and with power to dissolve cholesterol stones rapidly [187]. The solvent (3–7 ml) envelops the stone but should not overflow into the cystic and common bile duct. Computer-assisted pumps have been devised.

The gallstones are dissolved in 4–16 h and the catheter removed the same day or within 2–3 days in most cases. Side-effects include pain and nausea. The risk of bile leakage (which is small) can be reduced by plugging the trans-hepatic tract with gelfoam but cholecystectomy is necessary in 1–2% [72]. Toxic injury due to ether is rare [72].

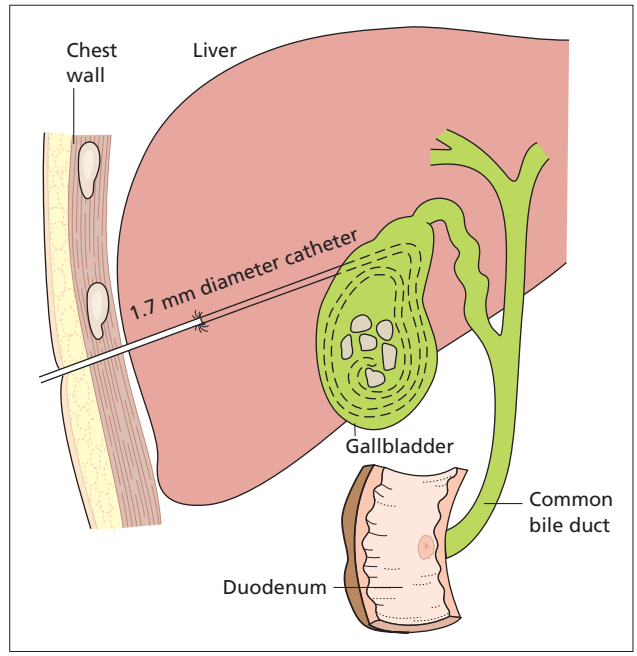


Fig. 34.9. Technique of percutaneous trans-hepatic gallbladder catheter placement for MTBE dissolution of cholesterol gallstones [187].

Shock-wave therapy [129]

Gallstones can be fragmented by shock waves generated extracorporeally by spark gap (electro-hydraulic), electro-magnetic or piezo-electric lithotripter machines using the same principle as that developed for kidney stones (fig. 34.10). By various methods the shock waves are directed towards a focal point. Ultrasound is usually used to compute the exact position of machine and patient such that the gallbladder stone lies at the point of highest energy (the focus). The waves pass through soft tissue with little absorption of energy but the solid stone absorbs the energy and is fragmented. Although the early prototypes required the patient to have a general anaesthetic, this is no longer necessary. Fragments, if small enough, may pass down the cystic and common bile duct into bowel. Oral bile acid therapy is given to dissolve those fragments remaining in the gallbladder, although when pulverization (fragmentation into very small sand-like particles) is achieved bile acid therapy is not necessary [129]. The gallbladder shows bruising and oedema after the shock waves but these are reversible.

Results

These vary from one machine, centre and protocol to another. Only 20–25% of patients referred satisfy the treatment criteria which included: three or fewer radiolucent gallbladder stones with a total diameter of less than 30 mm, in a functioning gallbladder (on cholecyst-

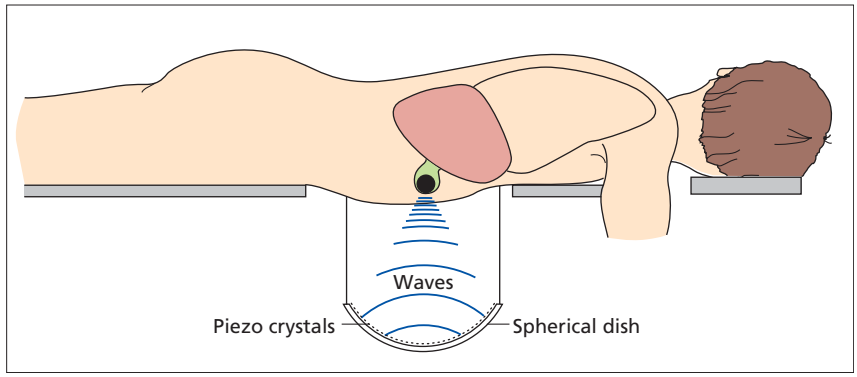


Fig. 34.10. Extracorporeal shock-wave lithotripsy (piezo-electric model). Patient lies face down and the shock waves are transmitted through a water-filled cushion to focus on a stone in the gallbladder.

ography), in a symptomatic patient who is otherwise healthy. The stones must be visible on ultrasound and are pin-pointed by this technique for the lithotripter. The shock-wave path should avoid any lung field or bone.

Shock waves successfully fragment stones in the majority of patients although with some machines, particularly the piezo-electric system, several sessions may be necessary. The latter system, however, carries a benefit of less patient discomfort and patients may be treated as outpatients. Adjuvant therapy with *oral bile acid* (ursodeoxycholic acid 10–12 mg/kg per day) has been found to increase the rate of stone/fragment disappearance, although with improved technology and successful pulverization this is not necessary. When used, adjuvant therapy is started a few weeks before lithotripsy and is continued for 3 months after complete clearance of the fragments.

Studies have shown overall complete clearance rates at 12 months of 70–90%. Protocols producing pulverization have greater success rates [129]. Stones recur in around 30% of patients after 5 years [158]. Two-thirds are symptomatic. Stone recurrence relates to incomplete gallbladder emptying and excessive deoxycholic acid in the bile acid pool [17]. As after cholecystectomy, non-specific abdominal symptoms (distension, flatulence, nausea) are not relieved despite successful lithotripsy.

Complications

Side-effects of treatment include biliary colic, skin petechiae, haematuria and pancreatitis (2%) due to fragments wedging in the low common bile duct.

Conclusions

The advent of laparoscopic cholecystectomy has reduced the contribution of this method to the treatment of gallbladder stones. Technical advances have widened the criteria that need to be satisfied for lithotripsy and improved results, but this technique remains appropriate for only a minority of patients.

Percutaneous cholecystolithotomy

Developed from percutaneous nephrolithotomy, this technique removes stones from the gallbladder transperitoneally. An oral cholecystogram is performed, timed to coincide with surgery. Under general anaesthesia the gallbladder is catheterized trans-peritoneally using fluoroscopy and ultrasound screening. The track is dilated to take a sheath wide enough to take the rigid operating cystoscope. The stones are removed after fragmentation by electro-hydraulic or laser lithotripsy if necessary. This technique also allows stones to be removed from a non-functioning gallbladder with catheterization being done under ultrasound. After the stones have been removed a balloon catheter is placed within the gallbladder and the balloon inflated so that there is drainage with little risk of leakage of bile. The catheter is removed after about 10 days.

Results

In a series of 113 patients, this method was successful in 90% with complications in 13%, but no mortality [28]. Stones recurred in 34% of patients at a mean follow-up of 26 months [46]. A similar recurrence rate is reported after laparoscopic cholecystotomy [86].

Conclusions

The procedure of choice for symptomatic gallstones is cholecystectomy. The laparoscopic method is now considered first and is acceptable to many patients who previously requested non-surgical treatment because of fear of open operation. For the patient who refuses any surgery, or who is judged unfit for general anaesthesia, oral bile acid therapy (with extra-corporeal shock-wave lithotripsy if available) is appropriate if the treatment criteria are met. Direct solvent dissolu-

tion therapy and percutaneous cholecystolithotomy are rarely used, and are best restricted to the expert enthusiastic operator.

Acute cholecystitis

Aetiology

In 96% of patients the cystic duct is obstructed by a gallstone. The imprisoned bile salts have a toxic action on the gallbladder wall. Lipids may penetrate the Rokitansky–Aschoff sinuses and exert an irritant reaction. The rise in pressure compresses blood vessels in the gallbladder wall; infarction and gangrene may follow.

Pancreatic enzymes may also cause acute cholecystitis, presumably by regurgitation into the biliary system when there is a common biliary and pancreatic channel. Such pancreatic regurgitation may account for some instances of acute cholecystitis developing in the absence of gallbladder stones.

Bacterial inflammation is an integral part of acute cholecystitis. Bacterial deconjugation of bile salts may produce toxic bile acids which can injure the mucosa.

Pathology

The gallbladder is greyish-red in colour with a lustreless surface. There are vascular adhesions to adjacent structures. The gallbladder is usually distended, but after previous inflammation the wall becomes thickened and contracted. It contains turbid fluid which may be frankly purulent (*empyema of the gallbladder*). A gallstone may be lodged in the neck.

Histology shows haemorrhage and moderate oedema reaching a peak by about the fourth day and diminishing by the seventh day. As the acute reaction subsides it is replaced by fibrosis.

Related lymph glands at the neck of the gallbladder and along the common bile duct are enlarged.

Bacteriology. Cultures of both gallbladder wall and bile usually show organisms of intestinal type, including anaerobes, in about three-quarters of cases.

Clinical features

These vary from those of mild inflammation to fulminating gangrene of the gallbladder wall. The acute attack is often an exacerbation of underlying chronic cholecystitis.

The sufferers are often obese, female and over 40, but no type, age or sex is immune.

Pain often occurs late at night or in the early morning, usually in the right upper abdomen or epigastrium and is referred to the angle of the right scapula, to the right shoulder [57], or rarely to the left side. It may simulate angina pectoris.

The pain usually rises to a plateau and can last 30–60 min without relief, unlike the short spasm of biliary colic. Attacks may be precipitated by late-night, heavy meals or fatty food, or even by such simple acts as abdominal palpation or yawning. The wretched, perspiring sufferer lies motionless in a curled-up posture, often with local heat applied to the abdomen.

Distension pain is due to the gallbladder contracting to overcome the blocked cystic duct. This visceral pain is deep seated, central and unaccompanied by muscular rigidity and superficial or deep tenderness.

Peritoneal pain is superficial with skin tenderness, hyperaesthesia and muscular rigidity. The fundus of the gallbladder is in apposition to the diaphragmatic peritoneum, which is supplied by the phrenic and last six intercostal nerves. Stimulation of the anterior branches produces right upper quadrant pain and of the posterior cutaneous branch leads to the characteristic right infrascapular pain.

The *spinal nerves* extend a short distance into the mesentery and gastro-hepatic ligament around the major bile ducts, and stimulation of these nerves is interpreted as pain and referred to the back and right upper quadrant. This explains the pain of stones in the common bile duct and of cholangitis.

Digestive system. Flatulence and nausea are common, but vomiting is unusual, unless there is a stone in the common bile duct.

Examination

The patient appears ill, with shallow, jerky respirations. The temperature rises with bacterial invasion. Jaundice usually indicates associated stones in the common bile duct.

The abdomen moves poorly. Spread of infection to peritoneal surfaces leads to gastric and duodenal distension. Hyperaesthesia is maximal in the 8th and 9th right thoracic segments, and the right upper abdominal muscles are rigid. The gallbladder is usually impalpable; occasionally a tender mass of gallbladder and adherent omentum may be felt. *Murphy's sign* is positive. The liver edge is tender.

The *leucocyte count* is raised to about 10×10^9/l, with a moderate increase in polymorphs. In the febrile patient blood cultures may be positive.

For the patient with acute abdominal pain of uncertain cause, a plain X-ray will be taken during the work-up, but if acute cholecystitis is suspected other imaging is of greater value.

Ultrasound (Chapter 32) may show gallstones, a thick-

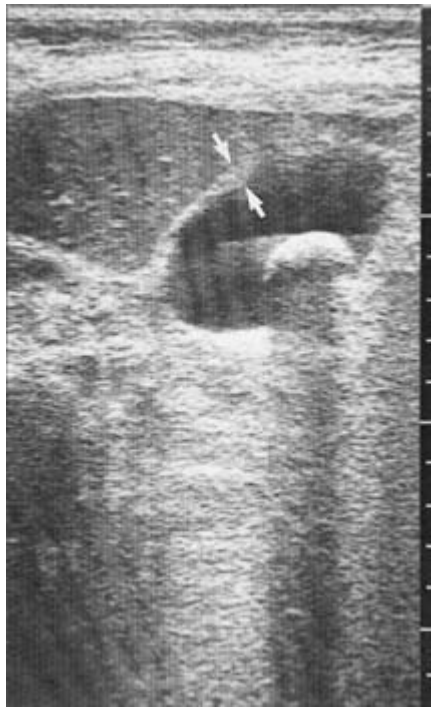


Fig. 34.11. Ultrasound scan of the gallbladder in a patient with right upper quadrant pain and fever. The gallbladder wall (arrowed) is irregularly thickened and a gallstone is present. There is a fluid–fluid level due to obstruction. Diagnosis: acute cholecystitis.

ened gallbladder wall (fig. 34.11), a sonographic Murphy's sign and pericholecystic fluid. *Cholescintigraphy* is also of value. Visualization of a completely normal gallbladder rules out acute cholecystitis whereas radioactivity in the common bile duct and intestine without filling of the gallbladder is reasonable evidence of an obstructed cystic duct (see fig. 32.9b). These two techniques have a similar accuracy in diagnosis of acute cholecystitis and the technique used will depend upon local facilities and expertise.

Differential diagnosis

Acute cholecystitis is liable to be confused with other causes of sudden pain and tenderness in the right hypochondrium. Below the diaphragm, acute retrocaecal appendicitis, intestinal obstruction, a perforated peptic ulcer or acute pancreatitis may produce similar clinical features.

Diaphragmatic pleurisy may be associated with tenderness in the gallbladder area and this is also characteristic of Bornholm disease. Myocardial infarction should always be considered.

Referred pain from muscular and spinal root lesions may cause similar pain.

Prognosis

Spontaneous recovery follows disimpaction of the stone in 85% of patients. However, the gallbladder remains shrunken, fibrotic, full of stones and non-functioning. Recurrent acute cholecystitis may follow—approximately a 30% chance over the next 3 months [148].

Rarely, acute cholecystitis proceeds rapidly to gangrene or empyema of the gallbladder, fistula formation, hepatic abscesses or even generalized peritonitis. The acute fulminating disease is becoming less common because of earlier antibiotic therapy and more frequent cholecystectomies for recurrent gallbladder symptoms.

Acute emergency surgery in the aged (over 75 years old) carries a bad prognosis with more frequent complications.

Treatment

General measures include bed rest, intravenous fluids, a light diet and relief of pain with pethidine (demerol) and buscopan.

Antibiotics

Antibiotics are given to treat septicaemia and prevent peritonitis and empyema. During the first 24 h, 30% of gallbladder cultures are positive. This rises to 80% after 72 h.

Common infecting organisms are *Escherichia coli*, *Streptococcus faecalis* and *Klebsiella*, often in combination. Anaerobes are present, if sought, and are usually found with aerobes. They include *Bacteroides* and *Clostridia*.

Antibiotic(s) should have a spectrum to cover the colonic type micro-organisms which are usually found with infection of the biliary tree. The choice depends upon the clinical picture. A cephalosporin is usually adequate for the stable patient with pain and mild fever. Patients with features of severe sepsis require broader spectrum antibiotics such as piperacillin/tazobactam combined if necessary with an aminoglycoside. These antibiotics are primarily given to treat septicaemia. They may penetrate and sterilize tissue but eradication of infection from the gallbladder should not be assumed, recurrent sepsis being possible later.

Surgery

Early cholecystectomy is preferred [108]. Morbidity, mortality and cost are less than with medical management followed by elective cholecystectomy 6–8 weeks later. If performed during the first 3 days, cholecystectomy has a mortality of about 0.5%. In around 50% of

patients the acute attack of cholecystitis will resolve without surgery. However, 20% have to be admitted later and may require urgent surgery. Emergency surgery is known to carry a higher risk than elective operation, particularly in elderly patients over 75 years old and in the diabetic patient where early elective cholecystectomy is preferred once symptoms have developed [75].

About 10% of patients with acute cholecystitis will have associated common duct stones. These are diagnosed by jaundice, dark urine and pale stools, fever, a raised serum bilirubin and alkaline phosphatase with operative findings of a large cystic and common bile duct with possible palpable stones. Pre-operative diagnosis based on laboratory tests and for scanning usually leads to endoscopic sphincterotomy and stone removal (see p. 619).

Percutaneous cholecystostomy

In the very severely ill patient, percutaneous transhepatic cholecystostomy is a safe and effective technique. It has a particular application in the elderly patient with acute complicated cholecystitis [193]. The method can either be done under ultrasound control or fluoroscopy after initial opacification using a skinny needle. A drainage catheter can be left to drain the gallbladder, or aspiration of the fluid and pus can be done without continued drainage [195]. Both methods are combined with intensive antibiotic therapy. Bile/pus is sent for culture. There is usually rapid relief of clinical symptoms. This technique may allow the patient to be brought to elective surgery in a better clinical condition. In the inoperable patient, after recovery, if a percutaneous catheter has been left in place, it can be removed and the patient treated conservatively, often without recurrence [193].

Empyema of the gallbladder

If the cystic duct remains blocked by a stone and infection sets in, empyema may develop. This can occur in cholangitic patients after endoscopic sphincterotomy, particularly if duct clearance is not achieved. It is also seen in patients with a malignant bile duct stricture (obstructing the cystic duct) after stent insertion.

Symptoms may be of an intra-abdominal abscess (fever, rigors, pain), although the elderly patient may appear relatively well.

Treatment is with antibiotics and surgery. There is a high post-operative rate of septic complications [30]. Percutaneous cholecystostomy is a valuable alternative.

Perforation of the gallbladder

Acute calculous cholecystitis may proceed to complete necrosis of the gallbladder wall and perforation. The gallstone may erode the necrotic wall; alternatively, dilated infected Rokitansky–Aschoff sinuses may provide a weak point for rupture.

Rupture usually takes place at the fundus which is the least well-vascularized part of the gallbladder. Rupture into the free peritoneal cavity is rare and, more usually, adhesions form between adjacent organs with local abscess formation. Rupture into adjacent viscera leads to internal biliary fistula.

The patient presents with nausea, right upper quadrant pain and vomiting. A right upper quadrant mass is palpable in 50%, and a similar number are febrile. The diagnosis is often overlooked. CT and ultrasound are of value in showing peritoneal fluid, abscess and gallstones.

There are three clinical types [156].

1 *Acute with bile peritonitis*. A history of gallbladder disease is rare. Associated systemic conditions include vascular insufficiency or immunodeficiency such as atherosclerosis, diabetes mellitus, collagen diseases, corticosteroid use or decompensated cirrhosis. The diagnosis should be suspected in any immunocompromised patient such as a patient with AIDS with an acute abdomen. Prognosis is poor with a mortality of about 30%. Treatment is by massive antibiotics and restoration of the fluid balance. The gangrenous gallbladder wall is removed or drained percutaneously or surgically. Any abscess must also be drained.

2 *Subacute with pericholecystic abscess*. These patients have chronic gallstone disease and the picture is intermediate between the acute and chronic types.

3 *Chronic* with cholecystenteric fistula formation, such as between the gallbladder and colon (see fig. 34.15).

Emphysematous cholecystitis

The term is used to denote infection of the gallbladder with gas-producing organisms (*Escherichia coli*, *Clostridium welchii*) or anaerobic streptococci. The primary lesion is occlusion of the cystic duct or cystic artery. Infection is secondary [184].

The condition classically affects male diabetics who develop features of severe, toxic, acute cholecystitis. An abdominal mass may be palpable.

Radiology. In the plain film the gallbladder may be seen as a sharply outlined pear-shaped gas shadow. Occasionally air may be seen infiltrating the wall and surrounding tissue. Gas is not apparent in the cystic duct which is blocked by a gallstone. In the erect position, a fluid level is seen in the gallbladder. However, plain abdominal X-ray may not show the characteristic changes. Ultrasound is diagnostic in around 50% of cases. CT may also show characteristic features.

Treatment. Antibiotics are given in large doses. Chole-

cystostomy and drainage are done either surgically or by the percutaneous method [206].

Chronic calculous cholecystitis

This is the commonest type of clinical gallbladder disease. The association of chronic cholecystitis with stones is almost constant.

Aetiological factors therefore include all those related to gallstones. The chronic inflammation may follow acute cholecystitis, but usually develops insidiously.

Pathology

The gallbladder is usually contracted with a thickened, sometimes calcified, wall. The contained bile is turbid with a sediment of biliary sludge. Stones are seen lying loosely embedded in the wall or in meshes of an organizing fibrotic network. One stone is usually lodged in the neck. The mucosa is ulcerated and scarred. Histologically the wall is thickened and congested with lymphocytic infiltration and occasionally complete destruction of the mucosa.

Clinical features

Chronic cholecystitis is difficult to diagnose because of the ill-defined symptoms. A familial incidence of gallstones, previous attacks of jaundice, multiparity and obesity form a suggestive background. Rarely, episodes of acute cholecystitis punctuate the course. The patient may experience episodes of biliary colic.

Abdominal distension or epigastric discomfort, especially after a fatty meal, may be temporarily relieved by belching. Nausea is common, but vomiting is unusual unless there are stones in the common bile duct. Apart from a constant dull ache in the right hypochondrium and epigastrium, pain may be experienced in the right scapular region, substernally or at the right shoulder. Post-prandial pain may be relieved by alkalis.

Local tenderness over the gallbladder and a positive Murphy sign are very suggestive.

Investigations

The temperature, leucocyte count, haemoglobin and erythrocyte sedimentation rate are within normal limits. A plain abdominal X-ray may show calcified gallstones. However, the imaging technique of first choice is ultrasound, which may show gallstones within a fibrosed gallbladder with a thickened wall. Non-visualization of the gallbladder is also a significant finding. CT scan may show gallstones but this technique is not appropriate in the diagnostic work-up of chronic cholecystitis.

Differential diagnosis

Fat intolerance, flatulence and post-prandial discomfort are common symptoms. Even if associated with imaging evidence of gallstones, the calculi are not necessarily responsible, for stones are frequently present in the symptom-free.

Other disorders producing a similar clinical picture must be excluded before cholecystectomy is advised, otherwise symptoms persist post-operatively. These include peptic ulceration, hiatus hernia, irritable bowel syndrome, chronic urinary tract infections and functional dyspepsias. A careful appraisal of the patient's psychological make-up is necessary.

Since approximately 10% of young to middle-aged adults have gallstones which can be shown by imaging, it is possible that symptomatic gallbladder disease may be over-diagnosed. Conversely, ultrasound is only about 95% accurate and symptomatic gallbladder disease may therefore sometimes be unrecognized.

Prognosis

This chronic disease is compatible with good life expectancy. However, once symptoms, particularly biliary colic, are experienced, the patients tend to remain symptomatic with about a 40% chance of recurrence within 2 years [186]. Gallbladder cancer is a rare, later development [198].

Treatment

Medical measures may be tried if the diagnosis is uncertain and a period of observation is desirable. This is especially so when indefinite symptoms are associated with a well-functioning gallbladder. The general condition of the patient may contraindicate surgery. The place of medical dissolution and shock-wave lithotripsy of radiolucent stones has already been discussed.

Obesity should be corrected. Fat intake will depend upon the functional state of the gallbladder: if it is non-functioning, a low-fat diet is advisable. Cooked fats are badly tolerated and should be avoided.

Cholecystectomy

This is indicated if the patient is symptomatic, particularly with repeated episodes of pain. If laparoscopic cholecystectomy is planned but there is a suspicion of a common duct calculus, pre-operative ultrasound is done followed if necessary by ERCP or MRCP and endoscopic sphincterotomy if a duct stone is shown. Laparoscopic removal of common duct stones is difficult, requires special equipment and is not yet within the capability of most operators. The same management applies if open

cholecystectomy is planned and common duct stones are suspected. Operative cholangiography, exploration of the bile duct and stone removal is the alternative, with insertion of a T-tube.

The T-tube is in position in the common bile duct for about 2 weeks. Culture of the bile is done, for postoperative complications are often due to sepsis. Cholangiography precedes removal of the T-tube.

Slight and transient increases in serum bilirubin and transaminase levels can be expected in the normal postoperative cholecystectomy course [69]. Greater increases indicate such complications as a retained duct stone or injury to the bile ducts.

Acalculous cholecystitis

Acute

About 5–10% of acute cholecystitis in adults and about 30% in children occurs in the absence of stones. The most frequent predisposing cause is an associated critical condition such as after major non-biliary surgery, multiple injuries, major burns, recent childbirth, severe sepsis, mechanical ventilation and parenteral nutrition.

The pathogenesis is unclear and probably multifactorial, but bile stasis (lack of gallbladder contraction), increased bile viscosity and lithogenicity, and gallbladder ischaemia are thought to play a role. Administration of opiates which increase sphincter of Oddi tone may also reduce gallbladder emptying. Shock impairs cystic arterial blood flow.

Clinical features should be those of acute calculous cholecystitis with fever, leucocytosis and right upper quadrant pain but diagnosis is often difficult because of the overall clinical state of the patient who may be intubated, ventilated and receiving narcotic analgesics.

There may be laboratory evidence of cholestasis with a raised bilirubin and alkaline phosphatase. Cholescintigraphy is reported to have a sensitivity of 60–90% for acalculous cholecystitis [88, 118]. Ultrasound and CT are complementary and useful in showing a thickened gallbladder wall (>4 mm), pericholecystic fluid or subserosal oedema without ascites, intramural gas, or a sloughed mucosal membrane. Because of the difficulties of diagnosis a high index of suspicion is needed, particularly in patients at risk. Gangrene and perforation of the gallbladder are common. The mortality is high, 41% in a recent series [88], often due to delayed diagnosis.

Treatment is emergency cholecystectomy. In the critically ill patient percutaneous cholecystostomy under ultrasound guidance may be life saving.

Chronic

This is a difficult diagnosis as the clinical condition resembles others, particularly the irritable bowel syndrome and the functional dyspepsias. Ultrasound scans and oral cholecystograms are normal. Nevertheless, chronic inflammation can be present in the gallbladder without gallstones and relief will follow cholecystectomy.

Cholescintigraphy with measurement of the gallbladder ejection factor 15 min after CCK infusion has been used to try and identify patients who would benefit from cholecystectomy. Normal individuals have an ejection fraction of 70% [34]. In those with a low ejection fraction (less than 40%) or who develop pain during the infusion, symptom relief after cholecystectomy is reported in between 70 and 90% of patients [103, 172, 174, 205]. However, decisions on management based on this test alone appear inappropriate and the result should be taken in the context of the other clinical features of the patient. In patients with acalculous gallbladder disease undergoing cholecystectomy, chronic cholecystitis, muscle hypertrophy and/or a narrowed cystic duct have been shown in patients in whom symptoms were relieved [205]. Management of this group of patients remains a clinical challenge.

Typhoid cholecystitis

Circulating typhoid bacilli are filtered by the liver and excreted in the bile. The biliary tract, however, is infected in only about 0.2% of patients with typhoid fever.

Acute typhoid cholecystitis is becoming very rare. Signs of acute cholecystitis appear at the end of the second week or even during convalescence, and are sometimes followed by perforation of the gallbladder.

Chronic typhoid fever cholecystitis and the typhoid carrier state. The typhoid carrier passes organisms in the faeces derived from a focus of infection in the gallbladder or biliary tract. Chronic typhoid cholecystitis is symptomless.

The carrier state is not cured by antibiotic therapy. Cholecystectomy is successful if there is not an associated infection of the biliary ducts. Chronic typhoid cholecystitis is not an important cause of gallstones, but carries an increased risk of gallbladder carcinoma [24].

Biliary carriers of other salmonellae have been reported and treated with ampicillin and cholecystectomy.

Acute cholecystitis in AIDS [25]

Four per cent of 904 patients with AIDS needed an abdominal operation over a 4-year period [147]. One-third of these cases had cholecystectomy for acute acalculous cholecystitis. This is thought to occur because of gallbladder stasis and increased bile lithogenicity in the critically ill patient, opportunistic pathogens, such as

cytomegalovirus (CMV) and cryptosporidium, or vascular insufficiency due to oedema or infection.

Patients present with fever, right upper quadrant pain and tenderness. The white cell count is often normal but with a left shift of neutrophils. Ultrasound shows features of acute cholecystitis (without stones).

Treatment is by cholecystectomy with a mortality of around 30% due to sepsis.

Other infections

Actinomycosis can very rarely involve the gallbladder, as may *Vibrio cholerae* [68] and *Leptospirosis* [197] which have been associated with acalculous cholecystitis. The pathological significance of *Helicobacter* spp. in the biliary tree is uncertain [59, 123].

Other associations

A *chemical cholecystitis* may follow long-term infusion of cytotoxic drugs, such as FUDR, into the hepatic artery.

Diseases involving the *cystic artery*, such as polyarteritis nodosa, may lead to cholecystitis [138].

The gallbladder may be involved in *Crohn's disease*.

Other gallbladder pathology

Cholesterolosis of the gallbladder

There is accumulation of cholesterol and triglyceride in the gallbladder wall. It is present in 50% of patients with gallstones, and 35% of symptomatic patients without stones having cholecystectomy for polyp or adenomyomatosis [160].

Cholesterol esters and other lipids are deposited in the submucosal and epithelial cells as small, yellow, lipid specks and, together with the intervening red bile-stained mucosa, give the appearance of a ripe strawberry. The deposits are at first found only on the mucosal ridges but later they extend into the troughs. As more lipid is deposited, it projects into the lumen as polyps which may become pedunculated. The change is confined to the gallbladder and never extends to the ducts.

The lipid is seen in reticulo-endothelial xanthoma cells of the mucosa, which is not inflamed. The cholesterolosis is related to the biliary, not blood, cholesterol concentration.

The aetiology is uncertain. The gallbladder mucosa may simply be taking up excess cholesterol from bile. Other possibilities are a defect in submucosal macrophages, impaired transport of cholesterol out of the mucosa [160], or increased cholesterol ester synthesis by the gallbladder mucosa [202].

There is controversy concerning the relation of cholesterolosis to symptoms. However, cholesterolosis may sometimes cause right upper quadrant pain and features causing confusion with the irritable bowel syndrome. Diagnosis is difficult. Oral cholecystography, preferably with CCK, shows filling defects in the gallbladder in only a third, and ultrasonography is usually negative.

Xanthogranulomatous cholecystitis

This is an uncommon inflammatory disease of the gallbladder characterized by a focal or diffuse destructive inflammatory process with lipid-laden macrophages. Macroscopically, areas of xanthogranulomatous cholecystitis appear as yellow masses within the wall of the gallbladder [154]. The gallbladder wall is invariably thickened and cholesterol or mixed gallstones are usually present.

The pathogenesis is uncertain, but an inflammatory response to extravasated bile, possibly from ruptured Rokitansky–Aschoff sinuses, is likely.

Symptoms often begin as an episode of acute cholecystitis and persist for up to 5 years. There is extension of yellow tissue into adjacent organs. Fistulae from gallbladder to skin or duodenum may develop [154]. At operation, carcinoma seems likely and frozen sections are usually required to make the differentiation.

Adenomyomatosis

This may affect the gallbladder wall profusely or locally. There is epithelial proliferation with muscular hypertrophy and mural diverticulae (Rokitansky–Aschoff sinuses), which may be seen as spots of contrast medium outside the lumen of the gallbladder on oral cholecystography after a fatty meal. Adenomyomatosis (*cholecystitis glandularis proliferans*) may cause chronic symptoms which are relieved by cholecystectomy.

Porcelain gallbladder

This rare condition (0.4–0.8% at cholecystectomy) is due to extensive calcification of the gallbladder wall. Circumferential calcification is seen on abdominal X-ray or CT. Ultrasound is helpful in showing the extent of involvement of the gallbladder wall. The condition is associated with a high frequency of cancer (12–61%) [171].

Post-cholecystectomy problems

Poor results after cholecystectomy can be expected in about one-third of patients. These may be due to wrong diagnosis. About 90–95% of those *with gallstones* are freed of symptoms or improved post-operatively. The absence of stones questions the original diagnosis. The

Table 34.3. Sphincter of Oddi dysfunction: classification

Group I (definite)	
Biliary-type pain	
Abnormal liver function tests (AST; alkaline phosphatase > 2 × normal) documented on two or more occasions	
Dilated common bile duct > 12 mm	
Delayed drainage of ERCP contrast > 45 min	Manometry unnecessary
Group II (presumptive)	
Biliary-type pain and one or two of other group I criteria	Manometry essential
Group III (possible)	
Biliary-type pain only. No other abnormalities	Manometry essential if intervention contemplated

patients may have been suffering from a psychosomatic or some other disorder including non-visceral pain [167]. Results of surgery are poor when done for vague symptoms such as abdominal bloating or dyspepsia, or in patients using psychiatric medication [110, 194]. A biliary cause is likely if stones are found at cholecystectomy and if a period of relief follows the operation. The colon and pancreas are common alternative culprits.

Symptoms may be related to technical difficulties at the time of surgery. These include traumatic *biliary stricture* (Chapter 35) and *residual calculi*.

Amputation neuromas can be demonstrated in some patients but removal offers no relief and this seems unlikely to be the cause of the symptoms.

Chronic pancreatitis, a common association of *choledocholithiasis*, may persist post-operatively.

US is the first test to image the bile duct. Depending on the result and the clinical features MRCP may be indicated. Despite all these efforts, ERCP is usually necessary. Residual calculi, stricture, ampullary stenosis, a cystic duct stump or normal appearances are significant findings.

Sphincter of Oddi dysfunction [34]

This has been an area of controversy but now appears to be a cause of post-cholecystectomy pain in some patients. Two forms exist.

Papillary stenosis is defined as narrowing of all or part of the sphincter of Oddi. There is fibrosis. It may follow injury due to stones [74], operative instrumentation, biliary infection or pancreatitis. There may be episodes of pain associated with abnormal liver function tests. On ERCP the bile duct is dilated and drains slowly. The basal sphincter tone is raised on manometry and is not reduced by smooth muscle relaxants. Endoscopic sphincterotomy is helpful [189].

Sphincter of Oddi (biliary) dyskinesia is a more difficult area. Biliary manometry shows a range of abnormalities including sphincter spasm, increased phasic contraction frequency (tachyoddia), paradoxical contraction response to CCK, and abnormal propagation of phasic waves.

There are clinical features (table 34.3) which are valuable in management decisions in patients with sphincter of Oddi dysfunction. Group I benefit from sphincterotomy in 90% of cases. In group II manometry is important. Patients with an elevated basal sphincter pressure have greater benefit from sphincterotomy than those with a normal pressure (91 vs. 42%) [64]. Studies continue in group III. Duodenal distension reproduces the symptoms in most patients [42]. Sphincterotomy in those with abnormal manometry may be beneficial in only 50% of patients [34]. Drug treatment with nitrates, nitroglycerin and calcium channel blockers which relax the sphincter are worth a trial, although the vasodilating side-effects limit their therapeutic use.

Gallstones in the common bile duct (choledocholithiasis)

The majority of stones in the common bile duct have migrated from the gallbladder and are associated with calculous cholecystitis. Migration is related to the size of the stone relative to the cystic and common bile duct. The stones grow in the common bile duct so causing biliary obstruction and facilitating the migration of further stones from the gallbladder.

Secondary stones that are not of gallbladder origin usually follow partial biliary obstruction due to such causes as residual calculus, traumatic stricture, sclerosing cholangitis or congenital biliary abnormalities. Infection may be the initial event. Stones are brown, single or multiple, oval and conforming to the long axis of the duct (fig. 34.1b).

Effects of common bile duct stones

Bile duct obstruction is usually partial and intermittent since the calculus exerts a ball-valve action at the lower

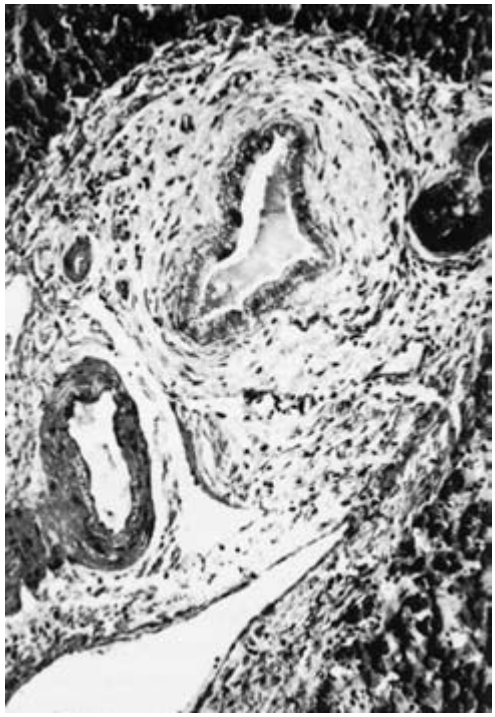


Fig. 34.12. Portal zone from operative liver biopsy of a patient with sclerosing cholangitis secondary to choledocholithiasis. The duct wall shows concentric fibrosis and the whole portal area is fibrosed. (PAS stain, ×126.)

end of the common bile duct. In the anicteric, hepatic histology is virtually normal. In the icteric, it shows cholestasis. In chronic cases, the bile ducts show concentric scarring (fig. 34.12) and eventually secondary sclerosing cholangitis and biliary cirrhosis.

Cholangitis. The stagnant bile is readily infected, probably from the duodenum. The bile becomes opaque and biliary sludge appears. Rarely the infection is more acute and the bile is purulent. The common bile duct is thickened and dilated, with desquamated or ulcerated mucosa, especially in the ampulla of Vater. The cholangitis may spread to the intra-hepatic bile ducts and, in severe and prolonged infections, cholangitic liver abscesses are seen. The cut section of liver shows cavities containing bile-stained pus, communicating with the bile ducts. *Escherichia coli* is the commonest infecting organism. Others include *Klebsiella*, *Streptococcus*, *Bacteroides* and *Clostridia*.

Acute or *chronic pancreatitis* may result from stones wedged in or passing through the ampulla of Vater.

Clinical syndromes

Choledocholithiasis may be silent and symptomless, discovered only by imaging at the time of a routine cholecystectomy for chronic calculous cholecystitis. Alternatively, the stones may cause an acute cholangitis with jaundice, pain and fever. In the elderly, they may present simply as mental and physical debility [33]. Residual stones detected early or late after cholecystectomy can be silent or symptomatic.

Acute jaundice and cholangitis

The classical picture is of an elderly, obese woman, with a previous history of flatulent indigestion, fat intolerance and mid-epigastric pain, presenting with jaundice, abdominal pain, chills and fever.

The *cholestatic jaundice* is usually mild, but may be deep or absent. Bile duct obstruction is rarely complete and the amount of pigment fluctuates in the stools.

Pain occurs in about three-quarters of patients, is usually severe, colicky and intermittent and needs analgesics for its relief. Sometimes it is a constant, sharp, severe pain. The site may be right upper quadrant or epigastric. It radiates to the back and to the right scapula. It is associated with vomiting. Palpation of the epigastrium is painful. *Fever* occurs in about a third of the patients, and there may be rigors. *Urine* is dark according to the degree of obstruction.

The *bile* shows a mixed growth of intestinal organisms, predominantly *E. coli*.

The *serum* has the changes of cholestasis with raised alkaline phosphatase, γ-glutamyl transpeptidase and conjugated bilirubin. In acute obstruction the transaminase levels may be briefly very high.

If a stone obstructs the main pancreatic duct, the serum amylase concentration may rise sharply and there may be clinical pancreatitis.

Haematological changes. The polymorph leucocyte count may be raised; the level depends on the acuteness and severity of the cholangitis.

Blood culture should be performed during the febrile period and the antibiotic sensitivity of any organism determined. Although the usual organisms encountered are the colonic ones, such as *E. coli* and anaerobic streptococci, other unusual ones such as *Pseudomonas* must be sought. Bile should be taken at ERCP for culture.

X-rays of the abdomen may show calculi in the gallbladder, or more medially and posteriorly in the common bile duct.

Ultrasound may show dilated intra-hepatic ducts although more often these are undilated. Stones in the lower end of the common bile duct are often missed by ultrasound.

Cholangiography, usually by the endoscopic route, confirms the presence of stones. Where the clinical features are equivocal, and ERCP is considered too invasive as a first test, MRCP is valuable in showing whether or not there is a duct stone.

Diagnosis

This is not difficult if jaundice follows biliary colic and febrile episodes. Too often, however, there is only vague indigestion, no fever, no gallbladder tenderness and an unhelpful white blood count. Alternatively, the patient may present with painless jaundice and sometimes itching. The condition must then be differentiated from other forms of cholestasis, including neoplastic, and acute viral hepatitis (see table 12.2). The bile in total biliary obstruction due to carcinoma is rarely infected and cholangitis is unusual unless there has been previous endoscopic cholangiography or stenting.

Residual common duct stones

Between 5 and 10% of patients having a cholecystectomy with exploration of the common bile duct will have retained stones. Calculi in the intra-hepatic ducts are especially liable to be overlooked. Residual bile duct calculi may be suspected if the patient experiences pain when the T-tube draining the bile duct is temporarily clamped. Cholangiography reveals filling defects. Sepsis and cholangitis occur post-operatively. In many instances, however, the residual bile duct calculi remain silent for many years.

Management of common duct stones

This depends on the clinical situation—emergency or elective—on the age and general condition of the patient and on the facilities and clinical expertise available. Antibiotics will be given for their systemic effect to treat or prevent septicaemia, and this is probably more relevant than their entry into bile. They are only temporarily effective in controlling the septicaemia if the bile duct is completely obstructed. Drainage is needed. Other measures include control of fluid and electrolyte balance and intravenous vitamin K, if the patient is jaundiced.

Acute obstructive suppurative cholangitis

Clinical features that identify this syndrome are fever, jaundice, pain, confusion and hypotension (*Reynold's pentad*) [151]. Renal failure and thrombocytopenia, as part of a disseminated intravascular coagulopathy, develop later. This situation is an emergency.

Laboratory tests should include blood cultures, as well as white cell and platelet count, prothrombin time and renal function tests. *Ultrasound* should show a dilated biliary system with or without stones. Even if ultrasound is negative, *endoscopic cholangiography* should be done if the clinical features suggest bile duct disease. MRCP is valuable if the clinical picture is equivocal.

Treatment is by intensive broad-spectrum antibiotics and emergency decompression of the biliary tract, as well as resuscitation with intravenous fluids. Antibiotics should cover Gram-negative colonic bacteria [179]. There are several alternatives but piperacillin/tazobactam is a good choice, with an aminoglycoside (gentamicin or netilmicin) if the clinical picture is life threatening. Aminoglycoside should only be used for a few days because of the risk of nephrotoxicity. Most cases are caused by common duct stones. ERCP is done with sphincterotomy and stone removal, if coagulation and anatomy permit. If not, then a naso-biliary tube is inserted.

The aim of any procedure is to *guarantee decompression of the biliary system*. The endoscopic approach is now accepted as the first choice, although there is still a mortality of around 5–10% [99, 104]. If this method fails, percutaneous trans-hepatic external bile drainage is the second choice. Surgical operation carries a greater mortality than non-surgical techniques, being between 16 and 40% [104]. After decompression there is usually rapid resolution of septicaemia and toxaemia. If not, drainage of the biliary system should be checked, or another source of sepsis sought, such as empyema of the gallbladder or liver abscess.

Antibiotics should be continued for 1 week, particularly if there are gallbladder stones, since empyema can be a complication of cholangitis.

Such severe cholangitis may also complicate malignant strictures after an interventional procedure, for example cholangiography without drainage, or previous endoprosthesis insertion. The management is the same: antibiotics and biliary decompression.

Acute cholangitis

The same principles govern the treatment of cholangitis of a lesser degree, but endoscopic therapy can be done electively if the patient's condition allows.

Malaise and fever are followed by shivering and sweating (*Charcot's intermittent biliary fever*). Not all features of Charcot's triad (fever, pain, jaundice) may be present. Laboratory tests include white cell count, renal and liver function tests and blood cultures. Ultrasound may show biliary tract disease.

The choice of antibiotic depends upon the state of the patient and local policy. A cephalosporin usually suffices [179]. Quinolones (e.g. ciprofloxacin) are an alternative. Cholangiography is timed according to the state of the patient and the response to antibiotics. Stones are removed after endoscopic sphincterotomy. If the stones cannot be extracted, bile drainage is provided by insertion of a naso-biliary tube or endoprosthesis (fig. 34.13). This management is necessary independent of whether the gallbladder is *in situ* or not. Subsequent decisions on cholecystectomy are discussed below.

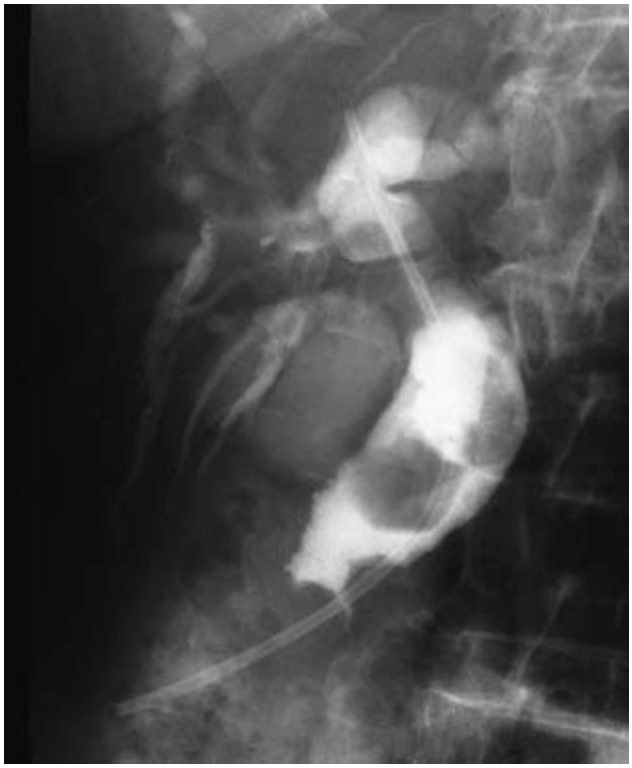


Fig. 34.13. ERCP in a patient with acute cholangitis. The common bile duct contains a large stone which could not be removed. A stent was inserted to provide drainage.

Multivariate analysis has identified seven features associated with a poor outcome in a mixed group of patients with cholangitis treated surgically and by non-surgical techniques. These were acute renal failure, cholangitis associated with liver abscess or liver cirrhosis, cholangitis secondary to high malignant biliary strictures or after percutaneous trans-hepatic cholangiography, female gender and age over 50 years [65].

Common duct stones without cholangitis

These are usually treated by elective endoscopic cholangiography, sphincterotomy and stone removal. Antibiotics are given to cover the procedure. Stone removal without sphincterotomy is possible, in most cases after balloon dilatation of the sphincter [15]. Pancreatitis occurs in 5–10%.

Patients with gallbladder *in situ*

Endoscopic sphincterotomy is definitive for residual post-cholecystectomy stones with only 10% having further biliary problems [70]—a similar outcome to surgical treatment.

If the gallbladder is still *in situ* and contains stones, subsequent management depends upon the age and clinical state of the patient. In the elderly, several studies have shown that, after endoscopic sphincterotomy, only 5–10% need cholecystectomy for gallbladder disease during 1–9 years follow-up [81]. However, a randomized trial of sphincterotomy alone versus open cholecystectomy with surgical removal of duct stones found that 15% of patients treated by sphincterotomy subsequently required cholecystectomy during a mean follow-up of 17 months [183]. This compared with 4% of the surgical group needing sphincterotomy after the cholecystectomy for a retained duct stone.

In an otherwise fit patient, the choices are endoscopic sphincterotomy (ES) followed by laparoscopic cholecystectomy, cholecystectomy with duct exploration, or ES without cholecystectomy unless gallbladder complications occur. The decision depends upon local expertise. In the patient who is unfit for surgery, ES without cholecystectomy is appropriate.

In younger patients—the age point is as yet undefined—cholecystectomy is generally recommended because of the concern that complications will occur in the long term.

Acute gallstone pancreatitis

Gallstones travelling down the bile duct may produce acute pancreatitis as they pass through the ampulla. The stones are usually small and pass into the faeces. The inflammation then subsides. Sometimes the stone does not pass out of the ampulla and pancreatitis persists and may be severe. Abnormal liver function tests, particularly transaminases, and ultrasound are the most useful tests to identify the patient with pancreatitis due to gallstones [40]. Early ERCP and sphincterotomy to remove the stone(s) has been shown to reduce complications and cholangitis in patients with severe, but not mild, pancreatitis [54, 166]. The optimal timing and selection of patients awaits further study.

Biliary sludge may also cause attacks of acute pancreatitis [101].

Large common duct stones

Stones greater than 15 mm in diameter are difficult or impossible to remove with a standard basket or balloon after sphincterotomy. Some may pass spontaneously. There are several options (table 34.4), which will depend upon local expertise and enthusiasm.

Mechanical lithotripsy may crush the stone but is limited by basket design and stone shape and size. With the latest baskets 90% success is possible [168].

The easiest method, particularly in the poor risk patient, is the insertion of an *endoprosthesis* (fig. 34.13), which may be long term, or temporary before surgical or

Table 34.4. Non-surgical treatment options for large common duct stones

Mechanical lithotripsy ('crushing basket')
Endoprosthesis
Extracorporeal shock-wave lithotripsy
Contact dissolution therapy
Electrohydraulic lithotripsy
Laser lithotripsy

endoscopic duct clearance. Early complications are seen in 12%, with a mortality of 4% [131]. Biliary colic, cholangitis and cholecystitis are late complications [139]. Stones may become smaller after stenting and may then be easier to remove at later ERCP [26].

Extracorporeal shock-wave lithotripsy can fragment 70–90% of large common duct stones with subsequent clearance of fragments through the sphincterotomy in the majority of patients, with less than a 1% 30-day mortality [52, 163].

Endoscopic electrohydraulic and laser lithotripsy remain experimental [133].

Trans T-tube tract removal of stones

Retained stones can be removed percutaneously along the T-tube tract in 77–96% of patients [135] with a complication rate of 2–4% (cholangitis, pancreatitis, tract perforation). The T-tube should have been in place for 4–5 weeks before stone removal to allow a fibrous tract to form. This method is complementary to endoscopic sphincterotomy, which with a T-tube in place is successful in about 75% [135]. The endoscopic approach may be favoured in the older patient, or when there is patient intolerance of the T-tube, or the size or path of the T-tube is not optimal.

Intra-hepatic gallstones

Stones in the intra-hepatic ducts are particularly common in certain parts of the world such as the Far East and Brazil where they are associated with parasitic infestation. Gallstones form in chronically obstructed bile ducts due to such conditions as anastomotic biliary–enteric stricture, primary sclerosing cholangitis or Caroli's disease. They are usually of brown pigment type. Secondary hepatic infection may result in multiple abscesses.

Percutaneous techniques using large-bore transhepatic catheters [132], combined with surgery if necessary, can clear stones in over 90% of patients, leaving the majority symptom-free [140]. The percutaneous transhepatic cholangioscopic approach can clear intra-hepatic stones in over 80% [83]. There is stone recurrence in 50% of patients with duct strictures.

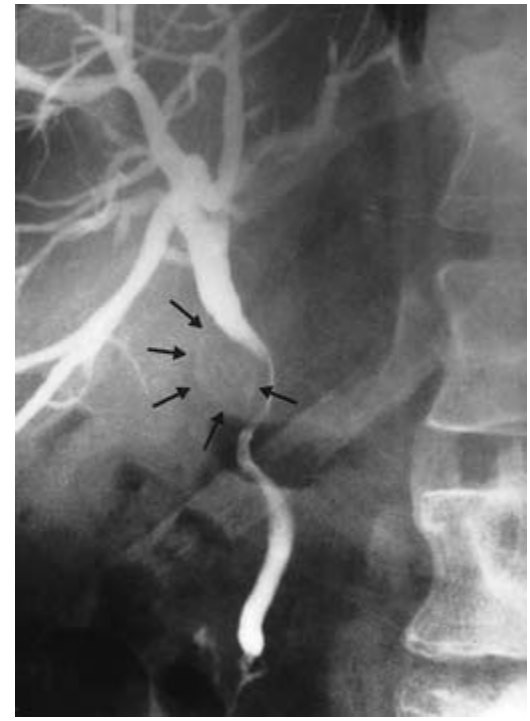


Fig. 34.14. Percutaneous cholangiography in Mirizzi's syndrome shows a large gallstone impacted in the cystic duct (arrowed) which has caused partial obstruction to the common hepatic duct.

Mirizzi's syndrome

Impaction of a gallstone in the cystic duct or neck of the gallbladder can cause partial common hepatic duct obstruction [60]. Recurrent cholangitis follows and the stone may erode into the common hepatic duct creating a single cavity [36].

Ultrasound shows dilated intra-hepatic and common hepatic ducts, but the cause may not been seen or correctly interpreted. Cholangiography shows mid duct obstruction (fig. 34.14). There may be the appearances of a stone, and from the outset it may be obvious that this is in cystic rather than bile duct. However, the appearances may initially suggest a common duct stone and only when attempts have failed to remove it does it become clear that the situation is more complicated. The operator must be alert to the possibility of a cystic duct stone and Mirizzi's syndrome. Endoscopic therapy is possible (stent insertion) to decompress the biliary system before surgery. Endoscopic stone retrieval is occasionally possible [53]. Surgery consists of removing the diseased gallbladder and the impacted stone.

A higher frequency of gallbladder carcinoma has been reported in Mirizzi's syndrome than with long-standing gallstone disease alone [146].

Biliary fistulae

External

These follow procedures such as cholecystotomy, transhepatic biliary drainage or T-tube choledochotomy. Very rarely they follow gallstones, carcinoma of the gallbladder or trauma.

Because of the sodium and bicarbonate content of bile, patients with external biliary fistulae run a risk of severe hyponatraemic acidosis and rise in blood urea levels.

Distal biliary obstruction contributes to the failure of the fistula to heal and the placement of an endoscopic or percutaneous biliary stent is followed by healing without the need for further difficult re-operations.

Internal

In 80% these are due to long-standing calculous cholecystitis. The inflamed gallbladder, containing stones, adheres and ruptures into a segment of the intestine, usually the duodenum and less often the colon (fig. 34.15). The ejected gallstones may be passed or cause intestinal obstruction (*gallstone ileus*), usually in the terminal ileum.

Post-operative biliary strictures, especially after multiple efforts at repair, may be complicated by fistula formation, usually hepatico-duodenal or hepatico-gastric. The fistulae are short, narrow and liable to block.

Biliary fistulae may also follow rupture of a chronic duodenal ulcer into the gallbladder or common bile duct. Fistulae may also develop between the colon and biliary tract in ulcerative colitis or Crohn's disease, especially if the patient is receiving corticosteroid therapy.

Clinical features

There is a long history of biliary disease. The fistula may be symptomless and, when the gallstones have discharged into the intestine successfully, the fistula closes. Such instances are often diagnosed only at the time of a later cholecystectomy.

About one-third give a history of jaundice or are jaundiced on admission. Pain may be absent or as severe as biliary colic. The features of cholangitis may be present. In cholecystocolic fistula the common bile duct may be filled with calculi, putrefying matter and faeces, which cause the severe cholangitis. Bile salts entering the colon produce severe diarrhoea. Weight loss is profound.

Radiological features

These include gas in the biliary tract and the presence of a gallstone in an unusual position. A barium meal, in the case of a cholecysto-duodenal fistula, or a barium enema, in the case of a cholecystocolic fistula, may fill the biliary tree. Small bowel distension may be noted.

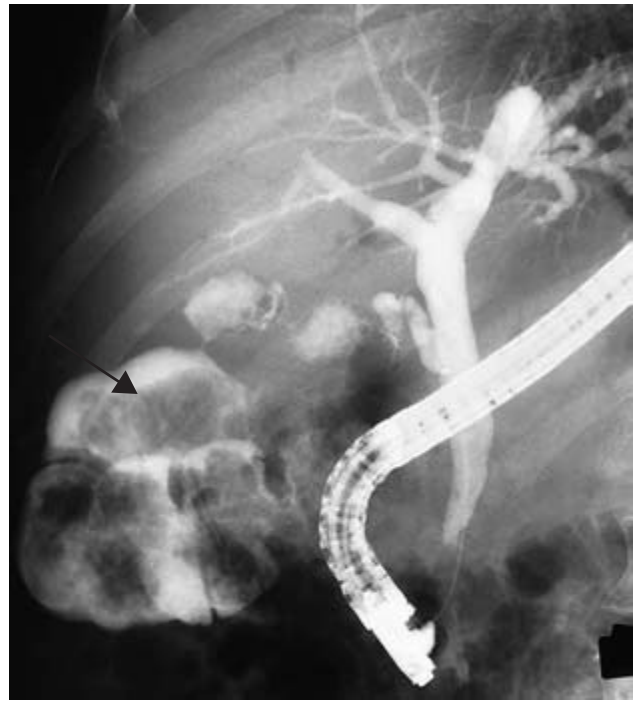


Fig. 34.15. ERCP showing a fistula between the gallbladder and colon (large arrow).

ERCP should be diagnostic (fig. 34.15).

Treatment

Fistulae due to gallbladder disease are treated surgically. Adherent viscera are separated and closed and cholecystectomy and drainage of the common bile duct performed. There is an operative mortality of around 10% [159].

Endoscopic treatment of common duct stones can result in closure of cholecystocolic and bronchobiliary fistulae [22, 121].

Gallstone ileus

A gallstone over 2.5 cm in diameter entering the intestine causes obstruction, usually of the ileum, less often of the duodeno-jejunal junction, duodenal bulb, pylorus or colon [32]. The impacted gallstone may excite an inflammatory reaction in the intestinal wall, or cause intussusception.

Gallstone ileus is very rare but is the cause of a quarter of all cases of non-strangulated intestinal obstruction in patients over 65 [98].

The patient is usually an elderly, afebrile female, possibly with a preceding history suggestive of chronic

cholecystitis. The onset is insidious, with nausea, occasional vomiting, colicky abdominal pain and a somewhat distended but flaccid abdomen. Complete intestinal obstruction leads to rapid physical deterioration.

A plain X-ray of the abdomen may reveal loops of distended bowel with fluid levels and possibly the obstructing stone. Gas may be seen in the biliary tract and gallbladder, indicating a biliary fistula.

The plain film on admission is diagnostic in about 50% of patients. Ultrasound, barium studies and CT provide diagnostic information in a further 25%. Leucocytosis is not usual unless there is associated cholangitis with pyrexia.

Pre-operative diagnosis is made in about 70% of cases [32].

Treatment

After the patient's general condition has been restored by intravenous fluids and electrolytes, the intestinal obstruction should be relieved surgically. This may be done by manual propulsion of the stone or by enterotomy. Whether fistula repair and cholecystectomy are also done at the time of the first operation to relieve intestinal obstruction depends upon the operative feasibility and the clinical state of the patient [32]. If not done at the initial operation, subsequent cholecystectomy is not mandatory [109]. Mortality is about 20%.

Haemobilia [19]

Haemorrhage into the biliary tract may follow trauma including surgical and needle liver biopsy, aneurysms of the hepatic artery or one of its branches, extra- or intrahepatic tumours of the biliary tract, hepatocellular carcinoma, gallstone disease, inflammation of the liver especially helminthic or pyogenic, and rarely varicose veins related to portal hypertension. Iatrogenic disease such as liver biopsy and percutaneous trans-hepatic cholangiography and bile drainage now accounts for 40%.

Clinical features are pain related to the passage of clots, jaundice and haematemesis and melaena. Minor episodes may be shown only by positive occult blood tests in faeces.

Diagnosis is suspected whenever upper gastrointestinal bleeding is associated with biliary colic, jaundice or a right upper quadrant mass or tenderness.

MRCP, ERCP or percutaneous cholangiography may show the clot in the ducts (fig. 34.16).

Treatment

Many resolve spontaneously. If bleeding continues angiography with embolization of a bleeding vessel if seen is indicated [38]. If clot obstructs the bile duct or gives colic, ERCP and drainage or sphincterotomy may be necessary [97].

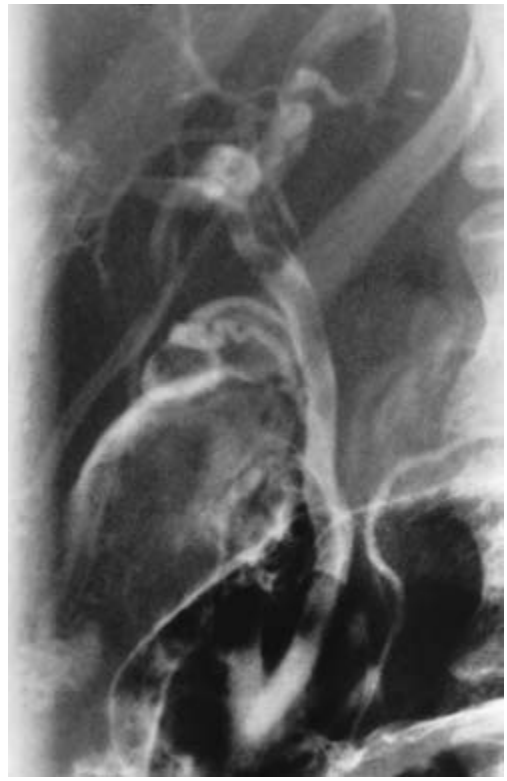


Fig. 34.16. ERCP in haemobilia shows filling defects, representing blood clot in the bile ducts.

Bile peritonitis

Aetiology

Post-cholecystectomy. Bile may leak from small bile channels between the gallbladder and liver or from an imperfectly ligated cystic duct. If the biliary pressure is raised, perhaps by a residual common duct stone or papillary stenosis, leakage is facilitated and the subsequent paraductal bile accumulation favours the development of biliary stricture.

Post-transplantation. Leakage of bile from the bile-duct anastomosis is a recognized complication of liver transplantation.

Rupture of the gallbladder. Empyema or gangrene of the gallbladder may lead to rupture and the formation of an abscess; this is localized by previous inflammatory adhesions.

Trauma. Crushing or gunshot wounds may involve the biliary tree. Needle biopsy of the liver or percutaneous cholangiography may rarely be complicated by puncture of the gallbladder or of a dilated intra-hepatic bile duct in a patient with deep cholestasis. Oozing of bile rarely follows operative liver biopsy.

Spontaneous. Biliary peritonitis may develop in patients

with prolonged, deep obstructive jaundice without demonstrable breach of the biliary tree. This is presumably due to bursting of minute superficial intra-hepatic bile ducts.

Common bile duct perforation is exceedingly rare. The factors concerned are similar to those for perforated gallbladder. They include increases of intra-ductal pressure, calculous erosion and necrosis of the duct wall secondary to thrombosis [89].

Spontaneous perforation of the extra-hepatic bile ducts is a rare cause of jaundice in infancy, the most common site being at the confluence of the cystic and common hepatic duct. Pathogenesis is unknown.

Clinical picture

This depends on whether the bile is localized or free in the peritoneal cavity, sterile or infected. Free rupture of bile into the peritoneal cavity causes severe shock. Due to the irritant effect of bile salts, large quantities of plasma are poured into the ascitic fluid. The onset is with excruciating, generalized, abdominal pain. Examination shows a shocked, pale, motionless patient, with low blood pressure and persistent tachycardia. There is board-like rigidity of the diffusely tender abdomen. Paralytic ileus is a frequent complication. Bile peritonitis should always be considered in any patient with unexplained intestinal obstruction. In a matter of hours secondary infection follows and the temperature rises while abdominal pain and tenderness persist.

Laboratory findings are non-contributory. There may be haemoconcentration. Abdominal paracentesis reveals bile, usually infected. Serum bilirubin rises and this is followed by an increase in alkaline phosphatase levels. Cholescintigraphy or cholangiography will show the leakage of bile. Bile drainage by the endoscopic or percutaneous route has improved the prognosis.

Treatment

Fluid replacement is imperative. Paralytic ileus may demand nasogastric intubation. Antibiotics are given to prevent secondary infection.

Rupture of the gallbladder is treated by cholecystectomy. Biliary leakage from the common bile duct can be treated by endoscopic stenting (with or without sphincterotomy) or naso-biliary drainage. If the leak does not seal over in 7–10 days, surgery may be necessary.

Association of gallstones with other diseases

Colorectal and other cancers

Population surveys show that gallstone sufferers do not seem at increased risk from other malignancies except perhaps that of the gallbladder [120] and extra-hepatic bile ducts [51].

Changes in faecal bile acids and cholesterol metabolites may promote colorectal oncogenesis [165]. Cholecystectomy may allow greater exposure of conjugated primary bile acids to anaerobic intestinal bacteria and so the increased production of carcinogens. Cholecystectomy and gallstones and colorectal cancer have been linked, although the association was not confirmed [2, 61]. The association may be related to increased diagnostic efforts in symptomatic post-cholecystectomy patients incidentally detecting early colorectal cancers.

Diabetes mellitus

About 30% of all diabetics over 20 years old have gallstones, compared with 11.6% of the general population of the same age. The older diabetic tends to be obese, and this may be the important factor in gallstone formation. Chronic pancreatitis and gallstones are associated and chronic pancreatitis can produce mild diabetes.

Patients with diabetes may have large, poorly contracting and poorly filling gallbladders [90]. A 'diabetic neurogenic gallbladder' syndrome has been postulated.

Patients with diabetes mellitus undergoing cholecystectomy, whether emergency or elective, have increased complications. These are probably related to associated cardiovascular or renal disease and to more advanced age.

References

1 Abei M, Nuutinen H, Kawczak P *et al*. Identification of human biliary alpha$_1$-acid glycoprotein as a cholesterol crystallization promoter. *Gastroenterology* 1994; **106**: 234.

2 Adami HO, Meirik O, Gustavsson S *et al*. Colorectal cancer after cholecystectomy: absence of risk increase within 11–14 years. *Gastroenterology* 1983; **85**: 859.

3 Apstein MD, Carey MC. Pathogenesis of cholesterol gallstones: a parsimonious hypothesis. *Eur. J. Clin. Invest*. 1996; **26**: 343.

4 Attili AF, Capocaccia R, Carulli N *et al*. Factors associated with gallstone disease in the MICOL experience. *Hepatology* 1997; **26**: 809.

5 Attili AF, Scafato E, Marchiolo R *et al*. Diet and gallstones in Italy: the cross-sectional MICOL results. *Hepatology* 1998; **27**: 1492.

6 Azzaroli F, Mazzella G, Mazelo P *et al*. Sluggish small bowel motility is involved in determining increased biliary deoxycholic acid in cholesterol gallstone patients. *Am. J. Gastroenterol*. 1999; **94**: 2453.

7 Barkun JS, Barkun AN, Sampalis JS *et al*. Randomised controlled trial of laparoscopic vs. mini cholecystectomy. *Lancet* 1992; **340**: 1116.

8 Barkun JS, Fried GM, Barkun AN *et al*. Cholecystectomy without operative cholangiography: implications for common bile duct injury and retained common bile duct stones. *Ann. Surg*. 1993; **218**: 371.

9 Barton JR, Russell RCG, Hatfield ARW. Management of bile leaks after laparoscopic cholecystectomy. *Br. J. Surg.* 1995; **82**: 980.

10 Bateson MC. Gallstone epidemiology. *Curr. Gastroenterol.* 1986; **5**: 120.

11 Bearcroft PW, Lomas DJ. Cholesterol crystallization in bile. *Gut* 1997; **41**: 138.

12 Behar J, Lee KY, Thompson WR *et al*. Gallbladder contraction in patients with pigment and cholesterol stones. *Gastroenterology* 1989; **97**: 1479.

13 Bennion LJ, Ginsberg RL, Garnick MB *et al*. Effects of oral contraceptives on the gallbladder bile of normal women. *N. Engl. J. Med.* 1976; **294**: 189.

14 Berger MY, van der Velden JJIM, Lijmer JG *et al*. Abdominal symptoms: do they predict gallstones? *Scand. J. Gastroenterol*. 2000; **35**: 70.

15 Bergman JJGHM, Rauws EAJ, Fockens P *et al*. Randomised trial of endoscopic balloon dilation vs. endoscopic sphincterotomy for removal of bileduct stones. *Lancet* 1997; **349**: 1124.

16 Bergman JJGHM, van den Brink JR, Rauws EAJ *et al*. Treatment of bile duct lesions after laparoscopic cholecystectomy. *Gut* 1996; **38**: 141.

17 Berr F, Mayer M, Sackmann MF *et al*. Pathogenic factors in early recurrence of cholesterol gallstones. *Gastroenterology* 1994; **106**: 215.

18 Bertomeu A, Ros E, Zambon D *et al*. Apolipoprotein E polymorphism and gallstones. *Gastroenterology* 1996; **111**: 1603.

19 Blochle C, Izbicki JR, Rashed MYT *et al*. Hemobilia: presentation, diagnosis and management. *Am. J. Gastroenterol*. 1994; **89**: 1537.

20 Boston Collaborative Drug Surveillance Program. Oral contraceptives and venous thromboembolic disease: surgically confirmed gall-bladder disease and breast tumours. *Lancet* 1973; **i**: 1399.

21 Boston Collaborative Drug Surveillance Program. Gallbladder disease, venous disorders, breast tumours: relation to oestrogens. *N. Engl. J. Med.* 1974; **290**: 15.

22 Brem H, Gibbons GD, Cobb G *et al*. The use of endoscopy to treat bronchobiliary fistula caused by choledocholithiasis. *Gastroenterology* 1990; **98**: 490.

23 Brink MA, Slors JFM, Keulemans YCA *et al*. Enterohepatic cycling of bilirubin: a putative mechanism for pigment gallstone formation in ileal Crohn's disease. *Gastroenterology* 1999; **116**: 1420.

24 Caygill CPJ, Hill MJ, Braddick M *et al*. Cancer mortality in chronic typhoid and paratyphoid carriers. *Lancet* 1994; **343**: 83.

25 Cello JP. AIDS-related biliary tract disease. *Gastrointest. Endosc. Clin. North Am.* 1998; **8**: 963.

26 Chan ACW, Ng EKW, Chung SCS *et al*. Common bile duct stones become smaller after endoscopic biliary stenting. *Endoscopy* 1998; **30**: 356.

27 Chapman BA, Wilson IR, Frampton CM *et al*. Prevalence of gallbladder disease in diabetes mellitus. *Dig. Dis. Sci.* 1996; **41**: 2222.

28 Cheslyn-Curtis S, Gillams AR, Russell RCG *et al*. Selection, management, and early outcome of 113 patients with symptomatic gall stones treated by percutaneous cholecystolithotomy. *Gut* 1992; **33**: 1253.

29 Chin PT, Boland S, Percy JP *et al*. 'Gallstone hip' and other sequelae of retained gallstones. *HBP Surg.* 1997; **10**: 165.

30 Chow WC, Ong CL, Png JC *et al*. Gall bladder empyema — another good reason for early cholecystectomy. *J. R. Coll. Surg. Edin.* 1993; **38**: 213.

31 Cicala M, Habib FI, Fiocca F *et al*. Increased sphincter of Oddi basal pressure in patients affected by gall stone disease: a role for biliary stasis and colicy pain? *Gut* 2001; **48**: 414.

32 Clavien P-A, Richon J, Burgan S *et al*. Gallstone ileus. *Br. J. Surg.* 1990; **77**: 737.

33 Cobden I, Lendrum R, Venables CLO *et al*. Gallstones presenting as mental and physical debility in the elderly. *Lancet* 1984; **i**: 1062.

34 Corazziari E, Jensen PF, Hogan WJ *et al*. Functional disorders of the biliary tract. *Gastroenterol. Int.* 1993; **6**: 129.

35 Cox MR, Wilson TG, Luck AJ *et al*. Laparoscopic cholecystectomy for acute inflammation of the gall bladder. *Ann. Surg.* 1993; **218**: 630.

36 Csendes A, Carlos Diaz J, Burdiles P *et al*. Mirizzi syndrome and cholecystobiliary fistula: a unifying classification. *Br. J. Surg.* 1989; **76**: 1139.

37 Cuschieri A, Berci G. *Laparoscopic Biliary Surgery*. Blackwell Scientific Publications, Oxford, 1990.

38 Czerniak A, Thompson JN, Hemingway AP *et al*. Hemobilia: a disease in evolution. *Arch. Surg.* 1988; **123**: 718.

39 Davidson BR, Neoptolemos JP, Carr-Locke DL. Endoscopic sphincterotomy for common bile duct calculi in patients with gallbladder *in situ* considered unfit for surgery. *Gut* 1988; **29**: 114.

40 Davidson BR, Neoptolemos JP, Leese T *et al*. Biochemical prediction of gallstones in acute pancreatitis: a prospective study of three systems. *Br. J. Surg.* 1988; **75**: 213.

41 De Santis A, Attili AF, Corradini SG *et al*. Gallstones and diabetes: a case-control study in a free-living population sample. *Hepatology* 1997; **25**: 787.

42 Desautels SG, Slivka A, Hutson WR *et al*. Postcholecystectomy pain syndrome: pathophysiology of abdominal pain in sphincter of Oddi type III. *Gastroenterology* 1999; **116**: 900.

43 Dhiman RK, Phanish MK, Chawla YK *et al*. Gallbladder motility and lithogenicity of bile in patients with choledocholithiasis after endoscopic sphincterotomy. *J. Hepatol.* 1997; **26**: 1300.

44 Diehl AK, Beral V. Cholecystectomy and changing mortality from gallbladder cancer. *Lancet* 1981; **i**: 187.

45 Doctor N, Dooley JS, Dick R *et al*. Multidisciplinary approach to biliary complications of laparoscopic cholecystectomy. *Br. J. Surg.* 1998; **85**: 627.

46 Donald JJ, Cheslyn-Curtis S, Gillams AR *et al*. Percutaneous cholecystolithotomy: is gall stone recurrence inevitable? *Gut* 1994; **35**: 692.

47 Donovan JM. Physical and metabolic factors in gallstone pathogenesis. *Gastroenterol. Clin. North Am.* 1994; **28**: 75.

48 Dowling RH. The enterohepatic circulation. *Gastroenterology* 1972; **62**: 122.

49 Dowling RH. Pathogenesis of gallstones. *Aliment. Pharmacol. Ther.* 2000; **14** (Suppl. 2): 39.

50 Dunn D, Fowler S, Nair R *et al*. Laparoscopic cholecystectomy in England and Wales: results of an audit by the Royal College of Surgeons of England. *Ann. R. Coll. Surg. Engl.* 1994; **76**: 269.

51 Ekborn A, Hsieh C, Yuen J *et al*. Risk of extrahepatic bile duct cancer after cholecystectomy. *Lancet* 1993; **342**: 1262.

52 Ellis RD, Jenkins AP, Thompson RP *et al*. Clearance of

refractory bile duct stones with extracorporeal shockwave lithotripsy. *Gut* 2000; **47**: 728.
53 England RE, Martin DF. Endoscopic management of Mirizzi's syndrome. *Gut* 1997; **40**: 272.
54 Enns R, Baillie J. The treatment of acute biliary pancreatitis. *Aliment. Pharmacol. Ther.* 1999; **11**: 1379.
55 Erlinger S, Go AL, Husson J-M *et al*. Franco-Belgian Cooperative Study of ursodeoxycholic acid in the medical dissolution of gallstones: a double-blind, randomized, dose–response study, and comparison with chenodeoxycholic acid. *Hepatology* 1984; **4**: 308.
56 Everhart JE, Khare M, Hill M *et al*. Prevalence and ethnic differences in gallbladder disease in the United States. *Gastroenterology* 1999; **117**: 632.
57 Festi D, Sottili S, Colecchia A *et al*. Clinical manifestations of gallstone disease: evidence from the multicentre Italian study on cholelithiasis (MICOL). *Hepatology* 1999; **30**: 839.
58 Fornari F, Imberti D, Squillante MM *et al*. Incidence of gallstones in a population of patients with cirrhosis. *J. Hepatol.* 1994; **20**: 797.
59 Fox JG, Dewhirst FE, Shen Z *et al*. Hepatic *Helicobacter* species identified in bile and gallbladder tissue from Chileans with chronic cholecystitis. *Gastroenterology* 1998; **114**: 755.
60 Freeman ME, Rose JL, Forsmark CE *et al*. Mirizzi syndrome: a rare cause of obstructive jaundice. *Dig. Dis.* 1999; **17**: 44.
61 Friedman GD, Goldhaber MK, Queensbury CP Jr. Cholecystectomy and large bowel cancer. *Lancet* 1987; **i**: 906.
62 Gadacz TR. Update on laparoscopic cholecystectomy, including a clinical pathway. *Surg. Clin. North Am.* 2000; **80**: 1127.
63 Gebhard RL, Prigge WF, Ansel HJ *et al*. The role of gallbladder emptying in gallstone formation during diet-induced rapid weight loss. *Hepatology* 1996; **24**: 544.
64 Geenen JE, Hogan WJ, Dodds WJ *et al*. The efficacy of endoscopic sphincterotomy after cholecystectomy in patients with sphincter of Oddi dysfunction. *N. Engl. J. Med.* 1989; **320**: 82.
65 Gigot JF, Leese T, Dereme T *et al*. Acute cholangitis: multivariate analysis of risk factors. *Ann. Surg.* 1989; **209**: 435.
66 Gilat T, Somjen GJ, Leikin-Frenkel A *et al*. Fatty acid bile acid conjugates (FABACs)—new molecules for the prevention of cholesterol crystallization in bile. *Gut* 2001; **48**: 75.
67 Gleeson D, Ruppin DC, Saunders A *et al*. Final outcome of ursodeoxycholic acid treatment in 126 patients with radiolucent gallstones. *Q. J. Med.* 1990; **279**: 711.
68 Gomez NA, Gutierrez J, Leon CJ. Acute acalculous cholecystitis due to *Vibrio cholerae*. *Lancet* 1994; **343**: 1156.
69 Halevy A, Gold-Deutch R, Negri M *et al*. Are elevated liver enzymes and bilirubin levels significant after laparoscopic cholecystectomy in the absence of bile duct injury? *Ann. Surg.* 1994; **219**: 362.
70 Hawes RH, Cotton PB, Vallon AG. Follow-up 6–11 years after duodenoscopic sphincterotomy for stones in patients with prior cholecystectomy. *Gastroenterology* 1990; **98**: 1008.
71 Heaton KW, Emmett PM, Symes CL *et al*. An explanation for gallstones in normal-weight women: slow intestinal transit. *Lancet* 1993; **341**: 8.
72 Hellstern A, Leuschner U, Benjaminov A *et al*. Dissolution of gallbladder stones with methyl tert-butyl ether and stone recurrence: a European study. *Dig. Dis. Sci.* 1998; **43**: 911.
73 Henriksson P, Einarsson K, Eriksson A *et al*. Estrogen-induced gallstone formation in males. *J. Clin. Invest.* 1989; **84**: 811.
74 Hernandez CA, Lerch MM. Sphincter stenosis and gallstone migration through the biliary tract. *Lancet* 1993; **341**: 1371.
75 Hickman MS, Schwesinger WH, Page CP. Acute cholecystitis in the diabetic. A case control study of outcome. *Arch. Surg.* 1988; **123**: 409.
76 Holzbach RT, Marsh M, Olszewski M *et al*. Cholesterol solubility in bile: evidence that supersaturated bile is frequent in healthy man. *J. Clin. Invest.* 1973; **52**: 1467.
77 Hood K, Gleeson D, Ruppin DC *et al*. Prevention of gallstone recurrence by nonsteroidal anti-inflammatory drugs. *Lancet* 1988; **ii**: 1223.
78 Hood KA, Gleeson D, Ruppin DC *et al*. Gall stone recurrence and its prevention: the British/Belgian gall stone study group's postdissolution trial. *Gut* 1993; **34**: 1277.
79 Hopman WPM, Jansen JBMJ, Rosenbusch G *et al*. Role of cholecystokinin and the cholinergic system in intestinal stimulation of gallbladder contraction in man. *J. Hepatol.* 1990; **11**: 261.
80 Howard DE, Fromm H. Nonsurgical management of gallstone disease. *Gastroenterol. Clin. North Am.* 1999; **28**: 133.
81 Ingoldby CJH, El-Saadi J, Hall RI *et al*. Late results of endoscopic sphincterotomy for bile duct stones in elderly patients with gallbladder *in situ*. *Gut* 1989; **30**: 1129.
82 Inoue K, Fuchigami A, Higashide S *et al*. Gallbladder sludge and stone formation in relation to contractile function after gastrectomy. *Ann. Surg.* 1992; **215**: 19.
83 Jan Y-Y, Chen M-F. Percutaneous trans-hepatic cholangioscopic lithotomy for hepatolithiasis: long-term results. *Gastrointest. Endosc.* 1995; **42**: 1.
84 Janowitz J, Kratzer W, Zemmler T *et al*. Gallbladder sludge: spontaneous course and incidence of complications in patients without stones. *Hepatology* 1994; **20**: 291.
85 Jazrawi RP, Pazzi P, Petroni ML *et al*. Postprandial gallbladder motor function: refilling and turnover of bile in health and cholelithiasis. *Gastroenterology* 1995; **109**: 582.
86 Jüngst D, Del Pozo R, Dolu MH *et al*. Rapid formation of cholesterol crystals in gallbladder bile is associated with stone recurrence after laparoscopic cholecystotomy. *Hepatology* 1997; **25**: 509.
87 Jüngst D, Lang T, von Ritter C *et al*. Cholesterol nucleation time in gallbladder bile of patients with solitary or multiple cholesterol gallstones. *Hepatology* 1992; **15**: 804.
88 Kalliafas S, Ziegler DW, Flancbaum L *et al*. Acute acalculous cholecystitis: incidence, risk factors, diagnosis, and outcome. *Am. Surg.* 1998; **64**: 471.
89 Kerstein MD, McSwain NE. Spontaneous rupture of the common bile duct. *Am. J. Gastroenterol.* 1985; **80**: 469.
90 Keshavarzian A, Dunne M, Iber FL. Gallbladder volume and emptying in insulin requiring male diabetics. *Dig. Dis. Sci.* 1987; **32**: 824.
91 Keulemans YCA, Mok KS, de Wit LTH *et al*. Hepatic bile vs. gallbladder bile: a comparison of protein and lipid concentration and composition in cholesterol gallstone patients. *Hepatology* 1998; **28**: 11.
92 Kibe A, Holzbach RT, LaRusso NF *et al*. Inhibition of cho-

lesterol crystal formation by apolipoproteins in supersaturated model bile. *Science* 1984; **225**: 514.
93 Kiviluoto T, Sirén J, Luukkonen P *et al*. Randomised trial of laparoscopic vs. open cholecystectomy for acute and gangrenous cholecystitis. *Lancet* 1998; **351**: 321.
94 Ko CW, Beresford SAA, Alderman B *et al*. Apolipoprotein E genotype and the risk of gallbladder disease in pregnancy. *Hepatology* 2000; **31**: 18.
95 Ko CW, Sekijima JH, Lee SP *et al*. Biliary sludge. *Ann. Intern. Med.* 1999; **130**: 301.
96 Konikoff FM, Danino D, Weihs D *et al*. Microstructural evolution of lipid aggregates in nucleating model and human biles visualized by cryogenic transmission electron microscopy. *Hepatology* 2000; **31**: 261.
97 Kroser J, Rothstein RD, Kochman ML. Endoscopic management of obstructive jaundice caused by haemobilia. *Gastrointest. Endosc.* 1996; **44**: 618.
98 Kurtz RJ, Heimann TM, Kurtz AB. Gallstone ileus: a diagnostic problem. *Am. J. Surg.* 1983; **146**: 344.
99 Lai ECS, Mok FPT, Tan ESY *et al*. Endoscopic biliary drainage for severe acute cholangitis. *N. Engl. J. Med.* 1992; **326**: 1582.
100 Lammert F, Carey MC, Paigen B. Chromosomal organization of candidate genes involved in cholesterol gallstone formation: a murine gallstone map. *Gastroenterology* 2001; **120**: 221.
101 Lee SP, Nicholls JF, Park HZ. Biliary sludge as a cause of acute pancreatitis. *N. Engl. J. Med.* 1992; **326**: 589.
102 Leitzmann MF, Rimm EB, Willett WC *et al*. Recreational physical activity and the risk of cholecystectomy in women. *N. Engl. J. Med.* 1999; **341**: 777.
103 Lennard TWJ, Farndon JR, Taylor RMR. Acalculous biliary pain: diagnosis and selection for cholecystectomy using the cholecystokinin test for pain reproduction. *Br. J. Surg.* 1984; **71**: 868.
104 Leung JWC, Sung JY, Chung SCS *et al*. Urgent endoscopic drainage for acute suppurative cholangitis. *Lancet* 1989; **i**: 1307.
105 Leung JWC, Sung JY, Costerton JW. Bacteriological and electron microscopy examination of brown pigment stones. *J. Clin. Microbiol.* 1989; **27**: 915.
106 Leuschner U, Güldütuna S, Hellstern A. Pathogenesis of pigment stones and medical treatment. *J. Gastroenterol. Hepatol.* 1994; **9**: 87.
107 Liddle RA, Goldstein RB, Saxton J. Gallstone formation during weight-reduction dieting. *Arch. Intern. Med.* 1989; **149**: 1750.
108 Lo C-M, Liu C-L, Fan S-T *et al*. Prospective randomized study of early vs. delayed laparoscopic cholecystectomy for acute cholecystitis. *Ann. Surg.* 1998; **227**: 461.
109 Lobo DN, Jobling JC, Balfour TW. Gallstone ileus: diagnostic pitfalls and therapeutic successes. *J. Clin. Gastroenterol.* 2000; **30**: 72.
110 Luman W, Adams WH, Nixon SN *et al*. Incidence of persistent symptoms after laparoscopic cholecystectomy: a prospective study. *Gut* 1996: **39**: 863.
111 Maclure KM, Hayes KC, Colditz GA *et al*. Weight, diet and the risk of symptomatic gallstones in middle-aged women. *N. Engl. J. Med.* 1989; **321**: 563.
112 McMahon AJ, Fischbacher CM, Frame SH *et al*. Impact of laparoscopic cholecystectomy: a population-based study. *Lancet* 2000; **356**: 1632.
113 McMahon AJ, Fullarton G, Baxter JN *et al*. Bile duct injury and bile leakage in laparoscopic cholecystectomy. *Br. J. Surg.* 1995; **82**: 307.
114 McMahon AJ, Russell IT, Baxter JN *et al*. Laparoscopic vs. minilaparotomy cholecystectomy: a randomised trial. *Lancet* 1994; **343**: 135.
115 McSherry CK, Ferstenberg H, Calhoun WF *et al*. The natural history of diagnosed gallstone disease in symptomatic and asymptomatic patients. *Ann. Surg.* 1985; **202**: 59.
116 Majeed AW, Troy G, Nicholl JP *et al*. A randomized, prospective, single-blind comparison of laparoscopic vs. small-incision cholecystectomy. *Lancet* 1996; **347**: 989.
117 Makino I, Chijiiwa K, Higashijima H *et al*. Rapid cholesterol nucleation time and cholesterol gall stone formation after subtotal or total colectomy in humans. *Gut* 1994; **35**: 1760.
118 Mariat G, Mahul P, Prev TN *et al*. Contribution of ultrasonography and cholescintigraphy to the diagnosis of acute acalculous cholecystitis in intensive care unit patients. *Intensive Care Med.* 2000; **26**: 1658.
119 Maringhini A, Ciambra M, Baccelliere P *et al*. Biliary sludge and gallstones in pregnancy: incidence, risk factors, and natural history. *Ann. Intern. Med.* 1993; **119**: 116.
120 Maringhini A, Moreau J, Melton J III *et al*. Gallstones, gallbladder cancer, and other gastrointestinal malignancies. An epidemiologic study in Rochester, Minnesota. *Ann. Intern. Med.* 1987; **107**: 30.
121 Marshall T, Kamalvand K, Cairns SR. Endoscopic treatment of biliary enteric fistula. *Br. Med. J.* 1990; **300**: 1176.
122 May GR, Sutherland LR, Shaffer EA. Efficacy of bile acid therapy for gallstone dissolution: a meta-analysis of randomised trials. *Aliment. Pharmacol. Ther.* 1993; **7**: 139.
123 Mendez-Sanchez N, Pichardo R, Gonzalez J *et al*. Lack of association between *Helicobacter* sp. colonization and gallstone disease. *J. Clin. Gastroenterol.* 2001; **32**: 138.
124 Mergener K, Strobel JC, Suhocki P *et al*. The role of ERCP in diagnosis and management of accessory bile duct leaks after cholecystectomy. *Gastrointest. Endosc.* 1999; **50**: 527.
125 Millat B, Fingerhut A, Deleuze A *et al*. Prospective evaluation in 121 consecutive unselected patients undergoing laparoscopic treatment of choledocholithiasis. *Br. J. Surg.* 1995; **82**: 1266.
126 Miquel JF, Covarrubias C, Villaroel L *et al*. Genetic epidemiology of cholesterol cholelithiasis among Chilean Hispanics, Amerindians and Maoris. *Gastroenterology* 1998; **115**: 937.
127 Misciagna G, Guerra V, Di Leo A *et al*. Insulin and gall stones: a population case control study in southern Italy. *Gut* 2000; **47**: 144.
128 Mok HYI, Druffel ERM, Rampone WH. Chronology of cholelithiasis. Dating gallstones from atmospheric radiocarbon produced by nuclear bomb explosions. *N. Engl. J. Med.* 1986; **344**: 1075.
129 Mulagha E, Fromm H. Extracorporeal shock wave lithotripsy of gallstones revisited: current status and future promises. *J. Gastroenterol. Hepatol.* 2000; **15**; 239.
130 National Institutes of Health Consensus Development Conference. Statement on gall stones and laparoscopic cholecystectomy. *Am. J. Surg.* 1993; **165**: 390.
131 Navicharen P, Rhodes M, Flook D *et al*. Endoscopic retrograde cholangiopancreatography (ERCP) and stent placement in the management of large common bile duct stones. *Aust. NZ J. Surg.* 1994; **64**: 840.

132 Neuhaus H. Intrahepatic stones: the percutaneous approach. *Can. J. Gastroenterol.* 1999; **13**: 467.

133 Neuhaus H, Hoffman W, Zillinger C *et al.* Laser lithotripsy of difficult bile duct stones under direct visual control. *Gut* 1993; **34**: 415.

134 Núñez L, Amigo L, Mingrone G *et al*. Biliary aminopeptidase-*N* and the cholesterol crystallization defect in cholelithiasis. *Gut* 1995; **37**: 422.

135 Nussinson E, Cairns SR, Vaira D *et al*. A 10-year single centre experience of percutaneous and endoscopic extraction of bile duct stones with T tube *in situ*. *Gut* 1991; **32**: 1040.

136 Ohya T, Schwarzendrube J, Busch N *et al*. Isolation of a human biliary glycoprotein inhibitor of cholesterol crystallization. *Gastroenterology* 1993; **104**: 527.

137 O'Leary DP. Biliary cholesterol transport and the nucleation defect in cholesterol gallstone formation. *J. Hepatol.* 1995; **22**: 239.

138 Parangi S, Oz MC, Blume RS *et al*. Hepatobiliary complications of polyarteritis nodosa. *Arch. Surg.* 1991; **126**: 909.

139 Peters R, Macmathuna P, Lombard M *et al*. Management of common bile duct stones with a biliary endoprosthesis. Report on 40 cases. *Gut* 1992; **33**: 1412.

140 Pitt HA, Venbrux AC, Coleman J *et al*. Intrahepatic stones: the transhepatic team approach. *Ann. Surg.* 1994; **219**: 527.

141 Pixley F, Wilson D, McPherson K *et al*. Effect of vegetarianism on development of gallstones in women. *Br. Med. J.* 1985; **291**: 11.

142 Plevris JN, Bouchier IAD. Defective acid base regulation by the gall bladder epithelium and its significance for gall stone formation. *Gut* 1995; **37**: 127.

143 Portincasa P, Di Ciaula A, Baldassarre G *et al*. Gallbladder motor function in gallstone patients: sonographic and *in vitro* studies on the role of gallstones, smooth muscle function and gallbladder wall inflammation. *J. Hepatol.* 1994; **21**: 430.

144 Portincasa P, van Erpecum KJ, van de Meeberg PC *et al*. Apolipoprotein E4 and genotype and gallbladder motility influence speed of gallstone clearance and risk of recurrence after extracorporeal shock-wave lithotripsy. *Hepatology* 1996; **24**: 580.

145 Portincasa P, van Erpecum KJ, Vanberge-Henegouwen GP *et al*. Cholesterol crystallization in bile. *Gut* 1997; **41**: 138.

146 Radaelli CA, Büchler MW, Schilling MK *et al.* High coincidence of Mirizzi syndrome and gallbladder carcinoma. *Surgery* 1997; **121**: 58.

147 Raja LA, Rothenberg RE, Odom JW *et al*. The incidence of intra-abdominal surgery in acquired immunodeficiency syndrome: a statistical review of 904 patients. *Surgery* 1989; **105**: 175.

148 Ransohoff DF, Gracie WA. Treatment of gallstones. *Ann. Intern. Med.* 1993; **119**: 606.

149 Ransohoff DF, Gracie WA, Wolfenson LB *et al*. Prophylactic cholecystectomy or expectant management for silent gallstones. *Ann. Intern. Med.* 1983; **99**: 199.

150 Rasmussen LB, Lundgren E, Osterberg J *et al*. Spilled gallstones: a complication of laparoscopic cholecystectomy. *Eur. J. Surg.* 1997; **163**: 147.

151 Reynolds BM, Dargan FL. Acute obstructive cholangitis: a distinct clinical syndrome. *Ann. Surg.* 1959: **150**: 299.

152 Rhodes M, Allen A, Dowling RH *et al.* Inhibition of human gall bladder mucus synthesis in patients undergoing cholecystectomy. *Gut* 1992; **33**: 1113.

153 Rhodes M, Sussman L, Cohen L *et al*. Randomised trial of laparoscopic exploration of common bile duct vs. postoperative endoscopic retrograde cholangiography for common bile duct stones. *Lancet* 1998; **351**: 159.

154 Roberts KM, Parsons MA. Xanthogranulomatous cholecystitis: clinico-pathological study of 13 cases. *J. Clin. Pathol.* 1987; **40**: 412.

155 Roslyn JJ, Binns GS, Hughes EFX *et al*. Open cholecystectomy: a contemporary analysis of 42 474 patients. *Ann. Surg.* 1993; **218**: 129.

156 Roslyn JJ, Thompson JE, Darvin H *et al*. Risk factors for gallbladder perforation. *Am. J. Gastroenterol.* 1987; **82**: 636.

157 Ruhl CE, Everhart JE. Association of diabetes, serum insulin, and C-peptide with gallbladder disease. *Hepatology* 2000; **31**: 299.

158 Sackmann M, Niller H, Klueppelberg U *et al*. Gallstone recurrence after shock-wave therapy. *Gastroenterology* 1994; **106**: 225.

159 Safaie-Shirazi S, Zike WL, Printen KJ. Spontaneous enterobiliary fistulas. *Surg. Gynecol. Obstet*. 1973; **137**: 769.

160 Sahlin S, Stahlberg D, Einarsson K. Cholesterol metabolism in liver and gallbladder mucosa of patients with cholesterolosis. *Hepatology* 1995; **21**: 1269.

161 Sandstad O, Osnes T, Skar V *et al*. Common bile duct stones are mainly brown and associated with duodenal diverticula. *Gut* 1994; **35**: 1464.

162 Sarin SK, Negi VS, Dewan R *et al*. High familial prevalence of gallstones in the first-degree relatives of gallstone patients. *Hepatology* 1995; **22**: 138.

163 Sauerbruch T, Holl J, Sackmann M *et al*. Fragmentation of bile duct stones by extracorporeal shock-wave lithotripsy: a five-year experience. *Hepatology* 1992; **15**: 208.

164 Savader SJ, Lillemoe KD, Prescott CA *et al*. Laparoscopic cholecystectomy-related bile duct injuries. *Ann. Surg.* 1997; **225**: 268.

165 Schottenfeld D, Winiwar SJ. Cholecystectomy and colorectal cancer. *Gastroenterology* 1983; **85**: 966.

166 Sharma VK, Howden CW. Metaanalysis of randomized controlled trials of endoscopic retrograde cholangiography and endoscopic sphincterotomy for the treatment of acute biliary pancreatitis. *Am. J. Gastroenterol.* 1999; **94**: 3211.

167 Sharpstone D, Colin-Jones DG. Chronic, nonvisceral abdominal pain. *Gut* 1994; **35**: 833.

168 Shaw MJ, Mackie RD, Moore JP *et al*. Result of a multicentre trial using a mechanical lithotripter for the treatment of large bile duct stones. *Am. J. Gastroenterol.* 1993; **88**: 730.

169 Shiesh S-C, Chen C-Y, Lin X-Z *et al*. Melatonin prevents pigment gallstone formation induced by bile duct ligation in guinea pigs. *Hepatology* 2000; **32**: 455.

170 Shiffman ML, Sugerman HJ, Moore EW. Human gallbladder mucosal function. *Gastroenterology* 1990; **99**: 1452.

171 Shimizu M, Miura J, Tanaka T *et al*. Porcelain gallbladder: relation between its type by ultrasound and incidence of cancer. *J. Clin. Gastroenterol.* 1989; **11**: 471.

172 Skipper K, Sligh S, Dunn E *et al*. Laparoscopic cholecystectomy for abnormal hepato-iminodiacetic acid scan: a worthwhile procedure. *Am. Surg.* 2000; **66**: 30.

173 Smit JJ, Schrinkel AH, Onde Elferink RP *et al*. Homozygous disruption of the murine mdr 2 P-glycoprotein gene leads to a complete absence of phospholipid from bile and to liver disease. *Cell* 1993; **75**: 451.

174 Smythe A, Majeed AW, Fitzhenry M *et al*. A requiem for the cholecystokinin provocation test? *Gut* 1998; **43**: 571.

175 Ståhlberg D, Rudling M, Angelin B *et al*. Hepatic cholesterol metabolism in human obesity. *Hepatology* 1997; **25**: 1447.

176 Stewart L, Way LW. Bile duct injuries during laparoscopic cholecystectomy: factors that influence the results of treatment. *Arch. Surg.* 1995; **130**: 1123.

177 Strasberg SM, Soper NJ. Management of choledocholithiasis in the laparoscopic era. *Gastroenterology* 1995; **109**: 320.

178 Strasberg SM, Toth JL, Gallinger S *et al*. High protein and total lipid concentration are associated with reduced metastability of bile in an early stage of cholesterol gallstone formation. *Gastroenterology* 1990; **98**: 739.

179 Subhani J, Kibbler C, Dooley JS. Antibiotic prophylaxis in ERCP. *Aliment. Pharmacol. Ther.* 1999; **13**: 103.

180 Sugerman HJ, Brewer WH, Schiffman ML *et al*. A multicentre, placebo-controlled, randomised, double-blind, prospective trial of prophylactic ursodiol for the prevention of gallstone formation following gastric-bypass-induced rapid weight loss. *Am. J. Surg.* 1995; **169**: 91.

181 Swidsinski A, Khilkin M, Pahlig H *et al*. Time dependent changes in the concentration and type of bacterial sequences found in cholesterol gallstones. *Hepatology* 1998; **27**: 662.

182 Tandon RK, Jain RK, Garg PK. Increased incidence of biliary sludge and normal gall bladder contractility in patients with high spinal cord injury. *Gut* 1997; **41**: 682.

183 Taragona EM, Perez Ayuso RM, Bordas JM *et al*. Randomised trial of endoscopic sphincterotomy with gallbladder left *in situ* vs. open surgery for common bileduct calculi in high-risk patients. *Lancet* 1996; **347**: 926.

184 Tellez G-S, Rodriquez-Montes JA, Fernandez de Lis S *et al*. Acute emphysematous cholecystitis. Report of 20 cases. *Hepatogastroenterology* 1999; **46**: 2144.

185 Thijs C, Knipschild P, Brombacher P. Serum lipids and gallstones: a case–control study. *Gastroenterology* 1990; **99**: 843.

186 Thistle JL, Cleary PA, Lachin JM *et al*. The natural history of untreated cholelithiasis during the National Cooperative Gallstone Study (NCGS). *Gastroenterology* 1982; **82**: 1197.

187 Thistle JL, May GR, Bender CE *et al*. Dissolution of cholesterol gallbladder stones by methyl *tert*-butyl ether administered by percutaneous transhepatic catheter. *N. Engl. J. Med.* 1989; **320**: 633.

188 Tomida S, Abel M, Yamaguchi T *et al*. Long-term ursodeoxycholic acid therapy is associated with reduced risk of biliary pain and acute cholecystitis in patients with gallbladder stones: a cohort analysis. *Hepatology* 1999; **30**: 6.

189 Toouli J, Roberts-Thomson IC, Kellow J *et al*. Manometry based randomised trial of endoscopic sphincterotomy for sphincter of Oddi dysfunction. *Gut* 2000; **46**: 98.

190 Valdivieso V, Covarrubias C, Siegel F *et al*. Pregnancy and cholelithiasis: pathogenesis and natural course of gallstones diagnosed in early puerperium. *Hepatology* 1993; **17**: 1.

191 Van Bodegraven AA, Böhmer CJM, Manoliu RA *et al*. Gallbladder contents and fasting gallbladder volumes during and after pregnancy. *Scand. J. Gastroenterol.* 1998; **33**: 993.

192 Van Erpecum KJ, Van Berge-Henegouwen GP. Gallstones: an intestinal disease? *Gut* 1999; **44**: 435.

193 Van Steenbergen W, Ponette E, Marchal G *et al*. Percutaneous transhepatic cholecystostomy for acute complicated cholecystitis in elderly patients. *Am. J. Gastroenterol.* 1990; **85**: 1363.

194 Vander Velpen GC, Shimi SM, Cuschieri A. Outcome after cholecystectomy for symptomatic gall stone disease and effect of surgical access: laparoscopic vs. open approach. *Gut* 1993; **34**: 1448.

195 Verbanck JJ, Demol JW, Ghillebert GL *et al*. Ultrasound-guided puncture of the gallbladder for acute cholecystitis. *Lancet* 1993; **341**: 1132.

196 Veysey MJ, Thomas LA, Mallet AI *et al*. Prolonged large bowel transit increases serum deoxycholic acid: a risk factor for octreotide induced gallstones. *Gut* 1999; **44**: 675.

197 Vilaichone RK, Mahachai V, Wilde H. Acute acalculous cholecystitis in leptospirosis. *J. Clin. Gastroenterol.* 1999; **29**: 280.

198 Vitetta L, Sali A, Little P *et al*. Gallstones and gall bladder carcinoma. *Aust. NZ J. Surg.* 2000; **70**: 667.

199 Vlahcevic ZR, Bell CC Jr, Gregory DH *et al*. Relationship of bile acid pool size to the formation of lithogenic bile in female Indians of the south-west. *Gastroenterology* 1972; **62**: 73.

200 Walters JRF, Hood KA, Gleeson D *et al*. Combination therapy with oral ursodeoxycholic and chenodeoxycholic acids: pretreatment computed tomography of the gall bladder improves gall stone dissolution efficacy. *Gut* 1992; **33**: 375.

201 Wang DQ, Cohen DE, Lammert F *et al*. No pathophysiologic relationship of soluble biliary proteins to cholesterol crystallization in human bile. *J. Lipid. Res.* 1999; **40**: 415.

202 Watanabe F, Hanai H, Kaneko E. Increased acylCoA-cholesterol ester acyltransferase activity in gallbladder mucosa in patients with gallbladder cholesterolosis. *Am. J. Gastroenterol.* 1998; **93**: 1518.

203 Wells JE, Berr F, Thomas LA *et al*. Isolation and characterization of cholic acid 7α-dehydroxylating fecal bacteria from cholesterol gallstone patients. *J. Hepatol.* 2000; **32**: 4.

204 Xiao ZL, Chen Q, Amaral J *et al*. CCK receptor dysfunction in muscle membranes from human gallbladder with cholesterol stones. *Am. J. Physiol.* 1999; **39**: G1401.

205 Yap L, Wycherley AG, Morphett AD *et al*. Acalculous biliary pain: cholecystectomy alleviates symptoms in patients with abnormal cholescintigraphy. *Gastroenterology* 1991; **101**: 786.

206 Zeebregts CJ, Wijffels RT, de Jong KP *et al*. Percutaneous drainage of emphysematous cholecystitis associated with pneumoperitoneum. *Hepatogastroenterology* 1999; **46**: 771.

Chapter 35
Benign Stricture of the Bile Ducts

Benign strictures of the biliary system are uncommon and usually follow surgery, in particular cholecystectomy, laparoscopic or open (table 35.1). They may also complicate liver transplantation. Other causes are primary sclerosing cholangitis (Chapter 15), chronic pancreatitis (Chapter 36) and abdominal trauma.

Clinical features are cholestasis with or without sepsis and pain. Diagnosis is by cholangiography. In most cases the underlying cause is clear from the clinical data.

Post-cholecystectomy

Pathogenesis

The bile duct may be ligated, sectioned, perforated by suture material, or damaged by cautery or laser. Several factors contribute to duct injury. There may be mistaken interpretation of the anatomy due to oedema or haemorrhage around an inflamed gallbladder, anomalies of the cystic duct or right hepatic duct (fig. 35.1), or lack of operator experience. Some surgeons advocate careful dissection of the neck of the bladder before dividing either the cystic duct or artery. Meticulous dissection of the cystic duct at the infundibulum of the gallbladder is crucial to avoid bile duct injury.

Table 35.1. Causes of benign bile duct stricture

Post-surgical
cholecystectomy
recurrence at bile duct/bowel anastomosis
extensive hepatic resection
liver transplantation
Inflammatory
primary sclerosing cholangitis
chronic pancreatitis
radiotherapy
Trauma
Idiopathic

Risk factors for *laparoscopic bile duct injury* include obesity, bleeding, acute cholecystitis and scarring in Calot's triangle (the area between the cystic duct and common hepatic duct). Uncertain anatomy, inexperience and a long procedure are also associated with damage [30, 31]. The threshold at which the decision is made to convert from laparoscopic to open surgery is also important.

A bile duct stricture may also follow prolonged T-tube drainage, rough probing of the duct for calculi and attempts at operative cholangiography especially with a normal-sized duct. A calculus in the common bile duct is an insufficient cause. Bile leakage after surgery may form peri-ductal collection or abscesses with constriction of the adjoining duct.

Pathology

Complete ligation, clipping or transection will become clear clinically in the immediate peri-operative period.

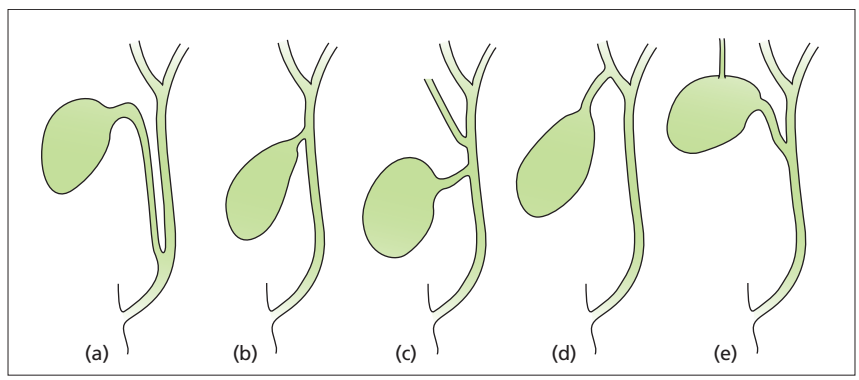


Fig. 35.1. Bile duct anatomy and anomalies associated with problems at cholecystectomy: (a) long cystic duct running adjacent to common duct; (b) short cystic duct; (c) anomalous right hepatic duct joins common duct outside liver; (d) cystic duct originates from right hepatic duct; (e) persistent duct between gallbladder and liver.

With partial injury, the occlusion develops slowly. The stricture is usually found in the common hepatic duct, or right hepatic duct particularly when the anatomy is anomalous.

The bile duct above a stricture is dilated and thickened, and below is replaced over a variable length by a fibrous cord difficult to identify at operation. The intra-hepatic ducts may be dilated depending on the completeness of the obstruction.

The obstructed bile is viscid and usually infected, with debris or biliary mud. Small calculi may form above the stricture and in the intra-hepatic ducts.

The liver shows cholestasis. Biliary cirrhosis with portal hypertension and splenomegaly will develop with time if the obstruction is not recognized and relieved.

Clinical features

Post-cholecystectomy strictures are more common in females because they have more biliary surgery. Seventy per cent of patients are less than 50 years old.

Bile duct damage occurs in approximately 1 in 400 open cholecystectomies [22]. The incidence is similar for laparoscopic cholecystectomy (1 in 200–400) [10, 21] although it is higher during the initial 'learning curve'.

About 60% of patients with bile duct injury present within 3 months of operation, and 80% within 1 year [16].

If unrecognized at the time of cholecystectomy, presentation depends upon the degree of damage. Post-operative anorexia, nausea, vomiting, pain, abdominal distension, ileus and delayed recovery should raise the possibility of damage [30], although the presentation is usually more obvious. Complete transection of the main bile duct usually gives pain (bile peritonitis), fever and cholestatic jaundice 3–7 days post-operatively. Bile-stained fluid may appear through a surgical drain. Alternatively, an external biliary fistula develops. Such a fistula, even for a few days, suggests that biliary damage has occurred and that there is a bile leak. A stricture may follow. The fistula may drain intermittently with episodes of jaundice when it is closed. Sub-hepatic abscesses may develop.

Ligation or clipping the main duct gives escalating cholestatic jaundice with or without cholangitis.

If the bile duct injury is partial, there may be cholestasis early after operation, but it may be several months before obvious jaundice is apparent. This is the period of slow, constrictive fibrosis. Intermittent attacks of cholangitis with or without jaundice usually accompany all grades of biliary stricture. The cholangitis is marked by fever, sometimes very high, with rigors, sweating and epigastric pain followed by dark urine and pale stools (*Charcot's intermittent biliary fever*). Itching may develop. Milder episodes are also seen which may be anicteric. The patient may think that they have caught a chill, or had a short-lived viral infection.

With current awareness of the complications of laparoscopic cholecystectomy, and the availability of ERCP and other imaging techniques, patients should not develop the chronic complications of biliary obstruction. The exception is the rare patient in whom multiple surgical attempts have been unsuccessful in providing unimpeded bile flow. Non-surgical methods should not be persisted with at the expense of long-term biliary cirrhosis, except after appropriate attempts have been made in a specialist tertiary referral centre to correct the stricture surgically.

With chronic cholestasis, secondary sclerosing cholangitis and then biliary cirrhosis follow, particularly when there is recurrent sepsis. The liver is enlarged and firm. The spleen becomes palpable. Gastrointestinal bleeding due to portal hypertension is a late event; liver failure is terminal. In this now rare circumstance, transplantation has to be considered although the multiple previous operations and biliary sepsis are relative contraindications.

Patients unfortunate enough to suffer bile duct damage at cholecystectomy may become increasingly introspective as the months pass. They keep the most detailed notes of their symptoms and, understandably, become querulous and suspicious of their medical advisors. They need considerable support.

Investigations

Serum biochemistry is of increasing or intermittent cholestasis. The alkaline phosphatase and γ-glutamyl transpeptidase may be raised even if the serum bilirubin, which is usually rising, is normal.

Haematological findings include a mild, normochromic, normocytic anaemia. A moderate leucocytosis accompanies the febrile episodes.

Blood cultures may show enteric organisms, in particular *Escherichia coli*, during attacks of cholangitis.

Radiology. The first step is scanning with ultrasound or CT. Where duct damage has led to a bile leak, ultrasound or CT will show an intra-abdominal collection which may be drained under scanning control. Bile ducts will not be dilated. Biliary scintigraphy detects around 50% of leaks (see fig. 32.9c) [13]. When there is a stricture without a leak dilated intra-hepatic bile ducts are seen.

The route of cholangiography depends upon the clinical data. For duct transection and discontinuity or a high stricture, percutaneous cholangiography and drainage are appropriate as part of the pre-operative work-up and management. If bile leakage from a cystic duct or a partial low duct stricture are suspected then ERCP is the first choice (fig. 35.2). A role for MRCP has not evolved in this clinical situation.

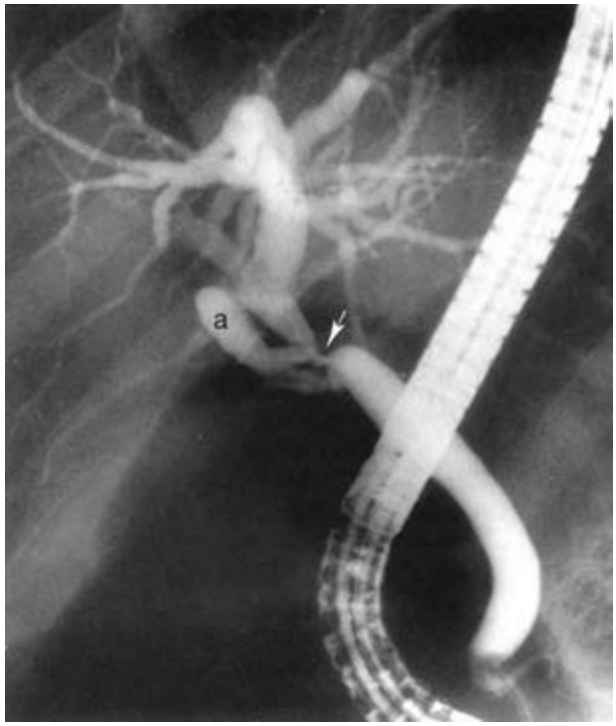


Fig. 35.2. Benign bile duct stricture following laparoscopic cholecystectomy (arrow). Note anomalous right-sided bile duct (a).

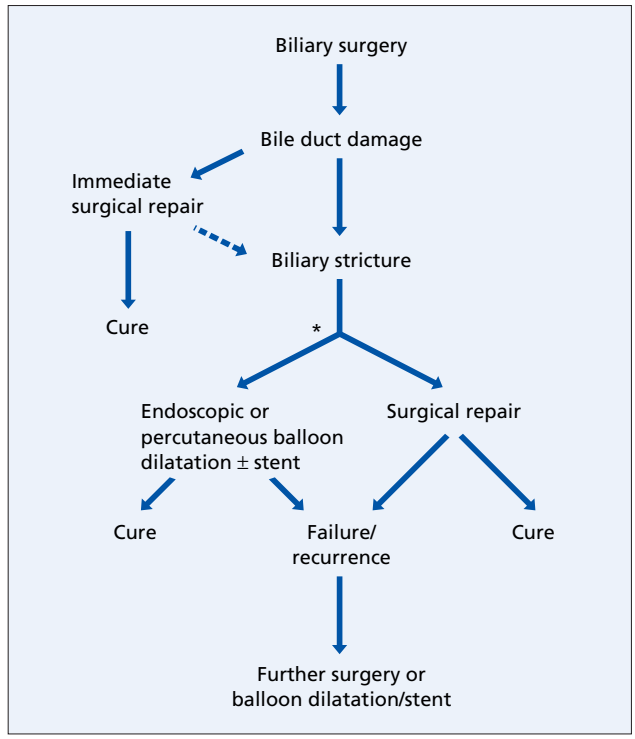


Fig. 35.3. The management of benign biliary stricture. *Choice depends on anatomy, clinical data and expertise available.

Diagnosis

The history of recent cholecystectomy, the post-operative features and the biochemical and imaging data should lead to cholangiography and the correct diagnosis.

The Bismuth classification is used to describe the level of the stricture:

Type 1: low common hepatic (>2 cm from hilum) or common bile duct.
Type 2: mid common hepatic duct (<2 cm from hilum).
Type 3: hilar stricture.
Type 4: destruction of hilar confluence.
Type 5: involvement of the right hepatic duct alone or with the bile duct.

Most post-cholecystectomy strictures are type 2 or 3 [16].

Treatment (fig. 35.3)

Prevention

The majority of strictures would be prevented if: (a) cholecystectomy was only performed by experienced surgeons; (b) the top-down approach was used with thorough dissection at the junction of the gallbladder infundibulum and cystic duct; and (c) there was an appropriate threshold for conversion from laparoscopic to open surgery. This is particularly so in the presence of acute cholecystitis.

No structure should be clamped or divided until the anatomy has been defined. Important technical points include good exposure, a dry operative field and adequate assistance. The cystic artery must be ligated *before* the cystic duct is tied. Traction on the gallbladder should be avoided.

The place of routine intra-operative cholangiography during laparoscopic cholecystectomy is controversial [5]. If a selective cholangiography policy is followed, the rate of residual stones is low. Some emphasize the importance of defining duct anatomy to reduce duct damage, but duct damage may still occur despite cholangiography.

Medical

Fluid and electrolyte balance must be maintained, particularly in the jaundiced patient and those with a biliary fistula. Antibiotic therapy, based if possible on blood and bile culture, will improve septicaemia but if there is bile duct obstruction or a leak, bile duct catheterization and drainage by the endoscopic or percutaneous route is essential to treat sepsis. Bile collections may need percutaneous drainage under scanning control.

Surgical vs. non-surgical intervention [1, 17]

The overriding principle is the importance of early referral to a specialist hepato-biliary centre where there will be a joint approach by surgeon, radiologist and endoscopist [8]. For the completely obstructed bile duct (or completely transected duct) surgery is necessary after investigation and preparatory percutaneous bile drainage, as appropriate to the individual patient. Bile leakage from a cystic duct stump or tiny ducts in the gallbladder bed can usually be managed endoscopically by stent insertion [1]. For the incomplete stricture, although some may be treated non-surgically, for example by endoscopic balloon dilatation and stenting, long-term results are awaited. Overall data from patients having operative treatment in a specialist centre show a good result in 75–90% with a mean follow-up of 5–7 years [3]. Thus although non-surgical treatment may be successful in the short and medium term [1, 2], the surgical option has to be considered throughout.

Balloon dilatation and stenting

For incomplete strictures a dilating balloon may be introduced by the endoscopic or percutaneous trans-hepatic route.

The *endoscopic route* is preferred if the papilla is accessible (Chapter 32). A large-channel endoscope is used to allow passage of the balloon catheter. After diagnostic cholangiography a guide-wire is placed through the stricture (see fig. 32.19). Over this the balloon catheter is passed. Radio-opaque markers on the catheter allow accurate positioning of the balloon across the stricture. A sphincterotomy is usually done to allow easy passage of the balloon catheter. The size of balloon chosen depends on the tightness of the stricture, but the eventual aim is to inflate a 6–8-mm diameter balloon. The time that the balloon is kept inflated is not standardized and depends upon the firmness of the stricture and how easily it dilates. In some percutaneous series 15–20 min of inflation is used but this depends upon the sedation and analgesia. Dilatation may be very painful. Long inflation times are not as practical with the endoscopic route.

After endoscopic balloon dilatation, one or more endoprostheses may be inserted to splint the stricture for 9–12 months (a period chosen empirically) to reduce the risk of re-stenosis [2]. Ideally the stent is replaced every 3–6 months.

The endoscopic route is of no value for the patient with duct transection and discontinuity, or for the complete duct stricture due to ligation. For these patients *percutaneous cholangiography* with catheter placement is done in the specialist centre prior to surgery. These are complex patients requiring a specialist multidisciplinary team. The intra-hepatic ducts are drained through a percutaneous catheter before surgery.

For the patient with an incomplete stricture which cannot be approached endoscopically, the *percutaneous trans-hepatic approach* is used, although results in the medium term (5 years) show this approach to be less effective than surgery [17].

The bile duct is catheterized percutaneously in the usual way (Chapter 32). A guide-wire, usually a steerable variety, is negotiated through the stricture, the balloon catheter passed across the stricture and the balloon inflated (fig. 35.4). Again, dilatation to 6–8 mm is usual. Smaller diameter balloons are available for the tighter stricture. After dilatation, an internal–external catheter with numerous side holes sitting above and below the dilated stricture is left in place. Dilatation can be repeated as often as necessary. The length of time that the balloon is left inflated varies from centre to centre, but is between 5 and 20 min. Similarly, there are wide differences in the time for which an internal–external drain is left in place after dilatation. Some centres do this only for a few days while others leave the tube in for 6–9 months. How these variables affect outcome is not known.

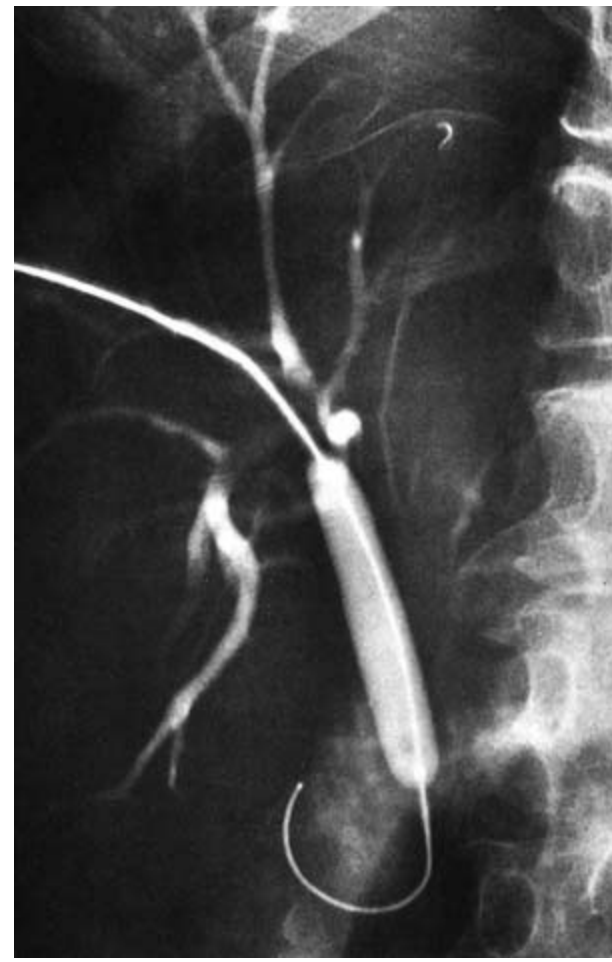


Fig. 35.4. A balloon, introduced trans-hepatically, has been inflated to dilate a benign biliary stricture.

Normally several sessions of dilatation are performed under local anaesthesia with intravenous sedation and analgesia as required. To reduce hospital stay and improve results, a study has been done of balloon dilatation under general anaesthesia at a single session. Results using this approach are as good as with intravenous sedation and multiple procedures [15].

Success rates vary considerably, between 60 and 90% patency with a mean follow-up of 3 years [2, 15, 17]. Differences in outcome reflect several factors including the definition of failure, the duration of follow-up and the features of the stricture.

Percutaneous balloon dilatation is usually used initially without endoprosthesis insertion, to avoid leaving a foreign body in the biliary system. In those patients where strictures recur after balloon dilatation, and surgery is not considered appropriate (by a specialist biliary surgeon), a stent may be inserted. With bile duct/bowel anastomotic strictures, the problem of this approach is the inaccessibility of the stent if it needs to be removed.

Many types of stent are available and there are insufficient data to recommend one over another. Success with metal stents is short-lived, with re-occlusion frequent. They are not recommended for post-operative bile duct strictures [9, 19].

The percutaneous trans-hepatic approach carries the risks of all other trans-hepatic procedures. Major complications include *sepsis*. 20% may have *haemobilia* for which hepatic arterial embolization may be necessary. Dilatation may produce *bile duct perforation*.

No trials compare surgery with balloon dilatation. A retrospective comparison has shown better results with surgical repair than with percutaneous balloon dilatation (90 vs. 65%) [17]. There remains little doubt that surgical repair is the first choice in most cases. Percutaneous, and where possible endoscopic, balloon dilatation has a role in selected patients, particularly those with many previous operations and portal hypertension.

Operative [16]

The timing of surgery for duct transection or complete obstruction depends upon the clinical situation. Patients are often septic and appropirate antibiotics are given. Pre-operative percutaneous trans-hepatic biliary drainage is performed. Intra-abdominal collections are drained. Collections resolve. Other pre-operative investigations are done, including angiography to detect vascular damage. Surgery may then be performed electively in the subsequent weeks under optimal conditions.

The surgeon attempting the first repair carries a great responsibility because failure reduces the chance of subsequent cure. The best surgeon should therefore be the first to re-operate rather than each intervention being undertaken by one of greater skill and reputation than his or her predecessor.

The operation chosen will depend mainly on two factors—the site and length of the stricture and the amount of duct available for repair. Any operation must provide excision of the stricture with mucosal apposition between the duct lining and the intestinal mucosa. The anastomosis must be as large as possible and not under tension.

Even if sufficient duct is available proximally, excision of the stricture and end-to-end anastomosis of the duct is rarely performed. Differences between the calibre of the duct above and below the stricture are too great for a satisfactory anastomosis. Recurrent stricture occurs in 60% of cases. End-to-end anastomosis should not be performed if: (a) the ends are greater than 2 cm apart; (b) the injury is not recognized at the time of surgery; and (c) the duct diameter is less than 4 mm [6].

The usual operation is between the bile duct and a Roux-en-Y segment of jejunum (*choledocho-jejunostomy*). In the case of high stricture, the hepatic duct is used (*hepatico-jejunostomy*) (fig. 35.5).

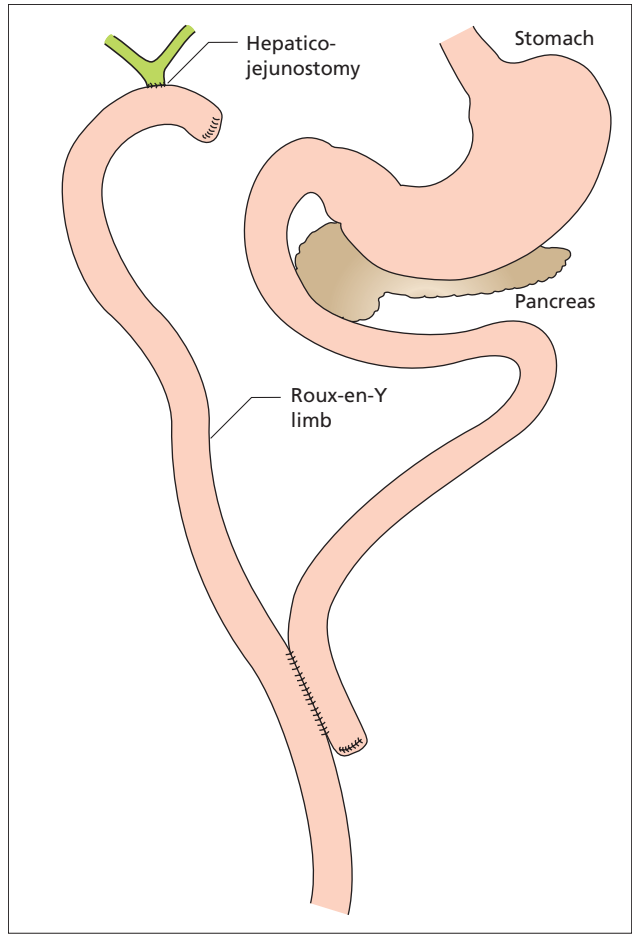


Fig. 35.5. Repair of a high biliary stricture by Roux-en-Y hepatico-jejunostomy.

The need for and duration of splinting of the anastomosis with silastic or other tubing is controversial. Some have recommended 6–12 months of splinting [16], but the impact of trans-anastomotic tubes on the long-term outcome of the repair is questionable [3].

Percutaneous access to the stricture can be made possible by the subcutaneous fixation of an extension of the Roux-en-Y loop beyond the biliary anastomosis. The position of this segment of bowel under the skin is marked by metal clips so that it can be found by X-ray fluoroscopy. Percutaneous entry into the loop allows cholangiography and, if necessary, further stricture dilatation [12].

Portal hypertension may be controlled by repairing the stricture, otherwise a porta-caval shunt may be necessary. This may be exceedingly difficult due to the adhesions from previous operations. A spleno-renal or meso-caval anastomosis may be the only shunt possible.

Outcome

Following surgical correction of a bile duct stricture in a specialist hepato-biliary unit, a good result, defined as loss of biliary symptoms and no further intervention necessary during a follow-up of 7.2 years, was achieved in 76% of 110 patients [3]. The operative mortality was low (1.8%). These results parallel reports from other specialist centres [18]. Factors associated with a poor outcome are discontinuity of right and left intra-hepatic ducts at the time of stricture repair, three or more attempts at operative repair before referral, hypoalbuminaemia, high serum bilirubin, the presence of liver disease and portal hypertension [3].

Bile duct/bowel anastomotic stricture

Choledocho-jejunostomies and hepatico-jejunostomies may stricture. Between 10 and 30% of patients with such anastomoses will need a further procedure—surgical or radiological. Of the recurrent strictures, two-thirds occur within 2 years and 90% by 5 years [25]. If the patient remains symptom-free for 4 years post-operatively, there is a 90% chance of complete cure. This happy result reduces with the number of operations, but *can* follow many attempts at repair.

Clinical features

Re-stricturing presents as fever, rigors and jaundice. There may be pain. Previous episodes of mild flu-like symptoms may precede the major attack. Cholangitis does not necessarily indicate re-stenosis, but can be due to intra-hepatic strictures or stones, or improperly constructed enteric loops up to the anastomosis [24].

Investigations

Investigations in the acute phase show leucocytosis and abnormal liver function tests, often with a transient rise in transaminase (due to short-term acute obstruction) with later elevation of alkaline phosphatase and γ-glutamyl transpeptidase.

Radiology

A plain film of the abdomen may show air in the biliary tree (see fig. 32.1) and the site of the stricture. Air in the ducts does not necessarily imply a fully patent anastomosis. Ultrasound may show dilated ducts but often does not because of the intermittent nature of the obstruction.

Cholangiography by the percutaneous trans-hepatic route shows whether the anastomosis is strictured (fig. 35.6); careful observation of the rate of flow of contrast across the anastomosis is more important than the X-ray film images examined later. If there has been prolonged partial obstruction with recurrent cholangitis, the

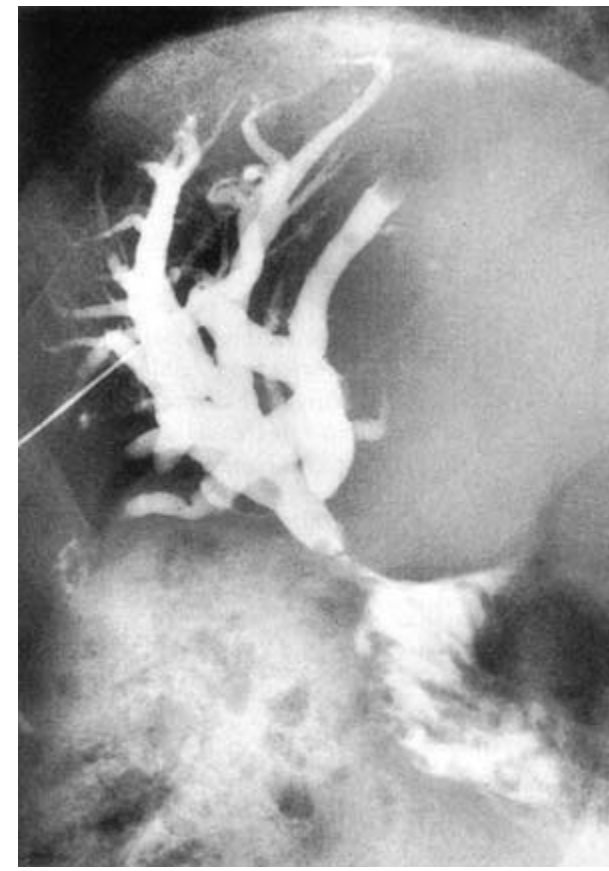


Fig. 35.6. Percutaneous trans-hepatic cholangiogram in a patient with hepatico-jejunostomy following post-cholecystectomy stricture. There is re-stenosis at the anastomosis with dilatation of the ducts in the right lobe.

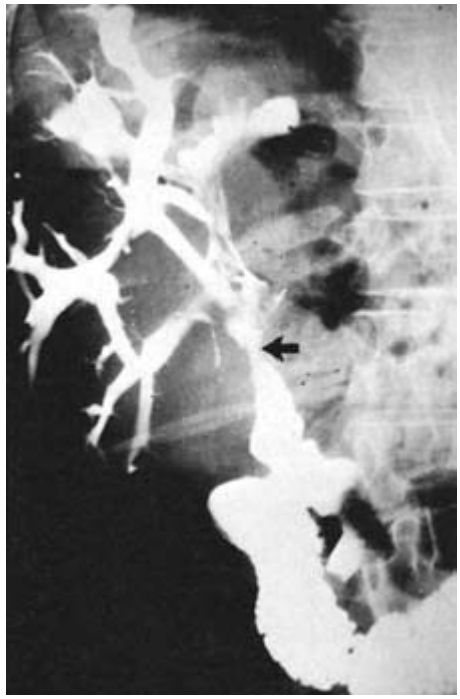


Fig. 35.7. Biliary stricture with patent choledocho-jejunostomy (arrow). Repeated attacks of cholangitis have led to secondary sclerosing cholangitis shown by irregular stenosis and dilatation of the intra-hepatic bile ducts.

changes of secondary sclerosing cholangitis may be seen (fig. 35.7).

ERCP can be used for investigation of choledocho-duodenostomies. Entry via a subcutaneous access loop of intestine is an alternative approach for the hilar anastomosis [11].

Investigation of the patient with cholangitis but an apparently patent anastomosis is a challenge, since no one imaging technique can be relied upon to demonstrate the cause [24].

Treatment

This is based on the surgical and non-surgical methods discussed above. Usually access to the biliary system is only possible percutaneously. Percutaneous balloon dilatation is effective in three-quarters of patients with a 30-month follow-up [33]. The importance of a specialist team of a surgeon and radiologist is critical [3].

Post liver transplantation

Pathogenesis

Biliary complications follow in 10–20% of patients and include stricture, bile leak, fistulae and cholangitis. Strictures may be *anastomotic* due to technical factors, inflammation after a leak and fibrosis, or *non-anastomotic*, forming above the anastomosis towards the hilum of the liver. The latter are sometimes due to duct ischaemia.

The blood supply to the distal (recipient) duct is rich due to collateral flow. That of the proximal (donor) duct is more tenuous [32], relying on the peri-biliary plexus derived from the reconstructed hepatic artery. Non-anastomotic duct necrosis with leakage of bile may follow hepatic artery thrombosis.

Development of non-anastomotic strictures seems to be independent of the method of bile duct reconstruction whether choledocho-choledochostomy or Roux-en-Y anastomosis. The majority of hilar strictures occur by 3 months after transplantation.

Apart from ischaemia, suggested mechanisms of non-anastomotic stricturing are decreased healing due to high-dose steroids, infection and chronic ductopenic arteriopathic rejection.

Biliary leaks are associated with T-tubes, either due to dislodgement, or occurring at the time of removal. T-tube splinting of the anastomosis has been used to reduce biliary problems, but if this is omitted the complication rate is no higher [29].

Clinical features

Liver function tests deteriorate with or without sepsis. Other causes of altered liver function tests will be considered and excluded by liver biopsy and viral serology. The differential diagnosis includes rejection, sepsis elsewhere, cytomegalovirus infection, recurrence of underlying disease and drug toxicity.

Investigations

Intermittent rises and falls in serum bilirubin and/or wide fluctuations in the serum transaminase level, unresponsive to changes in immunosuppressive therapy, may indicate biliary tract pathology.

Ultrasound may show duct dilatation or a collection. Doppler ultrasound is done to check hepatic arterial flow. If ultrasound is normal a clinical decision is taken between liver biopsy or cholangiography. ERCP will show a biliary leak or stricture. MRCP demonstrates late biliary complications, in particular anastomotic and non-anastomotic strictures [14].

Treatment

Endoscopic balloon dilatation and stenting has a success rate of 50–90% for anastomotic and 70–80% for non-anastomotic strictures assessed at a median follow-up of 2 years [26, 28]. Balloon dilatation alone was successful in 60% of one series of anastomotic strictures [23]. Percutaneous biliary intervention may be successful when the

endoscopic approach has failed. Thus an attempt at non-surgical therapy is worthwhile before considering surgical bypass. If these attempts fail surgical choledocho-jejunostomy is done. Failed non-surgical management does not increase the complication rate of reconstructive surgery [7].

Primary sclerosing cholangitis (Chapter 15)

Extra- and intra-hepatic bile ducts are diffusely involved in approximately 80% of patients. If the patient develops persistent jaundice or recurrent sepsis, investigations are necessary to show whether there is a dominant stricture, that is one which appears to be causing significant obstruction compared with the diffuse changes elsewhere. Ultrasound may show duct dilatation; MRCP or ERCP will show a dominant stricture if present. Brush cytology is necessary. Differentiation of benign stricturing from cholangiocarcinoma is difficult and often impossible.

Balloon dilatation with or without stenting can produce clinical improvement. Whether stenting needs to be maintained for 12 months, as for other benign duct strictures, has been questioned by the successful outcome in a series of patients with a dominant stricture who received stents for only 1–23 days [27]. 60% of 32 patients did not need further intervention after follow-up of 3 years. The differentiation between clinical deterioration caused by intra-hepatic disease and liver cell failure, and that due to remediable duct stricturing, is often difficult but important so as not to delay transplantation inappropriately.

Other causes

Chronic pancreatitis may cause low bile duct obstruction (Chapter 36), as may radiotherapy [4], a penetrating or sclerosed duodenal ulcer [20] and trauma. The stricture occurring after resection of the head of the pancreas is likely to be caused by recurrence of tumour, but benign strictures due to vascular insufficiency are also possible. This is related to the balance of blood supply to the bile duct proximally and distally. When necessary the bile duct should be divided as near to the ampulla as possible, where the blood supply is better.

Summary

In all benign strictures of the bile duct, the outcome depends on the experience and judgement of the team of surgeon, endoscopist and radiologist, in selecting and performing the most suitable corrective procedure tailored to the individual patient.

References

1 Bergman JJGHM, van der Brink GR, Rauws EAJ *et al*. Treatment of bile duct lesions after laparoscopic cholecystectomy. *Gut* 1996; **38**: 141.
2 Born P, Rösch T, Brühl K *et al*. Long-term results of endoscopic and percutaneous transhepatic treatment of benign biliary strictures. *Endoscopy* 1999; **31**: 725.
3 Chapman WC, Halevy A, Blumgart LH *et al*. Postcholecystectomy bile duct strictures: management and outcome in 130 patients. *Arch. Surg.* 1995; **130**: 597.
4 Cherqui D, Palazzo L, Piedbois P *et al*. Common bile duct stricture as a late complication of upper abdominal radiotherapy. *J. Hepatol.* 1994; **20**: 693.
5 Clair DG, Carr-Locke DL, Becker JM *et al*. Routine cholangiography is not warranted during laparoscopic cholecystectomy. *Arch. Surg.* 1993; **128**: 551.
6 Csendes A, Diaz JC, Burdiles P *et al*. Late results of immediate primary end to end repair in accidental section of the common bile duct. *Surg. Gynecol. Obstet.* 1989; **168**: 125.
7 Davidson BR, Bai R, Nandy A *et al*. Results of choledochojejunostomy in the treatment of biliary complications after liver transplantation in the era of nonsurgical therapies. *Liver Transplant* 2000; **6**: 201.
8 Doctor N, Dooley JS, Dick R *et al*. Multidisciplinary approach to biliary complications of laparoscopic cholecystectomy. *Br. J. Surg* 1998; **85**: 627.
9 Dumonceau J-M, Devière J, Delhaye M *et al*. Plastic and metal stents for postoperative benign bile duct strictures: the best and the worst. *Gastrointest. Endosc.* 1998; **47**: 8.
10 Dunn D, Fowler S, Nair R *et al*. Laparoscopic cholecystectomy in England and Wales: results of an audit by the Royal College of Surgeons of England. *Ann. R. Coll. Surg. Engl.* 1994; **76**: 269.
11 Hatfield ARW, Craig PI, Lanzon-Miller S *et al*. Percutaneous choledochoscopy in the management of benign biliary disease. *Gut* 1992; **33**: S34.
12 Hutson DG, Russell E, Schiff E *et al*. Balloon dilatation of biliary strictures through a choledochojejuno-cutaneous fistula. *Ann. Surg.* 1984; **199**: 637.
13 Kurzawinski TR, Selves L, Farouk M *et al*. Prospective study of hepatobiliary scintigraphy and endoscopic cholangiography for the detection of early biliary complications after orthotopic liver transplantation. *Br. J. Surg.* 1997; **84**: 620.
14 Laghi A, Pavone P, Catalano C *et al*. MR cholangiography of late biliary complications after liver transplantation. *Am. J. Roentgenol.* 1999; **172**: 1541.
15 Lee MJ, Mueller PR, Saini S *et al*. Percutaneous dilatation of benign biliary strictures: single-session therapy with general anaesthesia. *Am. J. Roentgenol.* 1991; **157**: 1263.
16 Lillemoe KD. Benign postoperative bile duct strictures. *Baillière's Clin. Gastroenterol.* 1997; **11**: 749.
17 Lillemoe KD, Martin SA, Cameron JA *et al*. Major bile duct injuries during laparoscopic cholecystectomy. *Ann. Surg.* 1997; **225**: 459.
18 Lillemoe KD, Melton GB, Cameron JL *et al*. Postoperative bile duct strictures: management and outcome in the 1990s. *Ann. Surg.* 2000; **232**: 430.
19 Lopez RR, Cosenza CA, Lois J *et al*. Long-term results of metallic stents for benign biliary strictures. *Arch. Surg.* 2001; **136**: 664.

20 Luman W, Hudson N, Choudari CP *et al*. Distal biliary stricture as a complication of sclerosant injection for bleeding duodenal ulcer. *Gut* 1994; **35**: 1665.
21 McMahon AJ, Fullarton G, Baxter JN *et al*. Bile duct injury and bile leakage in laparoscopic cholecystectomy. *Br. J. Surg.* 1995; **82**: 307.
22 McSherry CK. Cholecystectomy: the gold standard. *Am. J. Surg*. 1989; **158**: 174.
23 Mahajani RV, Cotler SJ, Uzer MF. Efficacy of endoscopic management of anastomotic biliary strictures after hepatic transplantation. *Endoscopy* 2000; **32**: 943.
24 Matthews JB, Baer HU, Schweizer WP *et al*. Recurrent cholangitis with and without anastomotic stricture after biliary-enteric bypass. *Arch. Surg*. 1993; **128**: 269.
25 Pellegrini CA, Thomas MJ, Way LW. Recurrent biliary stricture. Patterns of recurrence and outcome of surgical therapy. *Am. J. Surg.* 1984; **147**: 175.
26 Pfau PR, Kochman ML, Lewis JD *et al*. Endoscopic management of postoperative biliary complications in orthotopic liver transplantation. *Gastrointest. Endosc.* 2000; **52**: 55.
27 Ponsioen CY, Lam K, van Milligen de Wit AWM *et al*. Four years' experience with short-term stenting in primary sclerosing cholangitis. *Am. J. Gastroenterol.* 1999; **94**: 2403.
28 Rizk RS, McVicar JP, Emond MJ *et al*. Endoscopic management of biliary strictures in liver transplant recipients: effect on patient and graft survival. *Gastrointest. Endosc.* 1998; **47**: 128.
29 Rolles K, Dawson K, Novell R *et al*. Biliary anastomosis after liver transplantation does not benefit from T tube splintage. *Transplantation* 1994; **57**: 402.
30 Rossi RL, Schirmer WJ, Braasch JW *et al*. Laparoscopic bile duct injuries: risk factors, recognition, and repair. *Arch. Surg*. 1992; **127**: 596.
31 Schol FPG, Go PM, Gouma DJ. Risk factors for bile duct injury in laparoscopic cholecystectomy: analysis of 49 cases. *Br. J. Surg.* 1994; **81**: 1786.
32 Terblanche J, Allison HF, Northover JMA. An ischemic basis for biliary strictures. *Surgery* 1983; **94**: 52.
33 Vos PM, van Beek EJR, Smits NJ *et al*. Percutaneous balloon dilatation for benign hepaticojejunostomy strictures. *Abdom. Imaging* 2000; **25**: 134.

Chapter 36
Diseases of the Ampulla of Vater and Pancreas

Peri-ampullary carcinoma

The region of the head of the pancreas is a common site for carcinoma. The tumour may arise in the head of the pancreas itself, more often from ductular epithelium than acinar cells, the lining of the low bile duct, the ampulla (papilla) or rarely the duodenum. Tumours arising from any of these sites have the same overall effect (fig. 36.1), and will be considered as a group. They are often termed 'cancer of the head of the pancreas'. However, the prognosis is very different: 80% of patients with carcinoma of the ampulla and 50% of those with malignancy of the duodenum have a potentially operable tumour compared with only 20% of those arising in the head of the pancreas.

Genetic and environmental predisposition

In the majority of patients there is no clear aetiological factor. In a small number there is a genetic influence either through a strong family history or through hereditary pancreatitis. There is an 18-fold increased risk of pancreatic carcinoma among first-degree relatives in families with at least two other affected individuals [48]. Patients with hereditary pancreatitis have a cumulative risk of pancreatic carcinoma to age 70 of 40% [29]. There is no formal recommendation for screening patients with an increased risk, but spiral CT and endoscopic ultrasound have been suggested [14].

There is a low risk (two-fold) of carcinoma in diabetics of more than 1 year's duration [17]. Patients with chronic pancreatitis are reported to have a cumulative risk of 2% per decade [28]. Rarely intra-duct papillary mucinous tumour is found at ERCP and CT. This has a 25–50% incidence of invasive carcinoma [30].

Environmental risk factors include cigarette smoking and certain diets [14].

Molecular changes

K-*ras* gene mutation, particularly at codon 12, is found in the majority of pancreatic carcinomas and more frequently than in other tumours. Mutations can be detected by polymerase chain reaction on formalin-fixed paraffin-embedded tissue, or needle biopsy or aspirated material. Abnormally high *p53* gene expression is found in 60% of pancreatic carcinomas, predominantly in ductal tumours. These changes are common in other tumours, adding little to the understanding specifically of pancreatic carcinogenesis. Clinically K-*ras* mutation analysis remains a research rather than a clinical tool.

K-*ras* mutations may be detected in pancreatic duct brushings in patients with carcinoma [50]. They are also

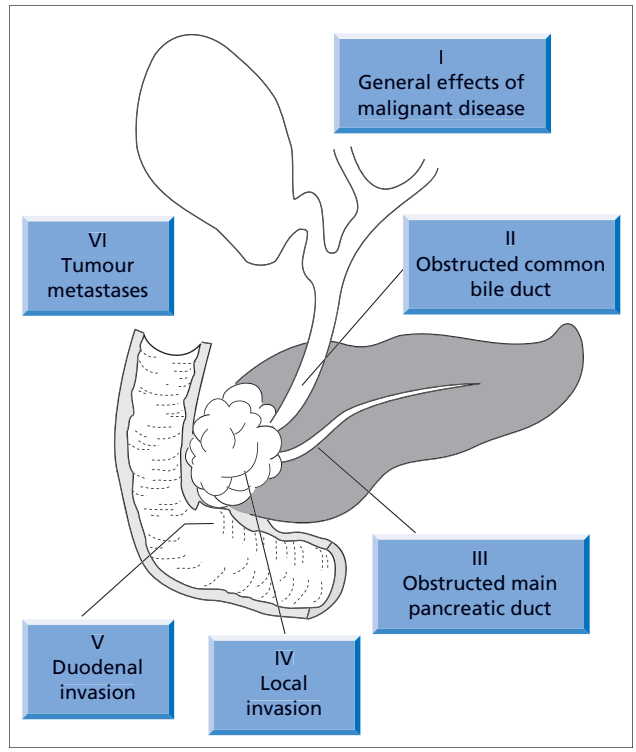


Fig. 36.1. The effects of carcinoma in the ampullary region.
I, General effects of malignant disease—weakness, weight loss.
II, Obstructed common bile duct. Dilated gallbladder and bile ducts—jaundice, pruritus.
III, Obstructed pancreatic duct—steatorrhoea, diabetes.
IV, Local invasion. Blood vessels (portal, superior mesenteric): encasement, thrombosis. Nerves: back and epigastric pain.
V, Duodenal invasion—occasional duodenal obstruction, positive occult blood.
VI, Tumour metastases—regional glands, liver, lungs, peritoneum.

found in the pancreatic juice of patients with chronic pancreatitis. This may relate to K-*ras* mutations in areas of duct hyperplasia [41]. Over a 2-year follow-up a minority develop pancreatic carcinoma [40].

Pathology

Histologically, the tumour is an adenocarcinoma, whether arising from pancreatic duct, acinus or bile duct. The ampullary tumours have a papillary arrangement and are often of low-grade malignancy; fibrosis is prominent. They tend to be polypoid and soft, whereas the acinar tumours are infiltrative, large and firm.

Obstruction of common bile duct

This results from direct invasion causing a scirrhous reaction, from annular stenosis, and from tumour tissue filling the lumen. The duct may also be compressed by the tumour mass.

The bile ducts dilate and the gallbladder enlarges. An ascending cholangitis in the obstructed duct is rare. The liver shows the changes of cholestasis.

Pancreatic changes

The main pancreatic duct may be obstructed as it enters the ampulla. The ducts and acini distal to the obstruction dilate and later rupture, causing focal areas of pancreatitis and fat necrosis. Later all the acinar tissue is replaced by fibrous tissue. Occasionally, particularly in the acinar type, fat necrosis and suppuration may occur in and around the pancreas.

Diabetes mellitus or impaired glucose tolerance is found in 60–80% of patients. Apart from destruction of insulin-producing cells by the tumour, this may be due to production of islet amyloid polypeptide (IAPP) by islet cells adjacent to the tumour [36].

Spread of the tumour

Direct extension in the wall of the bile duct and infiltration through the head of the pancreas is common with the acinar although not with the ampullary type. The second part of the duodenum may be invaded, with ulceration of the mucosa and secondary haemorrhage. The splenic and portal veins may be invaded and may thrombose with resultant splenomegaly.

Involvement of regional nodes is found in approximately a third of operated cases. Perineural lymphatic spread is common. Blood-borne metastases, with secondaries in liver and lungs, follow invasion of the splenic or portal veins. There may also be peritoneal and omental metastases.

Clinical features

Both sexes are affected, but males more frequently than females in a ratio of 2:1. The sufferer is usually between 50 and 69 years old.

The clinical picture is a composite one of cholestasis with pancreatic insufficiency, and the general and local effects of a malignant tumour (fig. 36.1).

Jaundice is of gradual onset, progressively deepening, but ampullary neoplasms can cause mild and intermittent jaundice. *Itching* is a common but not invariable feature, and when present comes after jaundice. Cholangitis is unusual.

Cancer of the head of the pancreas is not always painless. Pain may be experienced in the back, the epigastrium and right upper quadrant, usually as a continuous distress worse at night and sometimes ameliorated by crouching. It may be aggravated by eating.

Weakness and weight loss are progressive and have usually continued for at least 3 months before jaundice develops.

Although frank steatorrhoea is rare, the patient often complains of a change in bowel habit, usually diarrhoea.

Vomiting and intestinal obstruction follows invasion of the second part of the duodenum in 15–20% of patients. Ulceration of the duodenum can erode a vessel with haematemesis or, more commonly, occult bleeding.

Difficulty in making a diagnosis may make the patient depressed. It then becomes easy to believe mistakenly, that the patient is psychoneurotic.

Examination. The patient is jaundiced and shows evidence of recent weight loss. Theoretically, the gallbladder should be enlarged and palpable (*Courvoisier's law*). In practice, the gallbladder is only felt in about half the patients, although at subsequent laparotomy a dilated gallbladder is found in three-quarters. The liver is enlarged with a sharp, smooth, firm edge. The pancreatic tumour is usually impalpable.

The spleen is palpable if involvement of the splenic vein has caused thrombosis. Peritoneal invasion is followed by ascites.

Lymphatic metastases are more usual with cancer of the body rather than head of the pancreas [51]. Occasionally, however, axillary, cervical and inguinal glands may be enlarged and Virchow's gland in the left supraclavicular fossa may be palpable.

Sometimes, widespread venous thromboses simulate thrombophlebitis migrans.

Investigations

Glycosuria occurs in 60–80% and with it there is an impaired oral glucose tolerance test.

Blood biochemistry. The serum alkaline phosphatase level is raised. The serum amylase and lipase concentra-

tions are sometimes persistently elevated in carcinoma of the ampullary region. Hypoproteinaemia with, later, peripheral oedema may be found.

There is no reliable serum tumour marker with sufficient specificity or sensitivity. Using a cut-off of 70 U/ml (almost twice the upper limit of normal), CA 19-9 has the greatest sensitivity (around 70%) and specificity (90%) of current markers for carcinoma of the pancreas [14]. However its sensitivity in the detection of early tumour is lower [22]. It can be elevated in benign biliary obstruction.

Haematology. Anaemia is mild or absent. The leucocyte count may be normal or raised with a relative increase in neutrophils. The erythrocyte sedimentation rate is usually raised.

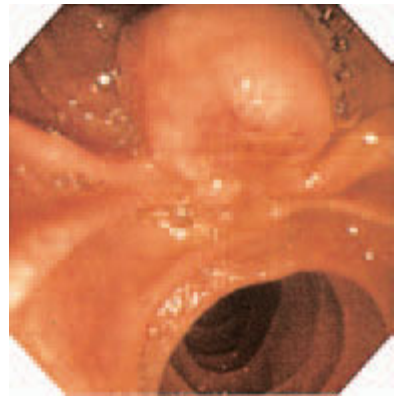


Fig. 36.2. Abnormal ampulla at ERCP. Note irregular surface with nodularity. Biopsy showed adenocarcinoma.

Differential diagnosis

The diagnosis must be considered in any patient over 40 years with progressive or even intermittent cholestasis. The suspicion is strengthened by persistent or unexplained abdominal pain, weakness and weight loss, diarrhoea, glycosuria, positive faecal occult blood, hepatomegaly, a palpable spleen or thrombophlebitis migrans.

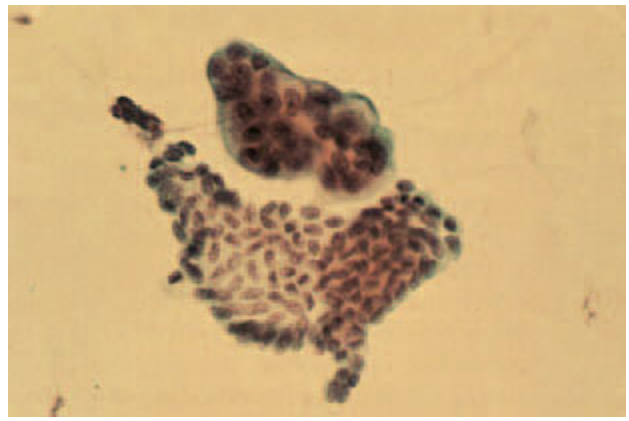


Fig. 36.3. Brush cytology taken from a low common bile duct stricture. There is a sheet of benign biliary epithelial cells and above this a small group of large polymorphic cells characteristic of adenocarcinoma.

Radiology

Most scanning techniques can detect pancreatic masses with high accuracy in specialist units. There are data supporting transabdominal ultrasound, spiral (helical) CT, dual-phase (arterial and venous) spiral CT, MRI, endoscopic ultrasound and PET scanning. The most effective initial technique is helical, dual-phase CT (see fig. 32.5) which has an accuracy of over 90% for tumours greater than 1.5 cm and 70% for smaller tumours [24]. This technique is widely available with expertise in interpretation [19]. MRI with angiography (gadolinium enhancement) and endoscopic ultrasound have a similar accuracy in some centres [2, 4, 16], but these techniques and expertise are not as widely available as spiral CT.

Scanning may also show dilatation of bile ducts and pancreatic duct, hepatic metastases and local spread of the primary lesion.

Percutaneous ultrasound or CT-guided *fine-needle aspiration* of the pancreatic mass is safe and has a sensitivity of over 90% in some units. There is a small risk of seeding of tumour cells along the needle track.

ERCP can usually demonstrate the pancreatic and bile ducts, allow biopsy of any ampullary lesion (fig. 36.2), and provide bile or pancreatic juice or brushings from the stricture for cytological examination (fig. 36.3). The appearance of the bile duct and/or pancreatic duct stricture (double duct sign) gives a good indication of the underlying malignant cause of the stricture (see fig. 32.12a) but occasionally appearances are deceptive [31] and tissue diagnosis should be sought. Biliary brush cytology has a sensitivity of around 60% for pancreatic carcinoma [23, 46]. Unusual tumours such as lymphoma need to be identified since they may respond to specific therapy.

In the patient with vomiting, barium meal and/or endoscopy will show the extent of duodenal invasion and obstruction.

Tumour staging

This gives an indication of whether the tumour is resectable or not. Clinical evidence, chest X ray, ultrasound or CT will show obvious metastatic disease.

Dual or triple-phase spiral CT is highly accurate in predicting irresectability (approximately 90%) [24] but

is less accurate in predicting resectability. Features suggesting irresectability are local extension of tumour, encasement of extra-pancreatic arteries or veins, invasion of adjacent organs and lymph node metastases (more than an isolated solitary node). Most irresectable lesions (70%) have three or four of these features—the minority having only one or two. Spiral CT may also show hepatic metastases but the detection rate is higher when combined with arterioportography.

Endoscopic ultrasound has a similar accuracy as dual phase helical CT in assessing irresectability, but expertise is not as widely available [24].

Experience with MRI is growing but it remains second choice to helical dual-phase CT.

For vascular involvement these techniques can give the same information as digital subtraction angiography (DSA) which is now used only when the data from scanning is inconclusive or conflicting.

Laparoscopy is valuable to show and biopsy minute hepatic metastases and peritoneal and omental seedings. Negative results from laparoscopy, CT and angiography correspond to a 78% resectability rate [51].

Prognosis

The prognosis of pancreatic carcinoma is grave. After biliary bypass surgery the mean survival is about 6 months. The acinar type carries a worse prognosis than the ductal type because regional lymph glands are involved earlier. Only the minority of tumours, between 5 and 20%, are resectable.

Resection has had an operative mortality of approximately 15–20%, but recent reports have shown this to fall to 5% and less in specialist centres with a few expert surgeons performing more operations [14]. A recent report from a superspecialist unit of zero mortality after 145 consecutive pancreatico-duodenal resections is exceptional [10].

Coincident with reduced operative mortality has been a rise in reported 5-year survival to around 20%. This may reflect earlier detection of disease through the newer scanning techniques, or selection of patients with less extensive spread of disease. Disease recurrence, however, remains a problem [14]. Total pancreatectomy does not lead to longer survival than the less extensive Whipple's procedure and produces exocrine insufficiency and brittle diabetes.

The overall outlook for carcinoma of the pancreas however, is grim with only 23 of 912 patients with carcinoma of the pancreas in one series surviving 3 years and only two of these being considered cures [11].

Prognosis for carcinoma of the ampulla is better. 85% or more of patients survive 5 years after resection if the tumour has not spread beyond the margins of the sphincter of Oddi. With more extensive tumour the 5-year survival falls to 11–35% [15, 52].

Treatment

Resection

A decision to attempt resection depends on the clinical state of the patient and the staging of the tumour derived from radiological imaging. Difficulties in removal arise because of the inaccessibility of the pancreas on the posterior wall of the abdomen in the vicinity of vital structures. The resectability rate is therefore low.

The classical procedure is *pancreatico-duodenectomy* (*Whipple's operation*) which is performed in one stage with removal of related regional lymph nodes, the entire duodenum and the distal third of the stomach. This operation was modified in 1978 [49] to preserve antral and pyloric function (pylorus-preserving pancreatico-duodenectomy). This reduces post-gastrectomy symptoms and marginal ulceration, and improves nutrition. Survival is the same as those having the classical procedure. The continuity of the biliary passages is restored by anastomosis of the common bile duct with the jejunum. Pancreatico-jejunostomy drains the duct of the remaining pancreas. The continuity of the intestinal tract is restored by duodeno-jejunostomy.

Frozen section examination of the resection margins is mandatory.

Prognostic factors are tumour size, resection margin and lymph node status [14]. The best indicator is lymph node histology. If negative at resection, 5-year survival is 40–50%, compared with 8% in those with nodes positive for metastasis [9]. Prognosis is also related to whether or not there is histological evidence of vascular invasion (median survival 11 vs. 39 months).

Carcinoma of the ampulla is also treated by pancreatico-duodenectomy. Local resection (ampullectomy) is an alternative in selected patients with premalignant or malignant ampullary lesions [5]. Endoscopic photodynamic therapy has produced remission or reduced tumour bulk in a series of patients with ampullary carcinoma unsuitable for surgery [1]. This technique uses endoscopic delivery of red light (630 nm) to tumour sensitized with haematoporphyrin given intravenously.

Palliative procedures

The choice lies between surgical bypass and endoscopic or percutaneous trans-hepatic insertion of an endoprosthesis (stent).

Palliative surgical biliary bypass is an option in irresectable patients with a predicted longer survival. For the jaundiced patient with vomiting due to duodenal

obstruction, choledocho-jejunostomy with gastroenterostomy is necessary. Gastric outlet and duodenal stenosis can be treated by endoscopically or radiologically placed expandable mesh metal stents [33, 43] although experience with this technique is limited. For the patient with bile duct obstruction alone, some argue for prophylactic gastric bypass surgery at the time of biliary bypass but most would make this decision at the time of operation, according to the size of the tumour.

Endoscopic stent insertion (fig. 36.4) is successful in up to 95% of patients (60% after the first session) and has a lower 30-day mortality than surgical bypass [42]. When the endoscopic approach fails, the percutaneous, or combined percutaneous/endoscopic approach can be used (Chapter 32).

Percutaneous stent insertion (see fig. 32.21) has a similar mortality, early morbidity and mean survival time (19 vs. 15 weeks) to palliative surgery partly due to the complications of the trans-hepatic approach (haemorrhage, bile leakage) [7]. Endoscopic stent insertion has a lower complication rate and mortality than the percutaneous route [44].

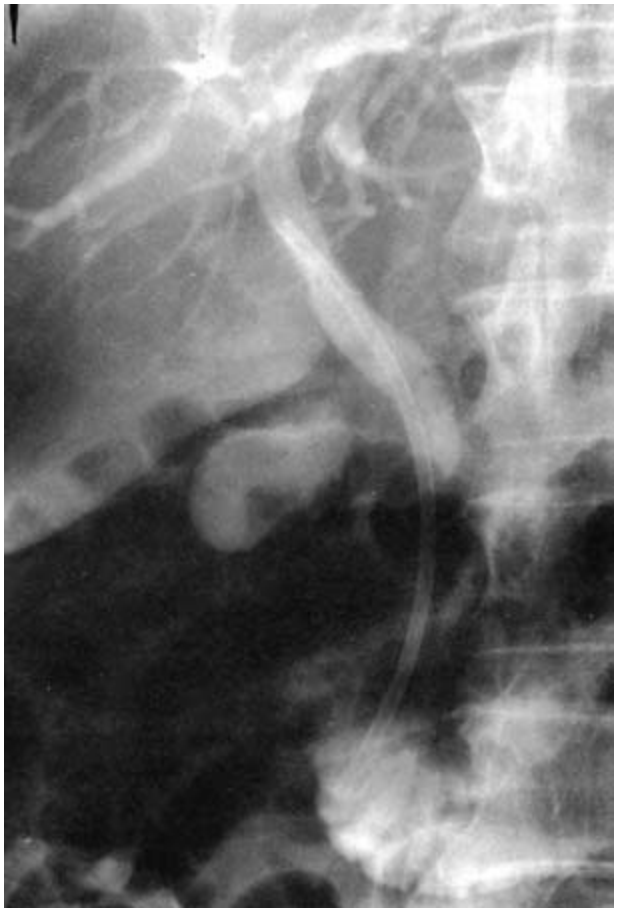


Fig. 36.4. Polyethylene 10 French endoprosthesis inserted across low common bile duct stricture by the endoscopic route. Note good flow of contrast into duodenum and decompressed biliary system.

Within 3 months of insertion 20–30% of plastic stents need to be replaced because of obstruction by biliary sludge. *Metal mesh expandable stents* can be inserted endoscopically or percutaneously (see fig. 32.17). They remain patent significantly longer than plastic stents (mean 273 vs. 126 days) [12]. However, because of their cost, they are best restricted to those patients with irresectable peri-ampullary carcinoma who at the time of first stent exchange because of blockage are judged likely to have slower progression and a longer survival [35]. This may be predicted to some extent by tumour size and weight loss [39]. If plastic stents are used, elective exchange of the stent every 3 months gives patients a longer complication-free interval than those having stent exchange only once blockage occurs [38].

The choice between surgical and non-surgical relief of biliary obstruction depends upon the expertise available and the clinical status of the patient.

The non-surgical insertion of a stent is particularly applicable to older, poor-risk patients especially when a large, clearly inoperable pancreatic mass has been imaged or where there is extensive metastatic disease. For the younger patient with irresectable disease, surgical bypass should still be considered if longer than average survival is expected.

With all the approaches now available, no patient with carcinoma of the pancreas should die jaundiced or with intolerable itching.

Chemotherapy: radiotherapy

Pre-operative adjuvant chemotherapy and radiotherapy have produced disappointing results. Selected patients may benefit from adjuvant combined radiotherapy and chemotherapy after radical resection [20]. For patients with irresectable tumour many chemotherapeutic regimes have been studied in randomized trials [14]. 5-fluorouracil (5-FU) has been used widely. Recent data suggest that treatment with gemcitabine may have some benefit on survival and the alleviation of disease-related symptoms [8]. Ideally all patients should participate in comparative studies. Otherwise gemcitabine may be considered for patients with advanced pancreatic carcinoma with or without metastases, who are still self-caring [14, 32]. For localized disease, radiotherapy and concomitant 5-FU is an alternative [14]. In patients who are no longer self-caring, management should focus on palliative measures rather than aggressive chemoradiation or chemotherapy.

For patients with pain, coeliac plexus block may be

more effective than oral or parenteral analgesia. Benefit is more immediate [37]. However, although coeliac plexus block either done percutaneously under X-ray screening or at operation can reduce pain for a few months, pain may return in over half of patients [27].

Benign villous adenoma of the ampulla of Vater

This leads to biliary colic and obstructive jaundice. The ampullary tumour is seen and biopsied at ERCP.

Dysplasia may be present on biopsy. Carcinoembryonic antigen (CEA) and CA19-9 are found on immunohistochemistry [53]. These lesions should be regarded as potentially premalignant. Local resection or pancreaticoduodenectomy is indicated [5]. In patients unfit for surgery, stenting is palliative. Endoscopic ablation may be successful using laser, monopolar or bipolar coagulation, or photodynamic therapy [1, 34].

Cystic tumours of the pancreas [18]

These may be benign or malignant and include cystic adenocarcinoma, cystic adenoma (serous and mucinous) and papillary cystic tumours. They may be misdiagnosed as pseudocysts. 40% of patients are asymptomatic. Work-up is by CT, endoscopic ultrasound, angiography and ERCP. Cyst fluid analysis (cytology, tumour markers) may be valuable in differentiating the type of tumour [26]. Around 40% of lesions are malignant. In general, resection should be attempted. Frozen and even routine histology may be misleading. Mucinous cystic neoplasm should be considered potentially malignant.

Endocrine tumours of the pancreas [3, 47]

These include insulinoma (70%), gastrinoma (20%), vaso-active intestinal polypeptide-secreting tumour (VIPoma), glucagonoma, polypeptide-secreting tumour (PPoma) and somatostatinoma. Some may be non-functioning [6]. They present with either the systemic effects of the hormone released or a mass effect with pain or jaundice as with pancreatic carcinoma. A variable proportion are malignant, depending on the endocrine type. Treatment is by surgical resection or debulking, and medical measures to counter the effect of any hormone released. Survival depends on the tumour type and stage.

Chronic pancreatitis

Pancreatitis, usually of alcoholic aetiology, can cause narrowing of the intra-pancreatic portion of the common bile duct. The resultant cholestasis may be transient during exacerbations of acute pancreatitis. It is presumably related to oedema and swelling of the pancreas. More persistent cholestasis follows encasement of the intra- and peri-pancreatic bile duct in a progressively fibrotic pancreatitis. Pseudocysts of the head of the pancreas and abscesses can also cause biliary obstruction and persistent cholestasis.

Bile duct stenosis affects about 8% of patients with chronic alcoholic pancreatitis and this figure would be higher if more cholangiograms were done. It should be suspected if the serum alkaline phosphatase is more than twice elevated for longer than 1 month. ERCP shows a smooth narrowing of the lower end of the common bile duct, sometimes adopting a 'rat tail' configuration (fig. 36.5). The main pancreatic duct may be tortuous, irregular and dilated. Pancreatic calcification may be present.

Liver biopsy shows portal fibrosis, features of biliary obstruction, and sometimes biliary cirrhosis. Features of alcoholic liver disease are unusual. Hepatic fibrosis regresses after biliary decompression [21].

Splenic vein thrombosis is a complication of chronic pancreatitis.

Management

Early diagnosis of a biliary stricture due to pancreatitis is essential as biliary cirrhosis and acute cholangitis can develop in the absence of clinical jaundice.

If alcohol is responsible for the pancreatitis the patient must abstain completely.

The place of surgery is controversial. Clinical, laboratory and imaging data do not necessarily distinguish

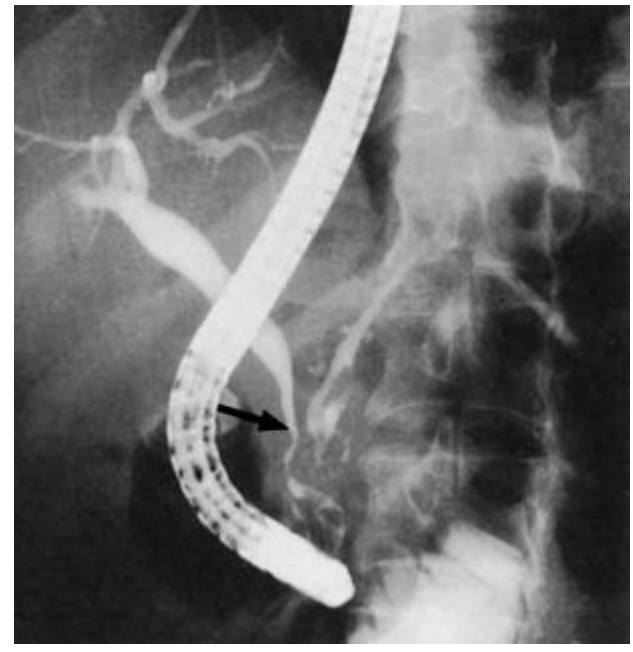


Fig. 36.5. ERCP in a patient with alcoholic chronic pancreatitis. Note the 'rat tail' narrowing of the distal common bile duct (arrow).

those patients with significant bile duct obstruction from those with alcoholic liver disease or normal liver histology [25]. Liver biopsy is valuable in deciding whether surgical decompression of the bile duct is necessary. Plastic and metal mesh stents successfully relieve bile duct obstruction due to chronic pancreatitis [13], but longer-term data are needed to judge whether this is an appropriate method of treatment. Acute cholangitis, biliary cirrhosis and protracted jaundice are strong indications for surgery [45]. Choledocho-enterostomy is the usual procedure.

Obstruction of the common bile duct by enlarged lymph glands

This is rare. The enlarged glands are nearly always metastatic, frequently from a primary in the alimentary tract, lung or breast, or from a hepato-cellular carcinoma.

Malignant glands in the porta hepatis are associated with deep jaundice, the main bile ducts usually being invaded rather than compressed. Secondary deposits in the hepatic parenchyma may also invade the bile ducts, causing segmental obstruction.

Glands along the common duct may be enlarged in non-malignant conditions, but the bile duct usually escapes compression. Jaundice in infections such as tuberculosis, sarcoidosis or infectious mononucleosis is not obstructive but due to direct hepatic involvement or haemolysis.

Glandular enlargement in the reticuloses does, very rarely, cause obstruction to the common bile duct, but jaundice complicating these diseases is more often due to hepatic parenchymal involvement, to increased haemolysis or loss of intra-hepatic bile ducts (Chapter 13).

Other causes of extrinsic pressure on the common bile duct

Duodenal ulceration

This is an extremely rare cause of obstructive jaundice. Perforation, so that the ulcer impinges against the bile duct or causes adhesive peritonitis, may rarely result in biliary obstruction. This can also follow scarring as the ulcer heals or endoscopic sclerosis for bleeding.

Duodenal diverticulum

Diverticula of the duodenum are often found near the ampulla of Vater, but rarely cause obstruction of the bile duct. They are associated with an increased rate of gallbladder and common bile duct stones, and the recurrence of duct stones [54].

References

1 Abulafi AM, Allardice JT, Williams NS *et al*. Photodynamic therapy for malignant tumours of the ampulla of Vater. *Gut* 1995; **36**: 853.

2 Adamek HE, Albert J, Breer H *et al*. Pancreatic cancer detection with magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography: a prospective controlled study. *Lancet* 2000: **356**; 190.

3 Aldridge MC. Islet cell tumours: surgical treatment. *Hosp. Med*. 2000; **61**: 830.

4 Arslan A, Buanes T, Geitung JT. Pancreatic carcinoma: MR, MR angiography and dynamic helical CT in the evaluation of vascular invasion. *Eur. J. Radiol*. 2001; **38**: 151.

5 Asbun HJ, Rossi RL, Munson JL. Local resection for ampullary tumours: is there a place for it? *Arch. Surg*. 1993; **128**: 515.

6 Bartsch DK, Schilling T, Ramaswamy A *et al*. Management of nonfunctioning islet cell carcinomas. *World J. Surg*. 2000; **24**: 1418.

7 Bornman PC, Harries-Jones EP, Tobias R *et al*. Prospective controlled trial of transhepatic biliary endoprosthesis vs. bypass surgery for incurable carcinoma of head of pancreas. *Lancet* 1986; **i**: 61.

8 Burris III HA, Moore MJ, Andersen J *et al*. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomised trial. *J. Clin. Oncol*. 1997: **15**; 2403.

9 Cameron JL, Crist DW, Sitzman JV *et al*. Factors influencing survival following pancreaticoduodenectomy for pancreatic cancer. *Am. J. Surg*. 1991; **161**: 120.

10 Cameron JL, Pitt HA, Yeo CJ *et al*. One hundred and forty-five consecutive pancreatico-duodenectomies without mortality. *Ann. Surg*. 1993; **217**: 430.

11 Connolly MM, Dawson PJ, Michelassi F *et al*. Survival in 1001 patients with carcinoma of the pancreas. *Ann. Surg*. 1987; **206**: 366.

12 Davids PHP, Groen AK, Rauws EAJ *et al*. Randomized trial of self-expanding metal stents vs. polyethylene stents for distal malignant biliary obstruction. *Lancet* 1992; **340**: 1488.

13 Deviere J, Cremer M, Baize M *et al*. Management of common bile duct stricture caused by chronic pancreatitis with metal mesh self expandable stents. *Gut* 1994; **35**: 122.

14 DiMagno EP, Reber HA, Tempero MA. AGA technical review on the epidemiology, diagnosis and treatment of pancreatic ductal adenocarcinoma. *Gastroenterology* 1999: **117**; 1464.

15 Dorandeu A, Raoul J-L, Siriser F *et al*. Carcinoma of the ampulla of Vater: prognostic factors after curative surgery: a series of 45 cases. *Gut* 1997; **40**: 350.

16 Erickson RA, Garza AA. Impact of endoscopic ultrasound on the management and outcome of pancreatic carcinoma. *Am. J. Gastroenterol*. 2000: **95**; 2248.

17 Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. *JAMA* 1995; **273**: 1605.

18 Fernandez-del Castillo C, Warshaw AL. Current management of cystic neoplasms of the pancreas. *Adv. Surg*. 2000; **34**: 237.

19 Freeny PC. Pancreatic carcinoma: imaging update 2001. *Dig. Dis*. 2001; **19**: 37.

20 Gastrointestinal Tumor Study Group, Kalser MH, Ellenberg SS. Further evidence of effective adjuvant combined radia-

tion and chemotherapy following curative resection of the pancreatic head. *Cancer* 1987; **59**: 2006.
21 Hammel P, Couvelard A, O'Toole D *et al*. Regression of liver fibrosis after biliary drainage in patients with chronic pancreatitis and stenosis of the common bile duct. *N. Engl. J. Med*. 2001; **344**: 418.
22 Kawa S, Tokoo M, Hasebe O *et al*. Comparative study of CA 242 and CA 19-9 for the diagnosis of pancreatic cancer. *Br. J. Cancer* 1994; **70**; 481.
23 Kurzawinski TR, Deery A, Dooley JS *et al*. A prospective study of biliary cytology in 100 patients with bile duct strictures. *Hepatology* 1993; **18**: 1399.
24 Legman P, Vignaus O, Dousser B *et al*. Pancreatic tumours: comparison of dual-phase helical CT and endoscopic sonography. *Am. J. Radiol*. 1998; **170**: 1315.
25 Lesur G, Levy P, Flejou J-F *et al*. Factors predictive of liver histopathological appearance in chronic alcoholic pancreatitis with common bile duct stenosis and increased serum alkaline phosphatase. *Hepatology* 1993; **18**: 1078.
26 Lewandrowski K, Lee J, Southern J *et al*. Cyst fluid analysis in the differential diagnosis of pancreatic cysts: a new approach to the preoperative assessment of pancreatic cystic lesions. *Am. J. Roentgenol*. 1995; **164**: 815.
27 Lillemoe KD, Cameron JL, Kaufman HS *et al*. Chemical splanchnicectomy in patients with unresectable pancreatic cancer: a prospective randomized trial. *Ann. Surg*. 1993; **217**: 447.
28 Lowenfels AB, Maisonneuve P, Cavallini G *et al*. Pancreatitis and the risk of pancreatic cancer. *N. Engl. J. Med*. 1993; **328**: 1433.
29 Lowenfels AB, Maisonneuve P, DiMagno EP *et al*. Hereditary pancreatitis and the risk of pancreatic cancer. *J. Natl. Cancer Inst*. 1997; **89**: 442.
30 McDowell RK, Gazelle GS, Murphy BL *et al*. Mucinous ductal ectasia of the pancreas. *J. Comput. Assist. Tomogr.* 1997; **21**: 383.
31 Menges M, Lerch MM, Zeitz M. The double duct sign in patients with malignant and benign pancreatic lesions. *Gastrointest. Endosc.* 2000; **52**: 74.
32 National Institute for Clinical Excellence (NICE) (2001). Guidance on gemcitabine for pancreatic cancer. HTTP://www.nice.org.uk. May 2001.
33 Nevitt AW, Vida F, Kozarek RA *et al*. Expandable metallic prostheses for malignant obstructions of gastric outlet and proximal small bowel. *Gastrointest. Endosc.* 1998; **47**: 271.
34 Norton ID, Geller A, Petersen BT *et al*. Endoscopic surveillance and ablative therapy for periampullary adenomas. *Am. J. Gastroenterol*. 2001; **96**: 101.
35 O'Brien S, Hatfield ARW, Craig PI *et al*. A three-year follow-up of self expanding metal stents in the endoscopic palliation of longterm survivors with malignant biliary obstruction. *Gut* 1995; **36**: 618.
36 Pemert J, Marsson J, Westermark GT *et al*. Islet amyloid polypeptide in patients with pancreatic cancer and diabetes. *N. Engl. J. Med*. 1994; **360**: 313.
37 Polati E, Finco G, Gottin L *et al*. Prospective randomized double-blind trial of neurolytic coeliac plexus block in patients with pancreatic cancer. *Br. J. Surg*. 1998; **85**: 199.
38 Prat F, Chapat O, Ducot B *et al*. A randomized trial of endoscopic drainage methods for inoperable malignant strictures of the common bile duct. *Gastrointest. Endosc.* 1998; **47**: 1.
39 Prat F, Chapat O, Ducot B *et al*. Predictive factors for survival of patients with inoperable malignant distal biliary strictures: a practical management guide. *Gut* 1998; **42**: 76.
40 Queneau P-E, Adessi G-L, Thibault P *et al*. Early detection of pancreatic cancer in patients with chronic pancreatitis: diagnostic utility of a K-*ras* point mutation in the pancreatic juice. *Am. J. Gastroenterol*. 2001: **96**; 700.
41 Rivera JA, Fernandez-del Castillo C, Rall CJN *et al*. Analysis of K-*ras* oncogene mutations in chronic pancreatitis with ductal hyperplasia. *Surgery* 1997; **121**: 42.
42 Smith AC, Dowsett JF, Russell RCG *et al*. Randomised trial of endoscopic stenting vs. surgical bypass in malignant low bileduct obstruction. *Lancet* 1994; **344**: 1655.
43 Soetikno RM, Lichtenstein DR, Vandervoort J *et al*. Palliation of malignant gastric outlet obstruction using an endoscopically placed Wallstent. *Gastrointest. Endosc.* 1998; **47**: 267.
44 Speer AG, Cotton PB, Russell RCG *et al*. Randomized trial of endoscopic vs. percutaneous stent insertion in malignant obstructive jaundice. *Lancet* 1987; **ii**: 57.
45 Stahl TJ, Allen MO'C, Ansel HJ *et al*. Partial biliary obstruction caused by chronic pancreatitis: an appraisal of indications for surgical biliary drainage. *Ann. Surg*. 1988; **207**: 26.
46 Stewart CJR, Mills PR, Carter R *et al*. Brush cytology in the assessment of pancreatico-biliary strictures: a review of 406 cases. *J. Clin. Pathol*. 2001; **54**: 449.
47 Taheri S, Meeran K. Islet cell tumours: diagnosis and medical management. *Hosp. Med*. 2000; **61**: 824.
48 Tersmette AC, Petersen GM, Offerhaus GJA *et al*. Increased risk of incident pancreatic cancer among first-degree relatives of patients with familial pancreatic cancer. *Clin. Cancer Res*. 2001; **7**: 738.
49 Traverso LW, Longmire WP Jr. Preservation of the pylorus in pancreaticoduodenectomy. *Surg. Gynecol. Obstet*. 1978; **146**: 959.
50 Van Laethem J-L, Vertongen P, Deviere J *et al*. Detection of c-K-*ras* gene codon 12 mutations from pancreatic duct brushings in the diagnosis of pancreatic tumours. *Gut* 1995; **36**: 781.
51 Warshaw AL, Zhuo-yun G, Wittenberg J *et al*. Preoperative staging and assessment of resectability of pancreatic cancer. *Arch. Surg*. 1990; **125**: 230.
52 Yamaguchi K, Enjoji M. Carcinoma of the ampulla of Vater. A clinico-pathologic study and pathologic staging of 109 cases of carcinoma and five cases of adenoma. *Cancer* 1987; **59**: 506.
53 Yamaguchi K, Enjoji M. Adenoma of the ampulla of Vater: putative precancerous lesion. *Gut* 1991; **32**: 1558.
54 Zoepf T, Zoepf D-S, Arnold JC *et al*. The relationship between juxtapapillary duodenal diverticula and disorders of the biliopancreatic system: analysis of 350 patients. *Gastrointest. Endosc.* 2001; **54**: 56.

Chapter 37
Tumours of the Gallbladder and Bile Ducts

Benign lesions of the gallbladder

At ultrasound, polypoid lesions of the gallbladder are occasionally seen and there is usually concern as to their nature and how to manage them. The vast majority are benign. They may be true tumours or pseudo-tumours. True tumours comprise adenoma, lipoma and leiomyoma. Pseudo-tumours include cholesterol polyps, inflammatory polyps and adenomyomatosis.

These lesions are seen most often as an echogeneic focus that projects into the gallbladder lumen, does not cast an acoustic shadow, and does not move when the patient is moved (unlike a stone). The diagnostic accuracy of ultrasound for the commonest lesions is 50–90% depending on the pathology [34].

Cholesterol polyps are usually multiple, with a higher echogenicity than liver, a pedicle and a mulberry-like surface [34]. They may contain a hyperechoic spot. Pathologically they consist of hypertrophied villi laden with cholesterol.

Adenoma is seen as a polypoid lesion which on ultrasound has an echogenicity similar to the liver, a smooth surface and usually no pedicle [34].

80%–90% of gallbladder polypoid lesions do not change in size on follow-up scans [41, 57]. However, they cause concern because of the low chance of malignancy in adenomas. Cholecystectomy will be done for the symptomatic patient. This is also appropriate for the lesion greater than 10 mm in diameter, where the risk of malignancy is greater [34]. Other features of malignant tumour are a sessile lesion, isoechoic with the liver, growing rapidly on serial ultrasounds.

Patients with a smaller lesion without these features should undergo a second scan. Some lesions disappear but the majority remain, and these patients may be offered a cholecystectomy for peace of mind. Alternatively, a repeat scan is done at 6-monthly intervals to detect any change in size [39]. In practice ultrasound lesions less than 10 mm in diameter with benign appearances in an asymptomatic patient tend to be treated conservatively but follow-up scanning is important. If the result of trans-abdominal ultrasound is inconclusive, endoscopic ultrasound if available is useful with a diagnostic accuracy for neoplastic lesions of 80% [10].

Carcinoma of the gallbladder [1]

This is an uncommon neoplasm. Gallstones coexist in about 75% of cases and chronic cholecystitis is a frequent association. There is a clear association with large, multiple gallbladder stones [62], but a causal relationship is unproven.

The calcified (porcelain) gallbladder is particularly likely to become cancerous [51]. An anomalous pancreatico-biliary ductal union, greater than 15 mm from the papilla of Vater, is associated with congenital cystic dilatation of the common bile duct and with gallbladder carcinoma [40]. Regurgitation of pancreatic juice may be tumorigenic. The common gallbladder cholesterol polyps are not precancerous.

Chronic typhoid infection of the gallbladder increases the risk of gallbladder carcinoma by 167-fold [6], emphasizing the need for antibiotic treatment to eradicate the chronic typhoid and paratyphoid carrier state, or for elective cholecystectomy.

Papillary adenocarcinoma starts as a wart-like excrescence. It grows slowly into, rather than through, the wall until a fungating mass fills the gallbladder. Mucoid change is associated with more rapid growth, early metastasis and gelatinous peritoneal carcinomatosis. *Squamous cell carcinoma* and *scirrhous* forms are recognized. The *anaplastic type* is particularly malignant. The most common tumour is a differentiated adenocarcinoma [1, 16] which may be papillary.

The tumour usually arises in the fundus or neck, but rapid spread may make the original site difficult to locate. The rich lymphatic and venous drainage of the gallbladder leads to early spread to related lymph nodes, causing cholestatic jaundice and widespread dissemination. The liver bed is invaded and there may also be local spread to the duodenum, stomach and colon resulting in fistulae or external compression.

Clinical. The patient is usually an elderly, white female, complaining of pain in the right upper quadrant, nausea, vomiting, weight loss and jaundice. Sometimes an unsuspected carcinoma is found in a cholecystectomy specimen at histology. These small lesions may not even be recognized at the time of operation [13].

Examination may reveal a hard and sometimes tender mass in the gallbladder area.

Serum, *urine* and *faeces* show the changes of cholestatic jaundice if the bile duct is compressed.

Ultrasound scanning shows a mass in the gallbladder lumen or totally replacing the gallbladder. With early lesions the differentiation between gallbladder carcinoma and a thickened wall due to acute or chronic cholecystitis is difficult.

CT may also show a mass in the area of the gallbladder. Ultrasound and CT detect carcinoma of the gallbladder in 60–70% of cases [45].

By the time an abnormality is shown by ultrasound or CT, extension is likely and the chance of total removal low. Endoscopic ultrasound images correlate with histological depth of invasion and are useful in staging [23].

ERCP shows external compression of the bile duct in the jaundiced patient. *Angiography* shows displacement of hepatic and portal blood vessels by the mass.

In only 50% of patients is a correct pre-operative diagnosis made [12].

Prognosis

This is generally hopeless because the majority are inoperable at the time of diagnosis. Distant metastases are already present in 50% of cases [16]. The only long-term survivors are those in whom the tumour was found incidentally at the time of cholecystectomy for gallstones (carcinoma *in situ*).

Median survival from diagnosis is 3 months, with only 14% alive at 1 year [12]. Patients with papillary and well-differentiated adenocarcinomas have longer survival than those with tubular and undifferentiated types [28]. The results of radical resection including partial hepatectomy and radical lymphadenectomy are conflicting [9, 16] with some series showing no survival benefit and others claiming increased survival.

Treatment

Cholecystectomy has been recommended for all patients with gallstones in an effort to prevent the development of carcinoma in the gallbladder. This seems drastic for a common condition, and would lead to a large number of unnecessary cholecystectomies.

The pre-operative diagnosis of carcinoma of the gallbladder should not preclude laparotomy although the results of surgical treatment are disappointing. Radical resection including partial hepatectomy has been attempted but with unsatisfactory results and no convincing evidence of improved survival [16]. The same applies to radiotherapy and chemotherapy [1].

Endoscopically or percutaneously placed biliary prostheses relieve bile duct obstruction.

Other tumours

Rarely other tumours develop in the gallbladder including leiomyosarcoma, rhabdomyosarcoma, oat cell carcinoma and carcinoid tumours.

Benign tumours of the extra-hepatic bile duct

These extremely rare tumours usually remain undetected until there is evidence of biliary obstruction and cholangitis. They are rarely diagnosed pre-operatively.

Recognition is important as resection is curative.

Papilloma is a polypoid tumour which projects into the lumen of the common bile duct. It is a small, soft, vascular tumour, which may be sessile or pedunculated. These tumours may be single or multiple; they may be cystic. Occasionally they undergo malignant change. Cholangiography may show a smooth mass projecting into the bile duct. Mucus secretion from the tumour can cause obstructive cholangitis.

Adenomyoma can be found anywhere in the biliary tract. It is firm and well circumscribed and varies in size up to 15 cm in diameter. It is cured by resection [11].

Fibroma is small and firm and causes early bile duct obstruction.

Granular cell tumour is of mesenchymal origin. It affects young women, usually black, causing cholestasis [5]. It must be distinguished from cholangiocarcinoma or localized sclerosing cholangitis. Tumours are uniformly resectable and curable.

Carcinoma of the bile duct (cholangiocarcinoma)

Carcinoma may arise at any point in the biliary tree from the small intra-hepatic bile ducts to the common bile duct (fig. 37.1).

The incidence of intra-hepatic cholangiocarcinoma is increasing. Studies from England and Wales [59] and the USA [48] show a 10-fold increase between the early 1970s and the mid-1990s. The explanation is unclear. Although improved diagnostic techniques for cholangiocarcinoma and primary sclerosing cholangitis may have played a part, they do not alone explain the marked increase in incidence and mortality. Mortality from extra-hepatic cholangiocarcinoma fell over the same period.

The treatment depends on the site. Resection is the rule for extra-hepatic tumours. For hilar cholangiocarcinoma surgical resection should always be considered but requires particular expertise because of the inaccessibility of hilar tumours, the proximity of the hepatic artery and portal vein and the need for hepatic resection in some patients. Even if not curative, surgical treatment may prolong survival with a good quality of life.

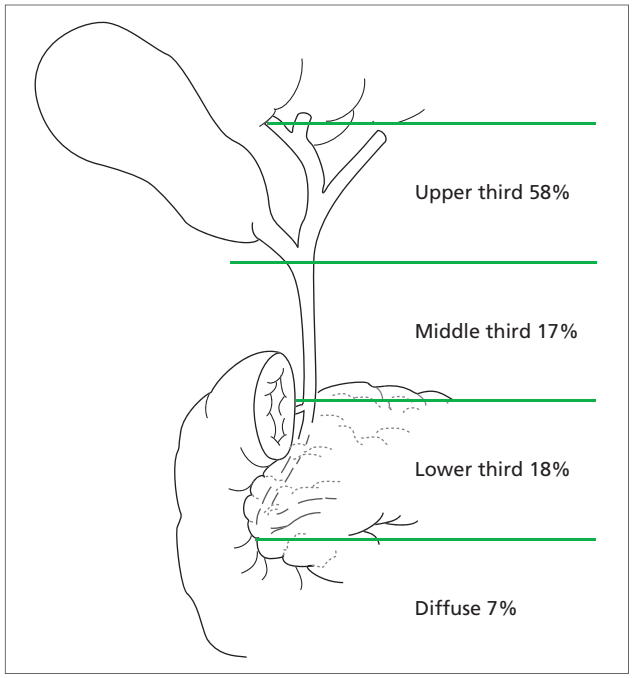


Fig. 37.1. Site of cholangiocarcinoma. The majority occur in the upper third of the bile duct [60].

Suspicion of cholangiocarcinoma, for example after ultrasound scan, should lead to referral to a specialist unit. This is to co-ordinate the work-up to evaluate resectability of the tumour. Modern CT techniques and MRI with MR cholangiography allow a high degree of non-invasive evaluation. The necessity and timing of invasive investigations depends on clinical circumstances. ERCP and non-operative drainage of bile percutaneously or after ERCP frequently introduce sepsis which may compromise later treatment [29, 42]. These aspects emphasize the importance of a multidisciplinary approach.

In those who are inoperable, biliary drainage by interventional radiologist or endoscopist relieves pruritus and usually jaundice to allow satisfactory palliation.

Associations

Bile duct cancer is associated with ulcerative colitis with or without sclerosing cholangitis (Chapter 15). The majority of patients with primary sclerosing cholangitis who develop cholangiocarcinoma have ulcerative colitis. Patients with primary sclerosing cholangitis and ulcerative colitis who also have colorectal neoplasia (dysplasia/carcinoma) are at greater risk of cholangiocarcinoma than those without colonic neoplasia [4].

In a group of 70 patients with primary sclerosing cholangitis followed prospectively for a mean of 30 months, 15 patients died of liver failure. Five of 12 patients (40%) having an autopsy had cholangiocarcinoma—7% of the total group [54].

Biliary malignancy is not necessarily a late complication of primary sclerosing cholangitis. 30% of patients in one series had a diagnosis of cholangiocarcinoma made within 1 year of the first evidence of underlying liver disease based on abnormal liver function tests [37]. Clinical features associated with malignancy were epigastric pain, weight loss and raised CA 19-9 and carcinoembryonic antigen (CEA) [37].

All members of the congenital fibropolycystic family may be complicated by adenocarcinoma (Chapter 33). These include congenital hepatic fibrosis, cystic dilatation (Caroli's syndrome), choledochal cyst, polycystic liver and von Meyenburg complexes. Cholangiocarcinoma may be associated with biliary cirrhosis due to biliary atresia.

The liver fluke infestations of the Orient may be complicated by intra-hepatic (cholangiocellular) cholangiocarcinoma. In the Far East (China, Hong Kong, Korea, Japan), where *Clonorchis sinensis* is prevalent, cholangiocarcinoma accounts for 20% of primary liver tumours. These arise in the heavily parasitized bile ducts near the hilum.

Opisthorchis viverrini infestation is important in Thailand, Laos and western Malaysia [35]. These parasites induce DNA changes and mutations through the production of carcinogens and free radicals, and the stimulation of cellular proliferation of intra-hepatic bile duct epithelium [46].

The risk of extra-hepatic bile duct carcinoma is significantly lower 10 years or more after cholecystectomy, suggesting a link with gallstones [17].

Pathology

The confluence of the cystic duct with the main hepatic duct or the right and left main hepatic ducts at the porta hepatis are common sites of origin (fig. 37.1). Tumours of the hepatic ducts extend into the liver. They cause complete obstruction of the extra-hepatic bile ducts with intra-hepatic biliary dilatation and enlargement of the liver. The gallbladder is collapsed and flaccid. If the tumour is restricted to one hepatic duct, biliary obstruction is incomplete and jaundice absent. The lobe of the liver drained by this duct atrophies and the other hypertrophies.

In the common bile duct the tumour presents as a firm nodule or plaque which causes an annular stricture which may ulcerate. It spreads along the bile duct and through its wall.

Local and distant metastases, even at autopsy, are found in only about half of the patients. They involve peritoneum, abdominal lymph nodes, diaphragm, liver

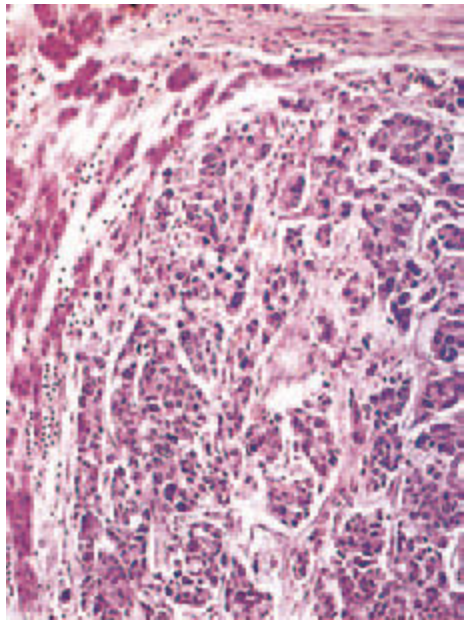


Fig. 37.2. Bile duct carcinoma: with irregular fibrous stroma. (H & E, × 40.)

or gallbladder. Blood vessel invasion is rare and extra-abdominal spread is unusual.

Histologically the tumour is usually a mucin-secreting adenocarcinoma with cuboidal or columnar epithelium (fig. 37.2). Spread along neural sheaths may be noted. Tumours around the hilum are sclerosing with an abundant fibrous stroma. More distal ones are nodular or papillary.

Molecular changes

Point mutations in codon 12 of the K-*ras* oncogene are found in cholangiocarcinoma [65]. *p53* protein is expressed particularly in high-grade mid and distal duct cholangiocarcinomas [15]. *Aneuploidy* (divergence from the normal chromosome content) is found in hilar cholangiocarcinoma [55] and is associated with neural invasion and shorter survival.

Cholangiocarcinoma cells contain *somatostatin receptor* RNA and cell lines have specific receptors. Cell growth is inhibited by somatostatin analogues.

Clinical features

This tumour tends to occur in the older age group, patients being about 60 years old. Slightly more males than females are affected.

Jaundice is the usual presenting feature, followed by pruritus—a point of distinction from primary biliary cirrhosis where itching usually comes first. Jaundice may be delayed if only one main hepatic duct is involved. The trend of the serum bilirubin level is always upward, but periods of clearing of jaundice are found in up to 50% [31].

Pain, usually epigastric and mild, is present in about one-third of patients. Diarrhoea may be related to steatorrhoea. Weakness and weight loss are marked.

The condition may be associated with chronic ulcerative colitis, often following long-standing cholestasis due to sclerosing cholangitis.

Examination. Jaundice is deep. Cholangitis is unusual unless the bile ducts have been interfered with surgically, endoscopically or percutaneously.

The liver is large and smooth, extending 5–12 cm below the costal margin. The spleen is not felt. Ascites is unusual.

Investigations

Serum biochemical findings are those of cholestatic jaundice. The serum bilirubin, alkaline phosphatase and γ-glutamyl transpeptidase levels may be very high. Fluctuations may reflect incomplete obstruction or primary involvement of one hepatic duct.

The serum mitochondrial antibody test is negative and α-fetoprotein is not increased.

The *faeces* are pale and fatty and occult blood is often present. *Glycosuria* is absent.

Anaemia may be greater than that seen with ampullary carcinoma; the explanation is unknown—it is not due to blood loss. The leucocyte count is high normal with increased polymorphs.

Liver biopsy shows features of large bile duct obstruction. In primary sclerosing cholangitis biliary dysplasia raises the possibility of coexistent cholangiocarcinoma [20].

Cytology taken at the time of ERCP or percutaneous drainage is worthwhile, but requires cytological expertise for interpretation. Brush cytology is better than analysis of aspirated bile, with a sensitivity of 60% [56]. Other approaches include fine-needle aspiration cytology from the suspected tumour, done under ultrasound or fluoroscopy. Aspiration cytology guided by endoscopic ultrasound is also valuable but this expertise is rare [22].

In primary sclerosing cholangitis, brush cytology of dominant strictures at ERCP has a sensitivity of 60% for cholangiocarcinoma [52]. *p53* and K-*ras* mutation analysis does not increase sensitivity. However, K-*ras* mutations may be found ahead of the diagnosis of cholangiocarcinoma in patients with primary sclerosing cholangitis [33].

The serum concentration of the tumour marker CA 19-9 is often increased in patients with biliary tract

malignancy. Levels are also increased by cholangitis and cholestasis. The sensitivity for detecting cholangiocarcinoma in primary sclerosing cholangitis is 50–60% [3, 47]. Combining CA 19-9 with CEA measurement does not increase sensitivity. Although CA 19-9 only has a moderate sensitivity, it has a role in surveillance of selected patients with primary sclerosing cholangitis if only because early detection of bile duct malignancy by any means is difficult.

Scanning

Ultrasound shows dilated intra-hepatic ducts with a normal extra-hepatic biliary tree. A tumour mass may be shown in up to 80% of cases. Ultrasound (real-time together with Doppler) accurately detects neoplastic involvement of the portal vein, both occlusion and wall infiltration, but is less good in showing hepatic arterial involvement [43]. Intra-duct ultrasound is still experimental but can provide important information on tumour extension in and around the bile duct [58].

Enhanced CT shows bile duct dilatation, and detects tumours in 40–70% of patients. Helical CT detects cholangiocarcinoma, as small as 15 mm diameter, in 90% of patients, and provides information on parenchymal, intra-hepatic bile duct and portal involvement [19]. It underestimates extra-hepatic bile duct involvement, hepatic arterial invasion and lymph node spread.

Overall, magnetic resonance cholangiography has an accuracy for bile duct stones and strictures of over 90%. In cholangiocarcinoma (fig. 37.3) it correctly delineates duct obstruction and the extent of hilar tumour extension in 80% of patients. It underestimates tumour extension in 20% [66]. MRI with MRCP is an important technique for planning the treatment of malignant hilar strictures but does not replace invasive cholangiography which also allows brushings to be taken for cytology and bile drainage if indicated.

CT and MRI therefore may show bile duct obstruction and a mass but differentiation between inflammatory and malignant biliary strictures generally depends upon invasive techniques to obtain cytology and biopsy. There is a diagnostic problem particularly in primary sclerosing cholangitis. PET scanning using [^{18}F] fluoro-2-deoxy-D-glucose has been reported to detect cholangiocarcinomas in patients with and without primary sclerosing cholangitis with a sensitivity of 90% [30, 32]. If substantiated this would represent an advance in the management particularly of patients with primary sclerosing cholangitis, although false-positive scans have been seen in normal individuals [32].

Cholangiography

With the newer non-invasive imaging modalities now available, the role of direct cholangiography has changed. Some specialist units rely on Doppler ultrasound and MRCP and avoid instrumentation of the biliary tree before surgery [7]. Hepatobiliary units have their individual approach and tailor this to the patient.

Endoscopic or percutaneous cholangiography, or both, still have a role (fig. 37.3). However, as emphasized above, they are not done immediately after ultrasound has shown a hilar bile duct obstruction. Jaundice is often felt to be dangerous, needing immediate treatment, but this is only so for the septic patient or when there is renal failure. It is prudent to investigate the patient non-invasively to judge the nature and extent of the hilar lesion, and then consider direct cholangiography, cytology and drainage when the management plan is clear. MRCP may be used to select the duct system for endoscopic stent drainage [27] or percutaneous puncture.

In hilar cholangiocarcinoma, ERCP shows the normal common bile duct and gallbladder with obstruction at the hilum (fig. 37.3c). Contrast usually passes through the stricture(s) into dilated bile ducts above. The stricture is passed with a guide-wire, cytology is done, and a stent placed.

Percutaneous cholangiography shows the dilated intra-hepatic ducts down to the stricture (fig. 37.3d). A drain is inserted. When right and left hepatic ducts are individually obstructed, puncture of both systems may be necessary to outline the obstruction accurately. Some specialist surgeons prefer the percutaneous rather than endoscopic approach to the system because it provides detailed information on tumour extension within the liver and intra-hepatic bile ducts. This is of more value than the appearances of the extra-hepatic biliary tree below the stricture.

Angiography

Digital subtraction angiography (DSA) shows the hepatic artery and portal vein and their intra-hepatic branches. Its use depends upon the information derived from ultrasound, CT and MRI.

Diagnosis

In the patient with deepening cholestatic jaundice the clinical diagnosis is likely to be carcinoma of the periampullary region. Other possibilities are drug jaundice, primary sclerosing cholangitis (Chapter 15) and primary biliary cirrhosis (Chapter 14). Cholangiocarcinoma is an

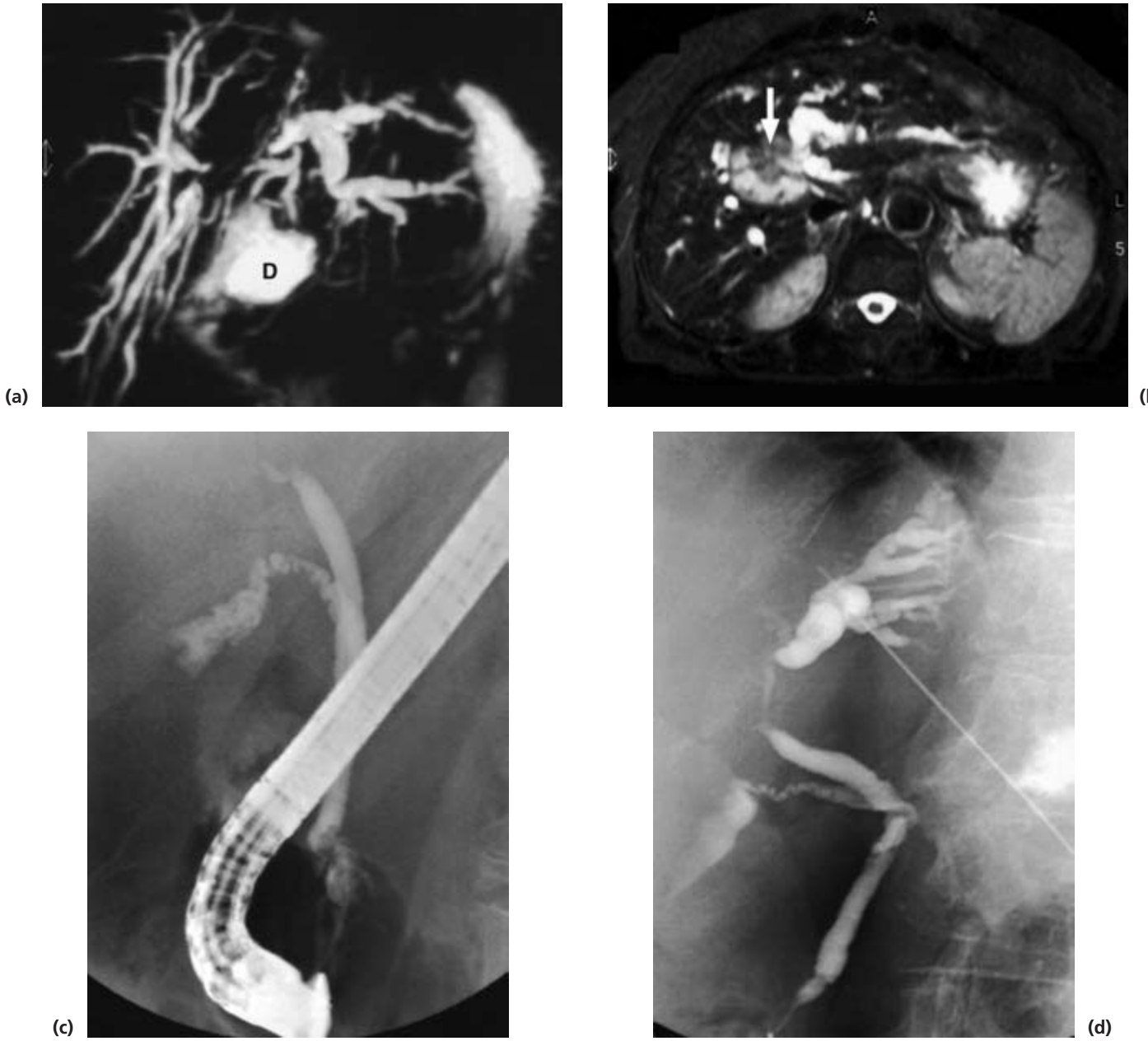


Fig. 37.3. A 75-year-old woman presenting with cholestatic jaundice. Ultrasound showed dilated intra-hepatic ducts, a hilar mass and a normal common bile duct. (a) MRCP shows dilated intra-hepatic ducts with at least three segments obstructed in the right lobe and the left hepatic system obstructed at the hilum. If non-surgical drainage is to be done, these appearances favour drainage of the left- rather than the right-sided system (D, duodenum). (b) MRI scan shows a mass in the liver (arrow) above the hilum. (c) Non-operative drainage was chosen since the patient was considered inoperable. ERCP shows a normal common duct with a hilar structure. A stent could not be placed. (d) Following on the MRCP appearances, the left-sided duct system was chosen for percutaneous cholangiography and a stent inserted.

unusual cause but it should be detected if an orderly work-up is used. History and examination are usually unhelpful.

The first step in the cholestatic patient is ultrasound scanning. Intra-hepatic bile ducts will be dilated in cholangiocarcinoma. The common duct is normal, equivocal or may be dilated down to an extra-hepatic tumour. If there is a suspicion of hilar cholangiocarcinoma and other clinical features do not indicate inoperability, the choice is MRCP or, if this is not available, referral to a specialist hepato-biliary unit.

If ultrasound does not show dilated bile ducts in the

cholestatic patient, other causes (Chapter 13) need to be considered including drug jaundice (history) and primary biliary cirrhosis (anti-mitochondrial antibody). Liver histology will help. If primary sclerosing cholangitis is possible, cholangiography is diagnostic.

With scanning and cholangiography it should be possible to diagnose the bile duct stricture due to cholangiocarcinoma. At the hilum, the differential diagnosis is a benign stricture [25] or metastatic gland, in the mid-duct carcinoma of the gallbladder, and in the peri-ampullary region carcinoma of the pancreas. Differentiation will depend upon history and other imaging techniques.

Prognosis

Prognosis depends on the site of the tumour. Those distally placed are more likely to be resectable than those at the hilum. The histologically differentiated do better than the undifferentiated. Polypoid cancers have the best prognosis.

If unresected, the 1-year survival for cholangio carcinoma is 50%, with 20% surviving at 2 years and 10% at 3 years [18]. This reflects that some tumours are slow growing and metastasize late. Jaundice can be relieved surgically or by endoscopic or percutaneous stenting. The tumour kills by its site making it inoperable, rather than by its malignancy. Average survival after resection is longer, making proper assessment in patients fit for surgery essential.

Staging [7]

If the clinical state of the patient does not rule out surgery the resectability and extent of tumour is assessed. Metastases, usually late, should be sought.

Low and mid common bile duct lesions are usually resectable although vascular imaging is needed to exclude invasion.

Hilar cholangiocarcinoma is more problematic (table 37.1). If cholangiography shows involvement of the secondary hepatic ducts in both hepatic lobes (fig. 37.4, type IV) or imaging shows encasement of the main portal vein or hepatic artery, the lesion is irresectable. A palliative procedure is needed.

If the tumour is limited to the hepatic duct bifurcation, affecting one lobe of the liver only, or only obstructs the portal vein or hepatic artery on the same side, the lesion may be resectable. Pre-operative imaging is aimed at establishing whether after surgical removal a viable unit of liver remains [7]. This must contain a biliary radicle large enough to anastomose to bowel, and a normal portal vein and hepatic arterial branch. At surgery, further assessment is done with intraoperative ultrasound and a search for lymph node involvement.

In a department with a high resection rate, preoperative cholangiography predicted clinical management in 62% of patients, and angiography determined management in 80% [38].

Treatment

Surgery

Tumours of the lower bile duct may be resected with a 1-year survival of about 70%. More proximal tumours may be resected by local or major liver surgery including excision of the whole bifurcation of the common hepatic duct, lobectomy if necessary and bilateral hepatico-jejunostomy.

Table 37.1. Criteria of irresectability for hilar cholangiocarcinoma

Bilateral bile duct involvement or multifocal disease on cholangiography
Main trunk of portal vein encased/occluded
Bilateral involvement of hepatic arterial or portal vein branches or both
Unilateral hepatic artery involvement and extensive contralateral bile duct involvement

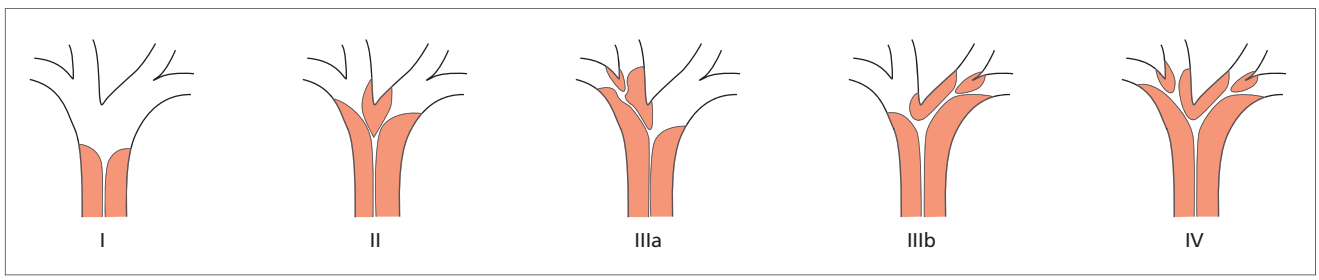


Fig. 37.4. Classification of hilar cholangiocarcinoma according to the involvement of bile ducts. Resectability of type I to III depends on angiographic findings. Type IV (bilateral involvement of secondary hepatic ducts) indicates incurable disease. In inoperable patients median survival after stent insertion depends upon the extent of tumour [53].

Some advocate caudate lobectomy, based on the observation that two to three bile ducts from this lobe drain directly into the main bile ducts adjacent to the confluence of the hepatic ducts and thus are likely to be involved by tumour.

The proportion of cholangiocarcinomas being resected has increased from 5–20% of patients in the 1970s to 30% or more in specialist centres in the 1990s. This relates to earlier diagnosis and referral to a tertiary centre, more accurate and complete pre-operative assessment, and a more aggressive surgical approach. The problem is to achieve a resection with tumour-negative margins. Median survival after aggressive resection of hilar cholangiocarcinoma is 18–40 months with good palliation for most of this time [7, 38]. Local resection of Bismuth type I and II tumours (fig. 37.4) carries a peri-operative mortality of 5% or less. Liver resection is needed for type III lesions, and carries a greater morbidity and mortality.

Liver transplantation is not appropriate for cholangiocarcinoma because of early recurrence in the majority [64].

Surgical palliative procedures include anastomosis of jejunum to the segment III duct in the left lobe which is usually accessible despite the hilar tumour (fig. 37.5). Jaundice is relieved for at least 3 months in 75% of patients [26]. If segment III bypass is not possible (atrophy, metastases), a right-sided intra-hepatic anastomosis to the segment V duct can be done.

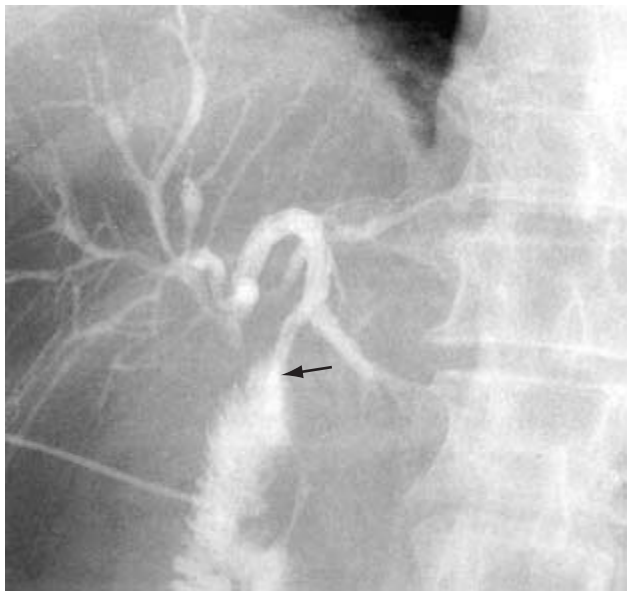


Fig. 37.5. Check cholangiogram after surgical bypass for hilar cholangiocarcinoma. The anastomosis is between the jejunum and the third segment duct of the left lobe (arrow).

Non-surgical palliation

In those patients unfit for surgery or with irresectable tumours, jaundice and itching may be relieved by placing an endoprosthesis across the stricture either by the endoscopic or percutaneous route.

By the endoscopic route, stents can be inserted successfully in about 90% of patients if a combined endoscopic/percutaneous procedure is included after a failed endoscopic attempt. The major early complication is cholangitis (7%). Thirty-day mortality is between 10 and 28% depending upon the extent of the tumour at the hilum and the mean survival is 20 weeks [53]. Stenting of only one lobe is necessary [14].

Percutaneous trans-hepatic endoprosthesis insertion is also successful but carries with it a higher risk of complications such as bleeding and bile leakage (Chapter 32). Metal mesh endoprostheses, which expand to 10 mm diameter in the stricture after insertion of a 5 or 7 French catheter, are more expensive than plastic types, but have longer patency for peri-ampullary strictures [36]. They may be used for hilar strictures. Studies suggest a similar advantage over plastic endoprostheses [63] but their insertion requires an experienced operator.

There are no trials comparing surgical versus non-surgical palliation. There are benefits and disadvantages of both approaches [44]. Generally, non-operative techniques are appropriate for high-risk patients expected to have a shorter survival. Because of recurrent stent blockage requiring replacement [24], surgical bypass should be considered as an alternative palliative approach.

Internal radiotherapy using an iridium-192 wire or radium needles may be combined with biliary drainage [21]. The value of this technique is unproven. Cytotoxic drugs are ineffective. External radiotherapy has appeared to show some benefit in retrospective studies but in a randomized trial showed no benefit [50]. Intra-duct photodynamic therapy combined with stenting has given encouraging results in Bismuth type III and IV cholangiocarcinoma [2]. There is a local tumour response of 30–75% and hilar bile ducts occlusion can be reversed. The treatment is costly and controlled studies are needed to establish survival benefit. Symptomatic treatment is that of chronic cholestasis (Chapter 13).

Cholangiocellular carcinoma

This intra-hepatic bile duct derived tumour is classified as a primary hepatic carcinoma. It becomes symptomatic as it enlarges producing abdominal pain rather than jaundice [8]. It grows rapidly with early metastasis and a particularly poor prognosis. There is an association with Thorotrast (thorium dioxide), an intravenous contrast medium used many years ago. Scanning shows an intra-hepatic mass. Distinction from hepato-cellular carci-

noma may be difficult. Hepatic venous and portal vein involvement is rare. Surgery is the only chance for effective treatment. Resection is possible in 30–60% of cases [8]. One-year survival after resection is 50–60%. Transplantation for irresectable tumour gives a median survival of 5 months [49].

Metastases at the hilum

Cholestatic jaundice developing following the diagnosis of carcinoma elsewhere (in particular the colon) may be due to diffuse metastases within the liver or duct obstruction by nodes at the hilum. Differentiation between the two is by ultrasound. If dilated bile ducts are shown and the patient is symptomatic with itching, biliary obstruction can be relieved by insertion of an endoprosthesis by the endoscopic or percutaneous approach [61]. Palliation is achieved depending upon the extent of tumour but the 30-day mortality is greater and the survival significantly shorter compared with endoprosthesis insertion for primary bile duct malignancy [53].

References

1 Bartlett DL. Gallbladder cancer. *Semin. Surg. Oncol.* 2000; **19**: 145.

2 Berr F, Wiedmann M, Tannapfel A *et al*. Photodynamic therapy for advanced bile duct cancer: evidence for improved palliation and extended survival. *Hepatology* 2000; **31**: 291.

3 Björnsson E, Kilander A, Olsson R. CA 19-9 and CEA are unreliable markers for cholangiocarcinoma in patients with primary sclerosing cholangitis. *Liver* 1999; **19**: 501.

4 Broomé U, Löfberg R, Veress B *et al*. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. *Hepatology* 1995; **22**: 1404.

5 Butterly LF, Schapiro RH, LaMuraglia GM *et al*. Biliary granular cell tumour: a little-known curable bile duct neoplasm of young people. *Surgery* 1988; **103**: 328.

6 Caygill CPJ, Hill MJ, Braddick M *et al*. Cancer mortality in chronic typhoid and paratyphoid carriers. *Lancet* 1994; **373**: 83.

7 Chamberlain RS, Blumgart LH. Hilar cholangiocarcinoma: a review and commentary. *Ann. Surg. Oncol.* 2000; **7**: 55.

8 Chen M-F. Peripheral cholangiocarcinoma (cholangiocellular carcinoma): clinical features, diagnosis and treatment. *J. Gastroenterol. Hepatol.* 1999; **14**: 1144.

9 Chijiiwa K, Tanaka M. Carcinoma of the gallbladder: an appraisal of surgical resection. *Surgery* 1994; **115**: 751.

10 Choi W-B, Lee S-K, Kim M-H *et al*. A new strategy to predict the neoplastic polyps of the gallbladder based on a scoring system using EUS. *Gastrointest. Endosc.* 2000; **52**: 372.

11 Cook DJ, Salena BJ, Vincic LM. Adenomyoma of the common bile duct. *Am. J. Gastroenterol.* 1988; **83**: 432.

12 Cubertafond P, Gainant A, Cucchiaro G. Surgical treatment of 724 carcinomas of the gallbladder. Results of the French Surgical Association Survey. *Ann. Surg.* 1994; **219**: 275.

13 De Aretxabala X, Roa I, Brugos L *et al*. Gallbladder cancer in Chile: a report on 54 potentially resectable tumours. *Cancer* 1992; **69**: 60.

14 De Palma GD, Galloro G, Siciliano S *et al*. Unilateral vs. bilateral endoscopic hepatic duct drainage in patients with malignant hilar biliary obstruction: results of a prospective, randomized, and controlled study. *Gastrointest. Endosc.* 2001; **53**: 547.

15 Diamantis I, Karamitopoulou E, Perentes E *et al*. p53 protein immunoreactivity in extrahepatic bile duct and gallbladder cancer: correlation with tumour grade and survival. *Hepatology* 1995; **22**: 774.

16 Donohue JH, Nagorney DM, Grant CS *et al*. Carcinoma of the gallbladder: does radical resection improve outcome? *Arch. Surg.* 1990; **125**: 237.

17 Ekbom A, Hsieh C, Yuen J *et al*. Risk of extra hepatic bile duct cancer after cholecystectomy. *Lancet* 1993; **372**: 1262.

18 Farley DR, Weaver AL, Nagorney DM. 'Natural history' of unresected cholangiocarcinoma: patient outcome after noncurative intervention. *Mayo Clin. Proc.* 1995; **70**: 425.

19 Feydy A, Vilgrain V, Denys A *et al*. Helical CT assessment in hilar cholangiocarcinoma: correlation with surgical and pathologic findings. *Am. J. Roentgenol.* 1999; **172**: 73.

20 Fleming KA, Boberg KM, Glaumann H *et al*. Biliary dysplasia as a marker of cholangiocarcinoma in primary sclerosing cholangitis. *J. Hepatol.* 2001; **34**: 360.

21 Fletcher MS, Brinkley D, Dawson JL *et al*. Treatment of hilar carcinoma by bile drainage combined with internal radiotherapy using 192-iridium wire. *Br. J. Surg.* 1983; **70**: 733.

22 Fritscher-Ravens A, Broering DC, Sriram PVJ *et al*. EUS-guided fine-needle aspiration cytodiagnosis of hilar cholangiocarcinoma: a case series. *Gastrointest. Endosc.* 2000; **52**: 534.

23 Fujita N, Noda Y, Kobayashi G *et al*. Diagnosis of the depth of invasion of gallbladder carcinoma by EUS. *Gastrointest. Endosc.* 1999; **50**: 659.

24 Gerhards MF, den Hartog D, Rauws EA *et al*. Palliative treatment in patients with unresectable hilar cholangiocarcinoma: results of endoscopic drainage in patients with type III and IV hilar cholangiocarcinoma. *Eur. J. Surg.* 2001; **167**: 274.

25 Gerhards MF, Vos P, van Gulik TM *et al*. Incidence of benign lesions in patients resected for suspicious hilar obstruction. *Br. J. Surg.* 2001; **88**: 48.

26 Guthrie CM, Banting SW, Garden OJ *et al*. Segment III cholangiojejunostomy for palliation of malignant hilar obstruction. *Br. J. Surg.* 1994; **81**: 1639.

27 Hintze RE, Abou-Rebyeh H, Adler A *et al*. Magnetic resonance cholangiopancreatography-guided unilateral endoscopic stent placement for Klatskin tumours. *Gastrointest. Endosc.* 2001; **53**: 40.

28 Hisatomi K, Haratake J, Horie A *et al*. Relation of histopathological features to prognosis of gallbladder cancer. *Am. J. Gastroenterol.* 1990; **85**: 567.

29 Hochwald SN, Burke EC, Jarnagin WR *et al*. Association of preoperative biliary stenting with increased postoperative infectious complications in proximal cholangiocarcinoma. *Arch. Surg.* 1999; **134**: 261.

30 Keiding S, Hansen SB, Rasmussen HH *et al*. Detection of cholangiocarcinoma in primary sclerosing cholangitis by positron emission tomography. *Hepatology* 1998; **28**: 700.

31 Klatskin G. Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis. An unusual tumour with

distinctive clinical and pathological features. *Am. J. Med.* 1965; **38**: 24.
32 Kluge R, Schmidt F, Caca K *et al*. Positron emission tomography with [^{18}F] fluoro-2-deoxy-D-glucose for diagnosis and staging of bile duct cancer. *Hepatology* 2001; **33**: 1029.
33 Kubicka S, Kohnel F, Flemming P *et al*. K-ras mutations in the bile of patients with primary sclerosing cholangitis. *Gut* 2001; **48**: 403.
34 Kubota K, Bandai Y, Noie T *et al*. How should polypoid lesions of the gallbladder be treated in the era of laparoscopic cholecystectomy? *Surgery* 1995; **117**: 481.
35 Kurathong S, Lerdverasirikul P, Wongpaitoon V *et al*. *Opisthorchis viverrini* infection and cholangiocarcinoma. A prospective, case-controlled study. *Gastroenterology* 1985; **89**: 151.
36 Lammer J, Hausegger KA, Flockiger F *et al*. Common bile duct obstruction due to malignancy: treatment with plastic vs. metal stents. *Radiology* 1996; **201**: 167.
37 Leidenius M, Höckerstedt K, Broomé U *et al*. Hepatobiliary carcinoma in primary sclerosing cholangitis: a case control study. *J. Hepatol.* 2001; **34**: 792
38 Lillemoe KD, Cameron JL. Surgery for hilar cholangiocarcinoma: the Johns Hopkins approach. *J. Hepatobil. Pancreat. Surg.* 2000; **7**: 115.
39 Mainprize KS, Gould SWT, Gilbert JM. Surgical management of polypoid lesions of the gallbladder. *Br. J. Surg.* 2000; **87**: 414.
40 Misra SP, Dwivedi M. Pancreaticobiliary ductal union. *Gut* 1990; **31**: 1144.
41 Moriguchi H, Tazawa J, Hayashi Y *et al*. Natural history of polypoid lesions in the gall bladder. *Gut* 1996; **39**: 860.
42 Nakeeb A, Pitt HA. The role of preoperative biliary decompression in obstructive jaundice. *Hepatogastroenterology* 1995; **42**: 332.
43 Neumaier CE, Bertolotto M, Perrone R *et al*. Staging of hilar cholangiocarcinoma with ultrasound. *J. Clin. Ultrasound* 1995; **23**: 173.
44 Nordback IH, Pitt HA, Coleman J *et al*. Unresectable hilar cholangiocarcinoma: percutaneous vs. operative palliation. *Surgery* 1994; **115**: 597.
45 Oikarinen H, Paivansalo M, Lahde S *et al*. Radiological findings in cases of gallbladder carcinoma. *Eur. J. Radiol.* 1993; **17**: 179.
46 Parkin DM, Ohshima H, Srivatanakul P *et al*. Cholangiocarcinoma: epidemiology, mechanisms of carcinogenesis and prevention. *Cancer Epidemiol. Biomarkers Prev.* 1993; **2**: 537.
47 Patel AH, Harnois DM, Klee GG *et al*. The utility of CA 19–9 in the diagnoses of cholangiocarcinoma in patients without primary sclerosing cholangitis. *Am. J. Gastroenterol.* 2000; **95**: 204.
48 Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. *Hepatology* 2001; **33**: 1353.
49 Pichlmayr R, Lamesch P, Weimann A *et al*. Surgical treatment of cholangiocellular carcinoma. *World J. Surg.* 1995; **19**: 83.
50 Pitt HA, Nakeeb A, Abrams RA *et al*. Perihilar cholangiocarcinoma. Postoperative radiotherapy does not improve survival. *Ann. Surg.* 1995; **221**: 788.
51 Polk HC. Carcinoma and calcified gallbladder. *Gastroenterology* 1966; **50**: 582.
52 Ponsioen CY, Vrouenraets SME, van Milligen de Wit AWM *et al*. Value of brush cytology for dominant strictures in primary sclerosing cholangitis. *Endoscopy* 1999; **31**: 305.
53 Polydorou AA, Cairns SR, Dowsett JF *et al*. Palliation of proximal malignant biliary obstruction by endoscopic endoprosthesis insertion. *Gut* 1991; **32**: 685.
54 Rosen CB, Nagorney DM, Wiesner RH *et al*. Cholangiocarcinoma complicating primary sclerosing cholangitis. *Ann. Surg.* 1991; **213**: 21.
55 Sato Y, van Gulik TM, Bosma A *et al*. Prognostic significance of tumour DNA content in carcinoma of the hepatic duct confluence. *Surgery* 1994; **115**: 488.
56 Stewart CJR, Mills PR, Carter R *et al*. Brush cytology in the assessment of pancreatico-biliary strictures: a review of 406 cases. *J. Clin. Pathol.* 2001; **54**: 449.
57 Sugiyama M, Atomi Y, Yamato T. Endoscopic ultrasonography for differential diagnosis of polypoid gall bladder lesions: analysis in surgical and follow up series. *Gut* 2000; **46**: 250.
58 Tamada K, Ido K, Ueno N *et al*. Preoperative staging of extrahepatic bile duct cancer with intraductal ultrasonography. *Am. J. Gastroenterol.* 1995; **90**: 239.
59 Taylor-Robinson SD, Toledano MB, Arora S *et al*. Increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968–98. *Gut* 2001; **48**: 816.
60 Tompkins RK, Saunders KD, Roslyn JJ *et al*. Changing patterns in diagnosis and management of bile duct cancer. *Ann. Surg.* 1990; **211**: 614.
61 Valiozis I, Zekry A, Williams SJ *et al*. Palliation of hilar biliary obstruction from colorectal metastases by endoscopic stent insertion. *Gastrointest. Endosc.* 2000; **51**: 412.
62 Vitetta L, Sali A, Little P *et al*. Gallstones and gall bladder carcinoma. *Aust. NZ J. Surg.* 2000; **70**: 667.
63 Wagner H-J, Knyrim K, Vakil N *et al*. Plastic endoprostheses vs. metal stents in the palliative treatment of malignant hilar biliary obstruction: a prospective randomized trial. *Endoscopy* 1993; **25**: 213.
64 Wall WJ. Liver transplantation for hepatic and biliary malignancy. *Semin. Liver Dis.* 2000; **20**: 425.
65 Watanabe M, Asaka M, Tanaka J *et al*. Point mutation of K-*ras* gene codon 12 in biliary tract tumours. *Gastroenterology* 1994; **107**: 1147.
66 Zidi SH, Prat F, Le Guen O *et al*. Performance characteristics of magnetic resonance cholangiography in the staging of malignant hilar strictures. *Gut* 2000; **46**: 103.

Chapter 38
Hepatic Transplantation

In 1955, Welch performed the first transplantation of the liver in dogs [118]. In 1963, Starzl and his group carried out the first successful hepatic transplant in man [101].

The number of transplants is escalating and, in 1997, 4099 patients were transplanted in the USA. Elective liver transplantation in low-risk patients has a 90% 1-year survival. Improved results can be related to more careful patient selection, to better surgical techniques and post-operative care, and to greater willingness to re-transplant after rejection. Better immunosuppression has contributed.

Selection of patients

The patient selected for transplant should suffer from irreversible, progressive disease for which there is no acceptable, alternative therapy. The patient and the family must understand the magnitude of the undertaking and be prepared to face the difficult early post-operative period and life-long immunosuppression.

Improved results have led to a greater acceptance of the procedure. Demand has exceeded supply of donor organs (fig. 38.1). The time spent awaiting transplant and deaths occurring before it can be performed have increased. The waiting time for low-risk patients is approximately 6–12 months. Although in general this may be longer for those of blood group B and AB, group O recipients may have the longest waiting time because group O is the universal donor type. Depending on the system of organ distribution, such livers can be given to recipients having any ABO group. Donor livers suitable for children are particularly rare and this has led to the split-liver technique (see fig. 38.5).

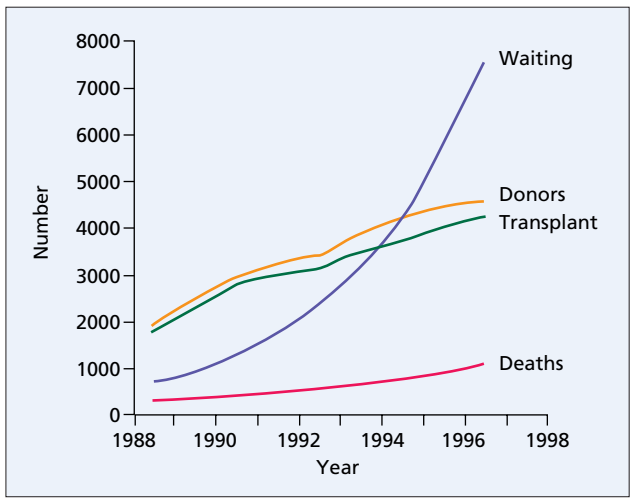


Fig. 38.1. Over the last 8 years availability of donors has not kept up with the demand for transplants. Waiting time and deaths have increased.

The equitable distribution of the precious donor livers is difficult. Results (and costs) are much better if the patient is low risk (ambulatory) compared with high risk (intensive care). Decisions are usually made by a multi-disciplinary panel including the patient and patient's family. In the USA, the United Network for Organ Sharing (UNOS) guidelines are followed (tables 38.1, 38.2) [63]. A modified Child–Pugh score is used as the basis by which to evaluate the severity of liver disease. The priorities expressed by the general public are not the same as those of clinicians. There has been a perceived lack of fairness in organ allocation [76]. The UNOS website (www.unos.org) allows the public and clinicians access to transplant activities and outcomes. Livers should be allocated for medical need and not on the basis of financial or other considerations. Unacceptable criteria include the patient's contribution to society, inability to comply with treatment (e.g. antisocial behaviour), the patient's contribution to the disorder (e.g. drug or alcohol abuse) and the past use of medical resources [27]. Recipients are broadly defined as having an intolerable quality of life because of liver disease or having an anticipated length of life of less than 1 year because of liver failure. There are few guidelines predicting survival. Patients more than 65 years old have a substantially worse 5-year survival, but age itself is not a contraindication.

Candidates: outcome (table 38.3)

In Europe, the pattern of primary indication for liver transplantation is changing. The main indication is cirrhosis, including primary biliary cirrhosis. More patients with acute and sub-acute hepatic failure are being

Table 38.1. Child–Pugh scoring system to assess severity of liver disease

	Points		
	1	2	3
Encephalopathy (grade)	None	1–2	3–4
Ascites	Absent	Slight or controlled by diuretics	At least moderate despite diuretic treatment
Bilirubin (mg/dl)	<2	2–3	>3
Albumin (g/dl)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged)	<4	4–6	>6
Or INR	<1.7	1.7–2.3	>2.3
For primary biliary cirrhosis, primary sclerosing cholangitis or other cholestatic liver diseases: bilirubin (mg/dl)	<4	4–10	>10

Table 38.2. Liver transplantation listing criteria for UNOS status 1, 2A, 2B and 3

Status 1

Fulminant hepatic failure. Onset within 8 weeks of initial symptoms and one of the following:
- stage 2 encephalopathy
- bilirubin >15 mg/dl
- INR >2.5
- hypoglycaemia (glucose level <50 mg/dl)

Primary non-function of graft transplanted within 7 days

Hepatic artery thrombosis occurring within 7 days of transplantation

Acute decompensated Wilson's disease

Status 2A

Patient with chronic liver failure and a Child–Pugh score ≥10, in the critical care unit, with a life expectancy without a liver transplant of less than 7 days, with at least one of the following criteria:
- unresponsive active variceal haemorrhage with failure or contraindication of surgical or transjugular intra-hepatic shunt
- hepato-renal syndrome
- refractory ascites/hepato-renal syndrome (hydrothorax)
- stage 3–4 encephalopathy unresponsive to therapy

Contraindications to status 2A listing:
- extra-hepatic sepsis unresponsive to antimicrobial therapy
- requirement for high dose or two or more pressor agents to maintain an adequate blood pressure
- severe, irreversible multi-organ failure

Status 2B

Patients with chronic liver disease and a Child–Pugh score ≥10, or ≥7 and one or more of the following clinical considerations:
- unresponsive variceal haemorrhage
- hepato-renal syndrome
- spontaneous bacterial peritonitis
- refractory ascites/hepato-renal syndrome (hydrothorax)

Liver transplant candidates with hepato-cellular carcinoma can be registered as status 2B if they meet the following criteria:
- thorough assessment has excluded metastatic disease
- recipient has one nodule ≤5 cm or three or fewer nodules all ≤3 cm
- patient is not a resection candidate

Status 3

Patients with chronic liver disease and a Child–Pugh score ≥7

Table 38.3. Possible candidates for hepatic transplantation

Cirrhosis
Cryptogenic
Autoimmune
Virus B (HBV DNA negative)
Virus D
Virus C
Alcoholic (Chapter 22)
Cholestatic liver disease
Primary biliary cirrhosis
Biliary atresia
Primary sclerosing cholangitis
Secondary sclerosing cholangitis
Graft-versus-host disease
Chronic hepatic rejection
Cholestatic sarcoidosis (Chapter 28)
Chronic drug reactions (rare)
Primary metabolic disease (see table 38.5)
Acute liver failure (Chapter 8)
Malignant disease (Chapter 31)
Hepato-cellular carcinoma
Epithelioid haemangio-endothelioma
Hepatoblastoma
Miscellaneous
Budd–Chiari syndrome (Chapter 11)
Short-bowel syndrome

included and fewer with cancer because of the poor survival due to recurrence of tumour (table 38.4).

Table 38.4. Percentage survival of 9966 patients according to diagnosis of cirrhosis, acute liver failure and cancer. (Data from European Liver Transplant Registry, 1993)

	Survival (%)		
Diagnosis	1 year	2 year	3 year
Cirrhosis	80	73	71
Acute liver failure	60	56	54
Cancer	64	42	36

Cirrhosis

All patients with end-stage cirrhosis should be considered for liver transplantation. Selection of the right time is difficult. The patient must not be moribund, so that the transplant will fail, or be capable of leading a relatively normal life for a long period so that transplant is unnecessary. Indications include a prothrombin time more than 5 s prolonged, a serum albumin concentration of less than 30 g/l, and intractable ascites. Bleeding oesophageal varices, after failure of medical treatment, is a good indication. The cost of transplant is little different from that of long-term medical and surgical management of complications such as bleeding, coma and ascites.

The patients are poor operative risks because of impaired blood coagulation and portal hypertension, so that blood loss is great. The technical difficulties are greater when cirrhosis is present, particularly when the liver is small and difficult to remove. Survival is much the same for all forms of cirrhosis.

Autoimmune chronic hepatitis

Post-transplant 5-year survival is 91% and graft survival 83% [85]. Despite triple immunosuppression, 33% develop recurrent chronic hepatitis of autoimmune type [30]. This is usually asymptomatic but may be severe, leading to graft failure [86]. Control is usually re-established by adjusting corticosteroid dose.

Chronic viral hepatitis

Hepatic transplantation performed for *acute* fulminant viral hepatitis (A, B, D and E) is not followed by graft re-infection as the viral levels are very low. In the chronic situation, however, graft re-infection is very common.

Hepatitis B

Post-transplant recurrence is usual and is related to viral replication in extra-hepatic sites, particularly monocytes. HBV-DNA is measured frequently. A severe *fibrosing cholestatic hepatitis* may develop with ballooning of hepatocytes and ground-glass change. This may be related to high cytoplasmic expression of viral antigens in the presence of immunosuppression [7, 31]. HBV may sometimes be cytopathic.

Hepatitis B immune globulin (*HBIG*), given before and after transplant, improves survival. However, it does not eliminate the virus and breakthrough replication can occur. It must be given indefinitely and is costly. Levels of protective antibody may be achieved by a new HBIG preparation (CMRI Hb) obtained from screened vaccinated donors [4].

HBV vaccination, following discontinuation of HBIG, may be associated with the development of protective serum titres of anti-HBs [93].

Lamivudine given before and after transplant may control re-infection. It has allowed transplant in HBV DNA and HBeAg-positive patients. The high development of lamivudine failure [71] with lamivudine-resistant mutants is associated with re-infection [55, 65, 73]. The combination of lamivudine and HBIG as prophylaxis against reinfection is effective, so long as lamuvidine resistance has not occurred pre-transplant [92].

Hepato-cellular cancer can develop in the transplanted liver.

Hepatitis delta

Transplantation is almost always followed by infection of the graft. HDV RNA and HDAg can be detected in the new liver and HDV RNA in the serum [124]. Hepatitis only develops if there is concomitant or superinfection with HBV.

Hepatitis B infection is inhibited by delta infection and hepatitis B recurrence may be reduced by delta infection. In general, survival is good after transplant for delta-infected patients.

Hepatitis C virus

Hepatitis C is the commonest indication for liver transplantation in most centres. All patients who are positive for HCV by PCR pre-transplant will remain positive, and 97% will develop recurrent hepatitis C post-transplant (fig. 38.2). Genetic sequencing of variable regions of the viral genome pre- and post-transplant will determine whether the infection is recurrent or acquired. Infection of the graft can come from infected mononuclear cells which contain negative strand viral RNA—the replicative intermediate of the viral genome. Early results suggested that the overall 5-year survival of patients with HCV was not worse than that with other liver diseases [40]. However, graft loss is increased and a 11–12% mortality is seen in the first year [24]. Whether long-term survival will decline due to recurrent disease awaits further study [13].

The post-transplant course is very variable; 50% of HCV-positive recipients, despite viraemia, will not have graft hepatitis within 2 years of the operation [13]. Lobular hepatitis, frequently asymptomatic, may develop 1–4 months post-transplant. It is unrelated to serum ALT. The hepatitis usually progresses to chronic hepatitis, which is often severe, with progressive fibrosis [8] and eventually graft loss [41]. Progressive fibrosing cholestatic hepatitis may be seen [95]. Re-grafting is usually necessary.

Patients with pre-treatment HCV viral titres exceeding 1×10^6 have a 5-year survival of 57% as opposed to 84% for those with lower titres [24].

Prediction of a severe course is difficult. Studies of the relationship to genotype and quasi-species are conflicting [8, 42]. Earlier recurrence of HCV relates to the number of rejection episodes [98], with consequent immunosuppression and hence, increasing HCV viraemia. The risk of severe fibrosis/cirrhosis may be greater with more aggressive immunosuppression [20]. There is no difference between cyclosporin- and tacrolimus-treated patients.

Interferon is ineffective in those with particularly high serum viral titres and so does not affect survival or graft loss [97]. It may increase the risk of graft rejection.

A pilot study has shown that interferon–ribavirin therapy can result in 50% clearance of HCV at the end of therapy. Of initial responders, 50% will relapse [12, 14]. Further controlled trials and longer follow-up are needed.

Neonatal hepatitis

This disease of unknown aetiology is associated with jaundice, giant cell hepatitis and rarely liver failure necessitating liver transplant which is curative [23].

Alcoholic liver disease

In the West, these patients are likely to provide the largest number of candidates for transplant. The selection and the results obtained are discussed in Chapter 22.

Cholestatic liver disease

End-stage biliary disease, usually involving the small intra-hepatic bile ducts, is an excellent indication for hepatic transplantation (fig. 38.3). Hepato-cellular function is usually preserved until late and the timing of

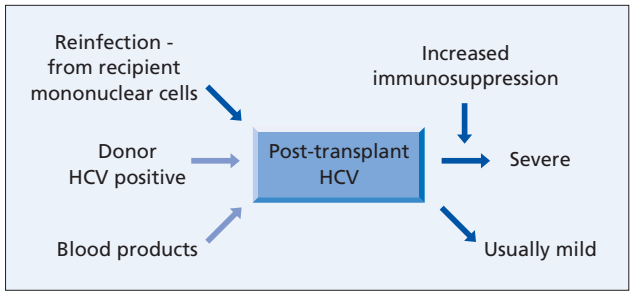


Fig. 38.2. Mechanisms for recurrent HCV hepatitis after liver transplantation.

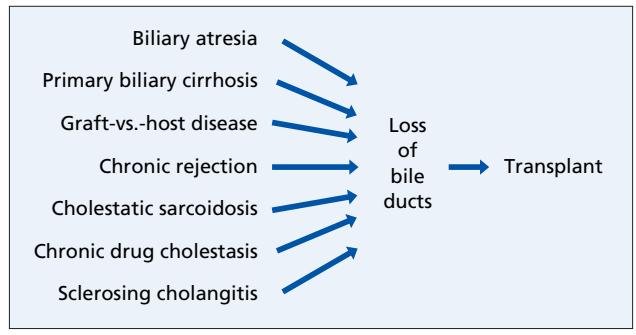


Fig. 38.3. Diseases with disappearing bile ducts treated by liver transplantation.

the transplant is easy. In every case the liver shows an advanced biliary cirrhosis, often combined with loss of bile ducts (‘*disappearing bile duct syndrome*’).

Primary biliary cirrhosis (Chapter 14)

One-year patient survival is 80% [96]. Recurrence is evident on hepatic histology, but there are no reports of subsequent graft failure.

Extra-hepatic biliary atresia (Chapter 26)

This indication comprises 35–67% of paediatric liver transplants. Calculated 1-year survival is 75%. Results are excellent and long-term survivors have good physical and mental development, although re-transplant and post-transplant surgery is often necessary.

A previous Kasai procedure increases the operative difficulty and the morbidity.

Alagille’s syndrome

Transplant is required only in very severe sufferers [22]. Associated cardio-pulmonary disease may be fatal and careful pre-operative assessment is necessary.

Primary sclerosing cholangitis (Chapter 15)

Sepsis and previous biliary surgery provide technical problems. Nevertheless, the results for transplantation are good, 1-year survival being 70% and 5-year survival 57%. Cholangiocarcinoma is a complication that greatly reduces long-term survival. Colon cancer is the most frequent cause of death [72].

Langerhans’ cell histiocytosis accounts for 15–39% of sclerosing cholangitis. It has been successfully treated by liver transplant [123].

Other end-stage cholestatic diseases

Hepatic transplantation has been performed for graft-versus-host cirrhosis in a bone marrow recipient. Other rare indications include cholestatic sarcoidosis (Chapter 28) and chronic drug reactions.

Primary metabolic disease

Liver homografts retain their original metabolic specificity. Consequently, liver transplantation is used for patients with inborn errors that result from defects in hepatic metabolism. Patients suffering from these conditions are good candidates. Selection depends on the prognosis and the likelihood of the later complication of primary liver tumours.

Liver transplantation for metabolic disorders is divided into those performed for *end-stage liver disease* or pre-malignant change and those performed for major *extra-hepatic features* (table 38.5). Overall survival is 85.9% over 5.5 years’ follow-up.

Table 38.5. Liver transplantation for metabolic disorders

End-stage disease or pre-malignant change
α_1-Antitrypsin deficiency
Wilson’s disease
Tyrosinaemia
Galactosaemia
Glycogen storage diseases
Protoporphyria
Neonatal haemochromatosis
β-thalassaemia
Cystic fibrosis
Byler’s disease
Major extra-hepatic features
Primary oxaluria type 1
Homozygous hypercholesterolaemia
Crigler–Najjar syndrome
Primary coagulation disorders (factor VIII, IX, protein C)
Urea cycle defects
Mitochondrial respiratory chain defects
Primary familial amyloidosis

End-stage liver disease

α_1-Antitrypsin deficiency

This is the most common metabolic disease leading to liver transplantation. Macronodular cirrhosis will develop in about 15% before the age of 20 years. Hepatocellular carcinoma is a complication. The plasma α_1-antitrypsin deficiency is corrected and the lung disease stabilizes after the transplant. Advanced pulmonary disease is a contraindication unless both lungs and liver are transplanted.

Genetic haemochromatosis (Chapter 23)

This is an uncommon indication for transplantation. Survival is lower than for other indications, because of infection and cardiac problems. Clear-cut recurrence of hepatic iron has not been reported but follow-ups are short [16].

Wilson’s disease (Chapter 24)

Liver transplants have to be considered in patients presenting with fulminant hepatitis, in young cirrhotic patients with severe hepatic decompensation who have failed to improve after 3 months’ adequate D-penicillamine treatment, and in effectively treated patients who have developed severe hepatic decompensation following discontinuance of penicillamine.

The overall survival is 72% increasing to 90% where the indication is fulminant Wilson’s disease [94].

Survivors transplanted for severe neurological complications showed significant improvement [37].

Glycogen storage diseases

Liver transplantation has been successfully performed for types I and IV, with survival and continued growth into adult life.

Galactosaemia

A few patients diagnosed late develop advanced cirrhosis in childhood and early adult life and are candidates for transplantation [81].

Protoporphyria

This can lead to end-stage cirrhosis and so be an indication for liver transplantation [52]. Post-operatively, the high level of protoporphyrin in erythrocytes and faeces persists and the disease is not cured.

Tyrosinaemia

Hepatic transplantation is curative and should be considered early before the development of hepato-cellular carcinoma [68].

β-Thalassaemia

Combined heart and liver transplantation has been reported for end-stage, iron-induced organ failure in an adult with homozygous β-thalassaemia [78].

Cystic fibrosis

Hepatic transplantation is indicated for predominant liver involvement. Combined liver–lung transplant is often necessary. The 3-year survival of young patients with end-stage respiratory failure complicated by cirrhosis is 70% [28].

Byler's disease

Byler's disease (Progressive Familial, Intra-hepatic Cholestasis type 1) results in death from cirrhosis or heart failure. The low serum apolipoprotein A1 concentration is corrected by transplant performed for cirrhosis [19].

Correction of extra-hepatic features

Oxaluria

Primary oxaluria type I, due to deficiency of hepatic peroxisomal alanine-glyoxylate aminotransferase, is corrected by simultaneous hepatic and renal transplantation [117]. Cardiac dysfunction reverses. The hepatic transplantation should possibly be done before renal damage has developed.

Homozygous hypercholesterolaemia

Liver transplant produces an 80% decrease in serum lipids. Cardiac transplant or coronary bypass are also usually necessary [88].

Crigler–Najjar syndrome

Liver transplant is indicated to prevent neurological sequelae when the serum bilirubin level is very high and cannot be controlled by phototherapy.

Primary coagulation disorders

The usual indication is HCV cirrhosis. Transplant cures the haemophilia but the effects of HIV infection and recurrent viral hepatitis remain post-transplant complications [46].

Urea cycle enzyme deficiencies

Transplantation has been performed for ornithine transcarbamylase deficiency as urea cycle enzymes are predominantly located in the liver [108]. The decision concerning the need for transplantation is difficult as some urea cycle disorders allow a normal lifestyle.

Mitochondrial respiratory chain defects

These may cause liver disease in neonates associated with hypoglycaemia and postprandial hyperlactic-acidaemia. They have been treated by liver transplant.

Primary familial amyloidosis

Transplant, often by the domino technique, is performed for intractable polyneuropathy. Neurological improvement is variable.

Acute liver failure (Chapter 8)

Indications include fulminant viral hepatitis, Wilson's disease, acute fatty liver of pregnancy, drug overdose (for instance, paracetamol), and drug-related hepatitis [11].

Malignant disease (Chapter 31)

Hepatic transplantation has been disappointing in patients with liver tumours despite pre-operative attempts at identifying extra-hepatic spread. Patients

with cancer have a low operative mortality, but the worst long-term survival. Carcinomatosis is the usual cause of death. Tumour recurs in 60%, perhaps because of the immunosuppressants necessary to prevent rejection.

The peri-operative survival is 76%, but the 1-year survival only 50% and the 2-year survival 31%. For all tumours transplanted, the overall actual 5-year survival is 20.4%.

Hepato-cellular carcinoma (Chapter 31)

The tumour must be 5 cm or less. If multifocal, only three tumours less than 3 cm each should be considered. Staging laparoscopy is important at the time of transplant. Vascular invasion, even microscopic, increases the recurrence rate and mortality.

The 2-year survival is 50 versus 83% for non-malignant conditions.

Transplantation may be preferable to resection for small tumours discovered incidentally in a patient with compensated cirrhosis.

Fibro-lamellar carcinoma

The tumour is localized to the liver and cirrhosis is absent. This may be the best tumour candidate for transplantation.

Epithelioid haemangio-endothelioma

This presents as multiple focal lesions in both lobes of an otherwise normal liver. The course is unpredictable and recurrence is likely in 50%. Metastatic spread does not contraindicate surgery and this does not correlate with survival. It can be successfully treated by liver transplantation.

Hepatoblastoma

Transplantation results in a 50% survival at 24–70 months. Microscopic vascular invasion and anaplastic epithelium with extra-hepatic spread are bad signs.

Neuro-endocrine tumours

When resection is not possible, worthwhile palliation can result from hepatic transplantation [62].

Abdominal cluster operations for right upper quadrant malignancy

Most of the organs derived from the embryonic foregut are removed including liver, duodenum, pancreas, stomach and intestine. With powerful immunosuppression, donor lympho-reticular cells circulate without causing clinical graft-versus-host disease and become those of the recipient without causing rejection [104]. The procedure is clearly very radical and patients usually die from recurrent tumour.

Cholangiocarcinoma

This is an unsatisfactory indication as tumour recurrence is usual and 3-year survival is poor, being zero in some series. In some countries, patients with cholangiocarcinoma are not accepted as transplant candidates.

Miscellaneous

Budd–Chiari syndrome (Chapter 11)

Hepatic transplantation is used in those who are too ill to perform decompressive surgery and where previous portal-systemic shunts have failed [89]. The 5-year survival is 67–69%. Recurrence of thrombosis is likely, especially in those who have an underlying coagulopathy.

Non-alcoholic fatty liver disease (NAFLD)

The end-stage is macronodular fatty cirrhosis. This is treated by transplantation, but 50% develop liver biopsy evidence of NAFLD post-transplant [79].

Absolute and relative contraindications

(table 38.6)

Absolute

These include uncorrectable cardio-pulmonary disease, ongoing infection, metastatic malignancy and severe brain damage.

Table 38.6. Absolute and relative contraindications to liver transplantation

Absolute
Psychological, physical and social inability to tolerate the procedure
Active sepsis
Metastatic malignancy
Cholangiocarcinoma
AIDS
Advanced cardiopulmonary disease
Relative (higher risk)
Age more than 60 or less than 2 years
Prior-porta-caval shunt
Prior complex hepato-biliary surgery
Portal vein thrombosis
Re-transplant
Multi-organ transplants
Obesity
HIV
Serum creatinine more than 2 mg/dl (180 μmol/l)
Cytomegalovirus mismatch
Advanced liver disease

Transplant should not be done if the patient cannot comprehend the magnitude of the undertaking and the exceptional physical and psychological commitment required [64].

Relative (higher risk)

Patients are at higher risk if they have advanced liver disease (UNOS status 2A) and are being treated in an intensive care unit and particularly if they are ventilation-dependent.

Children do particularly well but technical difficulties increase below the age of 2 years.

Risk increases with a body weight of more than 100 kg.

Multi-organ transplant adds to the risk.

A pre-transplant serum creatinine level exceeding 2.0 mg/dl (180 μmol/l) is the most accurate predictor of post-transplant death [29].

CMV mismatch (recipient negative, donor positive) adds to the risk.

Portal vein thrombosis makes the transplant more difficult and survival is reduced. However, the operation is usually possible [105]. An anastomosis is made between the donor portal vein and the recipient confluence of superior mesenteric vein and splenic vein, or a venous graft from the donor is used.

Previous surgical porta-caval shunts make the operation more difficult and a distal spleno-renal shunt creates least problems. TIPS for variceal bleeding is the most satisfactory preliminary to transplantation [2]. Careful positioning of the stent is important, avoiding an excessive length down the portal vein.

Previous complex surgery in the upper abdomen also makes the transplant technically very difficult.

Re-transplant

In Europe, primary transplant is associated with a 71% survival at 1 year. This is reduced to 47% for re-transplantation.

General preparation of the patient

The usual clinical, biochemical and serological investigation of any patient with liver disease is detailed.

Blood group, HLA and DR antigens are recorded. Antibodies to cytomegalovirus and hepatitis C are measured and markers of hepatitis B infection noted.

In patients with malignant disease, metastases must be sought by all possible techniques.

Cardio-pulmonary assessment should be thorough including the exclusion of hepato-pulmonary syndrome.

Imaging. Splanchnic vasculature and particularly the hepatic artery and portal vein must be visualized as a guide to surgery. Doppler ultrasound is routine. The hepatic arterial tree is also shown in contrast-enhanced helical CT [77].

MRI may be used as an alternative, or together with CT to exclude vascular abnormalities and silent malignancy.

The bile ducts are visualized by MRI cholangiography [44] or, if necessary, by ERCP.

The pre-transplant medical 'work-up' takes about 10 days. It includes psychiatric counselling and confirmation of the diagnosis. The patient may wait many months for a suitable donor liver and, during this period, intensive psychosocial support is necessary.

Donor selection and operation

Donation may be *informed with consent* from the family, the clinician ensuring that the family have been consulted, or *presumed consent* including the patient having specifically indicated their wish to donate. Those countries practising presumed consent tend to have higher transplant rates than those using informed consent. However, Spain, with the highest donation transplantation rate in Europe has the custom of informed consent, but a very well-resourced programme of trained co-ordinators. Better education, support and advice is needed for all clinical staff who have contact with potential donors [76].

Donor shortage has encouraged the use of livers formerly regarded as unsatisfactory. These include livers from donors with abnormal liver tests, elderly donors, those with prolonged ICU stay receiving inotropes, or with steatosis which was formerly an exclusion criterion. Use of these marginal livers does not seem to have increased graft loss.

Donors are considered between 2 months and 60–65 years of age, victims of brain injury that has resulted in brain death. Cardio-vascular and respiratory functions are sustained by mechanical ventilation. The recovery of livers and other vital organs from heart-beating cadavers minimizes the ischaemia that occurs at normal body temperatures and is a major contribution to graft success.

Transplant across A, B and O blood groups may be followed by severe rejection. It should be avoided unless necessitated by an emergency situation [48].

HLA matching is more difficult and indeed there is some evidence that selected HLA class II mismatches may be advantageous, particularly in preventing the vanishing bile duct syndrome [74].

Hepatitis B and C viral markers, CMV antibodies and HIV testing should be done.

The donor operation is as follows. The hepatic structures are dissected and the liver is pre-cooled through the portal vein with Ringer's lactate and 1000 ml of University of Wisconsin (UW) solution perfused through the aorta and portal vein. A cannula in the distal inferior

vena cava provides a vent for venous outflow. After removal, the cold liver is further flushed with an additional 1000 ml UW solution through the hepatic artery and portal vein and stored in this solution in a plastic bag on ice in a portable cooler. This routine has extended the preservation time to at least 18 h so that the recipient operation may be semi-elective and not performed at unsocial hours. Most centres now have designated multi-organ retrieval teams.

If possible, and particularly for elective procedures, the size of the donor liver should be matched to that of the recipient. This is based on a body weight within 10 kg of the recipient. Occasionally a small-sized liver is transplanted into a larger patient. The donor liver increases in size at the rate of about 70 ml/day until it achieves the volume expected for the recipient's size, age and sex [113].

The recipient operation (fig. 38.4)

The average operative time is 8 h. Blood loss is variable, volumes being minimal or massive. Cell savers have proven useful in transplants anticipated to have a high blood loss. The blood is aspirated from the abdominal cavity, washed repeatedly, re-suspended and infused.

The hilar structures and vena cava above and below the liver are dissected. The various vessels are cross-clamped and divided to allow removal of the liver.

During the implantation of the new liver, it is necessary to occlude the splanchnic and vena caval circulations. During this anhepatic phase, veno-venous bypass may be used to prevent pooling in the lower part of the body and splanchnic congestion. The cannulae are placed in the inferior vena cava (via the femoral vein) and the portal vein, and run to the subclavian vein.

The veno-venous bypass allows greater haemodynamic stability during the anhepatic phase of the operation.

Once all vascular anastomoses are completed, the preservation fluid is flushed out of the graft before opening the blood supply to the liver. Portal vein thrombosis must be excluded. Hepatic arterial anomalies are frequent, and vessel grafts from the donor should be available for arterial reconstructions.

The usual order of anastomases is: (a) supra-hepatic vena cava; (b) intra-hepatic vena cava; (c) portal vein; (d) hepatic artery; and (e) biliary system. The bile duct is usually reconstructed by direct anastomosis with external bile drainage through a T-tube in selected cases. If the recipient bile duct is diseased or absent, end-to-side Roux-en-Y choledocho-jejunostomy is chosen. Haemostasis is essential before closing the abdomen; perihepatic drains are placed.

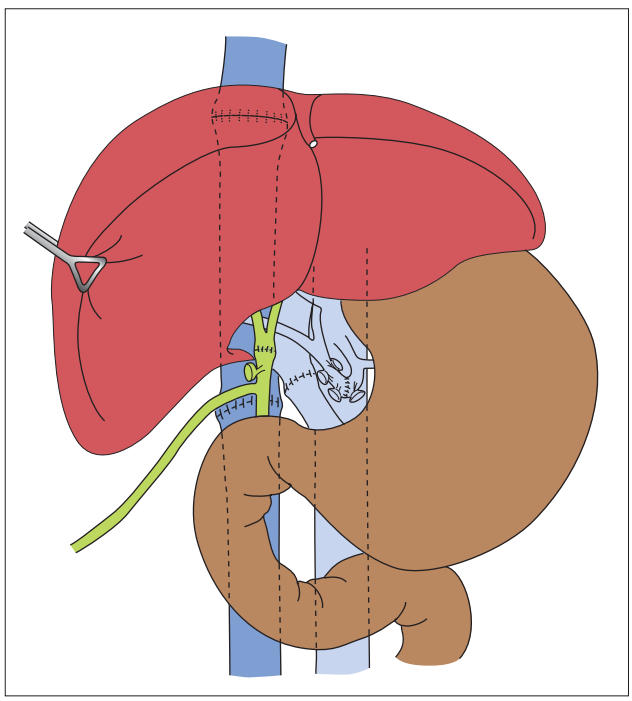


Fig. 38.4. Completed orthotopic liver transplantation. Biliary tract reconstruction is by duct-to-duct anastomosis.

Segmental (split) liver transplantation

Because of the difficulty in obtaining small donor livers for young children, segments of adult cadaveric livers have been used (fig. 38.5, table 38.7). Two viable grafts can be obtained from a single donor liver [38, 83]. Results are not quite as satisfactory as with full liver grafts (75 versus 85% 1-year survival) [17]. There are more complications including increased intra-operative blood loss and biliary problems [9, 10].

Cadaveric split liver grafts are also being used in the adult [21]. The split may be done *ex vivo* on the bench. Alternatively, the split may be done *in situ* with improved results for graft survival (85%) and patient survival (90%). Two grafts of optimal quality are obtained.

Live-related transplantation. This has been introduced because of the shortage of small cadaveric grafts. The liver is obtained from a live-related donor [59]. This technique was used originally largely in children, often with biliary atresia where small donor livers are not available.

Table 38.7. Strategies to overcome liver-donor shortage

Better clinician and public education
Presumed consent
Split livers
Live-related donors
Partial auxiliary grafts
Xeno-transplantation
Hepatocyte transplantation

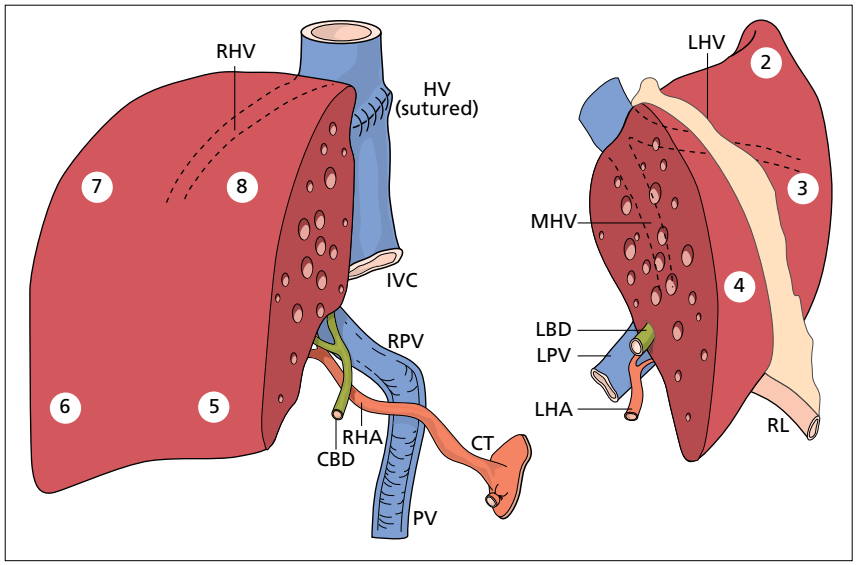


Fig. 38.5. Diagram of the two grafts prepared from one donor liver. In this example the main vascular and biliary structures are attached to the right lobe. CBD, common bile duct; CT, coeliac trunk; HV, hepatic vein; IVC, inferior vena cava; LBD, left bile duct; LHA, left branch of hepatic artery; LHV, left hepatic vein; LPV, left branch of portal vein; MHV, middle hepatic vein; PV, portal vein; RHA, right branch of hepatic artery; RHV, right hepatic vein; RL, round ligament; RPV, right branch of portal vein. Numbers indicate hepatic segments [38].

The over-all lack of cadaveric liver grafts also contributed to the development of this approach in some countries.

There are important ethical considerations concerning the donor, who is usually a relative, and must give free and informed consent. The transplant has the advantage of an elective operation. Ischaemia time is shortened and there is less re-perfusion injury. Living-related donation has been extended to the adult. It has been used in primary biliary cirrhosis [56] and in acute liver failure when a cadaveric donor was not available at short notice.

There is a recognised risk to the live donor of left hepatectomy to provide a paediatric graft. Operative stay averages 11 days and the blood loss is only about 200–300 ml. Rarely the donor may have operative and post-operative complications such as injury to the bile duct. There have been at least two reported deaths [47].

The required size of a donation is much greater for an adult than for a child. The critical limit of graft size is unknown, but is probably around 50% of the predicted liver volume, although it may be as low as 25%. This has led to the use of right lobe grafts [114]. In large adults with poor hepatic reserve, only the right lobe can provide the necessary hepatic mass. Problems are increased with postoperative cholestasis and biliary complications [86]. A combined kidney–right hepatic lobe transplant from a living donor has been performed [66]. The patient suffered transient hepatic impairment.

Auxiliary liver transplantation

Healthy liver tissue is introduced leaving the native liver *in situ* [69]. It may be indicated in acute liver failure where there is a chance that the patient's own liver will regenerate [111, 112]. It may also be used in the treatment of some metabolic defects [87].

A reduced size graft is usually used. The left lobe of the donor liver is excised and the right lobe anastomosed to the portal vein, inferior vena cava and aorta of the recipient. The donor liver hypertrophies and the recipient's own liver atrophies.

Complications, particularly portal vein thrombosis and primary graft non-function, are increased.

Auxiliary liver transplantation offers the possibility of a life-time free of immunosuppressive therapy. This is discontinued when the host liver has recovered. In time the auxiliary is likely to atrophy and should probably be removed.

Xeno-transplantation

Several non-human livers have been transplanted into humans. There are eight accounts of such transplants from pig, baboon or chimpanzee. No recipient has lived longer than 72 h [61]. The main limitation is immunological, including hyper-acute and delayed xeno-graft rejection and T-cell-dependent xeno-graft rejection. Various control strategies are under investigation [15] but the problems will be difficult to overcome.

Human infections, particularly viruses (especially porcine endogenous retroviruses) may be introduced with the xeno-transplant. There are ethical difficulties in accepting xeno-transplantation [102].

Domino liver transplantation

Structurally normal livers can be removed to control a metabolic defect such as familial amyloid polyneuropathy [36]. Such a liver may be offered for transplant to a recipient who has given full consent. The consequences of the metabolic defect will be delayed many years.

Hepatocyte transplantation

Transplantation of human hepatocytes is being developed to treat metabolic liver disease where a supply of normally functioning liver cells can correct a genetic deficiency [49]. However, the recipient may require long-term immunosuppression. Transplanted hepatocytes may be used to replace a missing or inactive enzyme, as in the Crigler–Najjar syndrome, or inactivate a disease-inducing gene or over-express a normal gene [25, 49].

Hepatocyte transplant may also be used in acute liver failure to sustain liver function until the native liver has regenerated.

Liver transplantation in paediatrics

The mean age is about 3 years, but successful transplant has been performed at less than 1 year old [5]. Scarcity of paediatric donors may necessitate adult reduced-liver or split-liver donations.

Post-transplant, growth is good and the quality of life excellent [119].

The small size of the vessels and bile ducts poses technical problems. Pre-transplant anatomy should be identified by CT or, preferably, MRI. Hepatic artery thrombosis occurs in at least 17% [106]. Re-transplants are frequent. Biliary complications are also common.

One-year survival is 75.5% for children who are less than 3 years old [82]. Renal function may deteriorate post-transplant and this is not solely due to cyclosporin A. Infections are frequent, particularly varicella, Epstein–Barr, mycobacteria, *Candida* and CMV.

Immunosuppression

There have been major advances in both scientific understanding and the therapy of rejection. Multiple therapy is usually given and the choice varies between centres and is nowadays tailored to both individual patient and to the underlying disease. Most immunosuppressive regimens include a calcineurin inhibitor—that is cyclosporin or tacrolimus. These are given with corticosteroids.

After the transplant the patient receives oral cyclosporin or tacrolimus. New formulations have improved oral absorption and can be given immediately after transplantation. Patients receive cyclosporin (5–10 mg/kg/day) in divided doses together with intravenous methylprednisolone, which is tapered to 0.3 mg/kg/day. For tacrolimus the equivalent dose is 0.1 mg/kg/day.

Some centres do not use a calcineurin inhibitor initially but use azathioprine and methylprednisolone, introducing cyclosporin or tacrolimus only when renal function is adequate.

Table 38.8. Interaction between cyclosporin (and tacrolimus) and other drugs

Increase cyclosporin levels
Erythromycin (clarithromycin)
Ketoconazole
Corticosteroids
Metoclopromide
Verapamil
Diltiazem
Tacrolimus
Decrease cyclosporin levels
Octreotide
Phenobarbitone
Phenytoin
Rifampicin
Septrin (Bactrim)
Omeprazole

Cyclosporin is continued for long-term maintenance orally with 5–10 mg/kg/day. In most, but not all, patients corticosteroids may be withdrawn during the first 3 months.

Cyclosporin side-effects include nephrotoxicity but the glomerular filtration usually stabilizes after a few months. Nephrotoxicity is enhanced by drugs such as the aminoglycosides. Electrolyte disturbances include hyperkalaemia, uricacidaemia and a fall in serum magnesium. Other complications include hypertension, weight gain, hirsuties, gingival hypertrophy and diabetes mellitus. Lymphoproliferative diseases can be seen long term. Cholestasis can develop. Neurotoxicity is shown by mood alterations, seizures, tremor and headaches.

Cyclosporin and tacrolimus can interact with other drugs leading to changing blood levels (table 38.8).

Cyclosporin is costly and has a narrow therapeutic index and its use has to be monitored carefully. Trough blood levels are taken, at first frequently, and then at regular intervals. Optimal levels at different times after transplant have not been clearly defined.

Tacrolimus (FK 506) is more powerful than cyclosporin in inhibiting IL2 synthesis and controlling rejection. It has been used to salvage patients with repeated liver rejection [103]. It is comparable to cyclosporin in terms of patient and graft survival [110, 120]. There are, however, fewer episodes of acute and refractory rejection and less need for corticosteroid immunosuppression. There are more adverse effects necessitating discontinuation. These include nephrotoxicity, diabetes, diarrhoea, nausea and vomiting. Neurological complications (tremors and headache) are more common with tacrolimus than cyclosporin.

Azathioprine side-effects include myelosuppression, cholestasis, peliosis hepatis, peri-sinusoidal fibrosis and veno-occlusive disease.

Both *mycophenolate mofetil* and *serolimus* are non-nephrotoxic. *Serolimus* inhibits B- and T-cell activity by inhibition of IL2 pathways [116]. These agents can be used in combination with calcineurin inhibitors (cyclosporin, tacrolimus) or alone.

Previously *antilymphocyte globulin* and *T-cell antibodies* were given to prevent acute rejection. They have been replaced by *specific monoclonal antibodies* directed against the IL2 receptor [33]. These receptors are expressed only by activated lymphocytes and the monoclonal antibodies are given early to reduce acute rejection. *Basilixiimab* and *diclizumab* have been licensed, but are costly.

The difficulties in balancing the risks of too much immunosuppression, which increases infections, with too little immunosuppression, which increases graft rejection, continue.

Tolerance

Donor cells have been identified in the blood of recipients of liver transplantation. This *chimerism* could influence the host immune system with development of tolerance to donor tissues. A donor liver may be spontaneously accepted more often than other organs [90]. This opens up the possibility of stopping immunosuppressive therapy. However, this is rarely possible. After a successful 5-year survival of a primary graft, only one-third of patients may be able to stop immunotherapy in the subsequent 3 years. The other two-thirds develop graft abnormalities [34]. Chimerism was not associated with tolerance. Factors suggesting successful withdrawal of immunosuppression were transplantation for a non-immunological condition, poor MHC mismatch and a low incidence of early acute rejection.

Post-operative course

This is not easy, particularly in the adult. Further surgery such as control of bleeding, biliary reconstruction or draining abscesses may be necessary.

Re-transplantation is required in 5–10% of patients. The main indications are primary graft failure, hepatic arterial thrombosis and chronic rejection. Renal dialysis may be required. Results are not so satisfactory as for the first transplant.

Factors determining an adverse result include poor pre-transplant nutrition, Child's grade C status, a raised serum creatinine level and severe coagulation abnormalities. Poor results are also related to the amount of blood products required during surgery, the need for renal dialysis post-transplant and severe rejection. The operation is easier in those without cirrhosis and portal hypertension, and the peri-operative mortality is considerably less.

The causes of death are surgical: technical complications (either immediate or late), biliary leaks and hepatic rejection, with or without infections often related to large doses of immunosuppressants.

The patient usually spends about 2 months in hospital or attending outpatients and is fully rehabilitated in 6 months.

Quality of life is usually excellent in the majority of patients with return to normal at home and work. Drug ingestion and monitoring are a burden. Social functioning improves in most [54]. However, only 43% of 9-month survivors are working [3]. The patient's age, duration of disability before transplant and type of job significantly affect the post-transplant employment status.

Those with recurrent disease, for instance HCV, have a worse quality of life than those without recurrent disease [100].

More than 87% of paediatric survivors are fully rehabilitated with normal growth, both physical and psychosexual.

Post-transplantation complications

(table 38.9)

The three major problems are:

1 primary graft non-function (days 1-2);
2 rejection (from 5–10 days); and
3 infections (days 3–14 and on).

Table 38.9. Complications of liver transplantation

Weeks	Complications
1	Primary graft non-function Bile leaks Renal Pulmonary CNS
1–4	Cellular rejection Cholestasis Hepatic artery thrombosis
5–12	CMV hepatitis Cellular rejection Biliary complications Hepatic artery thrombosis Hepatitis C
12–26	Cellular rejection Biliary complications Hepatitis B EBV hepatitis Drug-related hepatitis
>26	Ductopenic rejection (rare) EBV hepatitis Portal vein thrombosis Disease recurrence (HBV, HCV, tumours)

The presenting features of all three are very similar, namely a large, firm, tender liver, increasing jaundice, fever and leucocytosis. Specialist investigations must be available [53]. These include CT [35], MRI and Doppler imaging, HIDA scanning, angiography and percutaneous and endoscopic cholangiography.

Protocol liver biopsies are taken of the donor liver pre-transplant and 5 days, 3 weeks and 1 year after transplantation. No particular feature in the donor liver biopsy predicts function after transplantation. However, zonal or severe focal necrosis and neutrophil infiltration predicts a poor early course.

Primary graft non-function

This affects less than 5% of patients between the first 24 and 48 h (fig. 38.6). It is related to inadequate preservation of the donor liver, particularly a long (more than 30 h) cold preservation time and especially warm ischaemia time, to hypo-acute rejection or to shock in the recipient. It is marked by worsening state, hyperdynamic instability, renal dysfunction, lactic acidosis with increases in prothrombin time, bilirubin, transaminases and potassium. Blood glucose falls.

Re-transplantation is the only treatment and should not be delayed in the hope of spontaneous improvement.

Technical complications

Surgical complications will develop in about half of patients. They are most frequent in children with small vessels and bile ducts.

Doppler ultrasonography is used for detection of hepatic arterial, hepatic venous, portal venous or inferior vena caval stenosis or thrombosis [80].

Routine ultrasound, CT or MRI is used to evaluate hepatic parenchymal abnormalities, peri-hepatic collections and biliary dilatation.

Cholangiography through the T-tube is used to define biliary abnormalities. HIDA scanning or cholangiography may be used to show biliary leaks.

Guided biopsy allows aspiration of fluid collections.

Subcapsular hepatic necrosis. This is related to disproportionate size between donor and recipient. It can be visualized by CT scanning and usually resolves spontaneously [1].

Bleeding. This is more likely if the removal of a diseased liver has left a raw area on the diaphragm or if there have been adhesions from previous surgery or infec-tion. Treatment is by transfusion and re-operation if necessary.

Vascular complications

Hepatic artery thrombosis is most frequent in children. It may be acute, marked by clinical deterioration, fever and bacteraemia, a rise in enzymes and coagulopathy and hepatic necrosis (fig. 38.7). Alternatively it may be silent, presenting days to weeks later with biliary complications [109] including leaks and strictures, and recurrent bacteraemia and abscess.

Doppler ultrasound is diagnostic, although triple phase helical CT may be necessary to show intrahepatic branch occlusion. The findings may be confirmed by angiography. Re-transplantation is the usual treatment.

Hepatic arterial stenosis. This usually develops at the anastomotic site. If diagnosed early in the post-operative period it may be corrected surgically. Later, balloon angioplasty may be successful.

Portal vein thrombosis is uncommon in adults. It presents as graft dysfunction and massive ascites. Urgent

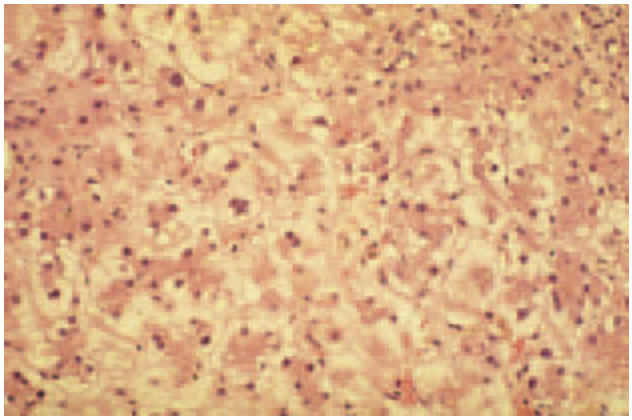


Fig. 38.6. Graft ischaemia 2 days after liver transplantation. Hepatocytes are swollen with loss of cytoplasm. (H & E, ×380.)

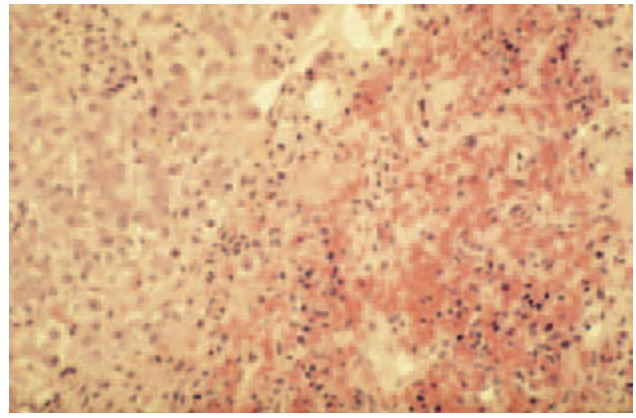


Fig. 38.7. Hepatic infarction, 3 days post-transplant, due to hepatic artery thrombosis. An area of necrotic, infarcted hepatocytes with haemorrhage adjoins normal liver tissue. (H & E, ×150.)

revascularization is essential. If not corrected, re-transplant is necessary.

Portal vein thrombosis is often silent, presenting as variceal bleeding weeks to months after the transplant.

Hepatic vein occlusion. This is common in patients who have had liver transplantation for the Budd–Chiari syndrome. Occasionally there is stricturing of the supra-hepatic–caval anastomosis and this can be treated by balloon dilatation.

Biliary tract complications

Bile secretion recovers spontaneously over a 10–12-day period and is strongly dependent upon bile salt secretion. The incidence of complication is 6–34% of all transplants usually during the first 3 months (table 38.10) [67, 109].

Bile leaks may be early (first 30 days) related to the bile duct anastomosis or late (about 4 months) after T-tube removal. Abdominal pain and peritoneal signs may be masked by immunosuppression.

Early leaks are diagnosed by ERCP or percutaneous cholangiography. HIDA scanning may be useful. They are usually treated by the endoscopic insertion of a stent or nasobiliary drain.

Extra-hepatic anastomotic strictures. These present after about 5 months as intermittent fever and fluctuating serum biochemical abnormalities. There is a wide differential diagnosis including rejection and sepsis. They are diagnosed by MRI cholangiography [44], ERCP or percutaneous cholangiopancreatography and treated by balloon dilatation (see fig. 32.19) and/or insertion of a plastic stent [109]. Hepatic arterial patency must be established.

Non-anastomotic or *'ischaemic-type' biliary strictures* develop in 2–19% [43]. They are associated with multifactorial damage to the hepatic arterial plexus around bile ducts. Factors include prolonged cold ischaemia time, hepatic arterial thrombosis, ABO blood group incompatibility, rejection, foam cell arteriopathy and a positive lymphocytotoxic cross-match. Peri-biliary arteriolar endothelial damage contributes to segmental microvascular thrombosis and hence to multiple segmental biliary ischaemic strictures.

Table 38.10. Biliary complications of liver transplantation

Leaks
Early (0–2 weeks)
anastomotic
Late (4 months) after T-tube removal
Strictures
Anastomotic (6–12 months)
Non-anastomotic/intra-hepatic (3 months)

Non-anastomotic strictures usually develop after several months. They develop in the donor common hepatic duct, with variable extension into the main intra-hepatic ducts. On cholangiography the wall of the duct may appear irregular and hazy, presumably reflecting areas of necrosis and oedema. Attempts are made to treat them by balloon dilatation and stenting. Hepatico-jejunostomy is sometimes possible. Re-transplant may be necessary.

Biliary stones, sludge and casts. These can develop any time following transplant. Obstruction, particularly biliary stricture, may be important. Foreign bodies such as T-tubes and stents may serve as a nidus for stone formation. Cyclosporin is lithogenic.

Treatment is by endoscopic sphincterotomy and stone extraction with naso-biliary irrigation if necessary.

Renal failure

Oliguria is virtually constant post-transplant, but in some renal failure is more serious. The causes include pre-existing kidney disease, hypotension and shock, sepsis, nephrotoxic antibiotics and cyclosporin or tacrolimus. Renal failure often accompanies severe graft rejection or overwhelming infection.

Pulmonary complications

In infants, death *during* liver transplantation may be related to platelet aggregates in small lung vessels. Intravascular catheters, platelet infusions and cell debris from the liver may contribute.

In the ICU, pulmonary infiltrates are most frequently due to pulmonary oedema and pneumonia. Other causes are atelectasis and respiratory distress syndrome [99]. In the first 30 days, pneumonia is usually due to methicillin-resistant *Staphylococcus aureus*, *Pseudomonas* and aspergillosis. After 4 weeks pneumonia due to CMV and *Pneumocystis* is seen. Later (more than 1 year), when the patient has developed recurrent HCV or HBV, lymphoproliferative disorder or chronic rejection are seen.

In one report, 87% of patients with pneumonia required ventilation and 40% were bacteraemic. Pyrexia, leucocytosis, poor oxygenation and cultures of the bronchial secretions indicate pneumonia and demand antibiotic therapy. The overall mortality for those having pulmonary infiltrates in the ICU is 28% [99].

Pleural effusion is virtually constant and in about 18% aspiration is necessary.

A post-transplant hyperdynamic syndrome tends to normalize with time.

The hepato-pulmonary syndrome (Chapter 6) is usually corrected by liver transplant but only after a stormy post-transplant course with prolonged hypoxaemia, mechanical ventilation and intensive care [60].

Non-specific cholestasis

This is frequently seen in the first few days, with the serum bilirubin peaking at 14–21 days. Liver biopsy suggests extra-hepatic biliary obstruction but cholangiography is normal. Factors involved include mild preservation injury, sepsis, haemorrhage and renal failure. If infection is controlled, liver and kidney function usually recover but a prolonged stay in the ICU is usually necessary.

Rejection

Immunologically, the liver is a privileged organ with regard to transplantation, having a higher resistance to immunological attack than other organs. The liver cell probably carries fewer surface antigens. Nevertheless, episodes of rejection, of varying severity, are virtually constant.

Cellular rejection is initiated through the presentation of donor HLA antigens by antigen-presenting cells to host helper T-cells in the graft. These helper T-cells secrete IL2 which activates other T-cells. The accumulation of activated T-cells in the graft leads to T-cell-mediated cytotoxicity and a generalized inflammatory response.

Hyper-acute rejection is rare and is due to pre-sensitization to donor antigens. Acute (cellular) rejection is fully reversible, but chronic (ductopenic) is not. The two may merge into one another. The diagnosis of rejection from opportunistic infections is difficult and protocol liver biopsies are essential. Increased immunosuppression to combat rejection favours infection.

Acute cellular rejection

64% of patients will have at least one episode, usually 5–20 days post-transplant and within the first 6 weeks [121]. Acute rejection does not have an adverse effect on patient or graft survival [51, 75]. There is little need to give higher immunosuppression during the first few days. The patient feels ill, there is mild pyrexia and tachycardia. The liver is enlarged and tender. Serum bilirubin, transaminases and prothrombin time increase. The liver enzyme changes lack specificity and a liver biopsy is essential.

Rejection is shown by the classical triad of portal inflammation, bile duct damage (fig. 38.8) and sub-endothelial inflammation of portal and terminal hepatic veins (endothelialitis) (fig. 38.9). Eosinophils may be conspicuous [50], and hepato-cellular necrosis may be seen.

Rejection may be graded into mild, moderate and severe (table 38.11) [32]. Follow-up biopsies may show eosinophils, resembling a drug reaction, and infarct-like areas of necrosis, perhaps secondary to portal venous obstruction by lymphocytes. Hepatic arteriography shows separation and narrowing of hepatic arteries (fig. 38.10). Histological severity correlates prognostically with steroid failure, early death or re-transplant [121]. In 85%, treatment is successful by increasing immunosuppression. Boluses of high dose methylprednisolone are given, for example 1 g intravenously daily for 3 days. Those who are steroid-resistant receive IL2 monoclonal antibody for 10–14 days. Tacrolimus rescue may also be tried. Those failing to respond to these measures proceed to ductopenic rejection. Re-transplant may be needed if the rejection continues.

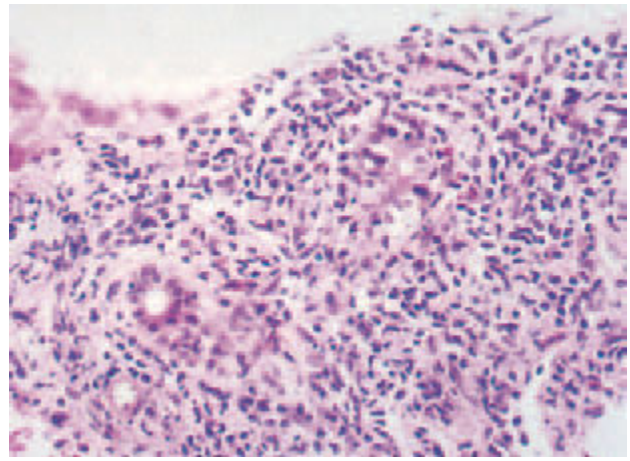


Fig. 38.8. Acute rejection: a damaged bile duct infiltrated with lymphocytes is seen in a densely cellular portal tract. (H & E, ×100.)

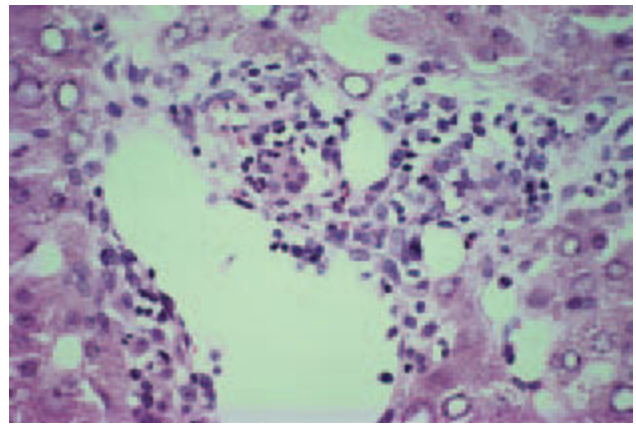


Fig. 38.9. Acute cellular rejection 8 days post-transplant. Liver biopsy shows portal zone infiltration with mononuclear cells and endothelialitis of cells lining the portal vein. (H & E, ×100.)

Chronic ductopenic rejection

Bile ducts are progressively damaged and ultimately

Table 38.11. NIDDK-LTD nomenclature and grading of liver allograft rejection [32]

Acute rejection*		Chronic (ductopenic) rejection†	
Grade	Histopathological findings	Grade	Histopathological findings
A0 (none)	No rejection	B1 (early or mild)	Bile duct loss, without centrilobular cholestasis, peri-venular sclerosis or hepato-cellular ballooning or necrosis and drop-out
A1 (mild)	Rejection infiltration in some, but not most, of the triads, confined within the portal spaces		
A2 (moderate)	Rejection infiltrate involving most or all of the triads, with or without spill-over into lobule. No evidence of centrilobular hepatocyte necrosis or drop-out	B2 (intermediate/moderate)	Bile duct loss, with one of the following four findings: centrilobular cholestasis, peri-venular sclerosis, hepato-cellular ballooning, necrosis and drop-out
A3 (severe)	Infiltrate in some or all of the triads, with or without spill-over into the lobule, with or without inflammatory cell linkage of the triads, associated with moderate–severe lobular inflammation and lobular necrosis and drop-out	B3 (late or severe)	Bile duct loss, with at least two of the following four findings: centrilobular cholestasis, peri-venular sclerosis, hepato-cellular ballooning, or centrilobular necrosis and drop-out

* The diagnosis of acute rejection is based on the presence of at least two of the following three findings: (a) predominantly mononuclear but mixed portal inflammation; (b) bile duct inflammation/damage; and (c) subendothelial localization of mononuclear cells in the portal and central veins. Thereafter, the severity of rejection is graded on the above findings.
† Bile duct loss in >50% of triads must be present for the diagnosis.

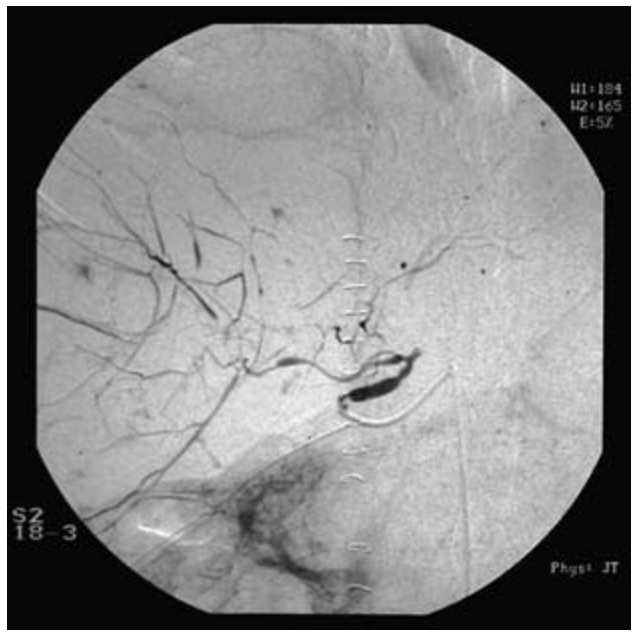


Fig. 38.10. Hepatic arteriogram in acute cellular rejection shows separation of intra-hepatic arterial tree with marked narrowing.

disappear [122]. The mechanism seems to be immunological with aberrant expression of HLA class II antigens on bile ducts. Donor–recipient HLA class I mismatch with class I antigen expression on bile ducts is contributory.

The incidence of chronic rejection has decreased from 20 to 15% in the 1980s to 5% currently [57]. This is due to better control of acute and early chronic rejection and to the unique regenerative capabilities of the liver.

Ductopenic rejection is defined as loss of interlobular and septal bile ducts in 50% of portal tracts. Duct loss is calculated from the ratio of the number of hepatic arteries to bile ducts within a portal tract (normal greater than 0.7). Preferably 20 portal tracts should be studied [58]. Foam cell obliterative arteriopathy increases the bile duct damage. Ductopenic rejection may be graded histologically into mild, moderate and severe (table 38.11) [32].

Bile duct epithelium is penetrated by mononuclear cells resulting in focal necrosis and rupture of the epithelium. Eventually bile ducts disappear and portal inflammation subsides (fig. 38.11). Larger arteries (not seen in a needle biopsy) show subintimal foam cells, intimal sclerosis and hyperplasia. Centrizonal necrosis and cholestasis develop and eventually biliary cirrhosis.

Ductopenic rejection usually follows early cellular rejection (at about 8 days) with bile duct degeneration (at about 10 days) and ductopenia (at about 60 days). The onset is usually within the first 3 months but can be sooner. Cholestasis is progressive.

Hepatic arterial occlusions may be a feature of chronic rejection (fig. 38.12), leading to bile duct stricturing shown by cholangiography. CMV cholangitis can also lead to the sclerosing cholangitis picture.

Features indicating that irreversible graft damage

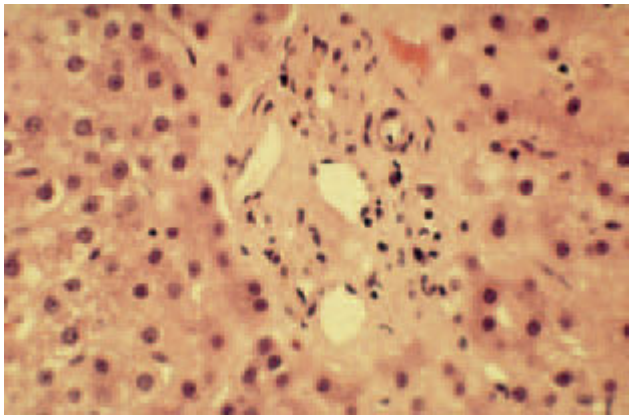


Fig. 38.11. Chronic ductopenic rejection. Bile ducts have disappeared from the portal tract which contains only a hepatic arterial branch, a portal vein and no inflammation. (H & E, × 380.)

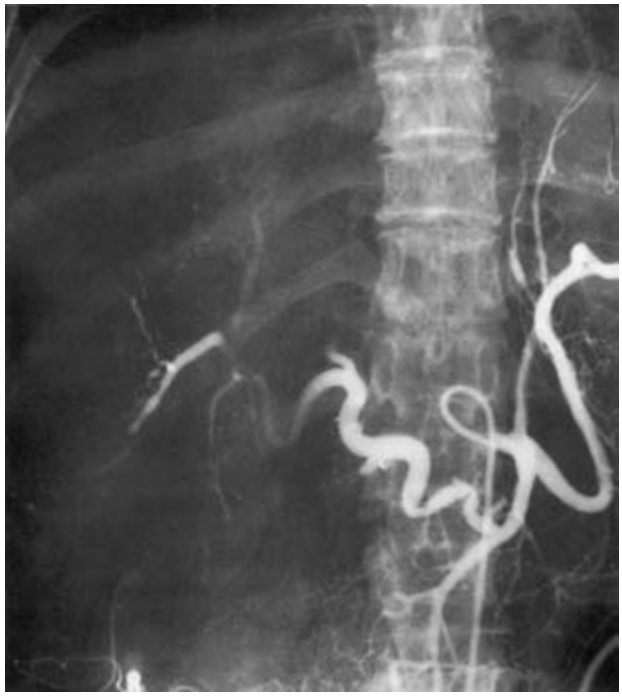


Fig. 38.12. Chronic rejection: coeliac angiogram shows pruning of the intra-hepatic arterial tree. Filling did not improve later in the series of films.

has occurred include absence of the features of acute rejection, bile duct loss in 80% of portal tracts, severe central-to-central bridging, peri-venular fibrosis and loss of small portal arterioles in 30% of portal tracts [57]. Some patients if seen early, respond to tacrolimus and corticosteroids but the ductopenic rejection is not usually reversed by increasing the immunosuppression. Re-transplant is the only effective treatment.

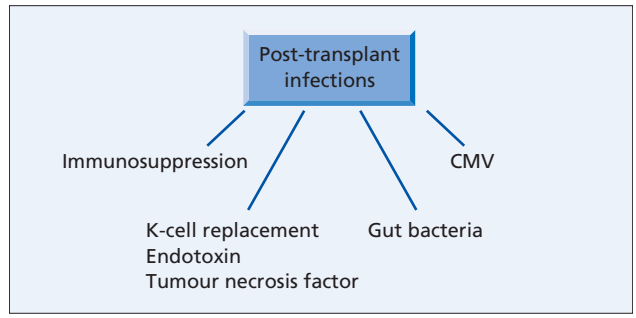


Fig. 38.13. Mechanisms of infection in liver transplant recipients.

Infections

Over 50% will experience an infection in the post-transplant period [51]. This may be primary, reactivation or related to opportunistic organisms (fig. 38.13). It is important to note the degree of immunosuppression and history of any previous infection [115].

Bacterial

These are seen during the first 2 months and are usually related to technical complications. They include pneumonia, wound sepsis, liver abscess and biliary sepsis. They may be related to invasive procedures and vascular lines. They are usually of endogenous origin and selective bowel decontamination is used prophylactically by some centres.

Deaths in transplant patients are almost always due to sepsis. There is a life-long risk of infections. This is reduced by early withdrawal of corticosteroid suppression.

Cytomegalovirus

This infection is a virtually constant complication and is symptomatic and serious in 30%. It may be primary (coming from the transfused blood or donor liver), or it may be a secondary reactivation. The single, most important risk factor is a positive donor with CMV antibodies.

Infection is increased in those having a re-transplant or with hepatic artery thrombosis. It is associated with reduced survival [39].

Infection presents within 90 days post-transplant, the peak being at 28–38 days. It continues for months or even years in those with poor graft function who require heavy immunosuppression. CMV is the most common cause of hepatitis in the liver allograft patient.

The picture is of a mononucleosis-like syndrome with fever and increased transaminases. The lungs are particularly involved in the severely affected. Chronic

infection is associated with cholestatic hepatitis and the vanishing bile duct syndrome.

'Pizza-pie' retinitis and gastroenteritis are other features.

Liver biopsy shows clusters of polymorphs and lymphocytes with CMV intranuclear inclusions (fig. 38.14). Bile duct atypia and endothelialitis are absent. Immunostaining, using a monoclonal antibody against an early CMV antigen, allows early diagnosis (fig. 38.15) [84]. Cell culture techniques, such as DEAFF (Detection of Early Antigen Fluorescent Foci), may be positive within 16 h. PCR techniques are now routine for diagnosis.

Routine prophylaxis for CMV with oral ganciclovir is effective [45] and is used in some centres, but there is concern over the appearance of resistant strains.

If possible, immunosuppression should be reduced. Re-transplant may be necessary.

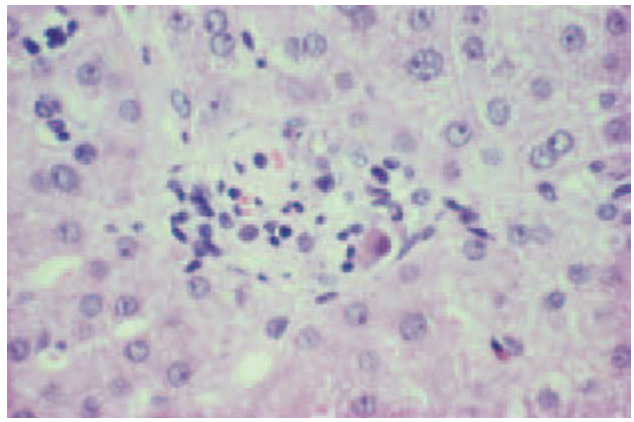


Fig. 38.14. CMV hepatitis 4 weeks post-transplant. A focus of inflammation shows hepatocytes containing inclusion bodies. (H & E, ×160.)

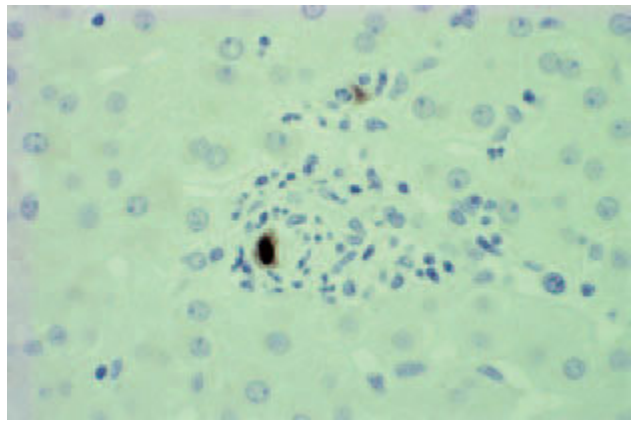


Fig. 38.15. Immunoperoxidase staining (×160) confirms the presence of CMV as a brown intranuclear deposit.

Herpes simplex virus

This infection is usually related to immunosuppression-induced reactivation. Liver biopsy shows confluent areas of necrosis with surrounding viral inclusions. This infection has virtually disappeared with prophylactic acyclovir.

Epstein–Barr virus

This is most frequent in children as a primary infection. It causes a mononucleosis–hepatitis picture (fig. 38.16). It is often asymptomatic. The diagnosis is made serologically (see Chapter 16).

Lymphoproliferative disorders

These complicate all solid organ transplants, the incidence being 1.8–4%. The tumour is usually a non-Hodgkin's B-cell lymphoma. It usually affects children but can also be seen in adults. There is a strong association with Epstein–Barr infection. The tumour presents 3–72 months post-transplant in lymph nodes or in the allograft itself. The prognosis is very poor. Treatment is by reducing immunosuppression and by giving antiviral therapy with acyclovir. Systemic chemotherapy may increase survival but has to be given cautiously as withdrawal may be followed by fulminant liver failure or reactivation of the hepatitis B virus. The outcome is poor [6].

Adenovirus

These infections are seen in children. They are usually

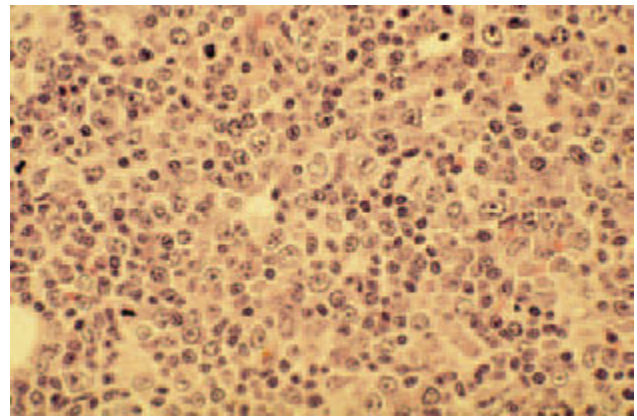


Fig. 38.16. Epstein–Barr-associated lymphoproliferative syndrome in a child aged 3 years, at 6 months post-transplant. A lymph node from the porta hepatis showing sheets of lymphocytes replacing the normal lymph gland architecture. (H & E, ×300.)

mild, but fatal hepatitis can develop. There is no recognized treatment.

Varicella

This can complicate transplants in children. It is treated with intravenous ganciclovir.

Nocardia

This infection usually affects the chest but skin and cerebral lesions may also occur.

Fungal infections

Aspergillosis has a high mortality with increases in serum bilirubin and renal failure. Brain abscess may be a complication. It may be treated by liposomal amphotericin.

Pneumocystis pneumonia

This presents in the first 6 months. It is diagnosed by bronchoscopy and broncho-alveolar lavage. It is prevented by Bactrim (Septrin) prophylaxis, one tablet daily for the first 6 months post-transplant.

Malignancies

Six per cent of organ transplant recipients will develop cancer, usually within 5 years of the transplant [107]. Many are related to immunosuppression. Malignancies include lymphoproliferative diseases, skin cancers and Kaposi's sarcoma [107]. Yearly cancer surveillance is essential for all patients post-transplant.

Drug-related toxicity

This must always be considered in any reaction whether hepatitic or cholestatic. Causative drugs include azathioprine, cyclosporin, tacrolimus, antibiotics, antihypertensives and antidepressants.

Disease recurrence

Hepatitis B appears at 2–12 months and may lead to cirrhosis and liver failure within 1–3 years (see p. 659). Hepatitis C is seen at any time after the first 4 weeks.

Hepato-cellular malignancies recur in the graft or as metastases, usually within the first 2 years.

The possible recurrence of primary biliary cirrhosis is discussed in Chapter 14. Budd–Chiari syndrome may re-appear quite soon after transplantation if anticoagulation is not well controlled.

Central nervous system toxicity

Several central nervous changes can follow liver transplantation [18]. Half the patients show fits, children being more susceptible than adults [26]. Cyclosporin-associated fits are controlled by phenytoin but this induces (accelerates) cyclosporin metabolism.

Central pontine myelinolysis is related to sudden alterations in serum electrolytes, perhaps in combination with cyclosporin. CT scan shows white-matter lucencies.

Cyclosporin is bound to lipoprotein fractions in the blood. Patients with low serum cholesterol values are at particular risk of central nervous system toxicity after the transplant.

Cerebral infarction is related to peri-operative hypotension, or air/micro-thrombus embolism.

Cerebral abscess is seen although rarely.

Headaches in the first few weeks can persist. Cyclosporin has been incriminated but in most instances the cause is obscure [18].

Tremor is a common side-effect of immunosuppressants including corticosteroids, tacrolimus and cyclosporin. It is usually mild, but occasionally requires reduction or cessation of medication.

A second transplant is associated with more and greater mental abnormalities, seizures and focal motor defects.

Bone disease

Patients having liver transplants usually have some previous degree of hepatic osteodystrophy. The bones deteriorate post-transplant with vertebral collapse in 38% during the second 3 months. The cause is multifactorial and includes cholestasis, cyclosporin, corticosteroid therapy and bed rest [91]. Recovery takes place with time.

Ectopic soft-tissue calcification [70]

This can develop diffusely and is associated with respiratory insufficiency and bone fractures. It is secondary to hypocalcaemia due to citrate infused in fresh frozen plasma, and, in addition, renal failure and secondary hyperparathyroidism. Tissue injury and administration of exogenous calcium lead to the soft-tissue calcium deposition.

Conclusion

Hepatic transplantation is a tremendous undertaking that does not begin or end with the surgery. The patient and family need psychiatric and social support. There must be a back-up programme to procure organs.

The survivor requires life-long medical and surgical supervision, together with costly drugs, both immunosuppressive and antibiotic.

Attending physicians must keep in touch with the transplant centre. They should be aware of possible late complications, particularly infections, chronic rejection, biliary complications, and lymphoproliferative and other malignancies.

It is not surprising that the cost is high. Technical advances, the training of more transplant teams and less costly immunosuppression will lower the cost. It must be compared with hospital costs of the last year of life of patients with liver disease who would have been candidates for transplantation had circumstances permitted.

References

1 Abecassis J-P, Pariente D, Hazebroucq V *et al*. Subcapsular hepatic necrosis in liver transplantation: CT appearance. *Am. J. Roentgenol*. 1991; **156**: 981.

2 Abouljoud MS, Levy MF, Rees CR *et al*. A comparison of treatment with transjugular intrahepatic portosystemic shunt or distal splenorenal shunt in the management of variceal bleeding prior to liver transplantation. *Transplantation* 1995; **59**: 226.

3 Adams PC, Ghent CN, Grant DR *et al*. Employment after liver transplantation. *Hepatology* 1995; **21**: 140.

4 Adler R, Safadi R, Caraco Y *et al*. Comparison of immune reactivity and pharmacokinetics of two hepatitis B immune globulins in patients after liver transplantation. *Hepatology* 1999; **29**: 1299.

5 Beath SV, Brook GD, Kelly DA *et al*. Successful liver transplantation in babies under 1 year. *Br. Med. J*. 1993; **307**: 825.

6 Ben-Ari Z, Amlot P, Lachmanan SR *et al*. Post-transplantation lymphoproliferative disorder in liver recipients: characteristics, management, and outcome. *Liver Transplant. Surg*. 1999; **5**: 184.

7 Benner KG, Lee RG, Keeffe EB *et al*. Fibrosing cytolytic liver failure secondary to recurrent hepatitis B after liver transplantation. *Gastroenterology* 1992; **103**: 1307.

8 Berenguer M, Ferrell L, Watson J *et al*. HCV-related fibrosis progression following liver transplantation: increase in recent years. *J. Hepatol*. 2000; **32**: 673.

9 Bismuth H, Azoulay D, Samuel D *et al*. Auxiliary partial orthotopic liver transplantation for fulminant hepatitis. The Paul Brousse experience. *Ann. Surg*. 1996; **224**: 712.

10 Bismuth H, Houssin D. Reduced sized orthotopic liver grafts in hepatic transplantation in children. *Surgery* 1984; **95**: 367.

11 Bismuth H, Samuel D, Castaing D *et al*. Orthotopic liver transplantation in fulminant and subfulminant hepatitis—the Paul Brousse experience. *Ann. Surg*. 1995; **222**: 109.

12 Bizollon T, Ducerf C, Trepo C. New approaches to treatment of hepatitis C virus infection after liver transplantation using ribavirin. *J. Hepatol*. 1995; **23** (Suppl. 2): 22.

13 Bizollon T, Ducerf C, Trepo C *et al*. Hepatitis C recurrence after liver transplantation. *Gut* 1999; **44**: 575.

14 Bizollon T, Palazzo U, Ducerf C *et al*. Pilot study of the combination of alfa interferon-alfa and ribavirin as therapy of recurrent hepatitis C after liver transplantation. *Hepatology* 1997; **26**: 500.

15 Bradley JA. Overcoming the immunological barriers to xenotransplantation. *Transplantation* 1999; **68**: 9.

16 Brandhagen DJ. Liver transplantation for hereditary hemochromatosis. *Liver Transplant*. 2001; **7**: 663.

17 Broelsch CE, Whitington PF, Emond JC *et al*. Liver transplantation in children from living related donors. Surgical techniques and results. *Ann. Surg*. 1991; **214**: 428.

18 Bronster DJ, Emre S, Mor E *et al*. Neurologic complications of orthotopic liver transplantation. *Mt Sinai J. Med*. 1994; **61**: 63.

19 Burdelski M, Rodeck B, Latta A *et al*. Treatment of inherited metabolic disorders by liver transplantation. *J. Inherit. Metab. Dis*. 1991; **14**: 604.

20 Burroughs AK. Post-transplanatation prevention and treatment of recurrent hepatitis C. *Liver Transplant*. 2000; **6** (Suppl. 2): S35.

21 Busuttil RW, Goss JA. Split liver transplantation. *Ann. Surg*. 1999; **229**: 313.

22 Cardona J, Houssin D, Gauthier F *et al*. Liver transplantation in children with Alagille syndrome—a study of 12 cases. *Transplantation* 1995; **60**: 339.

23 Casavilla FA, Reyes J, Tzakis A *et al*. Liver transplantation for neonatal hepatitis as compared to the other two leading indications for liver transplantation in children. *J. Hepatol*. 1994; **21**: 1038.

24 Charlton M, Seaberg E, Wiesner R *et al*. Predictors of patient and graft survival following liver transplantation for hepatitis C. *Hepatology* 1998; **28**: 823.

25 Chowdhury JR. Prospects of liver cell transplantation and liver-directed gene therapy. *Semin. Liver Dis.* 1999; **19**: 1.

26 Cilio MR, Danhaive O, Gadisseux JF *et al*. Unusual cyclosporin related neurological complications in recipients of liver transplants. *Arch. Dis. Child*. 1993; **68**: 405.

27 Council on Ethical and Judicial Affairs, American Medical Association. Ethical demand for liver transplantation. *Clin. Transplant*. 1997; **11**: 49.

28 Couteil JPA, Soubrane O, Houssin DP *et al*. Combined heart–lung–liver, double lung–liver and isolated liver transplantation for cystic fibrosis in children. *Transpl. Int*. 1997; **10**: 33.

29 Cuervas-Mas V, Millan J, Gavaler JJ *et al*. Prognostic value of preoperatively obtained clinical and laboratory data in predicting survival following liver transplantation. *Hepatology* 1986; **6**: 922.

30 Czaja AJ. The immunoreactive propensity of autoimmune hepatitis: is it corticosteroid-dependent after liver transplantation? *Liver Transplant. Surg*. 1999; **5**: 460.

31 Davies SE, Portmann BC, O'Grady JG *et al*. Hepatic histological findings after transplantation for chronic hepatitis B virus infection, including a unique pattern of fibrosing cholestatic hepatitis. *Hepatology* 1991; **13**: 150.

32 Demetris AJ, Seaberg EC, Batts KP *et al*. Reliability and predictive value of the National Institute of Diabetes and Digestive and Kidney Diseases liver transplantation database. Nomenclature and grading system for cellular rejection of liver allografts. *Hepatology* 1995; **21**: 408.

33 Denton MD, Magee CC, Sayegh MH. Immunosuppressive strategies in transplantation. *Lancet* 1999; **353**: 1083.

34 Devlin J, Doherty D, Thomson L *et al*. Defining the outcome of immunosuppression withdrawal after liver transplantation. *Hepatology* 1998; **27**: 926.

35 Dupuy D, Costello P, Lewis D *et al*. Abdominal CT findings after liver transplantation in 66 patients. *Am. J. Roentgenol*. 1991; **156**: 1167.

36 Dyer PA, Bobrow M. Domino hepatic transplantation using the liver from a patient with familial amyloid polyneuropathy. *Transplantation* 1999; **67**: 1202.

37 Eghtesad B, Nezakatgoo N, Geraci LC *et al*. Liver transplantation for Wilson's disease: a single centre experience. *Liver Transplant. Surg*. 1999; **5**: 467.

38 Emond JC, Whitington PF, Thistlethwaite JR *et al*. Transplantation of two patients with one liver: analysis of a preliminary experience with 'split-liver' grafting. *Ann. Surg*. 1990; **212**: 14.

39 Falagas ME, Paya C, Ruthazer R *et al*. Significance of cytomegalovirus for long-term survival after orthotopic liver transplantation. *Transplantation* 1998; **66**: 1020.

40 Feray C, Caccamo L, Alexander GJM *et al*. European Collaborative study on factors influencing outcome after liver transplantation for hepatitis C. *Gastroenterology* 1999; **117**: 619.

41 Feray C, Gigou M, Samuel D *et al*. The course of hepatitis C virus infection after liver transplantation. *Hepatology* 1994; **20**: 1137.

42 Feray C, Gigou M, Samuel D *et al*. Influence of the genotypes of hepatitis C virus on the severity of recurrent liver disease after liver transplantation. *Gastroenterology* 1995; **108**: 1088.

43 Fisher A, Miller CM. Ischemic-type biliary strictures in liver allografts—the Achilles heel revisited. *Hepatology* 1995; **21**: 589.

44 Fulcher AS, Turner MA. Orthotopic liver transplantation: evaluation with MR cholangiography. *Radiology* 1999; **211**: 715.

45 Gane E, Slaiba F, Valdecasas GJC *et al*. Randomized trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. *Lancet* 1997; **350**: 1729.

46 Gordon FH, Mistry PK, Sabin CA *et al*. Outcome of orthotopic liver transplantation in patients with haemophilia. *Gut* 1998; **42**: 744.

47 Grewal HP, Thistlethwaite JR, Loss GE *et al*. Complications in 100 living-liver donors. *Ann. Surg*. 1998; **228**: 214.

48 Gugenheim J, Samuel D, Reynes M *et al*. Liver transplantation across ABO blood group barriers. *Lancet* 1990; **336**: 519.

49 Gupta S. Hepatocyte transplantation: emerging insights into mechanisms of liver re-population and their relevance to potential therapies. *J. Hepatol*. 1999; **30**: 162.

50 Gupta SD, Hudson M, Burroughs AK *et al*. Grading of cellular rejection after orthotopic liver transplantation. *Hepatology* 1995; **21**: 46.

51 Hadley S, Samore MH, Lewis WD *et al*. Major infectious complications after orthotopic liver transplantation and comparison of outcomes in patients receiving cyclosporin or FK 506 as primary immunosuppression. *Transplantation* 1995; **59**: 851.

52 Herbert A, Corbin D, Williams A *et al*. Erythropoietic protoporphyria: unusual skin and neurological problems after liver transplantation. *Gastroenterology* 1991; **100**: 1753.

53 Holbert BL, Campbell WL, Skolnick ML. Evaluation of transplanted liver and postoperative complications. *Radiol. Clin. North Am*. 1995; **33**: 521.

54 Hunt CM, Camargo CA, Dominitz JA *et al*. Effect of postoperative complications on health and employment after liver transplantation. *Clin. Transplant*. 1998; **12**: 99.

55 Hunt CM, McGill JM, Allen MI *et al*. Clinical relevance of hepatitis B viral mutations. *Hepatology* 2000; **31**: 1037.

56 Ichida T, Matsunami H, Kawasaki S *et al*. Living related-donor liver transplantation from adult to adult for primary biliary cirrhosis. *Ann. Intern. Med*. 1995; **122**: 275.

57 International Panel. Update of the International Banff schema for liver allograft rejection: working recommendations for the histopathologic staging and reporting of chronic rejection. *Hepatology* 2000; **31**: 792.

58 International Working Party. Terminology of hepatic allograft rejection. *Hepatology* 1995; **22**: 648.

59 Jurim O, Shackleton CR, McDiarmid SV *et al*. Living-donor liver transplantation at UCLA. *Am. J. Surg*. 1995; **169**: 529.

60 Krowka MJ. Hepatopulmonary syndrome: what are we learning from interventional radiology, liver transplantation and other disorders? *Gastroenterology* 1995; **109**: 1009.

61 Lambrights D, Sachs DH, Cooper DK. Discordant organ xenotransplantation in primates: world experience and current status. *Transplantation* 1998; **68**: 547.

62 Le-Trent YP, Delpero JR, Dousset B *et al*. Results of liver transplantation in the treatment of metastatic neuroendocrine tumours: a 31-case French multicentre study. *Ann. Surg*. 1997; **225**: 355.

63 Lucey MR, Brown KA, Everson GT *et al*. Minimal criteria for placement of adults on the liver transplant waiting list. *Transplantation* 1998; **66**: 956.

64 Maddrey WC, ed., *Transplantation of the Liver* 2nd edn. Norwalk: Appleton & Lange, 1994.

65 Markowicz JS, Martin P, Contrad AJ *et al*. Prophylaxis against hepatitis B recurrence following liver transplantation using combination lamivudine and hepatitis B immune globulin. *Hepatology* 1998; **28**: 586.

66 Marujo WC, Barros MFA, Cory RA et al. Successful combined kidney–liver right lobe transplant from a living donor. *Lancet* 1999; **353**: 641.

67 Mazariegos GV, Molmenti EP, Kramer DJ. Early complications after orthotopic liver transplantation. *Surg. Clin. North Am*. 1999; **79**: 109.

68 Mieles LA, Esquivel CO, Van Thiel DH *et al*. Liver transplantation for tyrosinemia: a review of 10 cases from the University of Pittsburgh. *Dig. Dis. Sci*. 1990; **38**: 153.

69 Moritz MJ, Jarrell BE, Munoz SJ *et al*. Regeneration of the native liver after heterotopic liver transplantation for fulminant hepatic failure. *Transplantation* 1993; **55**: 952.

70 Munoz SJ, Nagelberg SB, Green PJ *et al*. Ectopic soft tissue calcium deposition following liver transplantation. *Hepatology* 1988; **8**: 476.

71 Mutimer D, Pillay D, Dragon E *et al*. High pretreatment serum hepatitis B virus titre predicts failure of lamivudine prophylaxis and graft re-infection after liver transplantation. *J. Hepatol*. 1999; **30**: 715.

72 Narumi S, Roberts JP, Emond JC *et al*. Liver transplantation for sclerosing cholangitis. *Hepatology* 1995; **22**: 451.

73 Nery JR, Wepler D, Rodriguez M *et al*. Efficacy of lamivu-

dine in controlled hepatitis B virus recurrence after liver transplantation. *Transplantation* 1998; **65**: 1615.
74 Neuberger JM, Adams DH. Is HLA matching important for liver transplantation? *J. Hepatol*. 1990; **11**: 1.
75 Neuberger J, Adams DH. What is the significance of acute liver allograft rejection? *J. Hepatol*. 1998; **29**: 143.
76 Neuberger J, James O. Guidelines for selection of patients for liver transplantation in the era of donor-organ shortage. *Lancet* 1999; **354**: 1636.
77 Nghiem HV. Imaging of hepatic transplantation. *Radiol. Clin. North Am*. 1998; **36**: 429.
78 Olivieri NF, Liu PP, Sher GD *et al*. Brief report: combined liver and heart transplantation for end-stage iron-induced organ failure in an adult with homozygous beta-thalassaemia. *N. Engl. J. Med*. 1994; **330**: 1125.
79 Ong JP, Reddy V, Gramlich TL *et al*. Cryptogenic cirrhosis and risk of recurrence of nonalcoholic fatty liver disease after liver transplantation. *Gastroenterology* 2000; **118**: A973.
80 Orons PD, Zajko AB. Angiography and interventional procedures in liver transplantation. *Radiol. Clin. North Am*. 1995; **33**: 541.
81 Otte G, Herfarth C, Senninger N *et al*. Hepatic transplantation in galactosaemia. *Transplantation* 1989; **47**: 902.
82 Otte JB. Recent developments in liver transplantation: lessons from a 5-year experience. *J. Hepatol*. 1991; **12**: 386.
83 Otte JB, de Ville de Goyet J, Sokal E *et al*. Size reduction of the donor liver is a safe way to alleviate the shortage of size-matched organs in paediatric liver transplantation. *Ann. Surg*. 1990; **211**: 146.
84 Paya CV, Holley KE, Wiesner RH *et al*. Early diagnosis of cytomegalovirus hepatitis in liver transplant recipients: role of immunostaining, DNA hybridization and culture of hepatic tissue. *Hepatology* 1990; **12**: 119.
85 Ratziu Y, Samuel D, Sebagh M *et al*. Long-term follow-up after liver transplantation for autoimmune hepatitis: evidence of recurrence of primary disease. *J. Hepatol*. 1999; **30**: 31.
86 Reding R, de Groyet J de V, Delbeke I *et al*. Paediatric liver transplantation with cadaveric or living related donors: comparative results in 90 elective recipients of primary grafts. *J. Pediatr*. 1999; **134**: 280.
87 Rela M, Musien P, Volea-Melendez H *et al*. Auxiliary partial orthotopic liver transplantation for Crigler–Najjar syndrome type 1. *Ann. Surg*. 1999; **239**: 565.
88 Revell SP, Noble-Jamieson G, Johnston P *et al*. Liver transplantation for homozygous familial hypercholesterolaemia. *Arch. Dis. Child*. 1995; **73**: 456.
89 Ringe B, Lang H, Oldhafter KJ *et al*. Which is the best surgery for Budd–Chiari syndrome: venous decompression or liver transplant action? A single-centre experience with 50 patients. *Hepatology* 1995; **21**: 1337.
90 Riordan SM, Williams R. Tolerance after liver transplantation: does it exist and can immunosuppression be withdrawn? *J. Hepatol*. 1999; **31**: 1106.
91 Roding MA, Shane E. Osteoporosis after organ transplantation. *Am. J. Med*. 1998; **104**: 459.
92 Rosenau J, Bahl MJ, Tillmann HL *et al*. Lamivudine and low-dose hepatitis B immune globulin for prophylaxis of hepatitis B reinfection after liver transplantation—possible role of mutations in the YMDD motif prior to transplantation as a risk factor for reinfection. *J. Hepatol*. 2001; **34**: 895.
93 Sanchez-Fuey OA, Rimola A, Grande L *et al*. Hepatitis B immunoglobulin discontinuation followed by hepatitis B virus vaccination: a new strategy in the prophylaxis of hepatitis B virus recurrence after liver transplantation. *Hepatology* 2000; **31**: 496.
94 Schissky ML, Scheinberg IH, Sternlieb I. Liver transplantation for Wilson's disease: indications and outcome. *Hepatology* 1994; **19**: 583.
95 Schluger LK, Sheiner PA, Thung SN *et al*. Severe recurrent cholestatis hepatitis C following orthotopic liver transplantation. *Hepatology* 1996; **23**: 971.
96 Seaberg EC, Belle SH, Beringer KC *et al*. Long-term patient and retransplantation-free survival by selected recipient and donor characteristics: an update from the Pitt-Unos liver transplant registry. *Clin. Transplant*. 1997; **18**: 15.
97 Sheiner PA, Boros P, Klion FM *et al*. The efficacy of prophylactic interferon alfa-2b in preventing recurrent hepatitis C after liver transplantation. *Hepatology* 1998; **28**: 831.
98 Sheiner PA, Schwartz ME, Mor E *et al*. Severe or multiple rejection episodes are associated with early recurrence of hepatitis C after orthotopic liver transplantation. *Hepatology* 1995; **21**: 30.
99 Singh N, Gayowski T, Wagener MM. Pulmonary infiltrates in liver transplant recipients in the intensive care unit. *Transplantation* 1999; **67**: 1138.
100 Singh N, Gayowski T, Wagener MM *et al*. Quality of life, functional status and depression in male liver transplant recipients with recurrent viral hepatitis C. *Transplantation* 1999; **67**: 69.
101 Starzl TE, Marchioro TL, von Kaulla KN *et al*. Homotransplantation of the liver in humans. *Surg. Gynecol. Obstet*. 1963; **117**: 659.
102 Starzl TE, Rao AS, Murase M *et al*. Will xenotransplantation ever be feasible? *J. Am. Coll. Surg*. 1998; **186**: 383.
103 Starzl TE, Todo S, Fung J *et al*. FK 506 for liver, kidney and pancreas transplantation. *Lancet* 1989; **ii**: 1000.
104 Starzl TE, Todo S, Tzakis A *et al*. The many faces of multivisceral transplantation. *Surg. Gynecol. Obstet*. 1991; **172**: 338.
105 Stieber AC, Zetti G, Todo S *et al*. The spectrum of portal vein thrombosis in liver transplantation. *Ann. Surg*. 1991; **213**: 199.
106 Tan KC, Yandza T, de Hemptinne B *et al*. Hepatic artery thrombosis in paediatric liver transplantation. *J. Pediatr. Surg*. 1988; **23**: 927.
107 Tan-Shalaby J, Tempero M. Malignancies after liver transplantation: a comparative review. *Semin. Liver Dis*. 1995; **15**: 156.
108 Todo S, Starzl ET, Tzakis A. Orthotopic liver transplantation for urea cycle enzyme deficiency. *Hepatology* 1992; **15**: 419.
109 Tung BY, Kimmey MB. Biliary complications of orthotopic liver transplantation. *Dig. Dis*. 1999; **17**: 133.
110 US Multicentre FK 506 Liver Study Group. A comparison of tacrolimus (FK 506) and cyclosporin for immunosuppression in liver transplantation. *N. Engl. J. Med*. 1994; **331**: 1110.
111 Van Hoek B, de Boer J, Boudjema K *et al*. Auxiliary vs. orthotopic liver transplantation for acute liver failure. *J. Hepatol*. 1999; **30**: 699.
112 Van Hoek B, Ringers J, Kroes ACM *et al*. Temporary heterotopic auxiliary liver transplantation for fulminant hepatitis B. *J. Hepatol*. 1995; **23**: 109.

113 Van Thiel DH, Gavaler JS, Kam I *et al*. Rapid growth of an intact human liver transplanted into a recipient larger than the donor. *Gastroenterology* 1987; **93**: 1414.
114 Wachs ME, Bak TE, Karrer FM *et al*. Adult living donor liver transplantation using a right hepatic lobe. *Transplantation* 1998; **68**: 1313.
115 Wade JJ, Rolando N, Hayllar K *et al*. Bacterial and fungal infections after liver transplantation: an analysis of 284 patients. *Hepatology* 1995; **21**: 1328.
116 Watson CJ, Friend PJ, Jamieson NY *et al*. Sirolimus: a potent new immunosuppressant for liver transplantation. *Transplantation* 1999; **67**: 505.
117 Watts RWE, Morgan SH, Danpure CJ *et al*. Combined hepatic and renal transplantation in primary hyperoxaluria type I: clinical report of nine cases. *Am. J. Med*. 1991; **90**: 179.
118 Welch CS. A note on transplantation of the whole liver in dogs. *Transpl. Bull*. 1955; **2**: 54.
119 Whitington PF, Balistreri WF. Liver transplantation in paediatrics: indications, contraindications, and pretransplant management. *J. Pediatr*. 1991; **118**: 169.
120 Wiesner RH. A long-term comparison for tacrolimus (FK506) vs. cyclosporin in liver transplantation. *Transplantation* 1998; **66**: 493.
121 Wiesner RH, Demetris AJ, Belle SH *et al*. Acute hepatic allograft rejection: incidence, risk factors, and impact on outcome. *Hepatology* 1998; **28**: 638.
122 Wiesner RH, Ludwig J, Vanhoek B *et al*. Current concepts in cell-mediated hepatic allograft rejection leading to ductopenia and liver failure. *Hepatology* 1991; **14**: 721.
123 Zandi P, Panis Y, Debray D *et al*. Paediatric liver transplantation for Langerhans' cell histiocytosis. *Hepatology* 1995; **21**: 129.
124 Zignego AL, Dubois F, Samuel D *et al*. Serum hepatitis delta virus RNA in patients with delta hepatitis and in liver graft recipients. *J. Hepatol.* 1990; **11**: 102.

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