30

The liver

Learning objectives

- ✓ To know the common causes of liver enlargement.
- ✓ To understand the different causes of jaundice, and how they may be diagnosed and treated.
- ✓ To have knowledge of cirrhosis, its various manifestations and their management.

Liver enlargement

Physical signs

The normal liver in the adult is impalpable. In contrast, an infant's liver is normally palpable two finger breadths below the right costal margin.

The enlarged liver extends downwards below the right costal margin and may fill the subcostal angle or even extend beneath the left costal margin in gross hepatomegaly. The liver moves with respiration, is dull to percussion and the liver dullness may extend above the normal upper level of the fifth right interspace.

Causes of hepatomegaly

1 *Congenital*:
- **a** Riedel's lobe;[1]
- **b** polycystic liver disease (which develops in adult life).

2 *Infective*:
- **a** viral hepatitis;
- **b** liver abscess;
- **c** malaria;
- **d** amoebic hepatitis and abscess;
- **e** hydatid;
- **f** leptospirosis (Weil's disease[2]);
- **g** actinomycosis.

3 *Vascular*:
- **a** right heart failure;
- **b** venous outflow obstruction, e.g. Budd–Chiari syndrome;

4 *Neoplastic*:
- **a** primary tumour;
- **b** secondary deposits.

5 *Haematological*:
- **a** Hodgkin's disease;[3]
- **b** non-Hodgkin's lymphoma;
- **c** leukaemia;
- **d** myeloproliferative disorders.

6 *Autoimmune*:
- **a** autoimmune hepatitis;

7 *Biliary tract disease*:
- **a** primary biliary cirrhosis;
- **b** primary sclerosing cholangitis.

8 *Metabolic diseases*:
- **a** fatty infiltration (non-alcoholic and alcoholic fatty liver disease);
- **b** haemochromatosis;
- **c** amyloid;
- **d** glycogen storage diseases (e.g. Gaucher's disease[4]).

[1]Bernhard Riedel (1846–1916), Professor of Surgery, Jena, Germany. Also described Riedel's thyroiditis.

[2]Adolf Weil (1848–1916), Professor of Medicine, Berlin, Germany.
[3]Thomas Hodgkin (1798–1866), Curator of Pathology, Guy's Hospital, London, UK.
[4]Phillipe Gaucher (1854–1918), Physician, Hôpital St Louis, Paris, France.

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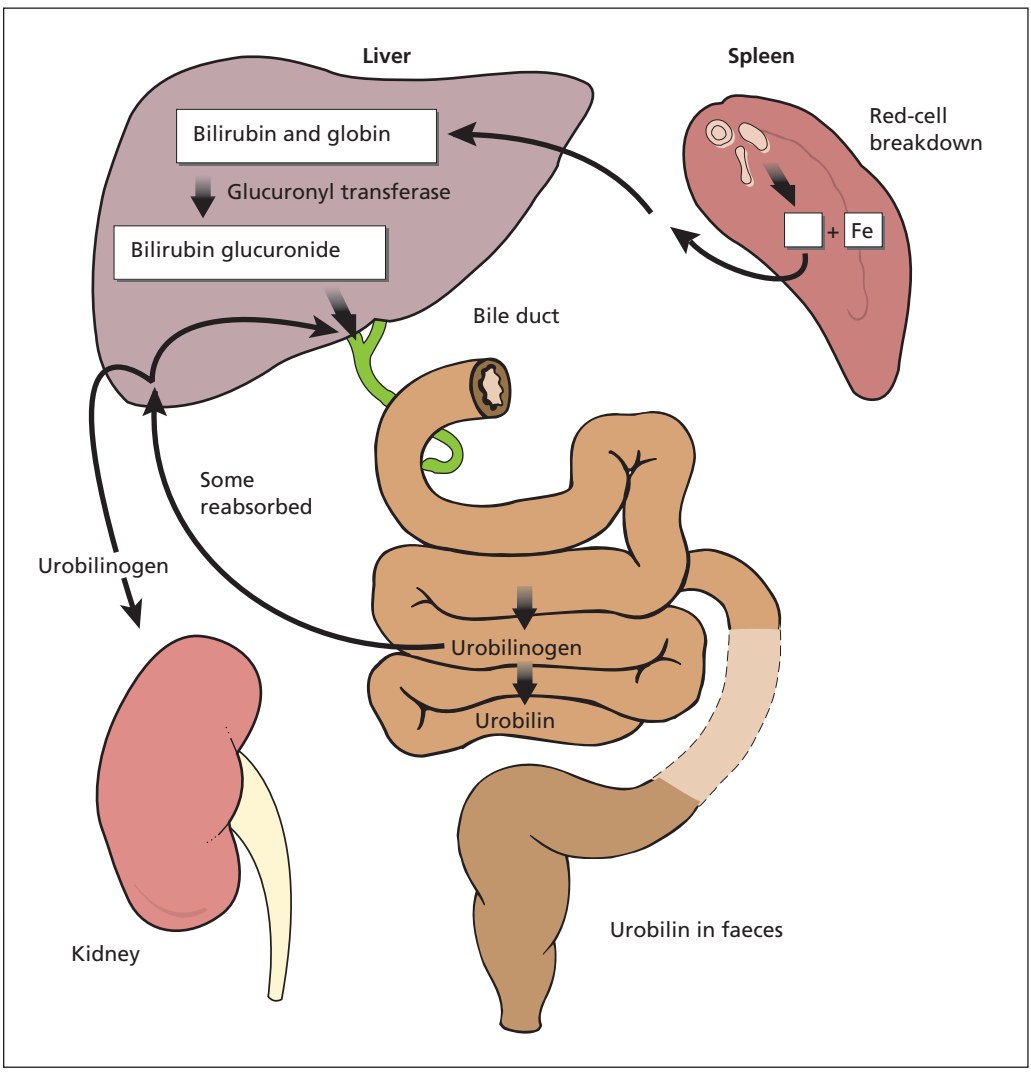

Figure 30.1 The metabolism of bilirubin.

Whenever the liver is palpable, the patient must be examined to detect any accompanying splenomegaly or lymphadenopathy. If the spleen is palpable in addition to the liver, consider cirrhosis, haematological malignancy or amyloid as possible diagnoses. If, in addition, the lymph nodes are enlarged, the diagnosis is often lymphoma, but may be due to viral infection such as Epstein–Barr virus.[5]

[5]Michael Anthony Epstein (b. 1921), Professor of Pathology, University of Bristol, Bristol, UK. Yvonne Barr (b. 1932), Epstein's assistant, Middlesex Hospital, London, UK.

Jaundice

The normal serum bilirubin is below 17 µmol/L (1 mg/dL). Excess bilirubin becomes clinically detectable when the serum level rises to over 35 µmol/L (2 mg/dL), and gives a yellow tinge to the sclera and skin, termed jaundice (or icterus).

Bilirubin metabolism (Figure 30.1)

Knowledge of bile pigment metabolism and excretion is essential if the pathogenesis, presentation,

investigation and treatment of jaundice are to be understood.

When red cells reach the end of their life in the circulation (approximately 120 days), they are destroyed in the reticuloendothelial system. The porphyrin ring of the haemoglobin molecule is disrupted and a bilirubin–iron–globin complex produced. The iron is released and used for further haemoglobin synthesis. The bilirubin–globin fraction reaches the liver as a lipid-soluble, water-insoluble substance. In the liver, the bilirubin is conjugated with glucuronic acid in the hepatocytes and excreted in the bile as the now water-soluble bilirubin glucuronide.

In the bowel lumen, bilirubin is reduced by bacterial action to the colourless urobilinogen. Most of the urobilinogen is excreted in the faeces, where it is broken down into urobilin, which is pigmented and which, with the other breakdown products of bilirubin, gives the stool its normal colour.

A small amount of urobilinogen is reabsorbed from the intestine into the portal venous tributaries and passes to the liver, where most of it is excreted once more in the bile back into the gut. Some, however, reaches the systemic circulation and this is excreted by the kidney into the urine. When urine is exposed to air, the urobilinogen it contains is oxidized to urobilin, which is darker.

Classification and pathogenesis

The causes of jaundice are classified according to which was the abnormal stage in the metabolism of bilirubin that resulted in its accumulation.

Prehepatic jaundice

Increased production of (unconjugated) bilirubin by the reticuloendothelial system, as may result from excessive destruction of red cells in haemolysis, exceeds the ability of the liver to conjugate; therefore, the unconjugated bilirubin accumulates in the blood. There is no increase in conjugated bilirubin in the blood, so none is found in the urine. However, there is an increase in the amount of urobilinogen produced in the gut, so more is resorbed and 'overflows' into the systemic circulation, where it is excreted by the kidney.

Hepatic jaundice

In the presence of hepatocellular damage, the liver is unable to conjugate bilirubin efficiently, and less is excreted into the canaliculi. Thus, both unconjugated and conjugated bilirubin accumulate in the blood.

Posthepatic (obstructive) jaundice

Obstruction of the intrahepatic or extrahepatic bile ducts prevents excretion of conjugated bilirubin. Without pigment, the stools become pale, and the conjugated bilirubin builds up in the blood and is excreted in the urine, turning it dark brown.

Sometimes the hepatic and posthepatic forms coexist. For example, a stone in the common bile duct may produce jaundice partly by obstructing the outflow of bile and partly by secondary damage to the liver (biliary cirrhosis). Similarly, tumour deposits in the liver and cirrhosis may both result in jaundice partly by actual destruction of liver tissue and partly by intrahepatic duct compression.

Causes

Prehepatic jaundice

This is caused by increased production of bilirubin owing to increased red blood cell destruction. The most common cause is haemolysis (e.g. spherocytosis or incompatible blood transfusion), but it may occur during reabsorption of a large haematoma.

Hepatic jaundice

This is a result of impaired bilirubin conjugation owing to the following:

- hepatitis: viral (hepatitis viruses A, B, C), leptospirosis, glandular fever;
- cirrhosis;
- cholestasis from drugs, e.g. chlorpromazine;
- liver poisons, e.g. paracetamol overdosage, chlorinated hydrocarbons such as carbon tetrachloride, chloroform and halothane; phosphorus;
- liver tumours.

Posthepatic jaundice

This is caused by obstruction to biliary drainage owing to the following:

1 *Obstruction within the lumen*: gallstones.
2 *Pathology in the wall*:

a congenital atresia of the common bile duct;
b traumatic stricture;
c primary or secondary sclerosing cholangitis;
d tumour of the bile duct (cholangiocarcinoma).

3 *External compression*:
a pancreatitis;
b tumour of the head of the pancreas;
c tumour of the ampulla of Vater;
d hilar lymphadenopathy.

Diagnosis

This is based on history, examination and special investigations.

History

A family history of anaemia, splenectomy or gallstones suggests a congenital red cell defect. Clay-coloured stools and dark urine accompanying the episodes of jaundice indicate hepatic or posthepatic causes. Enquire after recent blood transfusions, drugs (chlorpromazine, paracetamol, methyldopa, repeated exposure to halothane), injections and alcohol consumption. Has there been contact with cases of viral hepatitis? What is the patient's occupation? (Farmers and sewer workers are at risk of leptospirosis – Weil's disease.)

Usually painless jaundice of sudden onset with liver tenderness in a young person is viral in origin. Attacks of severe colic, rigors and intermittent jaundice suggest a stone. Remorselessly progressive jaundice, often accompanied by continuous pain radiating to the back, is suspicious of malignant disease. Recent onset of diabetes suggests carcinoma of the pancreas.

Examination

The colour of the jaundice is important; a lemon-yellow tinge suggests haemolytic jaundice (owing to combined anaemia and mild icterus). Deep jaundice suggests the hepatic or posthepatic types.

Other signs of cirrhosis should be sought: spider naevi, gynaecomastia, testicular atrophy, encephalopathy, splenomegaly, liver palms, flapping tremor, leuconychia (white nails) and, occasionally, finger clubbing. There may also be ascites and leg oedema, but these may be associated with intra-abdominal malignant disease as well as cirrhosis.

Examination of the liver itself is helpful. In viral hepatitis, the liver is slightly enlarged and tender; in cirrhosis, the liver edge is firm and may be irregular, although the liver may be shrunken and impalpable. A grossly enlarged, knobbly liver may also be present in malignant disease.

If the gallbladder is palpable and distended, it is probable that the cause of the jaundice is not a stone (Courvoisier's law,[6] Chapter 31, p. 271). The liver may be smoothly enlarged in posthepatic obstructive jaundice.

A pancreatic tumour may be palpable or a separate primary focus of malignant disease may be obvious, e.g. a melanoma.

Splenomegaly suggests cirrhosis of the liver, blood disease or a lymphoma. In the last, there may also be obvious lymphadenopathy.

Special investigations (Table 30.1)

The prehepatic causes of jaundice are relatively easy to distinguish from hepatic and posthepatic, but the last two are often very difficult to differentiate one from the other and, as already stated, may be associated with each other. Laboratory tests are of some help but are by no means diagnostic. Imaging techniques are valuable in visualizing the liver, gallbladder and pancreas, whereas endoscopic cannulation of the bile ducts or transhepatic duct puncture enable the bile duct system to be outlined. Percutaneous biopsy will usually confirm the hepatic cause of jaundice.

Bilirubin is not excreted by the kidney except in its water-soluble (conjugated) form. It is therefore absent from the urine in prehepatic jaundice (hence the old term 'acholuric jaundice'), although present when there is posthepatic obstruction.

In *prehepatic jaundice*, large amounts of bilirubin are excreted into the gut; therefore, the urobilinogen in the faeces is raised, the amount absorbed from the bowel increases and there is therefore greater spill over into the urine.

In *hepatic damage*, the urinary urobilinogen may also be raised because of the inability of the liver to re-excrete the urobilinogen reabsorbed from the bowel.

In *posthepatic obstruction*, very little bile can enter the gut; therefore, the urobilinogen must be low in both the faeces and the urine.

The important laboratory findings in the various types of jaundice can now be summarized:

[6]Ludwig Courvoisier (1843–1918), Professor of Surgery, Basle, Switzerland.

Table 30.1 Diagnosis of jaundice

Test	Prehepatic	Hepatic	Obstructive
Urine	Urobilinogen	Urobilinogen	No urobilinogen Bilirubin present
Serum bilirubin	Unconjugated bilirubin	Conjugated and unconjugated	Conjugated bilirubin
ALT (SGPT) and AST (SGOT)	Normal	Raised	Normal or moderately raised
ALP	Normal	Normal or moderately raised	Raised
Blood glucose	Normal	Low if liver failure	Sometimes raised if pancreatic tumour
Reticulocyte count	Raised in haemolysis	Normal	Normal
Haptoglobins	Low due to haemolysis	Normal or low if liver failure	Normal
Prothrombin time	Normal	Prolonged due to poor synthetic function	Prolonged due to vitamin K malabsorption; corrects with vitamin K
Ultrasound	Normal	May be abnormal liver texture, e.g. cirrhosis	Dilated bile ducts

- *Urine*: the presence of bilirubin indicates obstructive jaundice, either intra- or posthepatic. Excess of urobilinogen indicates prehepatic jaundice or sometimes liver damage, whereas an absence of urobilinogen suggests obstructive causes.
- *Faeces*: absence of bile pigment indicates intra- or posthepatic causes.
- *Haematological investigations*: red blood cell fragility, Coombs' test[7] and reticulocyte count confirm haemolytic causes.
- *Serum bilirubin* is rarely higher than 100 µmol/L (5 mg/dL) in prehepatic jaundice, but may be considerably higher in obstructive cases. In late malignant disease, it may exceed 1000 µmol/L.
- *Conjugated bilirubin*: in prehepatic jaundice, bilirubin is present in the unconjugated form. In pure posthepatic obstructive jaundice, the bilirubin is mainly in the conjugated form, whereas in hepatic jaundice it is present in the mixed conjugated and unconjugated forms owing to a combination of liver destruction and intrahepatic duct blockage.
- *Alkaline phosphatase (ALP)* is produced by cells lining the bile canaliculi. It is normal in prehepatic jaundice, raised in hepatic jaundice and considerably raised in posthepatic jaundice and in primary biliary cirrhosis. A raised ALP level and normal bilirubin are features of obstruction of some, but not necessarily all, of the intrahepatic bile ducts (note that a different isoenzyme of ALP is produced by bone and placenta, and isolated elevated levels should be isotyped to determine origin).
- *Serum proteins* are normal in prehepatic jaundice, have a reversed albumin/globulin ratio with depressed albumin synthesis in hepatic jaundice and are usually normal in posthepatic jaundice, unless associated with liver damage.
- *Haptoglobin* concentrations are low in haemolysis. Haptoglobin binds free haemoglobin released after haemolysis, and, once bound, the complex is catabolized faster than haptoglobin alone. It is also low in severe liver disease owing to impaired synthesis.
- *Serum transaminases* such as alanine transaminase (ALT) and aspartate transaminase (AST) are raised with hepatocyte inflammation such as occurs in viral hepatitis and in the active phase of cirrhosis. Gamma

[7]Robin Royston Amos Coombs (1921–2006), Professor of Immunology, Cambridge, UK. Described the test for detecting the presence of antibodies to red blood cells.

glutamyl transferase (GGT) is a more sensitive indicator of liver disease, and is often raised before the transaminases.

- *Prothrombin time* is normal in prehepatic jaundice, prolonged but correctable with vitamin K in posthepatic jaundice (in which functioning liver tissue is still present) and prolonged but not correctable in advanced hepatic jaundice, in which not only is absorption of fat-soluble vitamin K impaired but the damaged liver is also unable to synthesize prothrombin.
- *Ultrasound scanning* is extremely useful as well as non-invasive. Gallstones within the gallbladder can be demonstrated with a high degree of accuracy. Unfortunately, stones within the distal bile ducts are often missed because of overlying duodenal gas. Dilatation of the duct system within the liver is a good indication of duct obstruction; thus, if the ducts are not dilated, an obstructive cause for the jaundice is unlikely.
- *Computed tomography (CT)* and *magnetic resonance (MR)* scans are useful in addition to ultrasound in the demonstration of intrahepatic lesions (e.g. tumour deposits, abscess, cyst), which may then be accurately needle biopsied under imaging control. A mass in the pancreas may also be demonstrated, but differentiation between carcinoma and chronic pancreatitis is difficult.
- *Abdominal X-ray* may show gallstones (10% are radio-opaque).
- *Magnetic resonance cholangiopancreatography (MRCP)* affords non-invasive high-resolution imaging of the biliary tree. However, it does not permit therapeutic intervention.
- *Endoscopic retrograde cholangiopancreatography (ERCP)*, in which the ampulla of Vater[8] is cannulated using an endoscope passed via the mouth, may demonstrate the location and indicate the nature of an obstructing lesion within the bile ducts. A periampullary tumour is also directly visualized at this examination, and can be biopsied.
- *Percutaneous transhepatic cholangiography (PTC)*, in which a needle is passed percutaneously into the liver substance and a dilated bile duct is cannulated, may be necessary where ERCP is not possible.

  Both ERCP and PTC may be used to introduce stents across obstructing bile duct lesions to decompress the bile ducts and resolve jaundice.
- *Needle biopsy*. If the ultrasound scan reveals no dilatation of the duct system, an obstructive lesion is unlikely and needle biopsy of the liver may give valuable information regarding hepatic pathology (e.g. hepatitis or cirrhosis). If the ultrasound demonstrates focal lesions in the liver, an ultrasound-guided biopsy of one of the lesions can be obtained. Needle biopsy is potentially dangerous in the presence of jaundice, particularly where there is biliary dilatation or ascites. The prothrombin time, if prolonged, should first be corrected by administration of vitamin K, and fresh frozen plasma and platelet transfusions may also be indicated; a transjugular liver biopsy may be appropriate in the presence of severe coagulopathy. Should bleeding occur following biopsy, angiographic embolization or immediate laparotomy may be necessary.

Summary of investigations of jaundice

The investigations of jaundice may be grouped as follows:

- *Exclusion of prehepatic causes*: haptoglobin level, reticulocyte count, Coombs' test; split bilirubin (conjugated/unconjugated).
- *Liver synthetic function* (hepatocellular dysfunction): prothrombin time, albumin.
- *Liver cell damage*: transaminases, γ-glutamyl transferase.
- *Bile duct obstruction*: alkaline phosphatase, ultrasound of bile ducts, PTC, ERCP, MRCP and CT for pancreatic lesion.
- *Intrahepatic mass*: cross-sectional imaging, such as ultrasound and CT, with needle biopsy.

Congenital abnormalities

Riedel's lobe

This anatomical variant is a projection downwards from the right lobe of the liver of normally functioning liver tissue. It may present as a puzzling and symptomless abdominal mass.

[8]Abraham Vater (1648–1751), Professor of Anatomy, Wittenberg, Germany.

Polycystic liver

This is often associated with polycystic disease of the kidneys (and occasionally pancreas), and comprises multiple cysts within the liver parenchyma. The liver may reach a very large size, but functions normally. The commonest symptoms are discomfort and awareness of the grossly enlarged liver in the abdomen. Haemorrhage into the cysts and cholangitis are occasional complications.

Liver trauma

This may be due to penetrating wounds (gunshot or stab) or closed crush injuries, often associated with fractures of the ribs and injuries to other intra-abdominal viscera, especially the spleen. Severe abdominal trauma is becoming increasingly common, and accurate preoperative diagnosis of the source of the haemorrhage may be impossible.

Clinical features

Following injury, the patient complains of abdominal pain. Examination reveals shock (pallor, tachycardia, hypotension), generalized abdominal tenderness together with the signs of progressive bleeding.

CT is essential to assess the severity of the injury and to identify any additional injuries, such as a ruptured spleen. Occasionally, there is delayed rupture of a subcapsular haematoma, so that abdominal pain and shock may not be in evidence until some hours or days after the initial injury.

Treatment

If the patient's vital observations are stable, and a definite diagnosis made by CT, the patient can initially be managed conservatively with blood transfusion and careful observation. Repeat CT is undertaken to monitor progress.

If bleeding continues, as denoted by falling blood pressure, rising pulse and falling haemoglobin, and/or there is the risk of overlooking damage to other viscera, a laparotomy is performed. Minor liver tears can be sutured. Packing of the injury with gauze packs, removed after 48 hours, may be life-saving in severe trauma when the patient's condition is deteriorating. If bleeding continues, the relevant main hepatic arterial branch should be tied, and, if the bleeding continues in spite of this, major hepatic lobar resection may be necessary.

Antibiotic cover must be given because of the danger of infection of areas of devitalized liver, and is particularly important when packing is used.

Acute infections of the liver

Possible sources of infection are the following:

- *portal*, from an area of suppuration drained by the portal vein, usually diverticular sepsis or appendicitis;
- *biliary*, resulting from an ascending cholangitis;
- *arterial*, as part of a general septicaemia – this is unusual;
- *adjacent infections* spreading into the liver parenchyma, e.g. subphrenic abscess or acute cholecystitis.

Pyogenic liver abscess

Pyogenic liver abscess is a consequence of infection either in the portal territory, leading to a portal pyaemia (pyelophlebitis), or in the biliary tree. Multiple abscesses are common. Common infecting organisms include *Escherichia coli*, *Streptococcus faecalis* and *Streptococcus milleri*.

Clinical features

The condition should be suspected in patients who develop rigors, high swinging fever, a tender palpable liver and jaundice. A previous history of abdominal sepsis, such as Crohn's disease,[9] appendicitis or diverticulitis may be obtained. The clinical course is often insidious, with a non-specific malaise for over a month before presentation and diagnosis.

Special investigations

- *Blood culture*, carried out before treatment is commenced, is often positive.

[9]Burrill Bernard Crohn (1884–1983), Gastroenterologist, Mount Sinai Hospital, New York, NY, USA. The disease was first described by Morgagni (1682–1771).

- *Ultrasound or CT* of the liver may identify and localize hepatic abscesses, as well as identifying the source of the pyaemia.

Treatment

The originating site of sepsis should be dealt with appropriately. A large liver abscess can be drained percutaneously under ultrasound guidance; smaller abscesses are treated by parenteral antibiotic therapy alone.

Portal pyaemia (pyelophlebitis)

Infection may reach the liver via the portal tributaries from a focus of intra-abdominal sepsis, particularly acute appendicitis or diverticulitis. Multiple abscesses may permeate the liver; in addition, there may be septic thrombi in the intrahepatic radicles of the portal vein, and infected clot in the portal vein itself. The condition has become rare since the advent of antibiotics.

Biliary infection

Multiple abscesses in the liver may occur in association with severe suppurative cholangitis secondary to impaction of gallstones in the common bile duct. Clinically, the features are those of *Charcot's intermittent hepatic fever*[10] – pyrexia, rigors and jaundice. (Rigors represent a bacteraemia and are commonly due to infection in either the renal or biliary tract.)

Urgent drainage of the bile ducts is performed, by either endoscopic sphincterotomy or percutaneous transhepatic drainage.

Amoebic liver abscess

This particular type of portal infection is secondary to an *Entamoeba histolytica* infection of the large intestine. From there, amoebae travel via the portal circulation to the liver, where they proliferate. The amoeba produces a cytolytic enzyme that destroys the liver tissue, producing an amoebic abscess, which is sterile, although amoebae may be found in the abscess wall.

CT and ultrasound of the liver are the most valuable special investigations.

[10]Jean-Martin Charcot (1825–1893), First Professor of Neurology, Salpêtrière Hospital, Paris, France.

Treatment

The majority respond to medical treatment with metronidazole. Ultrasound-guided percutaneous drainage is required infrequently in non-responding cases.

Hydatid disease of the liver

The liver is the site of 75% of hydatid cysts in humans.

Pathology

Dogs are infected with the ova of *Echinococcus granulosus* (*Taenia echinococcus*) as a result of eating sheep offal. The tapeworms develop in the dog's small intestine from whence ova are discharged in the faeces. Humans (as well as sheep) ingest the ova from contaminated vegetables and the ova penetrate the stomach wall to invade the portal tributaries and thence pass to the liver. Occasionally, the hydatids may pass on to the lungs, brain, bones and other organs. Hydatid disease is therefore common in sheep-rearing communities, e.g. in Australia, Iceland, Cyprus, southern Europe, Africa and Wales.

Clinical features

A cyst may present as a symptomless mass. The contents may die and the walls become calcified so that this inactive structure may be a harmless postmortem finding.

The active cyst may, however,

- *rupture* into the peritoneal cavity, pleural cavity, alimentary canal or biliary tree;
- *become infected*;
- *produce obstructive jaundice* by pressure on intrahepatic bile ducts, although jaundice is much more often due to intrabiliary rupture and release of cysts into the bile ducts.

Special investigations

- *Plain X-ray* of the liver may show a clear zone produced by the cyst, or may show flecks of calcification in the cyst wall.
- *Ultrasound and CT scan* localize the cyst.

- *Serological tests* depend on the sensitization of the patient to hydatid fluid, which contains a specific antigen, leakage of which induces the production of antibodies.
- *Eosinophil count*: there may be *eosinophilia*, which, while not specific, should arouse clinical suspicion.

Treatment

A calcified cyst should be left alone. Other cysts should be treated to prevent complications. Treatment with albendazole may result in shrinkage or even disappearance of the cysts. Failure to respond or the presence of complications are indications for surgery. The cyst is exposed and aspirated. It is then possible to excise the cyst, taking care not to liberate daughter cysts that are present within the cyst.

Cirrhosis

Definition

Cirrhosis of the liver is a consequence of chronic hepatic injury, with healing by regeneration and fibrosis. Fibrosis leads to further cell damage and destruction of hepatic architecture, progressing to liver failure and portal hypertension.

Aetiology

A convenient classification of the cirrhoses is as follows:

1 *Parenchymal*:
- **a** alcohol;
- **b** viral, commonly following hepatitis B and C infections;
- **c** non-alcoholic fatty liver disease.

2 *Metabolic*:
- **a** iron overload – haemochromatosis;
- **b** copper overload – hepatolenticular degeneration (Kinnier Wilson's disease[11]).

3 *Biliary*:
- **a** primary biliary cirrhosis (Hanot's cirrhosis[12]) – an autoimmune disease characterized by raised serum antimitochondrial (M2) antibodies;
- **b** primary sclerosing cholangitis;
- **c** secondary to prolonged biliary obstruction (secondary biliary cirrhosis).

4 *Hepatic venous outflow obstruction*:
- **a** Budd–Chiari syndrome[13] (hepatic venous occlusion);
- **b** severe chronic congestive cardiac failure.

5 *Other causes*:
- **a** chronic active hepatitis, which is an autoimmune disease;
- **b** schistosomiasis;
- **c** nutritional (protein-deficient diet);
- **d** idiopathic (cryptogenic);
- **e** parenteral nutrition related – probably linked to the fat content.

In countries with a high consumption of alcohol (e.g. France), alcohol is the most common aetiological factor. In the tropics, schistosomiasis heads the list (Egyptian splenomegaly). In the UK, alcohol accounts for half of the cases of cirrhosis.

Consequences of cirrhosis

1 Hepatocellular failure:
- **a** impaired protein synthesis: prolonged prothrombin time and low albumin;
- **b** impaired metabolism of toxins: encephalopathy;
- **c** impaired bilirubin metabolism: jaundice.

2 Portal hypertension (see below).
3 Ascites due to portal hypertension.
4 Malignant change: hepatoma.

Clinical features of cirrhosis

A number of clinical signs, separate from those of portal hypertension, are seen in cirrhosis. These include gynaecomastia, testicular atrophy, amenorrhoea, spider naevi, finger clubbing and palmar erythema ('liver palms').

Hepatic encephalopathy

A neuropsychiatric condition characterized by mental changes, flapping tremor and hepatic coma. It occurs because the liver is unable to detoxify the nitrogenous breakdown products of protein metabolism combined with portosystemic shunts that divert these products directly into the systemic circulation.

[11]Samuel A. Kinnier Wilson (1877–1937), Neurologist, Hospital for Nervous Diseases, Queen Square, London, UK.
[12]Victor Charles Hanot (1844–96), Physician, Paris, France.
[13]George Budd (1808–1882), Professor of Medicine, King's College, London, UK. Hans Chiari (1851–1916), Professor of Pathology, Prague, Czech Republic.

Portal hypertension

The normal portal pressure is less than 5 mmHg. In portal hypertension, this pressure is raised.

Aetiology

Portal hypertension results from an obstruction to portal venous drainage. The causes are classified according to the site of the block.

1 *Prehepatic* (obstruction of the portal venous inflow into the liver):
   - **a** congenital malformation;
   - **b** portal vein thrombosis: often secondary to portal pyaemia, prothrombotic disorders, or, in the neonatal period, spreading infection from the umbilicus;
   - **c** occlusion by tumour or pancreatitis. In adults, there is a special case in which splenic vein thrombosis caused by pancreatic pathology can result in 'segmental portal hypertension' with diversion of the splenic drainage via the short gastric veins, which results in the development of gastric and oesophageal varices.

2 *Hepatic* (obstruction of the portal flow within the liver): e.g. cirrhosis.

3 *Posthepatic* (obstruction of the hepatic veins): Budd–Chiari syndrome.
   - **a** Idiopathic hepatic venous thrombosis in young adults of both sexes. A possible complication of oral contraceptives in women. In many cases, there is an underlying haematological cause, e.g. polycythaemia or monoclonal gammopathy.
   - **b** Congenital obliteration.
   - **c** Blockage of hepatic veins by tumour invasion.

By far, the commonest cause of portal hypertension is cirrhosis, yet there is no strict relationship between the severity of the liver disease and the extent of portal hypertension, which is not therefore entirely explained on the basis of mechanical obstruction.

Pathological effects

The four important effects of portal hypertension are the following:

1 collateral portosystemic venous drainage develops;
2 splenomegaly;
3 ascites (in hepatic and posthepatic portal hypertension only);
4 the manifestations of hepatic failure (in severe cirrhosis).

Collateral channels

Portal obstruction results in the development of collateral channels between the portal and systemic venous circulations (Figure 30.2). The sites of these channels are as follows:

- between the left gastric vein and the oesophageal veins, forming gastric and oesophageal varices; these are the largest and clinically the most important connections;
- along the obliterated umbilical vein to the superior and inferior epigastric veins, forming a *caput medusae* around the umbilicus;
- retroperitoneal and diaphragmatic anastomoses, which present technical hazards to the surgeon at the time of liver transplantation;
- between the superior and inferior rectal veins with development of anal canal varices;
- along any adhesions between the visceral and parietal peritoneum due to previous surgery or inflammation;
- at the site of a colostomy or ileostomy.

The oesophageal varices, and to a much lesser extent anal varices, may result in gastrointestinal haemorrhage, which is the most serious complication of portal hypertension.

Splenomegaly

Progressive splenic enlargement occurs as a result of portal congestion together with some degree of hypertrophy of the splenic substance itself. This is often associated with the haematological changes of hypersplenism: leucopenia and thrombocytopenia. Anaemia accompanying splenomegaly can be accounted for by gastrointestinal bleeding and is not necessarily a result of splenic enlargement.

Ascites

This is due to a combination of factors:

1 Splanchnic vasodilatation occurs owing to accumulation of vasoactive mediators in the splanchnic circulation secondary to the liver failure, resulting in pooling of blood. Systemic hypotension is a consequence, with renal hypoperfusion and activation of the renin–angiotensin–aldosterone system, resulting in raised serum aldosterone which leads to avid salt (sodium) and water retention.

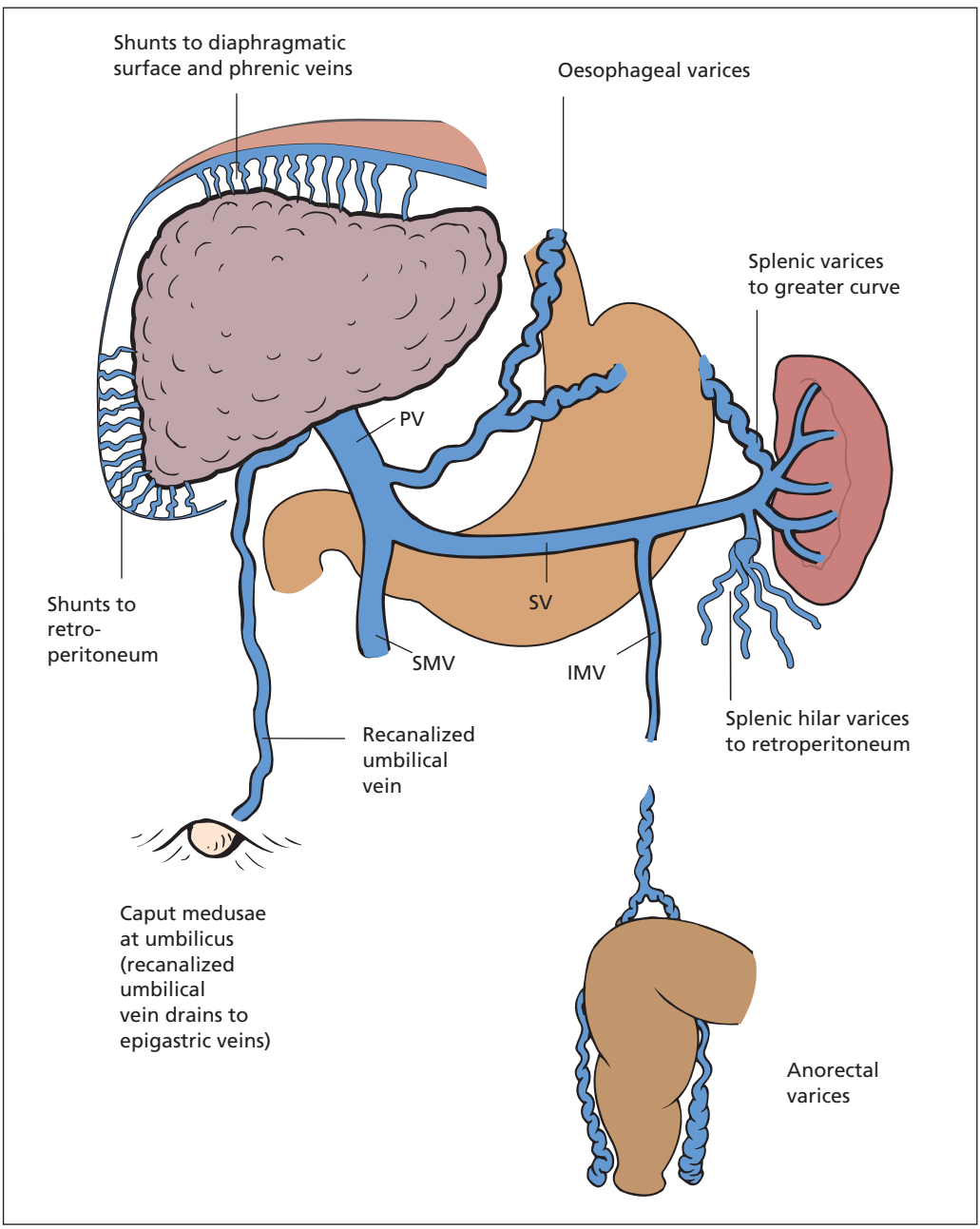

Figure 30.2 The sites of occurrence of portal–systemic communications in patients with portal hypertension. PV, portal vein; SMV, superior mesenteric vein; IMV, inferior mesenteric vein; SV, splenic vein.

2 The portal venous pressure is raised owing to compression of the portal venous radicles in the liver by the scarred surrounding hepatic tissue.
3 The serum albumin, which is synthesized by the liver, is reduced, resulting in lowering of the serum osmotic pressure.

The effects of liver failure

- Jaundice.
- Encephalopathy.

Clinical features

To the surgeon, portal hypertension presents as three problems:

1 as a differential diagnosis of jaundice or hepatomegaly;
2 as a cause of gastrointestinal haemorrhage;
3 as one of the causes of ascites (Box 30.1).

Special investigations

In addition to history and examination (which includes a careful search for the stigmata of liver disease), the following investigations are indicated:

- *Liver function tests*, particularly transaminases and alkaline phosphatase.
- *Liver synthetic function tests*, such as prothrombin time and albumin.
- *Liver biopsy* if necessary.
- *Fibreoptic endoscopy*, which may demonstrate varices and differentiate between bleeding from this source and from a peptic ulcer or multiple gastric erosions, all of which are common in patients with cirrhosis.

Box 30.1 The causes of ascites

- Liver failure and portal hypertension
- Carcinomatosis
- Heart failure
- Renal failure
- Chronic peritonitis, e.g. tuberculous
- Pancreatitis

- *Ultrasound* will demonstrate portal venous flow, splenomegaly, and the presence of intra-abdominal varices; it may also detect hepatic venous outflow occlusion.
- *Inferior vena cavagram*, which will demonstrate hepatic venous occlusion.
- *Portal pressure measurement*. This is achieved by means of a catheter passed via the transjugular route into the hepatic vein. The difference between the pressure in the vein with and without an occluding balloon inflated (the hepatic and hepatic wedge pressure) is the portal pressure, a technique akin to pulmonary pressure measurement with a Swan–Ganz catheter[14] (page 34).
- *Magnetic resonance angiography and CT angiography* for the accurate demonstration of the site of portal obstruction.

Treatment

The treatment of uncomplicated portal hypertension involves treatment of the underlying condition, e.g. cirrhosis is managed by a high-calorie, well-balanced diet with added protein in malnourished patients (provided liver damage is not severe), and with avoidance of precipitating factors such as alcohol. If oesophageal varices are visible on endoscopy, they are banded or injected with sclerosant, since the first episode of variceal haemorrhage is associated with a 15–20% mortality.

The management of haemorrhage from gastro-oesophageal varices

Haemorrhage from gastro-oesophageal varices is particularly dangerous, especially in patients with liver damage. In these subjects, the liver is further injured by the hypotension of blood loss, and encephalopathy may be precipitated owing to the absorption of large amounts of nitrogenous breakdown products from the 'meal of blood' within the intestine. Prognosis is better in the small group of patients with normal liver function and portal hypertension due to a prehepatic block, e.g. portal vein thrombosis.

[14]Harold James Charles ('Jeremy') Swan (1922–2005), Cardiologist, Cedars of Lebanon Hospital, Los Angles, CA, USA. William Ganz (1919–2009), Professor of Medicine, UCLA, and Senior Research Scientist, Cedars of Lebanon Hospital, Los Angeles, CA, USA.

Prophylaxis against haemorrhage

If varices are detected on screening endoscopy, pharmacological therapy with beta-blockers is instituted to reduce splanchnic blood flow and lower portal venous pressure. Large varices in patients at increased risk of haemorrhage (e.g. severe liver disease) may be treated by endoscopic band ligation (small rubber bands applied to ligate the varices) or injection with sclerosant.

Establishing the diagnosis

An attempt must be made to confirm the diagnosis. The presence of established liver disease, an enlarged spleen and proven varices does not necessarily mean that bleeding is from the varices. Such patients are prone to bleeding from gastric erosions and are commonly affected by peptic ulceration. Fibreoptic endoscopy should always be performed in order to visualize the bleeding point and to exclude non-variceal haemorrhage. Active bleeding may, however, prevent a satisfactory view at endoscopy.

Immediate treatment

The first priority is airway protection, emergency resuscitation and stabilizing the patient prior to emergency endoscopy:

- *Preventing aspiration*. Patients with liver disease have impaired consciousness and may be at risk of aspirating. They should be managed in conjunction with the critical care team.
- *Resuscitation with fluid and blood*. Coagulation abnormalities should be corrected with fresh frozen plasma and/or platelet transfusions.
- *Antimicrobial therapy*. Patients are at risk of bacterial infection and benefit from treatment with broad-spectrum antibiotics (e.g. third-generation cephalosporins) to reduce the risk of rebleeding and improve survival.

Stopping the haemorrhage

The bleeding may be arrested by a number of manoeuvres:

- *Endoscopic variceal band ligation or sclerotherapy*. These procedures can stop bleeding with minimal trauma to the patient, although there is a risk of perforation of the oesophagus, and repeated injections may produce ulceration or fibrosis and stenosis.
- *Intravenous terlipressin*, a vasopressin analogue, is given to reduce portal venous pressure and cause temporary cessation of bleeding by mesenteric arteriolar constriction. Therapeutic doses cause intestinal colic and myocardial ischaemia, which responds to glyceryl trinitrate infusion.
- *Balloon tamponade*, achieved by passing a Sengstaken–Blakemore tube[15] via the mouth into the oesophagus and cardia. The gastric balloon on the end is inflated, following which gentle traction is applied to the tube such that the balloon impacts on the oesophagogastric junction, which stops flow in the varices. Rebleeding after balloon decompression is common, so it is used to buy time pending definitive treatment.
- *Transjugular intrahepatic portosystemic shunt (TIPS)*: a metal stent is inserted via the jugular vein and, under radiological control, passed through the liver substance to open up a passage between the hepatic vein and the portal vein. The resultant portosystemic shunt decompresses the portal system. TIPS has reduced the necessity for oesophageal transection or operative portosystemic shunt formation. Unfortunately, shunt procedures (surgical or radiological), in which an anastomosis is made between the portal and systemic circulations, are likely to precipitate encephalopathy.
- *Oesophageal transection*, in which the oesophagus together with the varices are divided at the cardio-oesophageal junction using a circular stapling gun in order to interrupt the communications between the two systems of veins within the wall of the lower oesophagus.
- *Surgical portocaval shunt*, by surgical anastomosis of the portal vein to the inferior vena cava or by splenic vein to the left renal vein used to be commonplace. Such procedures have now been superseded by TIPS and endoscopic control of oesophageal varices. Laparotomy should be avoided when possible if a subsequent transplant is planned, as the resulting vascular adhesions will add greatly to the dangers of the transplant operation.

[15]Robert Sengstaken (b. 1923), Neurosurgeon, New York, NY, USA. Arthur H. Blakemore (1897–1970), Surgeon, Columbia Presbyterian Medical Center, New York, NY, USA.

Treatment of ascites

- *Paracentesis* gives immediate relief if discomfort is intense, but it has the disadvantage that the patient loses protein, which should therefore be replaced at the time (10 g albumin per litre of ascites removed).
- *Diet*: low-sodium, high-protein diet; intravenous albumin.
- *Diuretics*: spironolactone often combined with a thiazide or loop diuretic.
- *TIPS*: see above.

Intractable ascites due to hepatic cirrhosis is an indication for liver transplantation, which is performed after failure of medical therapy.

Hepatorenal syndrome

Renal failure is often associated with ascites and liver failure, particularly alcoholic cirrhosis. It is in part a consequence of depletion of the intravascular volume, as may be caused by diuretic therapy or surgery. There is a reduction in intrarenal blood flow brought about by increased glomerular afferent arteriolar tone, but the cause of this is unknown. The glomerular filtration rate falls as the blood flow is diverted away from the renal cortex. Established renal failure in the presence of liver disease is difficult to treat, and is best avoided by maintaining hydration during surgery.

Renal failure may occur in any patient with jaundice, particularly following surgery. It is best prevented by avoiding fluid depletion and maintaining a good diuresis intraoperatively.

Liver neoplasms

Classification

Benign

- Haemangioma.
- Adenoma.
- Focal nodular hyperplasia

Malignant

1 *Primary*:
   a hepatocellular carcinoma (hepatoma);
   b fibrolamellar carcinoma, uncommon variant of hepatoma affecting young adults and children;
   c cholangiocarcinoma.
2 *Secondary* (most common):
   a portal spread (from alimentary tract);
   b systemic blood spread (from lung, breast, testis, melanoma, etc.);
   c direct spread (from gallbladder, stomach and hepatic flexure of colon).

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) exhibits marked geographical variation in incidence, being uncommon in the West but common in central Africa and south-east Asia. This distribution largely reflects the prevalence of hepatitis B and C virus infection. In the UK, the incidence of HCC is increasing, a reflection of the increasing prevalence of viral hepatitis in particular, and cirrhosis in general.

Eighty per cent of cases of HCC arise in patients with cirrhosis of the liver, and it is most common when cirrhosis is caused by one of the following:

- hepatitis B infection, the commonest cause of HCC worldwide;
- hepatitis C infection, in which the lead-time from infection to HCC may be 25 years or more;
- alcoholic liver disease;
- haemochromatosis, in which the degree of iron overload is related to HCC;
- non-alcoholic fatty liver disease (NAFLD).

Pathology

The pathogenesis of HCC, when associated with cirrhosis, is related to the chronic inflammatory process within the liver. Macroscopically, the tumour either forms a large, solitary mass or there may be multiple foci throughout the liver.

Spread occurs through the liver substance and into the vessels, so that portal vein thrombosis is a common finding. Metastasis outside the liver is late.

Clinical features

The clinical presentation varies depending on the extent of liver disease. In the absence of cirrhosis, the presentation is with massive liver swelling and possibly ascites. In the presence of advanced liver disease, malignant change in the liver may be marked by rapid deterioration and decompensation with encephalopathy, ascites and impaired synthetic function.

Special investigations

- *Serum α-fetoprotein (AFP)* may be significantly raised, but it is neither sensitive nor specific for hepatocellular carcinoma and may rise in other diseases such as hepatitis C.
- *Cross-sectional imaging* with ultrasound, CT or MR will confirm the presence of a large tumour. Small tumours, 1 cm or less in diameter, are difficult to distinguish from regenerative nodules in the presence of cirrhosis.
- *Selective hepatic angiography* may distinguish regenerative nodules from small HCCs, or may reveal multifocal cancer.

Treatment

In the absence of cirrhosis, a primary hepatocellular carcinoma confined to one lobe can be treated by hemihepatectomy. In the presence of cirrhosis, removal of any liver substance is likely to precipitate hepatic decompensation and death. Localized treatments such as radiofrequency ablation or transarterial chemoembolization (TACE) may be used, but in this situation the whole liver is 'at risk' and, even after successful destruction of one lesion, further lesions are likely to develop. The only alternative is replacement of the diseased liver by liver transplantation. Results from this procedure are good providing the tumour load is limited.

Cholangiocarcinoma

This is much less common (20% of primary tumours). It is an adenocarcinoma arising from the bile duct system that usually presents with jaundice and may complicate primary sclerosing cholangitis. Spread occurs directly through the liver substance and regional nodes with a fatal outcome.

Some tumours present early and are amenable to resection, which usually involves an extended liver resection (see below). For the more usual inoperable cases it may be possible to relieve the jaundice at ERCP by passing a plastic or an expanding metal stent upwards along the common bile duct through the growth into the dilated radicles above the obstruction or downwards by percutaneous intubation. This relieves the jaundice, often for many months.

Secondaries

The liver is an extremely common site for secondary deposits, which are often found at autopsy on patients who have died of advanced malignant disease. Necrosis at the centre of metastases leads to the typical umbilication of these tumours.

The clinical effects of secondary deposits in the liver are as follows:

- hepatomegaly: the liver is large, hard and irregular;
- jaundice: a late sign due to liver destruction and intrahepatic duct compression;
- hepatic failure, also a late sign;
- portal vein obstruction: producing oesophageal varices and ascites;
- inferior vena cava obstruction: producing leg oedema.

Treatment of secondary tumours

Resection of secondary tumours is not appropriate in the case of disseminated malignancy. However, it may be considered when deposits can be surgically excised leaving an adequate residual liver volume in the absence of any demonstrable extrahepatic disease. Following resection, the liver will hypertrophy and regain normal functional capacity. This is mostly applicable to secondary deposits from a previous colonic carcinoma. For this reason, such patients should have regular ultrasound scans postoperatively to detect potentially curable metastatic disease early. Following such a policy, 10–20% of patients who develop colorectal liver metastases can undergo resection with a 30–40% 5 year disease-free survival.

Liver surgery

Anatomical considerations

The liver has remarkable regenerative powers and, as such, will tolerate resection of up to two-thirds of its mass. However, anatomically it is not suited to resection, since the inflow structures (portal vein, hepatic artery and bile duct tributaries) cross the hepatic venous outflow. Nevertheless, there are recognized planes of resection that follow from an understanding of the segmental anatomy of the liver (Figure 30.3).

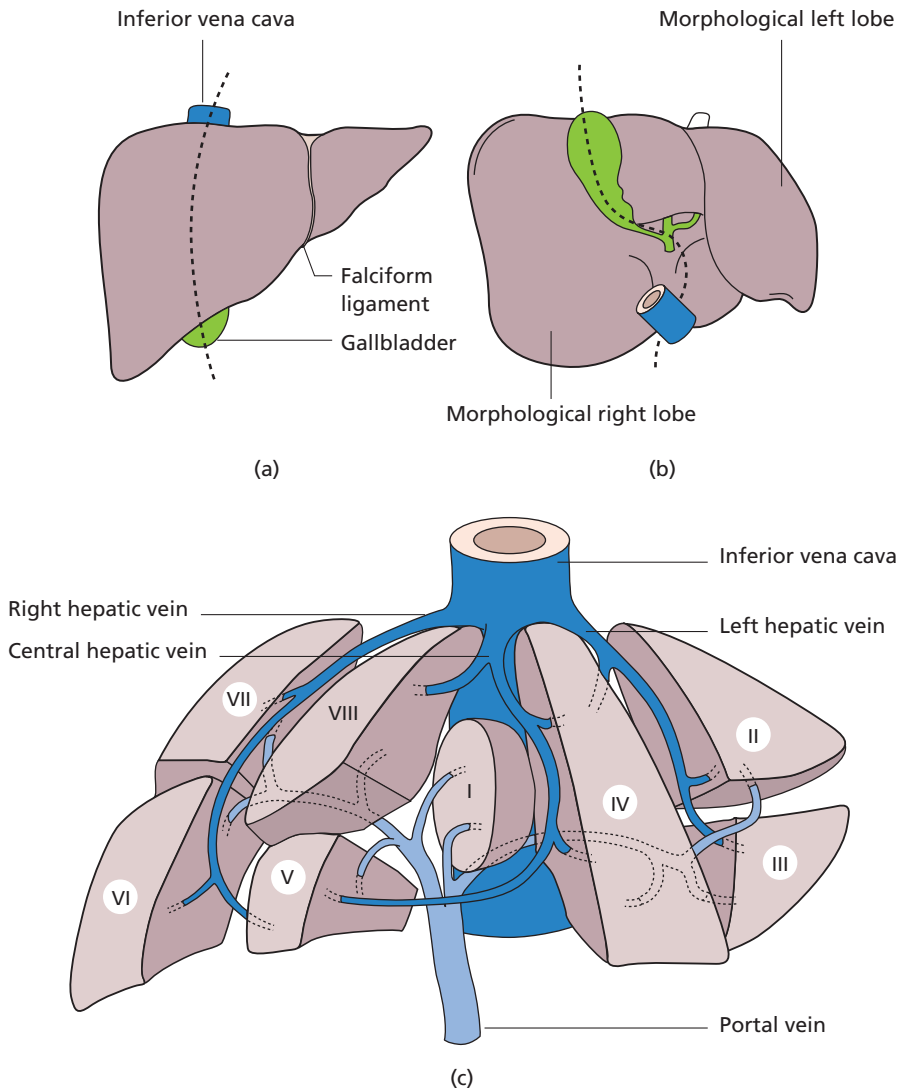

Figure 30.3 (a–c) Segmental anatomy of the liver showing inflow vessels (hepatic artery, portal vein and bile ducts) to the eight liver segments and the hepatic venous drainage via the three main hepatic veins. (Reproduced from Ellis H, Mahadevan V. (2010) *Clinical Anatomy*, 12th edn. Oxford: Wiley-Blackwell.)

Surgical resections

The following are the common liver resections performed for primary and secondary (usually colonic) tumours of the liver:

- right lobectomy involves removal of segments V to VIII by dividing the liver along a line between the gallbladder fossa and vena cava, and leaving the left lobe;
- left lobectomy involves resection of the left lobe segments II, III and IV; the caudate lobe (segment I) may also be removed;
- trisegmentectomy is a misnomer, but indicates resection of most of the liver but leaving just the left lateral segments (II and III); since this resection removes the most liver, care has to be taken to ensure that sufficient viable liver remains to sustain life.

31

The gallbladder and bile ducts

Learning objective

✓ To know the causes of gallstones, their varying presentations and treatment.

Congenital anomalies

Developmentally, a diverticulum grows out from the ventral wall of the foregut (primitive duodenum), which differentiates into the hepatic ducts and the liver. A lateral bud from this diverticulum becomes the gallbladder and cystic duct (Figure 31.1).

Anomalies are found in 10% of subjects and these are of importance to the surgeon during cholecystectomy.

The principal developmental abnormalities include the following:

- A long cystic duct travelling alongside the common hepatic duct to open near the duodenal orifice. This occurs in 10% of cases.
- Congenital absence (agenesis) of the gallbladder: one in 10 000, often associated with other congenital anomalies.
- Duplication of the gallbladder: one in 5000.
- Congenital obliteration of the ducts (biliary atresia, one of the causes of neonatal jaundice): one in 10 000.
- Absence of the cystic duct, the gallbladder opening directly into the side of the common bile duct.
- A long mesentery to the gallbladder, which allows acute torsion of the gallbladder to occur with consequent gangrene and rupture.
- Anomalies of the arrangement of the blood vessels supplying the gallbladder are common; for example, the right hepatic artery crosses in front of the common hepatic duct instead of behind it in 25% of subjects.
- Cystic dilatation of the main bile ducts (choledochal cyst): one in 200 000, but more common in people of Asian descent (one in 1000 Japanese).

Cholelithiasis (gallstones)

Gallstones are rare in children (although they should still be considered in the differential diagnosis of abdominal pain in children if the diagnosis is not to be overlooked, and should always be considered in children with spherocytosis or elliptocytosis), the incidence increasing with each decade. In the UK, they are found in approximately 10% of women in their forties, increasing to 30% after the age of 60 years. They are about half as common in men. Stones are particularly common in the Mediterranean races, and the highest incidence is found among the Indians of New Mexico.

The aphorism that gallstones occur in fair, fat, fertile women of 40 is only a distant approxima-

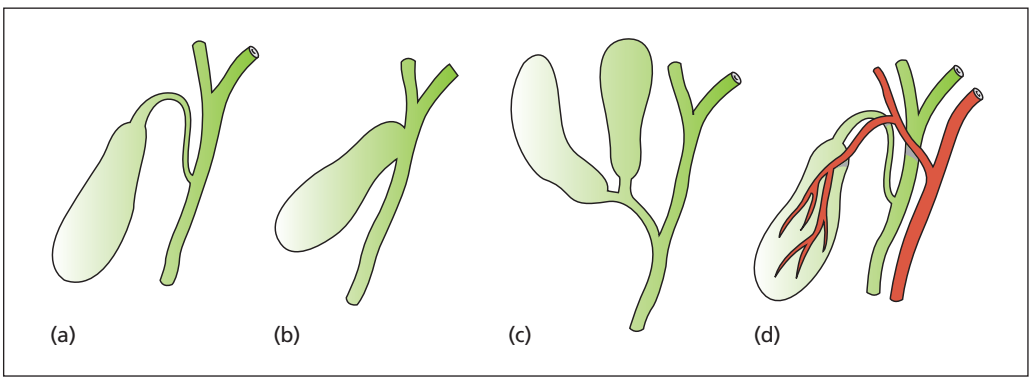

Figure 31.1 Developmental anomalies of the gallbladder. (a) A long cystic duct joining the hepatic duct low down behind the duodenum. (b) Absence of the cystic duct – the gallbladder opens directly into the common hepatic duct. (c) A double gallbladder, the result of a rare bifid embryonic diverticulum from the hepatic duct. (d) The right hepatic artery crosses in front of the common hepatic duct; this occurs in 25% of cases. (Reproduced from Ellis H, Mahadevan V. (2010) *Clinical Anatomy*, 12th edn. Oxford: Wiley-Blackwell.)

tion to the truth; people of either gender, and any age, colour, shape or fecundity may have gallstones, but certainly the incidence is higher in overweight, middle-aged women. To understand gallstones, it is first necessary to understand bile.

Bile composition and function

Bile is a combination of cholesterol, phospholipids (principally lecithin), bile salts (chenodeoxycholic acid and cholic acid) and water. Bile also contains conjugated bilirubin, the breakdown product of haemoglobin, which is quite distinct from bile salts. Cholesterol is not water soluble and is carried in the bile in water-soluble micelles, in which the hydrophobic cholesterol is carried within a 'shell' of phospholipid and bile salts. Once in the gut, bile salts act as a detergent, breaking up and emulsifying fats to facilitate their absorption. The bile salts themselves are resorbed in the distal small bowel, pass back via the portal venous system to the liver, from where they are once again secreted in the bile. This circulation of bile salts is termed the *enterohepatic circulation*, permitting a relatively small pool of bile salts to circulate up to 10 times a day. Diversion or absence of bile from the gut, as may occur in obstructive jaundice, results in a malabsorption of fat and the fat-soluble vitamins (A, D, E and K).

Gallstone types

There are three common varieties of stone (Figure 31.2).

1. *Cholesterol* (20%): these occur either as a solitary, oval stone (the cholesterol solitaire) or as two stones, one indenting the other, or as multiple mulberry stones associated with a strawberry gallbladder (see below). A cut section shows crystals radiating from the centre of the stone; the surface is yellow and greasy to the touch.
2. *Bile pigment* (5%): small, black, irregular, multiple, gritty and fragile.
3. *Mixed* (75%): multiple, faceted one against the other, and can often be grouped into two or more series, each of the same size, suggesting 'generations' of stones. The cut surface is laminated with alternate dark and light zones of pigment and cholesterol respectively.

This traditional classification into three groups is an oversimplification; calculi with widely different appearances simply represent different combinations of the same ingredients.

Cholesterol stones

These may be associated with elevated blood cholesterol, but there is little evidence to suggest this as a cause. There is a definite correlation between

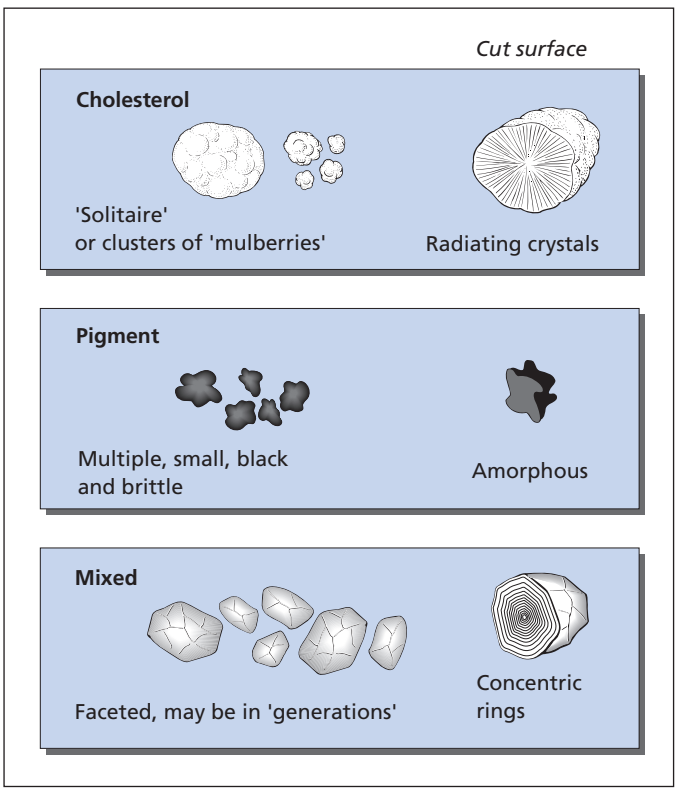

Figure 31.2 The varieties of gallstones.

cholesterol stones and the contraceptive pill and pregnancy, as well as an increase with age. Family history, obesity and low dietary fibre are also risk factors. The supersaturated bile from such patients is termed 'lithogenic' (stone-forming) bile. Bile may also become supersaturated with cholesterol owing to a deficiency of bile salts, which may occur as a result of interruption of the enterohepatic circulation after removal of the terminal ileum, which, for example, may occur following resection in the treatment of Crohn's disease.

Cholesterol stones form in the gallbladder when supersaturated bile is further concentrated. It may be that an excess of mucus production by the gallbladder wall is an important factor in forming calculi. In other cases, clumps of bacteria or desquamated mucosa, perhaps resulting from an episode of infection, may form the nucleus on which crystals may deposit. One rather picturesque view of the aetiology of gallstones states that every gallstone is the tombstone of a dead bacterium. When cholesterol precipitates on the gallbladder wall (cholesterosis), it forms yellow submucous aggregations of cholesterol with an appearance similar to a strawberry skin ('*strawberry gallbladder*').

Pigment stones

Pigment stones are composed of calcium bilirubinate, with some calcium carbonate. They occur in the haemolytic anaemias, e.g. spherocytosis and sickle-cell disease, in which excess of circulating bile pigment is deposited in the biliary tract. If such stones are found in the gallbladder of children or adolescents, haemolytic anaemia should be suspected, particularly if there is a family history of calculus.

Mixed stones

It is now considered that the majority of mixed stones have the same metabolic origin as cholesterol stones, i.e. some slight alteration in the composition of bile enabling precipitation of cholesterol together with bile pigment.

The pathological effects of gallstones

- *Silent*: gallstones lying free in the lumen of the gallbladder produce no pathological disturbance of the wall and the patient is symptom free.
- *Impaction in gallbladder*, either in Hartmann's pouch[1] or in the cystic duct. Water is absorbed from the contained bile, which becomes concentrated and produces a chemical cholecystitis. This is usually at first sterile, but may then become secondarily infected. If a stone impacts in Hartmann's pouch when the gallbladder is empty, the wall of the gallbladder may continue to secrete mucus and the gallbladder distends to form a mucocele.
- *Choledocholithiasis*: gallstones may migrate into the common bile duct. These may be silent, or produce an intermittent or complete obstruction of the common bile duct with pain and jaundice.
- *Gallstone ileus*: this is uncommon, and occurs when a large gallstone ulcerates through the wall of the gallbladder into the adjacent duodenum. The gallstone may pass per rectum or produce a gallstone ileus – this is impaction of the stone in the narrowest part of the small bowel (the distal ileum) with resulting intestinal obstruction. (Note that gallstone ileus is thus a misnomer and is in fact mechanical obstruction by an intraluminal stone, and not a paralytic ileus.) A key feature in such cases is the presence of air in the biliary tree that has entered the bile ducts via the fistula created when the gallstone ulcerates through into the gut and which can be readily seen on a plain abdominal radiograph provided the clinician looks closely in the appropriate area.

In addition, the presence of gallstones in the biliary tree is associated with the following:

- *acute and chronic pancreatitis*;
- *carcinoma of the gallbladder*.

Clinical features

The following syndromes can be recognized:

- biliary colic;
- acute cholecystitis;
- chronic cholecystitis;
- obstruction and/or infection of the common bile duct.

Two or more of these syndromes may occur in the same patient.

Biliary colic

The gallbladder contracts following stimulation by the hormone cholecystokinin, which is produced from the duodenum and small intestine in response to fat in the lumen of the bowel. Physiologically this delivers bile salts to aid the absorption of dietary fat, and the hormone also stimulates secretion of enzymes from the pancreas to aid digestion.

Biliary colic occurs when the gallbladder contracts against an obstruction, such as a stone impacted in either Hartmann's pouch or the cystic duct, producing severe pain, which usually comes on 2–3 hours after eating and often wakes the patient. It is a continuous pain, usually rising to a plateau, and may last for many hours. The pain is usually situated in the right subcostal region but may be epigastric, or it may spread as a band across the upper abdomen and be accompanied by vomiting and sweating. Radiation of the pain to the inferior angle of the right scapula is common. Characteristically, the patient tends to lie still. In contrast to acute cholecystitis the patient is usually not systemically unwell.

A variant of biliary colic occurs when a stone impacts in the sphincter of Oddi, in which case the patient is mildly jaundiced, the pain is colicky, and the patient is restless and rolls about in agony. Relief may be sudden as the stone passes into the duodenum.

Differential diagnosis is from the other acute colics, especially ureteric colic (Box 31.1).

Acute cholecystitis

If the stone remains impacted in the gallbladder outlet, the gallbladder wall becomes inflamed owing to the irritation of the concentrated bile contained within it producing a chemical cholecystitis. The gallbladder fills with pus, which is frequently sterile on culture. In these instances, the pain persists and progressively intensifies. There is a fever in the range of 38–39°C with marked toxaemia and leucocytosis. The upper

[1]Henri Hartmann (1860–1952), Professor of Surgery, Hôtel Dieu, Paris, France.

Box 31.1 Abdominal colic

Colicky pain is the result of smooth muscle contraction against a resistance. The common causes of colic occur in the uterus and tubes, renal tract, intestinal tract and biliary tract.

Biliary tract

- Stone in Hartmann's pouch
- Stone in cystic duct
- Stone in sphincter of Oddi

Renal tract

- Ureteric colic due to stone, blood clot or tumour
- Bladder colic in acute retention owing to enlarged prostate

Intestinal tract

- Mechanical obstruction
- Appendicular colic as appendix lumen occludes

Uterus and fallopian tubes

- Parturition
- Menstruation
- Ectopic pregnancy in a fallopian tube

abdomen is extremely tender, and often a palpable mass develops in the region of the gallbladder. This represents the distended, inflamed gallbladder wrapped in inflammatory adhesions to adjacent organs, especially the omentum. Occasionally, an empyema of the gallbladder develops or, rarely, gallbladder perforation into the general peritoneal cavity takes place. The swollen gallbladder may press against the adjacent common bile duct and produce a tinge of jaundice, even though stones may be absent from the duct system.

Ninety-five per cent of cases of acute cholecystitis are associated with gallstones. Occasionally, fulminating acalculous cholecystitis may occur and this may be associated with typhoid fever or gas gangrene.

The *differential diagnosis* is from acute appendicitis, perforated duodenal ulcer, acute pancreatitis, right-sided basal pneumonia and coronary thrombosis.

Chronic cholecystitis

This is almost invariably associated with the presence of gallstones. Repeated episodes of inflammation result in chronic fibrosis and thickening of the entire gallbladder wall, which may contain thick, sometimes infected, bile.

There are recurrent bouts of abdominal pain owing to mild cholecystitis, which may or may not be accompanied by fever. Discomfort is experienced after fatty meals as the gallbladder contracts onto the stones; there is often flatulence. The picture may be complicated by episodes of acute cholecystitis or symptoms produced by stones passing into the common bile duct.

The *differential diagnosis* is from other causes of chronic dyspepsia, including peptic ulceration and hiatus hernia. Occasionally, the symptoms closely mimic coronary insufficiency. It is as well to remain clinically suspicious – any or all of these common diseases may well occur in association with gallstones.

Stones in the common bile duct (choledocholithiasis)

This may be symptomless. More often, there are attacks of biliary colic accompanied by obstructive jaundice with clay-coloured stools and dark urine, the attacks lasting for hours or several days. The attack ceases either when a small stone is passed through the sphincter of Oddi or when it disimpacts and falls back into the dilated common duct. Above the impacted stone, other stones or biliary sludge may deposit. Occasionally, the jaundice is progressive and, rarely, it is painless.

If the obstruction is not relieved either spontaneously or by operation, the chronic back-pressure in the biliary system may result in secondary biliary cirrhosis and liver failure.

The *differential diagnosis* of stones in the common bile duct is as follows:

1 With jaundice (75% of cases):
   - **a** carcinoma of the pancreas or other malignant obstructions of the common bile duct;
   - **b** acute hepatitis;
   - **c** other causes of jaundice (Chapter 30, p. 252).

2 Without jaundice (25% of cases):
   - **a** renal colic;
   - **b** intestinal obstruction;
   - **c** angina pectoris.

Ascending cholangitis

Infection of the common bile duct, which occurs in the presence of an obstruction to the normal biliary drainage, usually as a complication of

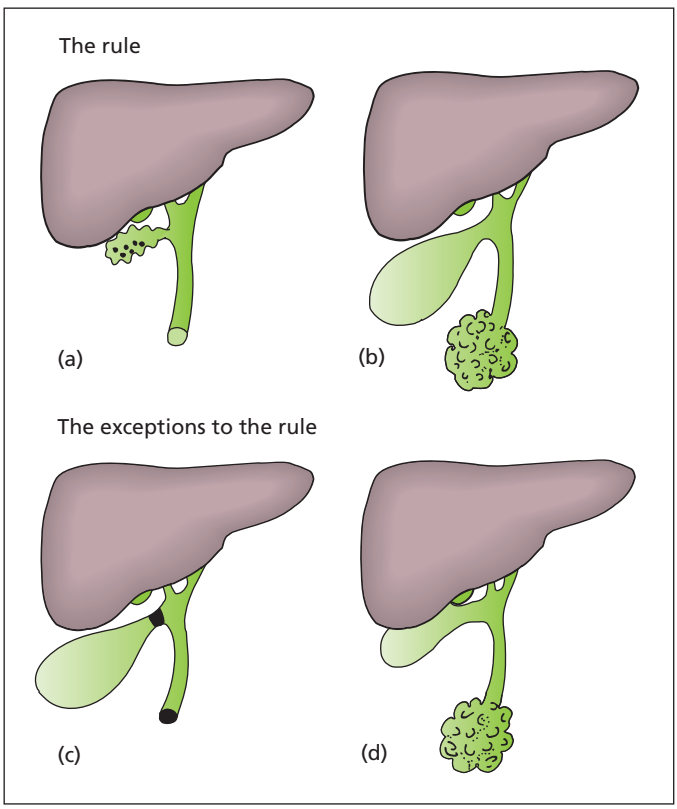

Figure 31.3 Obstructive jaundice due to stone is usually associated with a small, contracted gallbladder (a). Therefore, in the presence of jaundice, a palpable gallbladder indicates that the obstruction is probably due to some other cause – the most common being carcinoma of the pancreas (b). Exceptions are a palpable gallbladder produced by one stone impacted in Hartmann's pouch resulting in a mucocele, another in the common duct causing obstruction (c), which is very rare, or, more commonly, the gallbladder is indeed distended but is clinically impalpable (d).

stones in the duct. Jaundice and pain are accompanied by rigors, a high intermittent fever and severe toxaemia (the intermittent hepatic fever of Charcot[2]). In these instances, the duct system is severely inflamed and filled with pus, and the liver may be dotted with multiple small abscesses. Treatment is with appropriate antibiotics and urgent biliary drainage (e.g. endoscopic sphincterotomy).

Courvoisier's law[3] (Figure 31.3)

'If in the presence of jaundice the gallbladder is palpable, then the jaundice is unlikely to be due to stone.' This is an extremely useful rule provided it is quoted correctly. The principle on which it is based is that, if the obstruction is due to stone, the gallbladder is usually thickened and fibrotic and therefore does not distend. Moreover, unlike obstruction due to malignant disease, calculus obstruction is not usually complete. This allows some escape of bile into the duodenum, with decompression of the gallbladder. Obstruction of the common bile duct due to other causes (e.g. carcinoma of the head of the pancreas) is usually associated with a normal gallbladder, which can dilate. However, in carcinoma of the bile ducts arising above the origin of the cystic duct, the gallbladder, distal to the obstruction, will be collapsed and empty.

Note that the law is not phrased the other way round – 'If the gallbladder is *not* palpable, the jaundice is due to stone' – as 50% of dilated gallbladders cannot be palpated on clinical examination, owing to either the patient's obesity or overlap by the liver, which itself is usually enlarged as a result of bile engorgement.

Only rarely is the gallbladder dilated when jaundice is due to stone. These circumstances occur when a stone impacts in Hartmann's pouch to produce a mucocele while at the same time jaundice is produced by a second stone in the common duct, or when a stone forms *in situ* in the common

[2]Jean Charcot (1825–1893), Neurologist, Paris, France.
[3]Ludwig Courvoisier (1843–1918), Professor of Surgery, Basle, Switzerland.

bile duct, the gallbladder itself being normal and therefore distensible.

Special investigations

- *Ultrasound*: this non-invasive technique gives three pieces of information:
  - the presence of gallstones within the gallbladder, revealed as intensely echogenic foci, which cast a clear acoustic shadow beyond them;
  - the thickened wall of the gallbladder in acute or chronic inflammation;
  - the diameter of the common bile duct which, if over 7 mm, is suggestive of the presence of stones within.

  Unfortunately, ultrasound, like computed tomography (CT), is unreliable in detecting stones in the bile ducts, especially at the lower end where they are obscured by the overlying duodenal gas.
- *Plain abdominal X-ray* reveals radio-opaque gallstones in only 10% of cases. These usually appear as rings due to calcium deposited on a central translucent organic core. Occasionally, the gallbladder may be seen to be calcified ('porcelain gallbladder').
- *Upper gastrointestinal endoscopy* may be advisable to exclude an associated peptic ulcer or hiatus hernia when there is any degree of uncertainty in the clinical picture, even though gallstones have been noted on ultrasound.
- *Liver function tests* are performed whenever jaundice, present or past, is a feature. Persistently raised alkaline phosphatase is suspicious of choledocholithiasis. Prothrombin time should also be checked in the presence of jaundice lest any invasive procedure be required.
- *Magnetic resonance cholangiopancreatography (MRCP)* permits visualization of the biliary tree and contained calculi can be detected. This non-invasive procedure provides the same diagnostic information as can be obtained with ERCP but without the small but important risk of complications (perforation, bleeding, pancreatitis) associated with ERCP.
- *Endoscopic retrograde cholangiopancreatography (ERCP)*: endoscopic intubation of the bile ducts through the ampulla of Vater is more invasive than MRCP, but in addition to visualizing the ducts and contained stones it also permits their extraction, often after first carrying out a diathermy sphincterotomy opening up the sphincter of Oddi[4] to facilitate instrumentation of the bile duct. ERCP has been largely replaced by MRCP for diagnosis but remains an essential part of hepatobiliary management in offering endoscopic therapeutic options and removing the reliance on open surgical procedures.

Treatment

Acute cholecystitis

At least 90% resolve on bed rest with antibiotics and pain relief. Elective cholecystectomy is commonly performed about 6 weeks later because of the undoubted danger of further attacks although early urgent cholecystectomy during the first 72 hours of admission offers an excellent alternative to the patient, optimizing recovery and minimizing the disruption to their normal lifestyle. Cholecystectomy is routinely performed laparoscopically, with the advantages of minimal scarring of the abdominal wall and rapid convalescence compared with an open procedure. Nevertheless, operative difficulties, anatomical aberrations and equipment failures may necessitate conversion to an open operation in approximately 2–5% of cases.

An *empyema of the gallbladder* usually requires more active intervention, with emergency drainage (cholecystostomy), either percutaneously under ultrasound guidance or at cholecystectomy.

Perforation of the acutely inflamed gallbladder is rare and requires urgent surgery. This complication carries a high mortality.

If diagnosis is in doubt in the early stages of acute cholecystitis, laparoscopy is performed. Cholecystectomy is comparatively easy in the first 24–48 hours of the illness; dissection is facilitated by the oedema of adjacent tissues, although after this time operation becomes difficult because of the inflammatory adhesions. Many surgeons advise early surgical intervention in acute cholecystitis with early resolution of the presenting illness and its underlying cause.

[4]Ruggero Oddi (1864–1913), Surgeon, Genoa, Italy. The sphincter was first described in 1654 by Francis Glisson (1597–1677), Regius Professor of Physic, Cambridge, UK.

Chronic cholecystitis

Cholecystectomy is performed, usually laparoscopically. The cystic duct is intubated and an operative cholangiogram performed by injecting radio-opaque contrast medium into the common duct. If stones are demonstrated at laparoscopic operation an MRCP is performed following recovery; many will have passed spontaneously. If they are still present they are removed at ERCP. If an open cholecystectomy has been performed, the common bile duct is explored, the stones removed and the bile duct drained using a latex T-tube inserted into the common duct. The T-tube is removed 10 days postoperatively, provided a check cholangiogram taken through the tube confirms that the ducts are clear and that there is free flow of contrast into the duodenum. Alternatively, at laparoscopic cholecystectomy, the surgeon may perform a laparoscopic exploration of the bile ducts, but this is uncommon and most small stones seem to pass spontaneously following cholecystectomy.

Obstructive jaundice due to stones

Impacted stones are removed using a balloon or Dormia[5] basket at ERCP. Subsequent cholecystectomy is performed as soon as possible lest new stones pass into the ducts. The presence of high fever makes removal of the impacted stones and drainage of the obstructed common bile duct imperative as an emergency procedure. Any intervention is preceded by giving intravenous vitamin K, since a lack of bile salts in the gut reduces absorption of this fat-soluble vitamin; hence, serum prothrombin is lowered with consequent bleeding tendency.

Non-surgical treatment of gallstones

- *Gallstone dissolution.* Because cholesterol is held in solution by bile salts, dissolution of small cholesterol stones is possible by administering bile salts orally in the form of chenodeoxycholic or ursodeoxycholic acid. This therapy may be used for small, non-calcified stones in a functioning gallbladder. Treatment must be continued for many months and may be interrupted by attacks of biliary colic as small fragments of calculus pass through the bile ducts. Moreover, recurrences commonly occur after therapy is discontinued since an abnormal gallbladder remains. The indications for this treatment are limited and may be appropriate in less than 10% of cases. It is largely reserved as an option in elderly medically unfit patients in whom there is a strong contraindication to laparoscopic cholecystectomy.
- *Lithotripsy.* Ultrasonic destruction of small stones as used in the renal tract appeared to be an attractive option, but there is the problem of the passage of small fragments of stone through the duct system that may cause biliary colic, biliary obstruction and pancreatitis. Additionally, the residual fragments in the gallbladder appeared to provide a nidus for further stone formation. Lithotripsy has thus been abandoned in routine practice.

The symptomless gallstone

The incidental diagnosis of gallstones is becoming increasingly common during routine ultrasound examination of the abdomen for a variety of non-biliary reasons. Cholecystectomy may be recommended when the patient is at significantly increased risk of complications owing to concomitant comorbidities such as diabetes or chronic renal failure, but will not normally prompt surgical intervention unless they become symptomatic; the risks (albeit low) of elective cholecystectomy need to be balanced against the long-term risks of complications of cholelithiasis (acute cholecystitis, obstructive jaundice, pancreatitis and gallbladder cancer). In younger patients, in whom the likelihood of complications over time is high and the risks of surgery low, cholecystectomy is advised; in older patients with asymptomatic stones and a shorter life expectancy, it is often unwise to intervene.

Complications of cholecystectomy

There are two special dangers after cholecystectomy, whether performed by laparotomy or laparoscopy.

1 *Leakage of bile.* This may result from the following:
   a injury to bile canaliculi in the gallbladder bed of the liver;

[5]Enrico Dormia (1928-2009), Professor of Urology, Milan, Italy.

b injury to the common hepatic or common bile duct;
c slipping of the ligature or clip from the cystic duct;
d leakage from the common bile duct after exploration.

ERCP may identify the site of the leak, and temporary stenting[6] will ensure adequate biliary drainage, thus allowing the bile fistula to close spontaneously; if this does not occur, further exploration may be required. A percutaneous drain is usually placed to prevent generalized biliary peritonitis.

2 *Jaundice.* This may be due to the following:
a missed stones in the common bile duct;
b inadvertent injury to the common bile duct;
c cholangitis or associated pancreatitis.

Residual stones in the common duct can usually be removed by ERCP; if a T tube is still present in the common duct they can be removed by means of a Burhenne basket[7] passed along the track formed by the tube under X-ray control.

Gallbladder polyps

Pathology

Gallbladder polyps may be single or multiple and are increasingly being detected by ultrasound examination. They appear as lesions within the gallbladder which do not cast an acoustic shadow (as stones do) and which do not move when the patient rolls onto one side, indicating that they are attached to the gallbladder wall. When multiple, they represent the ultrasonographic appearance of cholesterosis of the gallbladder wall and are of no other significance. When a single polyp is present, it may represent a premalignant lesion, the risk of malignancy rising with increasing size of polyp, becoming significant when the size reaches 1 cm and probable when the size reaches 1.5 cm.

Clinical features

Gallbladder polyps may be entirely asymptomatic and simply represent an incidental finding on an ultrasound examination performed for reasons other than biliary symptoms; if they are situated distally in the gallbladder close to Hartmann's pouch they may produce symptoms identical to those of gallstones.

Treatment

Polyps causing symptoms similar to those of cholelithiasis are appropriately managed by cholecystectomy. If there are three or fewer polyps detected in an otherwise asymptomatic patient, then the possible malignant potential is the key management issue. In these cases, 6 monthly surveillance using ultrasound is recommended with cholecystectomy being indicated if the polyps are increasing in size and particularly when they reach or exceed 1 cm in diameter. The management of multiple polyps is more controversial and, since they usually represent cholesterosis, it can be argued that intensive follow-up is therefore unnecessary. When the gallbladder is removed it is common to find that the polyps were in fact small gallstones adherent to the gallbladder wall.

Carcinoma of the gallbladder

Pathology

This is a relatively uncommon tumour, but it is associated in about 85% of cases with the presence of gallstones. It is debatable whether this is due to chronic irritation or to the carcinogenic effect of cholic acid derivatives. Fifty per cent of 'porcelain' gallbladders are associated with carcinoma. As gallstones are commoner in women, carcinoma of the gallbladder is, not surprisingly, four times commoner in women than men. Ninety per cent are adenocarcinoma and 10% squamous carcinoma.

There is local invasion of the liver and its ducts and lymphatic spread to the nodes in the porta hepatis; portal vein dissemination to the liver may occur.

Clinical features

Carcinoma of the gallbladder usually presents with a picture closely resembling chronic cholecystitis, with right upper quadrant pain, nausea

[6]Charles Stent (1845–1901), English Dentist.
[7]H. Joachim Burhenne (1925–1996), Radiologist, Vancouver, Canada.

and vomiting, in addition to weight loss and, later, progressing to obstructive jaundice. At this stage, a palpable mass may be present in the gallbladder region.

Treatment

Occasionally, cholecystectomy performed for stones reveals the presence of an unexpected tumour. Under these circumstances, long-term survival may follow. Sadly, most cases present late with liver involvement and nodal spread leaving few surgical options. If direct infiltration into the liver has already occurred, as is common, local excision or radical liver resection is only rarely possible and the prognosis is therefore usually poor, with death within months.

Cholangiocarcinoma

Pathology

The incidence of carcinoma of the bile ducts, cholangiocarcinoma, is increasing. The disease commonly occurs after 50 years of age and is more common in men. It is associated with inflammatory bowel disease, particularly in the presence of sclerosing cholangitis. Congenital hepatic fibrosis, choledochal cysts and polycystic liver are all associations.

Macroscopically, cholangiocarcinomas may occur within the liver substance, or in the larger extrahepatic bile ducts. The confluence of the left and right hepatic ducts, or the common hepatic duct with the cystic duct, are common sites.

Microscopically, they are mucin-secreting adenocarcinomas.

Clinical features

The usual presentation is with painless progressive jaundice, with dark urine and pale stools. Epigastric pain, steatorrhoea and weight loss are common. There may be hepatomegaly, usually without a palpable gallbladder because the tumour is proximal to, or at, the cystic duct confluence. Confirmation is by MRCP, ERCP or percutaneous transhepatic cholangiography and brush cytology (poor sensitivity), and CT-guided needle biopsy if possible.

Treatment

The tumours are slow growing, and palliation is often achieved by endoluminal stenting at ERCP, or surgical bypass. The prognosis is poor, and curative resection is seldom possible, although, in a small percentage of cases with early presentation of hilar tumours (Klatskin tumour[8]), good results have been reported with extended right hepatectomy together with excision of the adjacent portal vein and venous reconstruction. In the rarer cases in which the tumour is located distally in the common bile duct, a Whipple's resection (see Figure 32.2) may be possible.

[8]Gerald Klatskin (1910–1986), Liver Physician, Yale, New Haven, CT, USA; pioneered the liver biopsy and was considered to be one of the fathers of hepatology.

32

The pancreas

Learning objectives

- ✓ To know the causes and management of acute pancreatitis, and the factors that predict its severity.
- ✓ To have knowledge of pancreatic cancer, its presentation and the surgical approach to treatment of carcinoma of the head of the pancreas.

Congenital anomalies

The pancreas develops as a dorsal and a ventral bud from the duodenum (Figure 32.1). The ventral bud rotates posteriorly, thus enclosing the superior mesenteric vessels; it forms the major part of the head of the pancreas and its duct becomes the main duct of Wirsung,[1] which in the great majority of cases has a shared opening with the common bile duct in the ampulla of Vater.[2] The larger dorsal bud becomes the body and tail and its duct becomes the accessory duct of Santorini.[3]

Annular pancreas

The two developmental buds may envelop the second part of the duodenum, producing this rare form of extrinsic duodenal obstruction.

Heterotopic pancreas

This is produced occasionally by an accessory budding from the primitive foregut. A nodule of pancreatic tissue may be found in the stomach, duodenum or jejunum. This may produce obstructive or dyspeptic symptoms.

[1]Johann Georg Wirsung (1589–1643), Professor of Anatomy, University of Padua, Italy, where he was murdered.
[2]Abraham Vater (1684–1751), Professor of Anatomy, Wittenberg, Germany.
[3]Giovanni Domenico Santorini (1681–1737), Professor of Anatomy and Medicine, Venice, Italy.

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Acute pancreatitis

Acute inflammation of the pancreas is a common cause of acute abdominal pain, with significant morbidity and mortality.

Aetiology

Most cases of acute pancreatitis are associated with either gallstones or alcohol, although a number of less common causes have been identified.

- *Gallstones* are present in half of the cases in the UK, and, indeed, small gallstones can be recovered from the faeces of many patients with acute pancreatitis.
- *Alcohol*: the majority of cases of non-gallstone pancreatitis are alcohol related. This is particularly common in France and North America. Alcohol is also the most common cause of recurrent pancreatitis. The mechanism is unclear, and it may follow either chronic alcohol abuse or binge drinking.

Other less common causes of pancreatitis include the following:

- *Postoperative*: particularly after cardiopulmonary bypass or damage to the

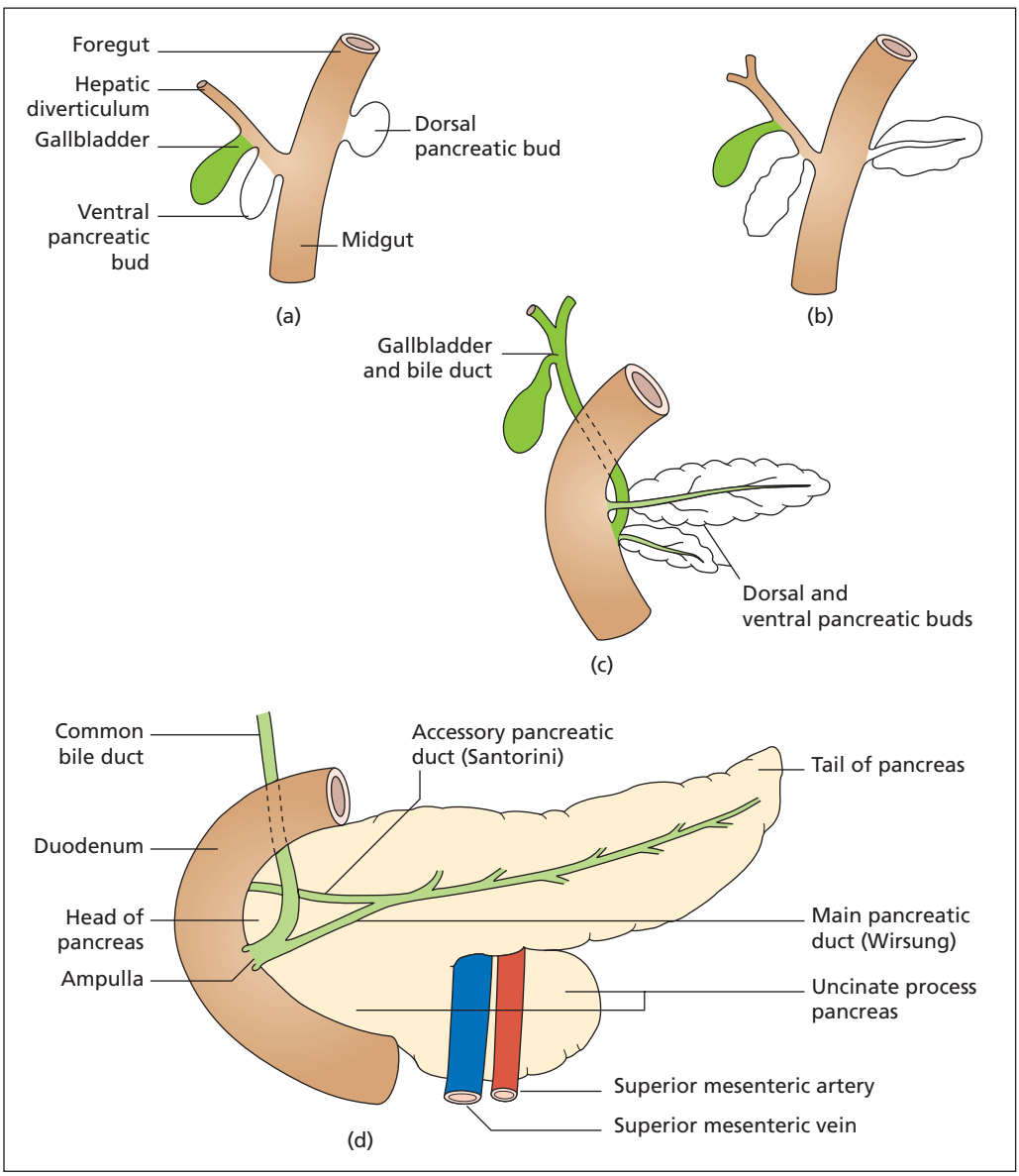

Figure 32.1 (a–d) The development of the pancreas and biliary tree. (Reproduced from Ellis H, Mahadevan V. (2010) *Clinical Anatomy*, 12th edn. Oxford: Wiley-Blackwell.)

pancreas during mobilization of the duodenum at partial gastrectomy or splenectomy.

- *After endoscopic retrograde cholangiopancreatography (ERCP)*: particularly if pancreatography was performed or there was difficulty cannulating the papilla with subsequent oedema and obstruction.
- *Carcinoma of the pancreas.*
- *Infection*, e.g. mumps, cytomegalovirus or coxsackie infection.
- *Trauma*: particularly blunt trauma or crush injury.
- *Drugs*, e.g. corticosteroids, sodium valproate.
- *Hypothermia.*
- *Hypercalcaemia.*

- *Hyperlipidaemia*.
- *Vascular*: pancreatitis may occur in malignant hypertension, cholesterol emboli and polyarteritis nodosa, probably as a result of local infarction causing enzyme liberation.

Pathology

Acute pancreatitis differs from other inflammatory conditions because of the autodigestion that may result from liberation of digestive enzymes. The pancreas is normally protected from autodigestion by storing its enzymes in intracellular zymogen granules before secreting them as proenzymes. Trypsin, for example, is secreted as trypsinogen and converted to trypsin by the action of enterokinase in the gut. Trypsin itself then cleaves other proenzymes, thus activating them. One such enzyme is phospholipase A which, in pancreatitis, is involved in cell wall damage and fat necrosis along with pancreatic lipase.

The mechanisms initiating autodigestion are multiple. Duodenopancreatic reflux is an important factor that may occur as a result of injury to the papilla following endoscopic cannulation, trauma or surgery in this region, or as a result of damage to the sphincter owing to the recent passage of a stone (hence the strong association of pancreatitis and biliary calculi). Duodenal fluid containing enterokinase then refluxes into the duct, activating the pancreatic proenzymes. Duodenal reflux can be shown experimentally to produce pancreatitis, and may be a common factor that underlies many of the aetiological associations mentioned above. As inflammation proceeds, local infarction may occur as arterioles thrombose, and more proenzymes leak out of the necrotic cells to be activated. Once started, pancreatitis can be rapidly progressive, with widespread autodigestion not only confined to the pancreas.

As inflammation and autodigestion progress, liquefying necrotic material and inflammatory exudate collect in the lesser sac. This fluid, walled off by the stomach in front and necrotic pancreas behind, is the pancreas pseudocyst, and commonly appears from day 10 onwards.

Macroscopic pathology

At operation, the appearances are quite typical. There is a blood-stained peritoneal effusion. White spots of fat necrosis are scattered throughout the peritoneal cavity; these are produced by lipase released from the pancreas, which liberates fatty acids and glycerol from fat; these acids combine with calcium to produce insoluble calcium soaps. The pancreas is swollen, haemorrhagic or, in severe cases, actually necrotic. Occasionally, suppurative pancreatitis may occur.

Clinical features

The condition can present at any age but is uncommon in childhood and in young adults. The patient presenting with gallstone pancreatitis is commonly middle aged or elderly. By contrast, the alcohol-related form commonly first presents in patients who are younger than 40. Pain is of rapid onset, is severe, constant, usually epigastric and often radiates into the back. The patient typically sits forward, and repeated retching is common. Vomiting is early and profuse. The patient may be shocked with a rapid pulse, cyanosis (indicating circulatory collapse) and a temperature that may be either subnormal or raised up to 39.5°C (103°F). The abdomen reveals generalized tenderness and guarding. About 30% of patients are jaundiced owing to oedema of the pancreatic head obstructing the common bile duct.

On rare occasions, a few days after a severe attack, the patient may develop a bluish discoloration in the loins from extravasation of blood-stained pancreatic juice into the retroperitoneal tissues (Grey Turner's sign[4]). The tracking of fluid that results in this sign can often be seen on computed tomography (CT) imaging of patients with acute pancreatitis even when it is not clinically apparent.

Differential diagnosis

The less severe episode of acute pancreatitis simulates acute cholecystitis; the more severe attack, with a marked degree of shock, is usually mistaken for a perforated peptic ulcer or coronary thrombosis. Differentiation must also be made from high intestinal obstruction and from other causes of peritonitis.

Special investigations

The investigation comprises tests to confirm the diagnosis and tests to assess the severity of the disease (i.e. diagnostic and prognostic).

[4]George Grey Turner (1877–1951), Professor of Surgery, University of Durham, then Foundation Professor of Surgery at the Royal Postgraduate Medical School, London, UK.

- *Serum amylase*. Amylase is liberated into the circulation by the damaged pancreas, and exceeds the kidney's ability to excrete it, so the serum concentration rises. It is usually significantly raised (fivefold or more) in the acute phase, but returns to normal within 2–3 days; the urinary amylase is elevated for a longer period and may be useful in the diagnosis of cases presenting late. Occasionally, an overwhelming attack of pancreatitis with extensive destruction of the gland, or an attack occurring as an acute exacerbation of chronic pancreatitis, is associated with a normal serum amylase. Other causes of raised serum amylase need to be borne in mind before assuming a diagnosis of pancreatitis (Box 32.1).
- *Full blood count*: there is a moderate leucocytosis, and anaemia in severe cases.
- *Blood glucose* is often raised, with glycosuria in 15% of cases.
- *Serum bilirubin* is often raised.
- *Arterial blood gases*: hypoxia occurs in severe cases.
- *Serum calcium* may be lowered, partly as a result of fat saponification; tetany may occur. The prognosis is bad in such cases.
- *CT* may confirm pancreatitis if the amylase is normal or the diagnosis otherwise unclear. At a later stage, necrotic pancreas, abscess or pseudocyst may be visualized.
- *Electrocardiography (ECG)* may show diminished T waves, or arrhythmia, and can cause confusion with cardiac ischaemia.
- *Abdominal X-rays* often give no direct help. The absence of free gas or of localized fluid levels assists in the differential diagnosis of perforated duodenal ulcer or high intestinal obstruction. In some cases, a solitary dilated loop of proximal jejunum may be seen (the 'sentinel loop sign'). Radio-opaque pancreatic calculi may be present in cases of chronic pancreatitis.
- *Ultrasound* will demonstrate associated gallstones and dilatation of the common bile duct suggestive of choledocholithiasis. It may also show enlargement of the pancreas, although overlying bowel gas often prevents a good view of the pancreas.

Note that each of the three enzymes liberated by the pancreas plays a part in the overall picture of acute pancreatitis:

Box 32.1 Raised serum amylase

The causes of raised serum amylase are listed below. Only those marked with an asterisk cause a marked increase in amylase (fivefold or more).

Impaired renal excretion

- Renal failure*
- Macroamylasaemia (amylase not cleared by kidneys owing to complexing or protein binding)

Salivary gland disease

- Salivary calculi
- Parotitis

Metabolic causes

- Severe diabetic ketoacidosis*
- Acute alcoholic intoxication
- Morphine administration (causing sphincter of Oddi spasm[5])

Abdominal causes

- Acute pancreatitis*
- Perforated peptic ulcer
- Acute cholecystitis
- Intestinal obstruction
- Afferent loop obstruction following partial gastrectomy
- Ruptured abdominal aortic aneurysm
- Ruptured ectopic pregnancy
- Mesenteric infarction
- Trauma, open or blunt

1 *Trypsin* produces the autodigestion of the pancreas.
2 *Lipase* results in the typical fat necrosis.
3 *Amylase* absorbed from the peritoneal cavity produces a rise in the serum level and is thus a helpful test in diagnosis.

Management

The management of a patient with suspected pancreatitis involves first confirming the diagnosis (serum amylase and/or CT) and determining the

[5]Ruggero Oddi (1864–1913). Identified the sphincter while a medical student in Perugia, Italy.

severity of the attack. Mortality in severe pancreatitis is high, so severe cases should be managed in an intensive care environment where pulmonary, renal and abdominal complications can be promptly diagnosed and treated.

Severe acute pancreatitis

Severe pancreatitis is associated with haemorrhagic necrosis of the pancreas and systemic release of many vasoactive peptides and enzymes, as well as sequestration of large volumes of fluid within the abdomen. Acute lung failure occurs, characterized by increased capillary permeability and reduced oxygen transfer, and the combination of toxins and loss of circulating fluid results in acute renal failure. Several criteria predictive of the development of severe pancreatitis have been identified (Box 32.2); the presence of three or more is predictive of severe pancreatitis. Both a raised C-reactive protein (>140 mg/L) and non-perfusion of areas of the pancreas on a contrast-enhanced CT also predict a poor prognosis. Identification of such high-risk cases enables aggressive intensive management to be instituted at an early stage. Nevertheless, severe acute pancreatitis has a mortality of over 25%.

Box 32.2 Glasgow criteria for severe acute pancreatitis

The factors are assessed over the first 48 hours. Presence of three or more factors indicates severe pancreatitis with a high mortality.

- Age over 55 years
- Hyperglycaemia (glucose >10 mmol/L in the absence of a history of diabetes)
- Leucocytosis (>15 × 10^9/L)
- Urea >16 mmol/L (no response to intravenous fluids)
- Po_2 <8 kPa (60 mmHg)
- Calcium <2.0 mmol/L
- Albumin <32 g/L
- Lactate dehydrogenase >600 IU/L
- Raised liver transaminases (aspartate transaminase >100 IU/L)

Supportive treatment

In the established case, treatment is initially non-operative and consists of the following:

- *Analgesia*: relief of pain, traditionally with pethidine to avoid the sphincter spasm associated with morphine.
- *Fluid replacement* with colloid or blood transfusion, to treat shock and establish a diuresis. In less severe cases, electrolyte and water replacement alone may suffice.
- *Resting the pancreas* by removing stimuli for secretion: the patient is not allowed to take fluid or food by mouth, and nasogastric aspiration is started if the patient is vomiting.
- *Nutrition*: total parenteral nutrition (TPN) may be instituted early in severe cases. There is good evidence that nasojejunal feeding may be superior to TPN in the absence of an ileus probably because of improved maintenance of the gut mucosal integrity decreasing bacterial translocation and reducing septic complications.
- *Antibiotics* (e.g. co-amoxiclav) are commenced in severe cases and if the pancreatitis is associated with gallstones.
- *Prophylaxis against gastric erosions* with sucralfate or an H_2-receptor antagonist (e.g. ranitidine) or proton pump inhibitor (e.g. omeprazole).
- *Endoscopic sphincterotomy* performed early in the admission may be indicated in severe gallstone pancreatitis; a dilated common bile duct on ultrasound associated with deranged liver function tests also represents an indication for urgent ERCP and sphincterotomy.

Attempts at treatment with drugs that reduce pancreatic enzyme activation (e.g. aprotonin) or secretion (e.g. probanthine or atropine) are of no proven benefit.

Surgery

Surgery should be avoided early in the acute attack when possible. Later in the disease percutaneous drainage of collections or abscesses may be indicated, often requiring multiple drains; failure to resolve in spite of adequate drainage may be an indication for operative debridement of the necrotic pancreas (necrosectomy). Operative drainage of a pseudocyst may also be required at

a later stage (peripancreatic collections in the lesser sac are common in the early stages but usually resolve without intervention). In the case of gallstone pancreatitis, cholecystectomy should be performed as soon as the patient recovers from the acute attack, preferably during the same admission.

Prognosis

Mortality is in the region of 10% and is directly proportional to the severity of the attack.

Complications

- *Abscess formation* with pancreatic necrosis, characterized by pyrexia and persistent leucocytosis.
- *Peripancreatic collections and pseudocyst formation*, characterized by symptoms attributable to the pressure effect on the stomach with fullness and discomfort commonly associated with a palpable epigastric mass.
- *Gastrointestinal bleeding* from acute gastric erosions or peptic ulceration.
- *Renal failure* associated with shock and pancreatic necrosis.
- *Pulmonary insufficiency*: acute lung injury.
- *Further attacks* (relapsing pancreatitis).
- *Diabetes mellitus*, resulting from a severe attack with pancreatic necrosis, or chronic relapsing pancreatitis.

Chronic pancreatitis

Chronic and acute pancreatitis are clinically distinct entities, although bouts of acute pancreatitis may occur in the course of the development of chronic pancreatitis, and the pathogenesis of chronic pancreatitis has much in common with alcoholic acute pancreatitis. In acute pancreatitis the gland is normal before the attack; chronic pancreatitis is characterized by gradual destruction of the functional pancreatic tissue.

Aetiology

In the Western world, alcoholism is the main cause of chronic pancreatitis. In parts of Asia and Africa, chronic pancreatitis is associated with malnutrition; hereditary pancreatitis and hypercalcaemia are uncommon causes.

Clinical features

The patient may present with one or more of the following:

- *asymptomatic* (X-ray diagnosis only from pancreatic calcification);
- *recurrent abdominal pain* radiating through to the upper lumbar region, relieved by sitting forward;
- *steatorrhoea* due to pancreatic insufficiency, resulting in malabsorption and weight loss;
- *diabetes* due to β-cell damage;
- *obstructive jaundice*, which even at operation can be very difficult to differentiate from carcinoma of the head of the pancreas.

Special investigations

- *Serum amylase* estimations performed during attacks of pain may be elevated, but in long-standing disease are often normal, there being insufficient pancreatic tissue remaining to cause a large rise.
- *Abdominal X-ray* may show evidence of calcification or calculi.
- *CT* may demonstrate enlargement and irregular consistency of the gland together with calcification and ductal changes, although the latter may be better appreciated by the use of magnetic resonance cholangiopancreatography (MRCP).
- *ERCP* may show dilatation and irregularity of the pancreatic duct and compression of the bile duct by the inflamed pancreatic head.
- *Endoscopic ultrasound* has become the standard technique for examining the head of the pancreas, and aspiration cytology can be carried out from any suspicious areas to help differentiate chronic pancreatitis or areas of focal pancreatitis from carcinoma.
- *Exocrine function tests*, such as the faecal elastase test, have largely replaced older techniques such as faecal fat estimation.

However, despite preoperative investigation, it is still true that at times the differential diagnosis from a pancreatic carcinoma may only be established following laparotomy and resection when formal histology is obtained.

Treatment

The principal treatment is to remove causative factors such as alcohol consumption. Alcohol should be avoided by anyone with pancreatitis.

- *Analgesics*: the pain is often sufficient to warrant opiate analgesia, but long-term use may result in addiction. Getting the analgesia right is often one of the most difficult aspects of management.
- *Diet*: a low-fat diet with pancreatic enzyme supplements (pancreatin) by mouth.
- *Insulin* when diabetes mellitus occurs.
- *Surgery* if attacks are very frequent or if there is severe pain. Partial pancreatectomy or, in patients in whom the pancreatic duct is grossly dilated, drainage of the whole length of the pancreatic duct into a loop of intestine may be required (Puestow procedure[6]). Occasionally, total pancreatectomy is required, with consequent diabetes and steatorrhoea. In these patients, the diabetes may be very difficult to control partly because of their poor compliance and partly because of the loss of the glucagon-secreting function when the whole pancreas has been removed.
- *Painless obstructive jaundice* may be relieved by a bypass using a Roux-en-Y reconstruction, usually to the common hepatic duct. However, if diagnostic uncertainty remains or if there is a coincident problem with gastric emptying, a Whipple's operation (pancreaticodoudenectomy) may be appropriate.

Pancreatic cysts

Classification

True (20%)

- Congenital polycystic disease of pancreas.
- Retention.
- Hydatid.
- Neoplastic: cystadenoma or cystadenocarcinoma.

False

A collection of fluid in the lesser sac (80%):

- after trauma to the pancreas;
- following acute pancreatitis;
- owing to perforation of a posterior gastric ulcer (rare).

Clinical features

A pancreatic cyst presents as a firm, large, rounded, upper abdominal swelling. Initially, the cyst is apparently resonant because of loops of gas-filled bowel in front of it, but as it increases in size the intestine is pushed away and the mass becomes dull to percussion.

Treatment

True cysts require surgical excision; false cysts are drained. This may be performed internally (by anastomosis either into the stomach or into the small intestine), or percutaneously, under ultrasound control.

Pancreatic tumours

Classification

Benign

1 Adenoma.
2 Cystadenoma.
3 Islet cell tumour (see Box 38.1, p. 324):
  a Zollinger–Ellison tumour;
  b insulinoma (β-cell tumour);
  c glucagonoma (α-cell tumour).

Malignant

1 *Primary*:
  a adenocarcinoma;
  b cystadenocarcinoma;
  c malignant islet cell tumour.
2 *Secondary*: invasion from carcinoma of the stomach or bile duct.

[6]Charles Puestow (1902–73), Professor of Surgery, College of Medicine, University of Illinois, Chicago, IL, USA.

Pancreatic neuroendocrine tumours

These tumours arise from cell types within the islets of Langerhans and, although rare (less than 2% of pancreatic neoplasms), are of great interest because of their metabolic effects, even from small lesions, which may be difficult to localize even with CT and magnetic resonance (MR) imaging or selective angiography.

Types of tumours

Pancreatic neuroendocrine tumours are derived from amine precursor uptake and decarboxylation (APUD) cells, and are thus sometimes termed APUD-omas. They secrete a number of polypeptides according to the cell type of origin. These may be active hormones and present relatively early, or polypeptides for which no function has been identified; often, more than one polypeptide is secreted. A pancreatic islet contains many cell types of which the alpha (α) cells (producing glucagon), beta (β) cells (insulin) and delta (δ) cells (somatostatin) are best known. In addition, interacinar cells produce pancreatic polypeptide (F cells) and serotonin (enterochromaffin cells). The islet cells may also produce hormones not normally found in the pancreas, such as gastrin (gastrinoma), vasoactive intestinal polypeptide (VIP-oma), and adrenocorticotrophic hormone (ACTH) (Cushing's syndrome[7]).

The islet cell tumours may be associated with other endocrine tumours elsewhere as part of a multiple endocrine neoplasia (MEN) syndrome, often involving the parathyroid and the anterior pituitary gland (see Box 38.1, p. 324).

Insulinoma (β-cell tumour)

Ninety per cent are benign, 10% malignant and about 10% are multiple tumours. Because of the high production of insulin by the tumour, two groups of hypoglycaemic symptoms may be produced.

1 *Central nervous system phenomena*: weakness, sweating, trembling, epilepsy, confusion, hemiplegia and eventually coma, which may be fatal.
2 *Gastrointestinal phenomena*: hunger, abdominal pain and diarrhoea.

These symptoms appear particularly when the patient is hungry, or during physical exercise. They are often present early in the morning before breakfast and are relieved by eating. Often, there is excessive appetite with gross weight gain. Although once the diagnosis has been made the cause of the symptomatology is clear, it is not uncommon for diagnosis to be delayed, and psychiatric diagnoses and referrals being made during the course of the illness is common.

Diagnosis: Whipple's triad[8]

The main diagnostic characteristics of the syndrome are as follows:

- The attacks are induced by starvation or exercise.
- During the attack, hypoglycaemia is present.
- Symptoms are relieved by sugar given orally or intravenously.

Differential diagnosis of spontaneous hypoglycaemia in adults includes self-administration of insulin or alcohol, and suprarenal, pituitary or hepatic insufficiency.

Special investigations

- *Insulin levels*: raised insulin levels in the presence of hypoglycaemia. The hypoglycaemia can be prompted by a period of prolonged fasting (14–16 hours).
- *C-peptide levels* may be measured to rule out exogenous insulin administration, as these will be high with insulinoma and low when exogenous insulin is administered.
- *Localization tests* include CT, MR, endoscopic ultrasound (EUS) and selective angiography. Occasionally, localization is not achieved until laparotomy is performed, when the tumour can usually be located using careful palpation and intraoperative ultrasound.

[7]Harvey Cushing (1869–1939), Professor of Surgery, Harvard Medical School, Boston, MA, USA.

[8]Allen Oldfather Whipple (1881–1963), Professor of Surgery, Columbia University, New York, NY, USA. Also described the operation for carcinoma of the head of the pancreas.

Treatment

Treatment is excision of the tumour. Depending on the site, this may require either a Whipple's procedure or a distal pancreatectomy, but in patients in whom the insulinoma is well defined and superficial, simple enucleation is often possible.

Gastrinoma (Zollinger–Ellison syndrome,[9] non-β-cell islet tumour)

This tumour of non-β-cells may be benign or malignant, solitary or multiple, and a quarter are part of an MEN syndrome. Malignant tumours are less common in sporadic forms (30%) than in those related to MEN syndromes (60%); the malignant tumours are also relatively slow growing, although they eventually produce hepatic metastases. The gastrinoma secretes a gastrin-like substance into the bloodstream, which produces an extremely high gastric secretion of HCl. Many patients also develop oesophagitis owing to the high acid secretion; diarrhoea is common (probably related to the high acid output). The majority of patients develop fulminating peptic ulceration, presenting with bleeding or perforation, and have multiple duodenal ulcers. Symptoms relapse after cessation of medical therapy.

Special investigations

- *Serum gastrin* concentration in the blood is 10 times normal.
- *Basal acid output*, measured by nasogastric aspiration, is very high (>15 mmol/h).
- *Localization*: as for insulinoma.

Treatment

Treatment comprises excision of the tumour or, if this is not possible, control of the high acid secretion by means of proton pump inhibitors (e.g. omeprazole) or high doses of histamine H_2-receptor antagonists (cimetidine, ranitidine). Modern acid suppression therapy has largely replaced surgical treatment by total gastrectomy.

[9]Robert Milton Zollinger (1903–1992), Professor of Surgery, Ohio State University, Columbus, OH, USA. Edward Horner Ellison (1918–1970), Associate Professor at the same institution.

Pancreatic carcinoma

Pathology

Sixty per cent are situated in the head of the pancreas, 25% in the body and 15% in the tail.

Of the tumours of the head of the pancreas, one-third are periampullary, arising from the ampulla of Vater, the duodenal mucosa or the lower end of the common bile duct.

The incidence in the UK is 10 per 100 000 population, with men and women now almost equally affected. It affects the middle-aged and elderly, and the disease is more common in those who smoke.

Macroscopically, the growth is infiltrating, hard and irregular; rarer types are characterized by cystic lesions near the tail of the pancreas.

Microscopically, the tumours may be

- ductal adenocarcinomas (most common): tumours arising in the cells lining the pancreatic ducts;
- acinar cell carcinoma;
- undifferentiated.

Less common tumours include:

- mucinous cystic neoplasm (MCN): cystic tumours that predominantly affect the tail of the pancreas and occur in middle-aged women;
- intraductal papillary mucinous tumour (IPMN): ductal tumours that are characterized by the production of a large amount of mucus. They are slow-growing tumours that may be benign or malignant, and occur more commonly in older men.

Spread

1 *Direct invasion into*:
   - **a** common bile duct – obstructive jaundice;
   - **b** duodenum – occult or overt intestinal bleeding and duodenal obstruction;
   - **c** portal vein – portal vein thrombosis, portal hypertension and ascites;
   - **d** inferior vena cava – bilateral leg oedema.

2 *Lymphatic*: to adjacent lymph nodes and nodes in the porta hepatis.

3 *Bloodstream*: to the liver and then to the lungs.
4 *Transcoelomic*: with peritoneal seeding and ascites.

Clinical features

Carcinoma of the pancreas may present in a variety of ways:

- *Painless progressive jaundice* is the classical presentation, but this form is rather uncommon and is most often found in the periampullary type of tumour. This is because the bile duct is compressed at an early stage, before extensive painful invasion of surrounding tissues.
- *Pain*: at least 50% of patients present with epigastric pain of a dull, continuous, aching nature, which frequently radiates into the upper lumbar region. This pain often precedes the development of jaundice.
- *Diabetes*: recent-onset diabetes in the elderly is suspicious.
- *Thrombophlebitis migrans* (Trousseau's sign[10]); the pathogenesis of this is unknown.
- *The general features of malignant disease*: anorexia and, in particular, loss of weight.

Examination

The patient is frequently jaundiced, and half have a palpable gallbladder (Courvoisier's law; see Figure 31.3, p. 271). If the tumour is large, an epigastric mass may be palpable. The liver is frequently enlarged, either because of back-pressure from biliary obstruction or because of secondary deposits.

Special investigations

- *Ultrasound* will confirm dilated bile ducts and a distended gallbladder, but should not be relied on to obtain adequate views of the pancreas.
- *CT* may demonstrate the tumour mass and facilitate fine-needle biopsy.
- *Endoscopy* may visualize a periampullary growth, which can then be biopsied.
- *EUS*, in which a specialized endoscope is used to obtain ultrasound images of the pancreatic head from within the duodenum, will give detailed information about the location of the tumour and its relationship to the portal vein and superior mesenteric artery and will demonstrate local extent of spread and also visualize enlarged lymph nodes. EUS is thus a key step in defining the operability of a tumour in terms of local invasion and spread.
  - Needle aspiration under EUS control will allow cytological diagnosis of the tumour itself and lymph node metastases.
  - Needle aspiration of cystic lesions may distinguish between pseudocysts (high amylase content) and mucinous tumours (high Ca 19.9 and CEA; see Chapter 7, Table 7.1, p. 37).
- *MRCP and ERCP* will demonstrate an obstruction in the bile duct.
- *Barium studies* may show widening of the duodenal loop and a filling defect or irregularity of the duodenum resulting from invasion by the tumour, but have largely been replaced by CT imaging with three-dimensional reconstruction when necessary.
- *Occult blood* may be present in the stools, especially from a periampullary tumour ulcerating into the duodenum. The stools are pale in the presence of jaundice, and may have a silvery appearance owing to the periampullary bleeding (the silvery stools of Ogilvie[11]).
- *Serum amylase* is rarely elevated.
- *Biochemical analysis* confirms the changes of obstructive jaundice (high bilirubin and alkaline phosphatase). The tumour marker Ca 19.9 may be elevated.

Differential diagnosis

This is from other causes of obstructive jaundice and from other causes of upper abdominal pain. Carcinoma of the body and tail of the pancreas, in which obstructive jaundice does not occur, is notoriously difficult to diagnose, the diagnosis often only being made at a late stage following many weeks or months of upper abdominal pain when a CT scan is performed. The tumour at this stage is usually inoperable.

Treatment

Treatment of carcinoma of the pancreas is usually symptomatic, and thus applicable to tumours of the head of the pancreas, which present with

[10]Armand Trousseau (1801–1867), Physician, Hôpital St. Antoine and Hôpital Dieu, Paris, France.

[11]Sir William Heneage Ogilvie (1887–1971), Surgeon, Guy's Hospital, London, UK.

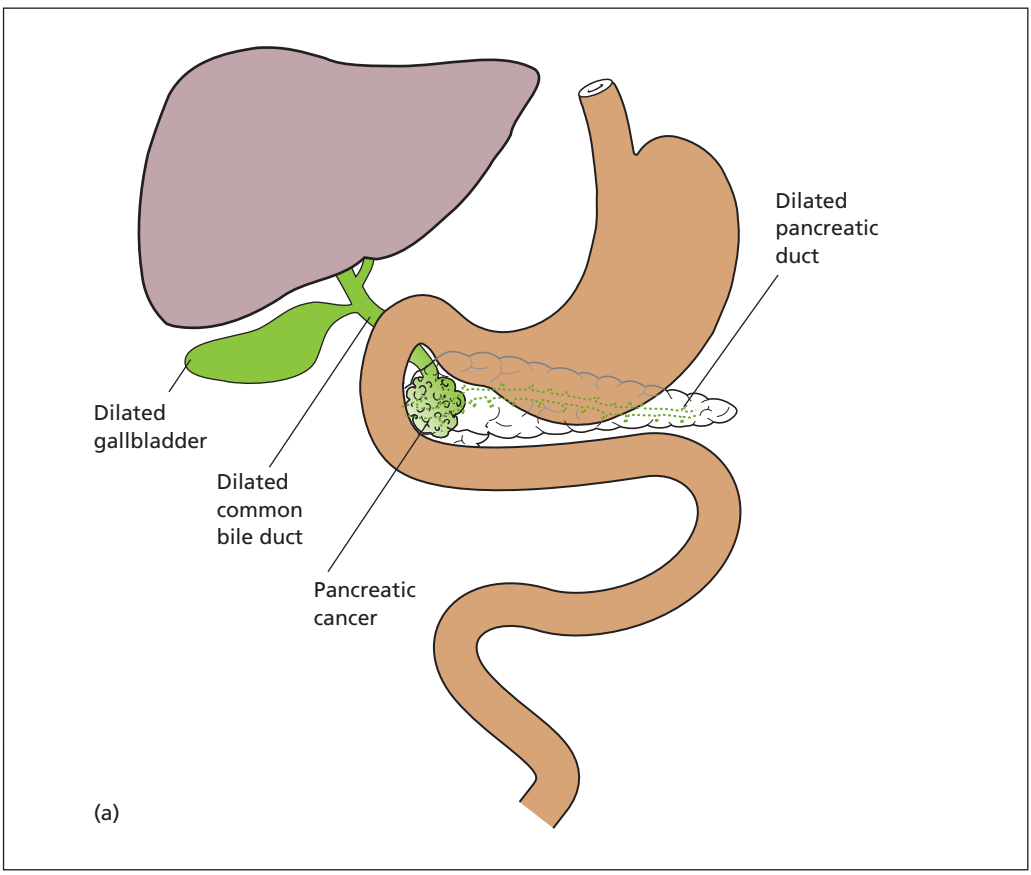

Figure 32.2 Whipple's pancreaticoduodenectomy. (a) The initial appearance characterized by a distended gallbladder, dilated bile duct and pancreatic duct, and mass in the head of the pancreas. (b) Following resection, the stomach remnant is anastomosed to the proximal jejunum as a gastrojejunostomy; the common hepatic duct is anastomosed to a Roux-en-Y loop of jejunum, the end of which is anastomosed to the pancreatic duct.

obstructive jaundice and duodenal obstruction. In approximately 15% of cases, attempted curative resection may be possible; otherwise, palliation is more appropriate.

- *Curative surgical resection* is possible when disease is confined to the periampullary region. The procedure (Whipple's pancreaticoduodenectomy; Figure 32.2) involves removal of the duodenal 'C' along with the pancreatic head and common bile duct; a gastroenterostomy and biliary drainage using a Roux loop[12] of jejunum are fashioned to restore continuity, together with the implantation of the pancreatic duct into the jejunal Roux loop. However, most tumours are inoperable and, even among the 15% which are operable, the long-term prognosis is poor except in early periampullary tumours without lymph node involvement.
- *Palliative surgical bypass* comprises a short circuit between the distended bile duct and a loop of jejunum (choledochojejunostomy), together with a duodenal bypass by a gastroenterostomy if duodenal obstruction is present.
- *Palliative intubation*, by passage of a stent across the ampulla and through the obstructed common bile duct, is the other alternative to treat the obstructive jaundice. This may be performed either endoscopically (ERCP) or transhepatically (percutaneous transhepatic

[12]Cesar Roux (1857–1934), Professor of Surgery, Lausanne, Switzerland.

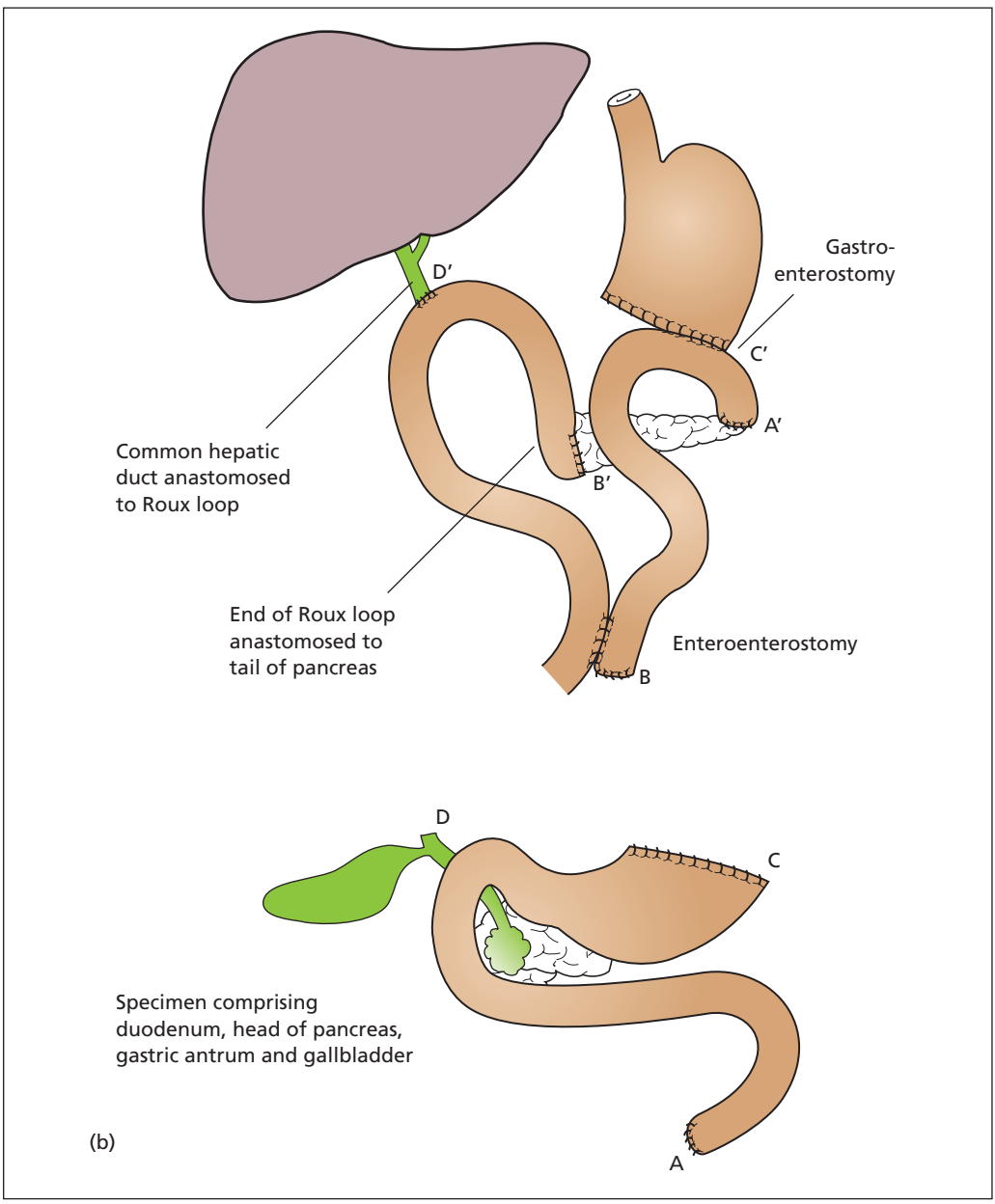

Figure 32.2 *Continued*

cholangiography). Plastic stents are commonly used when the diagnosis has not been established or when operative resection is planned, but expanding metal stents can be used in the palliative situation when the diagnosis is clear because they have better patency rates. Duodenal obstruction can now also be treated by endoscopic stenting, potentially allowing the terminally ill patient to be spared the additional morbidity of a laparotomy and surgical bypass. Alternatively, laparoscopic gastroenterostomy can be used to palliate duodenal obstruction.

- *Severe pain* often requires management with opiates, but coeliac plexus block performed either via the percutaneous approach or under EUS guidance can offer good pain control in some cases.

Prognosis

The outlook for patients with carcinoma of the pancreas itself is gloomy; even if the growth is resectable, the operation has a mortality of about 2–5% and only a small percentage survive for 5 years. Periampullary growths, however, which present relatively early, have a reasonably good prognosis after resection, with about a 25% 5 year survival.

Palliative chemotherapy currently uses protocols based on gemcitabine. The place of radiotherapy is unclear, although some centres do use a combination of radiotherapy and chemotherapy in selected patients. Recent trials have shown a definite survival benefit in patients who have undergone attempted curative resection and who receive postoperative chemotherapy.

Occasionally, a patient has a surprisingly prolonged survival after a palliative bypass operation. In such a case, the diagnosis was more likely to have been chronic pancreatitis mistaken for carcinoma.

33

The spleen

Learning objective

✓ To know the common causes of splenomegaly, the presentations of a ruptured spleen and the prophylaxis and treatment of post-splenectomy syndrome.

Splenomegaly

Physical signs

The spleen must be enlarged to about three times its normal size before it becomes clinically palpable. It then forms a swelling that descends below the left costal margin, moves on respiration and has a firm lower margin, which may or may not be notched. The mass is dull to percussion, the dullness extending above the costal margin.

There are three important differential diagnoses:

1 An enlarged left kidney; unless this is enormous, there is resonance over the swelling anteriorly, as it is covered by the gas-containing colon.
2 Carcinoma of the cardia or upper part of the body of the stomach; by the time such a tumour reaches palpable proportions, there are usually symptoms of gastric obstruction, which suggest the site of the lesion.
3 An enlarged left lobe of liver.

Classification

It is essential to have a working classification of enlargements of the spleen.

1 *Infections.*
   a Viruses: glandular fever.
   b Bacterial: typhus, typhoid, septicaemia ('septic spleen').
   c Protozoal: malaria, kala-azar, Egyptian splenomegaly (schistosomiasis).
   d Parasitic: hydatid.
2 *Haematological diseases.*
   a Leukaemia: chronic myeloid and chronic lymphocytic.
   b Lymphoma: Hodgkin's and non-Hodgkin's lymphoma.
   c Myelofibrosis, idiopathic thrombocytopenia, polycythaemia rubra vera.
   d Haemolytic anaemias, e.g. spherocytosis, β-thalassaemia.
3 *Portal hypertension.* Increased pressure in the portal system causes progressive enlargement of the spleen and may lead to hypersplenism with overactivity of the normal splenic functions such as removal of platelets, resulting in thrombocytopenia.
4 *Metabolic and collagen disease.*
   a Amyloid: secondary to rheumatoid arthritis, collagen diseases, chronic sepsis.
   b Storage diseases, e.g. Gaucher's disease.[1]
5 *Cysts, abscesses and tumours of the spleen*: all uncommon.

Massive splenomegaly in the UK is likely to be due to one of the following: chronic myeloid leukaemia, myelofibrosis, lymphoma, polycythaemia or portal hypertension.

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[1]Phillipe Gaucher (1854–1918), Physician, Hôpital St Louis, Paris, France.

If the spleen is palpable, special attention must be paid to detecting the presence of hepatomegaly and lymphadenopathy (Chapter 34, p. 292).

Splenectomy

Splenectomy is indicated under the following circumstances:

- *Rupture*: either from closed or open trauma or from accidental damage during abdominal surgery.
- *Haematological disease*: haemolytic anaemia, thrombocytopenic purpura.
- *Tumours and cysts*.
- *Part of another operative procedure*, e.g. radical excision of carcinoma of the stomach, distal pancreatectomy, splenorenal anastomosis for portal hypertension.

Complications of splenectomy

Gastric dilatation

Following splenectomy, there may be a gastric ileus. Swallowed air causes rapid dilatation of the stomach, which may tear ligatures on the short gastric vessels on the greater curve of the stomach, which are tied during splenectomy; haemorrhage results. To prevent this, a nasogastric tube is placed and regularly aspirated.

Thrombocytosis

Following splenectomy, the platelet count rises, often to a level of 1000×10^9/L (normal is $<400 \times 10^9$/L). In time, the count falls, but while it is high the patient is at a greater than normal risk of deep vein thrombosis and pulmonary embolus. Antiplatelet agents such as aspirin are given as prophylaxis in addition to low-molecular-weight heparin.

Postsplenectomy sepsis

One of the spleen's functions is to clear capsulated microorganisms (such as *Pneumococcus*, *Meningococcus* and *Haemophilus influenzae*) from the bloodstream after they have been opsonized by the binding of host antibodies to their surface as part of the normal immune response. The spleen also has important phagocytic properties, as well as being the largest repository of lymphoid tissue in the body.

Removal of the spleen in splenectomy predisposes the patient, especially a child, to infection with organisms such as the *Pneumococcus*. The clinical course is of a fulminant bacterial infection, with shock and circulatory collapse, termed overwhelming postsplenectomy sepsis.

Prophylactic immunization with pneumococcal, meningococcal and *H. influenzae* type B vaccines should be administered, preoperatively when possible. In addition, children should have prophylactic daily low-dose penicillin at least until they reach adulthood. Adults should have penicillin for at least the first 2 years after splenectomy, and longer if immunosuppressed. Annual flu immunizations are also recommended to minimize the additional risk of bacterial superinfection and special care is required if the patient is to travel to malarial areas.

Ruptured spleen

This is the commonest internal injury produced by non-penetrating trauma to the abdominal wall. It usually occurs in isolation, but may coexist with fractures of the ribs, or rupture of the liver, the left kidney, the diaphragm or the tail of the pancreas.

Clinical features

Rupture of the spleen manifests in one of the following ways:

1. *Immediate massive bleeding* with rapid death from shock. This results from a complete shattering of the spleen or its avulsion from the splenic pedicle, and death may occur in a few minutes. Fortunately, this is rare.
2. *Peritonism from progressive blood loss*. Following injury, there are the symptoms and signs of progressive blood loss together with evidence of peritoneal irritation. Over a period of several hours after the accident, the patient becomes increasingly pale, the pulse rises and the blood pressure falls. There is abdominal pain, which is either diffuse or confined to the left flank. The patient may complain of pain referred to the left shoulder tip or admit to this only on direct questioning.

   On examination, the abdomen is generally tender, particularly on the left side. There may

be marked generalized rigidity, or it may be confined to slight guarding in the left flank. Bruising of the abdominal wall is often absent or only slight.

3 *Delayed rupture*. This may occur from hours up to several days after trauma. Following the initial injury the concomitant pain soon settles. Then, following a completely asymptomatic interval, the signs and symptoms described above become manifest. This picture is produced by a subcapsular haematoma of the spleen, which increases in size and then ruptures the thin overlying peritoneal capsule with a resultant sudden, sharp haemorrhage.

4 *Spontaneous rupture*. A spleen diseased by, for example, malaria, glandular fever or leukaemia may rupture spontaneously or after only trivial trauma.

Special investigations

The diagnosis of a ruptured spleen is a clinical one, and an unstable patient must be resuscitated aggressively and the surgeon proceed at once to laparotomy. In the less acute situation, and only after resuscitation has begun, the following investigations are useful:

- *Chest X-ray* may reveal associated rib fractures, rupture of the diaphragm or injury to the left lung.
- *Abdominal X-ray*: the stomach bubble may be displaced to the right and there may be indentation of its gas shadow. The splenic flexure of the colon, if containing gas, may be seen to be displaced downwards by the haematoma.
- *Ultrasound* may reveal free fluid, an intrasplenic haematoma or a laceration of the capsule, although the last may be overlooked. Ultrasound is increasingly used as a diagnostic tool in the accident and emergency department for such cases.
- *Computed tomography* is the investigation of choice in all cases of abdominal trauma, and will demonstrate the laceration of the spleen, the presence of intra-abdominal fluid and identify traumatic injuries to other organs.
- *Urinalysis for blood*: haematuria will suggest associated coincidental renal damage.

Treatment

Resuscitation with plasma expanders initially and blood replacement as soon as blood is available is commenced, and laparotomy performed. If the spleen is found to be avulsed or hopelessly pulped, emergency splenectomy is required. If there is minor laceration of the spleen, an attempt is made to preserve it, especially in children and young adults, in whom there is a greater risk of post-splenectomy sepsis. This may be carried out by using fine sutures, fibrin glues and haemostatic absorbable gauze.

Having controlled the bleeding at laparotomy, it is important to carry out a full examination to exclude injury to other organs.