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846 • HEPATOLOGY Clinical examination of the abdomen for liver and biliary disease Observation Face Jaundice Spider naevi Parotid swelling Chest Loss of body hair Abdomen: inspection Scars Distension Veins Testicular atrophy • Unkempt • Smell of alcohol or fetor hepaticus • Encephalopathy • Weight loss • Scratch marks from itching Hands Clubbing Dupuytren’s contracture Leuconychia Bruising Flapping tremor (hepatic encephalopathy) Legs Bruising Oedema Xanthelasma and jaundiced sclera in a patient with chronic cholestasis Palmar erythema Spider naevi Aspiration of ascitic fluid Gynaecomastia Abdomen: palpation/ percussion/auscultation Hepatomegaly Splenomegaly Ascites Palpable gallbladder Hepatic bruit (rare) Tumour Dilated abdominal wall veins (caput medusae) Kayser–Fleischer rings in Wilson’s disease

Insets (Spider naevi) From Hayes P, Simpson K. Gastroenterology and liver disease. Edinburgh: Churchill Livingstone, Elsevier Ltd; 1995; (Aspiration) Strachan M. Davidson’s Clinical cases. Edinburgh: Churchill Livingstone, Elsevier Ltd; 2008; (Palmar erythema) Goldman L, Schafter AI.

Goldman’s Cecil medicine, 24th edn. Philadelphia: WB Saunders, Elsevier Inc.; 2012.

Clinical examination of the abdomen for liver and biliary disease • 847

5 Assessment of liver size Clinical assessment of hepatomegaly is important in diagnosing liver disease. • Start in the right iliac fossa. • Progress up the abdomen 2 cm with each breath (through open mouth). • Confirm the lower border of the liver by percussion. • Detect if smooth or irregular, tender or non-tender; ascertain the shape. • Identify the upper border by percussion. 1 Assessment of encephalopathy Flapping tremor. Jerky forward movements every 5–10 secs, when arms are outstretched and hands are dorsiflexed, suggest hepatic encephalopathy. The movements are coarser than those seen in tremor. Number connection test. These 25 numbered circles can normally be joined together within 30 secs. Serial observations may provide useful information, as long as the position of the numbers is varied to avoid the patient learning their pattern. Begin End

Constructional apraxia. Drawing stars and clocks may reveal marked abnormality. Doctor Patient Ascites Causes Associated clinical findings Exudative (high protein) Carcinoma Weight loss ± hepatomegaly Tuberculosis Weight loss ± fever Transudative (low protein) Cirrhosis Hepatomegaly Splenomegaly Spider naevi Renal failure (including nephrotic syndrome) Generalised oedema Peripheral oedema Congestive heart failure Elevated jugular venous pressure It is important to note that patients with liver disease can present silently following detection of abnormality on screening investigation. This occurs frequently in practice in three settings: Biochemical abnormality • Liver enzyme abnormality detected during health screening or drug monitoring Radiological abnormality • Observation of an unexpected structural lesion (liver mass most usually) following ultrasound, computed tomography or other imaging assessment undertaken for reasons unrelated to the liver Serological abnormality • Detection of a liver-related autoantibody Silent presentation of liver disease History and significance of abdominal signs These represent the combined effects of: Impairment of liver function and its metabolic sequelae • Jaundice (failure of bilirubin clearance) • Encephalopathy (failure of clearance of by-products of metabolism) • Bleeding (impaired liver synthesis of clotting factors) • Hypoglycaemia Ongoing presence of aetiological factors (e.g. alcohol) • Effects of aetiological agent, e.g. intoxication, withdrawal, cognitive impairment versus • Effects of liver injury from agent, e.g. encephalopathy Effects of chronic liver injury (> 6 months) Catabolic status (± poor nutrition) • Skin thinning (‘paper-money skin’) • Loss of muscle bulk • Leuconychia Impaired albumin synthesis • Reduced oncotic pressure (contributes to ascites) Reduced aldosterone clearance • Na+ retention (contributes to ascites) Reduced oestrogen clearance • Mild feminisation of males (loss of body hair, gynaecomastia) Presenting clinical features of liver disease

848 • HEPATOLOGY biliary tree. The segmental anatomy of the liver has an important influence on imaging and treatment of liver tumours, given the increasing use of surgical resection. A liver segment is made up of multiple smaller units known as lobules, comprised of a central vein, radiating sinusoids separated from each other by single liver cell (hepatocyte) plates, and peripheral portal tracts. The functional unit of the liver is the hepatic acinus (Fig. 22.2). Blood flows into the acinus via a single branch of the portal vein and hepatic artery situated centrally in the portal tracts. Blood flows outwards along the hepatic sinusoids into one of several tributaries of the hepatic vein at the periphery of the acinus. Bile, formed by active and passive excretion by hepatocytes into channels called cholangioles, which lie between them, flows in the opposite

direction from the periphery of the acinus. The cholangioles converge in interlobular bile ducts in the portal tracts. The hepatocytes in each acinus lie in three zones, depending on their position relative to the portal tract. Those in zone 1 are closest to the terminal branches of the portal vein and hepatic artery, and are richly supplied with oxygenated blood, and with blood containing the highest concentration of nutrients and toxins. Conversely, hepatocytes in zone 3 are furthest from the portal tracts and closest to the hepatic veins, and are therefore relatively hypoxic and exposed to lower concentrations of nutrients and toxins compared to zone 1. The different perfusion and toxin exposure patterns, and thus vulnerability, of hepatocytes in the different zones contribute to the often patchy nature of liver injury. Liver cells Hepatocytes comprise 80% of liver cells. The remaining 20% are the endothelial cells lining the sinusoids, epithelial cells lining the intrahepatic bile ducts, cells of the immune system (including macrophages (Kupffer cells) and unique populations of atypical lymphocytes), and a key population of non-parenchymal cells called stellate or Ito cells. Fig. 22.1 Liver blood supply. Inferior vena cava VIII VII II I VI V IV III Left hemiliver (LHL) Right hemiliver (RHL) Hepatic vein Portal vein Fig. 22.2 Liver structure and microstructure. A Liver anatomy showing relationship with pancreas, bile duct and duodenum. B Hepatic lobule. C Hepatic acinus. Hepatic acinus Right hepatic duct Common hepatic duct Left hepatic duct Common bile duct Portal vein Central vein Hepatic lobule Hepatic artery Bile duct Sphincter of Oddi Pancreatic duct Pancreas Cholangiole A B C Liver Gallbladder Cystic duct Portal vein Hepatic artery Bile duct Central vein Zone 3 (pericentral) Mono-oxygenation Glycolysis Lipolysis Glucuronidation Zone 2 Zone 1 (perivenous) Good O2 supply Gluconeogenesis Bile salt formation Bile flow Blood flow Duodenum Functional anatomy and physiology Applied anatomy Normal liver structure and blood supply The liver weighs 1.2–1.5 kg and has multiple functions, including key roles in metabolism, control of infection, and elimination of toxins and by-products of metabolism. It is classically divided into left and right lobes by the falciform ligament, but a more useful functional division is into the right and left hemilivers, based on blood supply (Fig. 22.1). These are further divided into eight segments, according to subdivisions of the hepatic and portal veins. Each segment has its own branch of the hepatic artery and

to the hepatocytes. Individual hepatocytes are separated from the leaky sinusoids by the space of Disse, which contains stellate cells that store vitamin A and play an important part in regulating liver blood flow. They may also be immunologically active and play a role in the liver’s contribution to defence against pathogens. The key role of stellate cells in terms of pathology is in the development of hepatic fibrosis, the precursor of cirrhosis. They undergo activation in response to cytokines produced following liver injury, differentiating into myofibroblasts, which are the major producers of the collagen-rich matrix that forms fibrous tissue (Fig. 22.4). Blood supply The liver is unique as an organ, as it has dual perfusion: it receives a majority of its supply via the portal vein, which drains blood from the gut via the splanchnic circulation and is the principal route for nutrient trafficking to the liver, and a minority from the hepatic artery. The portal venous contribution is 50–90%. The dual perfusion system, and the variable contribution from portal vein and hepatic artery, can have important effects on the clinical expression of liver ischaemia (which typically exhibits a less dramatic pattern than ischaemia in other organs, a fact that can sometimes lead to it being missed clinically), and can raise practical challenges in liver transplant surgery. Biliary system and gallbladder Hepatocytes provide the driving force for bile flow by creating osmotic gradients of bile acids, which form micelles in bile (bile Fig. 22.3 Non-parenchymal liver cells. (B

cell = B lymphocyte; NK cell = natural killer cell; PMN cell = polymorphonuclear leucocyte; T cell = T lymphocyte). Space of Disse Hepatocyte Kupffer cell B cell Stellate cell Sinusoid lumen PMN cell Endothelial cell NK cell T cell Fig. 22.4 Pathogenic mechanisms in hepatic fibrosis. Stellate cell activation occurs under the influence of cytokines released by other cell types in the liver, including hepatocytes, Kupffer cells (tissue macrophages), platelets and lymphocytes. Once stellate cells become activated, they can perpetuate their own activation by synthesis of transforming growth factor beta (TGF-β1), and platelet-derived growth factor (PDGF) through autocrine loops. Activated stellate cells produce TGF-β1, stimulating the production of collagen matrix, as well as inhibitors of collagen breakdown. The inhibitors of collagen breakdown, matrix metalloproteinase 2 and 9 (MMP2 and MMP9), are inactivated in turn by tissue inhibitors TIMP1 and TIMP2, which are increased in fibrosis. Inflammation also contributes to fibrosis, with the cytokine profile produced by Th2 lymphocytes, such as interleukin-6 and 13 (IL-6 and IL-13). Activated stellate cells also produce endothelin 1 (ET1), which may contribute to portal hypertension. (EGF = epidermal growth factor; IGF1 = insulin-like growth factor 1; ROS = reactive oxygen species) Stellate cell Activated stellate cell Peroxide products IGF1 TGF-α Injured hepatocyte EGF Platelets TGF-β1 PDGF Initiation Activated Kupffer cell Chemotaxis Vasoconstriction (ET1) Cytokine production (IL-10) Perpetuation TGF-β1 PDGF ROS PDGF ROS Matrix degeneration (MMP2, TIMP1+ 2) Fibrogenesis (TGF-β1) TGF-β1 Endothelial cells line the sinusoids (Fig. 22.3), a network of capillary vessels that differ from other capillary beds in the body, in that there is no basement membrane. The endothelial cells have gaps between them (fenestrae) of about 0.1 micron in diameter, allowing free flow of fluid and particulate matter

 converted to glycerol and fatty acids, thus preventing hyperglycaemia. During fasting, glucose is synthesised (gluconeogenesis) or released from glycogen in the liver, thereby preventing hypoglycaemia (p. 724). • The liver plays a central role in lipid metabolism, producing very low-density lipoproteins and further metabolising low- and high-density lipoproteins (see Fig. 14.13, p. 372). Dysregulation of lipid metabolism is thought to have a critical role in the pathogenesis of NAFLD. Lipids are now recognised to play a key part in the pathogenesis of hepatitis C, facilitating viral entry into hepatocytes. Clotting factors The liver produces key proteins that are involved in the coagulation cascade. Many of these coagulation factors (II, VII, IX and X) are post-translationally modified by vitamin K-dependent enzymes, and their synthesis is impaired in vitamin K deficiency (p. 918). Reduced clotting factor synthesis is an important and easily accessible biomarker of liver function in the setting of liver injury. Prothrombin time (PT; or the International Normalised Ratio, INR) is therefore one of the most important clinical tools available for the assessment of hepatocyte function. Note that the deranged PT or INR seen in liver disease may not directly equate to increased bleeding risk, as these tests do not capture the concurrent reduced synthesis of anticoagulant factors, including protein C and protein S. In general, therefore, correction of PT using blood products before minor invasive procedures should be guided by clinical risk rather than the absolute value of the PT. Bilirubin metabolism and bile The liver plays a central role in the metabolism of bilirubin and is responsible for the production of bile (Fig. 22.6). Between 425 and 510 mmol (250–300 mg) of unconjugated bilirubin is produced from the catabolism of haem daily. Bilirubin in the acid-dependent bile flow), and of sodium (bile acid-independent bile flow). Bile is secreted by hepatocytes and flows from cholangioles to the biliary canaliculi. The canaliculi join to form larger intrahepatic bile ducts, which in turn merge to form the right and left hepatic ducts. These ducts join as they emerge from the liver to form the common hepatic duct, which becomes the common bile duct after joining the cystic duct (see Fig. 22.2). The common bile

duct is approximately 5 cm long and 4–6 mm wide. The distal portion of the duct passes through the head of the pancreas and usually joins the pancreatic duct before entering the duodenum through the ampullary sphincter (sphincter of Oddi). It should be noted, though, that the anatomy of the lower common bile duct can vary widely. Common bile duct pressure is maintained by rhythmic contraction and relaxation of the sphincter of Oddi; this pressure exceeds gallbladder pressure in the fasting state, so that bile normally flows into the gallbladder, where it is concentrated 10-fold by resorption of water and electrolytes. The gallbladder is a pear-shaped sac typically lying under the right hemiliver, with its fundus located anteriorly behind the tip of the 9th costal cartilage. Anatomical variation is common and should be considered when assessing patients clinically and radiologically. The function of the gallbladder is to concentrate, and provide a reservoir for, bile. Gallbladder tone is maintained by vagal activity, and cholecystokinin released from the duodenal mucosa during feeding causes gallbladder contraction and reduces sphincter pressure, so that bile flows into the duodenum. The body and neck of the gallbladder pass posteromedially towards the porta hepatis, and the cystic duct then joins it to the common hepatic duct. The cystic duct mucosa has prominent crescentic folds (valves of Heister), giving it a beaded appearance on cholangiography. Hepatic function Carbohydrate, amino acid and lipid metabolism The liver plays a central role in carbohydrate, lipid and amino acid metabolism, and is also involved in metabolising drugs and environmental toxins (Fig. 22.5). An important and increasingly recognised role for the liver is in the integration of metabolic pathways, regulating the response of the body to feeding and starvation. Abnormality in metabolic pathways and their regulation can play an important role both in liver disease (e.g. non-alcoholic fatty liver disease, NAFLD) and in diseases that are not conventionally regarded as diseases of the liver (such as type 2 diabetes and inborn errors of metabolism). Hepatocytes have specific pathways to handle each of the nutrients absorbed from the gut and carried to the liver via the portal vein: • Amino acids from dietary proteins are used for synthesis of plasma proteins, including albumin. The liver produces 8–14 g of albumin per day, and this plays a critical role in maintaining oncotic pressure in the vascular space and in the transport of small molecules like bilirubin, hormones and drugs throughout the body. Amino acids that are not required for the production of new proteins are broken down, with the amino group being converted ultimately to urea. • Following a meal, more than half of the glucose absorbed is taken up by the liver and stored as glycogen or Fig. 22.5 Important liver functions. Excretion Bile salts Bilirubin Drugs Phospholipid Cholesterol Storage Iron Copper Vitamins A, D and B12 Nutrient metabolism Carbohydrate Protein Lipids Protein synthesis Albumin Coagulation factors Complement factors Haptoglobin Caeruloplasmin Transferrin Protease inhibitors, e.g. α1-antitrypsin Immune functions Local cells (Kupffer cells) Innate factors (defensins etc.)

fat-soluble vitamins, as occurs in biliary obstruction, results in a coagulopathy. The liver also stores minerals such as iron, in ferritin and haemosiderin, and copper, which is excreted in bile. Immune regulation Approximately 9% of the normal liver is composed of immune cells (see Fig. 22.3). Cells of the innate immune system include Kupffer cells derived from blood monocytes, the liver macrophages and natural killer (NK) cells, as well as ‘classical’ B and T cells of the adaptive immune response (p. 67). An additional type of atypical lymphocyte, with phenotypic features of both T cells and NK cells, is thought to play an important role in host defence through linking of innate and adaptive immunity. The enrichment of such cells in the liver reflects the unique importance of the liver in preventing microorganisms from the gut from entering the systemic

circulation. Kupffer cells constitute the largest single mass of tissue-resident macrophages in the body and account for 80% of the phagocytic capacity of this system. They remove aged and damaged red blood cells, bacteria, viruses, antigen–antibody complexes and endotoxin. They also produce a wide variety of inflammatory mediators that can act locally or may be released into the systemic circulation. The immunological environment of the liver is unique in that antigens presented within it tend to induce immunological tolerance. This is of importance in liver transplantation, where classical major histocompatibility (MHC) barriers may be crossed, and also in chronic viral infections, when immune responses may be attenuated. The mechanisms that underlie this phenomenon have not been fully defined. blood is normally almost all unconjugated and, because it is not water-soluble, is bound to albumin and does not pass into the urine. Unconjugated bilirubin is taken up by hepatocytes at the sinusoidal membrane, where it is conjugated in the endoplasmic reticulum by UDP-glucuronyl transferase, producing bilirubin mono- and diglucuronide. Impaired conjugation by this enzyme is a cause of inherited hyperbilirubinaemias (see Box 22.17). These bilirubin conjugates are water-soluble and are exported into the bile canaliculi by specific carriers on the hepatocyte membranes. The conjugated bilirubin is excreted in the bile and passes into the duodenal lumen. Once in the intestine, conjugated bilirubin is metabolised by colonic bacteria to form stercobilinogen, which may be further oxidised to stercobilin. Both stercobilinogen and stercobilin are then excreted in the stool, contributing to its brown colour. Biliary obstruction results in reduced stercobilinogen in the stool, and the stools become pale. A small amount of stercobilinogen (4 mg/day) is absorbed from the bowel, passes through the liver and is excreted in the urine, where it is known as urobilinogen or, following further oxidisation, urobilin. The liver secretes 1–2 L of bile daily. Bile contains bile acids (formed from cholesterol), phospholipids, bilirubin and cholesterol. Several biliary transporter proteins have been identified (Fig. 22.7). Mutations in genes encoding these proteins have been identified in inherited intrahepatic biliary diseases presenting in childhood, and in adult-onset disease such as intrahepatic cholestasis of pregnancy and gallstone formation. Storage of vitamins and minerals Vitamins A, D and B12 are stored by the liver in large amounts, while others, such as vitamin K and folate, are stored in smaller amounts and disappear rapidly if dietary intake is reduced. The liver is also able to metabolise vitamins to more active compounds, e.g. 7-dehydrocholesterol to 25(OH) vitamin D. Vitamin K is a fat-soluble vitamin and so the inability to absorb Fig. 22.6 Pathway of bilirubin excretion. Liver Kidney Urobilinogen (4 mg/day) Urobilin Bilirubin mono- or diglucuronide (conjugated) Bile Stercobilinogen (100 –200 mg/day) Stercobilin Stool Colonic bacteria Large intestine Bilirubin (unconjugated) Urobilinogen (enterohepatic circulation) Blood Fig. 22.7 Biliary transporter proteins. On the hepatocyte basolateral membrane, sodium taurocholate co-transporting polypeptide (NTCP) mediates uptake of conjugated bile acids from portal blood. At the canalicular membrane, these bile acids are secreted via the bile salt export pump (BSEP) into bile. Multidrug resistance protein 3 (MDR3), also situated on the canalicular membrane, transports phospholipid to the outer side of the membrane. This solubilises bile acids, forming micelles and protecting bile duct membranes from bile salt damage. Familial intrahepatic cholestasis 1 (FIC1) moves phosphatidylserine from the inside to the outside of the canalicular membrane; mutations result in familial cholestasis syndrome in childhood. MDR2 (multidrug resistance 2) regulates transport of glutathione. Multidrug resistance protein 2 (MRP2) transports bilirubin and is induced by rifampicin. Organic anion transporter protein (OATP) transports bilirubin and organic anions. Bile duct NTCP Bile acids Bilirubin and organic anions OATP MDR3 BSEP Hepatocytes MDR2 Sinusoid Bile canaliculus MRP2 FIC1

852 • HEPATOLOGY Bilirubin and albumin The degree of elevation of bilirubin can reflect the degree of liver damage. A raised bilirubin often occurs earlier in the natural history of biliary disease (e.g. PBC) than in disease of the liver parenchyma (e.g. cirrhosis), where the hepatocytes are primarily involved. Swelling of the liver within its capsule in inflammation can, however, sometimes impair bile flow and cause an elevation of bilirubin level that is disproportionate to the degree of liver injury. Caution is therefore needed in interpreting the level of liver injury purely on the basis of bilirubin elevation. Serum albumin levels are often low in patients with liver disease. This is due to a change in the volume of distribution of albumin, and to reduced synthesis. Since the plasma half-life of albumin is about 2 weeks, albumin levels may be normal in acute liver failure but are almost always reduced in chronic liver failure. Alanine aminotransferase and aspartate aminotransferase Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are located in the cytoplasm of the hepatocyte; AST is also located in the hepatocyte mitochondria. Although both transaminase enzymes are widely distributed, expression of ALT outside the liver is relatively low and this enzyme is therefore considered more specific for hepatocellular damage. Large increases of aminotransferase activity favour hepatocellular damage, and this pattern of LFT abnormality is known as ‘hepatitic’. Alkaline phosphatase and γ-glutamyl transferase Alkaline phosphatase (ALP) is the collective name given to several different enzymes that hydrolyse phosphate esters at alkaline pH. These enzymes are widely distributed in the body but the main sites of production are the liver, gastrointestinal tract, bone, placenta and kidney. ALPs are post-translationally modified, resulting in the production of several different isoenzymes, which differ in abundance in different tissues. ALP enzymes in the liver are located in cell membranes of the hepatic sinusoids and the biliary canaliculi. Accordingly, levels rise with intrahepatic and extrahepatic biliary obstruction and with sinusoidal obstruction, as occurs in infiltrative liver disease. Gamma-glutamyl transferase (GGT) is a microsomal enzyme found in many cells and tissues of the body. The highest concentrations are located in the liver, where it is produced by hepatocytes and by the epithelium lining small bile ducts. The function of GGT is to transfer glutamyl groups from γ-glutamyl peptides to other peptides and amino acids. The pattern of a modest increase in aminotransferase activity and large increases in ALP and GGT activity favours biliary obstruction and is commonly described as ‘cholestatic’ or ‘obstructive’ (Box 22.2). Isolated elevation of the serum GGT is relatively common and may occur during ingestion of microsomal enzyme-inducing drugs, including alcohol (Box 22.3), but also in NAFLD. Other biochemical tests Other widely available biochemical tests may become altered in patients with liver disease: • Hyponatraemia occurs in severe liver disease due to increased production of vasopressin (antidiuretic hormone, Investigation of liver and hepatobiliary disease Investigations play an important role in the management of liver disease in three settings: • identifying the presence of liver disease • establishing the aetiology • understanding disease severity (in particular, identification of cirrhosis with its complications). When planning investigations, it is important to be clear as to which of these goals is being addressed. Suspicion of the presence of liver disease is normally based on blood biochemistry abnormality (‘liver function tests’, or ‘LFTs’). Aetiology is typically established through a combination of history, specific blood tests and, where appropriate, imaging and liver biopsy. Staging of disease (in essence, the identification of cirrhosis) is largely histological, although there is increasing interest in noninvasive approaches, including novel imaging modalities, serum markers of fibrosis and the use of predictive scoring systems. The aims of investigation in patients with suspected liver disease are shown in Box 22.1. Liver blood biochemistry Liver blood biochemistry (LFTs) includes the measurement of serum bilirubin, aminotransferases, alkaline phosphatase, γ-glutamyl transferase and albumin. Most analytes

measured by LFTs are not truly ‘function’ tests but instead, given that they are released by injured hepatocytes, provide biochemical evidence of liver cell damage. Liver function per se is best assessed by the serum albumin, PT and bilirubin because of the role played by the liver in synthesis of albumin and clotting factors and in clearance of bilirubin. Although LFT abnormalities are often non-specific, the patterns are frequently helpful in directing further investigations. In addition, levels of bilirubin and albumin and the PT are related to clinical outcome in patients with severe liver disease, reflected by their use in several prognostic scores: the Child–Pugh and MELD scores in cirrhosis (see Boxes 22.29 and 22.30, pp. 867 and 868), the Glasgow score in alcoholic hepatitis (see Box 22.47, p. 882) and the King’s College Hospital criteria for liver transplantation in acute liver failure (see Box 22.11, p. 858). These established predictive models, together with emerging disease-specific scoring systems in conditions such as non-alcoholic steatohepatitis (the NASH fibrosis score) and primary biliary cholangitis (PBC, formerly known as primary biliary cirrhosis; the UK-PBC risk score), systematise the approach to assessing abnormal LFTs and can be important for the targeting of more expensive and/or invasive confirmatory diagnostic tests. 22.1 Aims of investigations in patients with suspected liver disease • Detect hepatic abnormality • Measure the severity of liver damage • Detect the pattern of liver function test abnormality: hepatitic or obstructive/cholestatic • Identify the specific cause • Investigate possible complications

A low platelet count is often an indicator of chronic liver disease, particularly in the context of hepatomegaly. Thrombocytosis is unusual in patients with liver disease but may occur in those with active gastrointestinal haemorrhage and, rarely, in hepatocellular carcinoma. Coagulation tests These are often abnormal in patients with liver disease. The normal half-lives of the vitamin K-dependent coagulation factors in the blood are short (5–72 hours), and so changes in the PT occur relatively quickly following liver damage; these changes provide valuable prognostic information in patients with both acute and chronic liver failure. An increased PT is evidence of severe liver damage in chronic liver disease. Vitamin K does not reverse this deficiency if it is due to liver disease, but will correct the PT if the cause is vitamin K deficiency, as may occur with biliary obstruction due to non-absorption of fat-soluble vitamins. Immunological tests A variety of tests are available to evaluate the aetiology of hepatic disease (Boxes 22.4 and 22.5). The presence of liverrelated autoantibodies can be suggestive of the presence of autoimmune liver disease (although false-positive results can occur in non-autoimmune inflammatory disease such as NAFLD). Elevation in overall serum immunoglobulin levels can also indicate autoimmunity (immunoglobulin G (IgG) and IgM). Elevated serum IgA can be seen, often in more advanced alcoholic liver disease and NAFLD, although the association is not specific. ADH; see Fig. 14.8, p. 359). Hyponatraemia can be a significant clinical problem in liver disease with aspects that are distinct from hyponatraemia of other causes. • Serum urea may be reduced in hepatic failure, whereas levels of urea may be increased following gastrointestinal haemorrhage. • When high levels of urea are accompanied by raised bilirubin, high serum creatinine and low urinary sodium, this suggests hepatorenal failure, which carries a grave prognosis. • Significantly elevated ferritin suggests haemochromatosis. Modest elevations can be seen in inflammatory disease, NAFLD and alcohol excess. Haematological tests Blood count The peripheral blood count is often abnormal and can give a clue to the underlying diagnosis: • A normochromic normocytic anaemia may reflect recent gastrointestinal haemorrhage, whereas chronic blood loss is characterised by a hypochromic

microcytic anaemia secondary to iron deficiency. A high erythrocyte mean cell volume (macrocytosis) is associated with alcohol misuse, but target cells in any jaundiced patient also result in a macrocytosis. Macrocytosis can persist for a long period of time after alcohol cessation, making it a poor marker of ongoing consumption. • Leucopenia may complicate portal hypertension and hypersplenism, whereas leucocytosis may occur with cholangitis, alcoholic hepatitis and hepatic abscesses. Atypical lymphocytes are seen in infectious mononucleosis, which may be complicated by an acute hepatitis. • Thrombocytopenia is common in cirrhosis and is due to reduced platelet production and increased breakdown because of hypersplenism. Thrombopoietin, required for platelet production, is produced in the liver and levels fall with worsening liver function. Thus platelet levels are usually more depressed than white cells and haemoglobin in the presence of hypersplenism in patients with cirrhosis. 22.2 ‘Hepatitic’ and ‘cholestatic’/‘obstructive’ liver function tests Pattern AST/ALT GGT ALP Biliary obstruction ↑ ↑↑ ↑↑↑ Hepatitis ↑↑↑ ↑ ↑ Alcohol/enzyme-inducing drugs N/↑ ↑↑ N N = normal; ↑ mild elevation (< twice normal); ↑↑ moderate elevation (2–5 times normal); ↑↑↑ marked elevation (> 5 times normal). (ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase) 22.3 Drugs that increase levels of γ-glutamyltransferase • Barbiturates • Carbamazepine • Ethanol • Griseofulvin • Rifampicin • Phenytoin 22.4 Chronic liver disease screen • Hepatitis B surface antigen • Hepatitis C antibody • Liver autoantibodies (antinuclear antibody, smooth muscle antibody, antimitochondrial antibody) • Immunoglobulins • Ferritin • α1-antitrypsin • Caeruloplasmin Imaging Several imaging techniques can be used to determine the site and general nature of structural lesions in the liver and biliary tree. In general, however, imaging techniques are unable to identify hepatic inflammation and have poor sensitivity for liver fibrosis unless advanced cirrhosis with portal hypertension is present. Ultrasound Ultrasound is non-invasive and most commonly used as a ‘first-line’ test to identify gallstones, biliary obstruction (Fig. 22.8) or thrombosis in the hepatic vasculature. Ultrasound is good for the identification of splenomegaly and abnormalities in liver texture but is less effective at identifying diffuse parenchymal disease. Focal lesions, such as tumours, may not be detected if they are less than 2 cm in diameter and have similar echogenicity to normal liver tissue. Bubble-based contrast media are now used routinely and can enhance discriminant capability. Doppler ultrasound allows blood flow in the hepatic artery, portal vein

 Hepatic angiography is seldom used nowadays as a diagnostic tool, since CT and MRI are both able to provide images of hepatic vasculature, but it still has a therapeutic role in the embolisation of vascular tumours, such as hepatocellular carcinoma. Hepatic venography is now rarely performed. Cholangiography Cholangiography can be undertaken by magnetic resonance cholangiopancreatography (MRCP; Fig. 22.10), endoscopy (endoscopic retrograde cholangiopancreatography, ERCP) or the percutaneous approach (percutaneous transhepatic and hepatic veins to be investigated. Endoscopic ultrasound provides high-resolution images of the pancreas, biliary tree and liver (see below and Fig. 22.46, p. 906). Computed tomography and magnetic resonance imaging Computed tomography (CT) detects smaller focal lesions in the liver, especially when combined with contrast injection (Fig. 22.9). Magnetic resonance imaging (MRI) can also be used to localise and confirm the aetiology of focal liver lesions, particularly primary and secondary tumours. Fig. 22.8 Ultrasound showing a stone in the gallbladder (A) with acoustic shadow (S). S T 22.5 How to identify the cause of liver function test (LFT) abnormality Diagnosis Clinical clue Initial test Additional tests Alcoholic liver disease History LFTs AST > ALT; high MCV Random blood alcohol Non-alcoholic fatty liver disease (NAFLD) Metabolic syndrome (central

obesity, diabetes, hypertension) LFTs Liver biopsy Chronic hepatitis B Injection drug use; blood transfusion HBsAg HBeAg, HBeAb HBV-DNA Chronic hepatitis C Injection drug use; blood transfusion HCV antibody HCV-RNA Primary biliary cholangitis Itching; raised ALP AMA Liver biopsy Primary sclerosing cholangitis Inflammatory bowel disease MRCP ANCA Autoimmune hepatitis Other autoimmune diseases ASMA, ANA, LKM, immunoglobulin Liver biopsy Haemochromatosis Diabetes/joint pain Transferrin saturation, ferritin HFE gene test Wilson's disease Neurological signs; haemolysis Caeruloplasmin 24-hour urinary copper α1-antitrypsin Lung disease α1-antitrypsin level α1-antitrypsin genotype Drug-induced liver disease Drug/herbal remedy history LFTs Liver biopsy Coeliac disease Malabsorption Tissue transglutaminase Duodenal biopsy (ALP = alkaline phosphatase; ALT = alanine aminotransferase; AMA = antimitochondrial antibody; ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; ASMA = anti-smooth muscle antibody; AST = aspartate aminotransferase; HBeAb = antibody to hepatitis B e antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HFE = haemochromatosis (high iron/Fe); LKM = liver–kidney microsomal antibody; MCV = mean cell volume; MRCP = magnetic resonance cholangiopancreatography) Fig. 22.9 Computed tomography in a patient with cirrhosis. The liver is small and has an irregular outline (black arrow), the spleen is enlarged (long white arrow), fluid (ascites) is seen around the liver, and collateral vessels are present around the proximal stomach (short white arrow).

• the procedure is conducted percutaneously under ultrasound control and the needle track is then plugged with procoagulant material. In patients with potentially resectable malignancy, biopsy should be avoided due to the potential risk of tumour dissemination. Operative or laparoscopic liver biopsy may sometimes be valuable. Although the pathological features of liver disease are complex, with several features occurring together, liver disorders can be broadly classified histologically into fatty liver (steatosis), hepatitis (inflammation, 'grade') and cirrhosis (fibrosis, 'stage'). The use of special histological stains can help in determining aetiology. The clinical features and prognosis of these changes are dependent on the underlying aetiology and are discussed in the relevant sections below. Non-invasive markers of hepatic fibrosis Non-invasive markers of liver fibrosis can reduce the need for liver biopsy to assess the extent of fibrosis in some settings. In general, they have high negative predictive value, being able to exclude the presence of advanced fibrosis, but a relatively low positive predictive value. It is important to note that many of these tests have been validated only in certain aetiologies of liver disease and therefore results cannot be extrapolated to all other liver diseases. Alcohol-related liver disease is particularly poorly served in this respect. Serological markers of hepatic fibrosis, such as α2-macroglobulin, haptoglobin and routine clinical biochemistry tests, are used in the Fibrotest®. The Enhanced Liver Fibrosis (ELF®) serological assay uses a combination of hyaluronic acid, procollagen peptide III (PIIINP) and tissue inhibitor of metalloproteinase 1 (TIMP1). These tests are good at differentiating severe fibrosis from mild scarring but are limited in their ability to detect subtle changes. A number of non-commercial scores based on standard biochemical and anthropometric indices have also been described that provide similar levels of sensitivity and specificity (e.g. the FIB4 score, which is based on age, ALT/AST ratio and platelet count). An alternative to serological markers is vibration-controlled transient elastography (Fibroscan®), in which ultrasound-based shock waves are sent through the liver to measure liver stiffness as a surrogate for hepatic fibrosis. Once again, this test is good at differentiating severe fibrosis from

mild scarring, but it is limited in its ability to detect subtle changes and validity may be affected by obesity. Similar techniques, including magnetic resonance elastography, are promising but not yet widely available. Presenting problems in liver disease Liver injury may be either acute or chronic. The main causes are listed in Figure 22.11 and discussed in detail later in the chapter. In Fig. 22.10 Magnetic resonance cholangiopancreatography showing a biliary stricture due to cholangiocarcinoma in the distal common bile duct (arrow). The proximal common bile duct (CBD) is dilated but the pancreatic duct (PD) is normal. cholangiography, PTC). The latter does not allow the ampulla of Vater or pancreatic duct to be visualised. Endoscopic ultrasound can also provide high-quality biliary imaging safely (see below). MRCP is as good as ERCP at providing images of the biliary tree but is safer, and there is now little, if any, role for diagnostic ERCP. Both endoscopic and percutaneous approaches allow therapeutic interventions, such as the insertion of biliary stents across bile duct strictures. The percutaneous approach is used only if it is not possible to access the bile duct endoscopically. Endoscopic ultrasound Endoscopic ultrasound (EUS; p. 774) is complementary to MRCP in the diagnostic evaluation of the extrahepatic biliary tree, ampulla of Vater and pancreas. With the ultrasonic probe in the duodenum, high-quality images are obtained, tissue sampling can be performed and, increasingly, therapeutic drainage of biliary obstruction can be performed. EUS has the advantage over ERCP of not exposing patients to the risk of pancreatitis, among other complications of bile duct cannulation. Histological examination An ultrasound-guided liver biopsy can confirm the severity of liver damage and provide aetiological information. It is performed percutaneously with a Trucut or Menghini needle, usually through an intercostal space under local anaesthesia, or radiologically using a transjugular approach. Percutaneous liver biopsy is a relatively safe procedure if the conditions detailed in Box 22.6 are met, but carries a mortality of about 0.01%. The main complications are abdominal and/or shoulder pain, bleeding and biliary peritonitis. Biliary peritonitis is rare and usually occurs when a biopsy is performed in a patient with obstruction of a large bile duct. Liver biopsies can be carried out in patients with defective haemostasis if: • the defect is corrected with fresh frozen plasma and platelet transfusion • the biopsy is obtained by the transjugular route, or 22.6 Conditions required for safe percutaneous liver biopsy • Cooperative patient • Prothrombin time < 4 secs prolonged • Platelet count > 80 × 109/L • Exclusion of bile duct obstruction, localised skin infection, advanced chronic obstructive pulmonary disease, marked ascites and severe anaemia

 significantly increased risk, whereas decompensation can be a complication in all cases and the presence of portal hypertension with intra-abdominal varices can make abdominal surgery more hazardous. The possibility of undiagnosed liver disease should be borne in mind in all patients in at-risk groups undergoing significant surgery. Acute liver failure Acute liver failure is an uncommon but serious condition characterised by a relatively rapid progressive deterioration in liver function. The presence of encephalopathy is a cardinal feature, with mental changes progressing from delirium to coma. The syndrome was originally defined further as occurring within 8 weeks of onset of the precipitating illness, in the absence of evidence of pre-existing liver disease. This distinguishes it from instances in which hepatic encephalopathy represents a deterioration in chronic liver disease. Liver failure occurs when there is insufficient metabolic and synthetic function for the needs of the patient. Although the direct cause is usually acute loss of functional hepatocytes, this can occur in different settings, which have implications for outcome and treatment. In a patient whose liver was previously normal (fulminant liver failure), the level of injury needed to cause liver Fig. 22.11 Causes of acute and chronic liver injury. *Although there is often evidence of chronic liver disease at presentation, may present acutely with*

jaundice. In alcoholic liver disease this is due to superimposed alcoholic hepatitis. (NAFLD = non-alcoholic fatty liver disease; PBC = primary biliary cholangitis; PSC = primary sclerosing cholangitis) Acute liver injury Viral hepatitis (A, B, E) Alcoholic liver disease Autoimmune hepatitis* Drugs Chronic liver injury Chronic viral hepatitis (B + C) PBC PSC NAFLD Haemochromatosis a1-antitrypsin deficiency Cryptogenic (unknown) Wilson's disease Fig. 22.12 Standardised UK mortality rates showing the rise in liver-related mortality. From Williams R, Aspinall R, Bellis M, et al. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. Reprinted with permission from Elsevier (The Lancet 2014; 384:1953–1997). Circulatory Ischaemic heart Cerebrovascular Neoplasms Respiratory Liver Endocrine or metabolic Diabetes

Year

Disease Standardised mortality (% change) the UK, liver disease is the only one of the top causes of mortality that is steadily increasing (Fig. 22.12). Mortality rates have risen substantially over the last 30 years, with a near-fivefold increase in liver-related mortality in people younger than 65 years. The rate of increase is substantially higher in the UK than in other countries in Western Europe. • Acute liver injury may present with non-specific symptoms of fatigue and abnormal LFTs, or with jaundice and acute liver failure. • Chronic liver injury is defined as hepatic injury, inflammation and/or fibrosis occurring in the liver for more than 6 months. In the early stages, patients can be asymptomatic with fluctuating abnormal LFTs. With more severe liver damage, however, the presentation can be with jaundice, portal hypertension or other signs of cirrhosis and hepatic decompensation (Box 22.7). Patients with clinically silent chronic liver disease frequently present when abnormalities in liver function are observed on routine blood testing, or when clinical events, such as an intercurrent infection or surgical intervention, cause the liver to decompensate. Patients with compensated cirrhosis can undergo most forms of surgery without 22.7 Presentation of liver disease Severity Acute liver injury Chronic liver injury Mild/moderate Abnormal liver function tests Abnormal liver function tests Severe Jaundice Signs of cirrhosis ± portal hypertension Very severe Acute liver failure Chronic liver failure* Jaundice Ascites Hepatic encephalopathy Portal hypertension with variceal bleeding *May not occur until several years after cirrhosis has presented.

Clinical assessment Cerebral disturbance (hepatic encephalopathy and/or cerebral oedema) is the cardinal manifestation of acute liver failure, but in the early stages this can be mild and episodic, and so its absence does not exclude a significant acute liver injury. The initial clinical features are often subtle and include reduced alertness and poor concentration, progressing through behavioural abnormalities, such as restlessness and aggressive outbursts, to drowsiness and coma (Box 22.9). Cerebral oedema may occur due to increased intracranial pressure, causing unequal or abnormally reacting pupils, fixed pupils, hypertensive episodes, bradycardia, hyperventilation, profuse sweating, local or general myoclonus, focal fits or decerebrate posturing. Papilloedema occurs rarely and is a late sign. More general symptoms include weakness, nausea and vomiting. Right hypochondrial discomfort is an occasional feature. The patient may be jaundiced but jaundice may not be present at the outset (e.g. in paracetamol overdose), and there are a number of exceptions, including Reye's syndrome, in which jaundice is rare. Occasionally, death may occur in

fulminant cases of acute liver failure before jaundice develops. Fetor hepaticus can be present. The liver is usually of normal size but later becomes smaller. Hepatomegaly is unusual and, in failure, and thus the patient risk, is very high. In a patient with pre-existing chronic liver disease, the additional acute insult needed to precipitate liver failure is much less. It is critical, therefore, to understand whether liver failure is a true acute event or an acute deterioration on a background of pre-existing injury (which may itself not have been diagnosed). Although liver biopsy may ultimately be necessary, it is the presence or absence of the clinical features suggesting chronicity that guides the clinician. More recently, newer classifications have been developed to reflect differences in presentation and outcome of acute liver failure. One such classification divides acute liver failure into hyperacute, acute and subacute, according to the interval between onset of jaundice and encephalopathy (Box 22.8). Pathophysiology Any cause of liver damage can produce acute liver failure, provided it is sufficiently severe (Fig. 22.13). Acute viral hepatitis is the most common cause worldwide, whereas paracetamol toxicity (p. 137) is the most frequent cause in the UK. Acute liver failure occurs occasionally with other drugs, or from Amanita phalloides (mushroom) poisoning, in pregnancy, in Wilson’s disease, following shock (p. 199) and, rarely, in extensive malignant disease of the liver. In 10% of cases, the cause of acute liver failure remains unknown and these patients are often labelled as having ‘non-A–E viral hepatitis’ or ‘cryptogenic’ acute liver failure. Fig. 22.13 Causes of acute liver failure in the UK. The relative frequency of the different causes varies according to geographical area. Miscellaneous (< 5%) Acute liver failure Viral infections (5%) Drugs (70–80%) Poisons (< 5%) Amanita phalloides Paracetamol Halothane Antituberculous drugs Methylenedioxymethamphetamine (MDMA, 'ecstasy') Herbal remedies Hepatitis A, B, E (rare) Wilson's disease Acute fatty liver of pregnancy Shock and cardiac failure Budd–Chiari syndrome Leptospirosis Liver metastases Lymphoma Cryptogenic (5–10%) Non-A–E viral hepatitis 22.8 Classification of acute liver failure Type Time: jaundice to encephalopathy Cerebral oedema Common causes Hyperacute < 7 days Common Viral, paracetamol Acute 8–28 days Common Cryptogenic, drugs Subacute 29 days to 12 weeks Uncommon Cryptogenic, drugs 22.9 How to assess clinical grade of hepatic encephalopathy Clinical grade Clinical signs Grade 1 Poor concentration, slurred speech, slow mentation, disordered sleep rhythm Grade 2 Drowsy but easily rousable, occasional aggressive behaviour, lethargic Grade 3 Marked delirium, drowsy, sleepy but responds to pain and voice, gross disorientation Grade 4 Unresponsive to voice, may or may not respond to painful stimuli, unconscious

858 • HEPATOLOGY bilirubin reflects the degree of jaundice. Plasma aminotransferase activity is particularly high after paracetamol overdose, reaching 100–500 times normal, but falls as liver damage progresses and is not helpful in determining prognosis. Plasma albumin remains normal unless the course is prolonged. Percutaneous liver biopsy is contraindicated because of the severe coagulopathy, but biopsy can be undertaken using the transjugular route if appropriate. Management Patients with acute liver failure should be treated in a highdependency or intensive care unit as soon as progressive prolongation of the PT occurs or hepatic encephalopathy is identified (Box 22.12), so that prompt treatment of complications can be initiated (Box 22.13). Conservative treatment aims to maintain life in the hope that hepatic regeneration will occur, but early transfer to a specialised transplant unit should always be considered. N-acetylcysteine therapy may improve outcome, particularly in patients with acute liver failure due to paracetamol poisoning. Liver transplantation is an increasingly important treatment option for acute liver failure, and criteria have been developed to identify patients unlikely to survive without a transplant (see Box 22.11). Patients should, wherever possible, be transferred to a transplant centre before these

criteria are met to allow time for assessment and to maximise the time for a donor liver to become available. Survival following liver transplantation *Predict a mortality rate of ≥ 90% and are an indication for referral for possible liver transplantation. 22.11 Adverse prognostic criteria in acute liver failure* Paracetamol overdose • H+ > 50 nmol/L (pH < 7.3) at or beyond 24 hours following the overdose Or • Serum creatinine > 300 µmol/L (≅ 3.38 mg/dL) plus prothrombin time > 100 secs plus encephalopathy grade 3 or 4 Non-paracetamol cases • Prothrombin time > 100 secs Or • Any three of the following: Jaundice to encephalopathy time > 7 days Age < 10 or > 40 years Indeterminate or drug-induced causes Bilirubin > 300 µmol/L (≅ 17.6 mg/dL) Prothrombin time > 50 secs Or • Factor V level < 15% and encephalopathy grade 3 or 4 22.10 Investigations to determine the cause of acute liver failure • Toxicology screen of blood and urine • HBsAg, IgM anti-HBc • IgM anti-HAV • Anti-HEV, HCV, cytomegalovirus, herpes simplex, Epstein–Barr virus • Caeruloplasmin, serum copper, urinary copper, slit-lamp eye examination • Autoantibodies: ANA, ASMA, LKM, SLA • Immunoglobulins • Ultrasound of liver and Doppler of hepatic veins (ANA = antinuclear antibody; anti-HBc = antibody to hepatitis B core antigen; ASMA = anti-smooth muscle antibody; HAV = hepatitis A virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; IgM = immunoglobulin M; LKM = liver–kidney microsomal antibody; SLA = soluble liver antigen) 22.12 Monitoring in acute liver failure Cardiorespiratory • Pulse • Blood pressure • Central venous pressure • Respiratory rate Neurological • Intracranial pressure monitoring (specialist units, p. 208) • Conscious level Fluid balance • Hourly output (urine, vomiting, diarrhoea) • Input: oral, intravenous Blood analyses • Arterial blood gases • Peripheral blood count (including platelets) • Sodium, potassium, HCO_3^-, calcium, magnesium • Creatinine, urea • Glucose (2-hourly in acute phase) • Prothrombin time Infection surveillance • Cultures: blood, urine, throat, sputum, cannula sites • Chest X-ray • Temperature the presence of a sudden onset of ascites, suggests venous outflow obstruction as the cause (Budd–Chiari syndrome, p. 898). Splenomegaly is uncommon and never prominent. Ascites and oedema are late developments and may be a consequence of fluid therapy. Other features are related to the development of complications (see below). Investigations The patient should be investigated to determine the cause of the liver failure and the prognosis (Boxes 22.10 and 22.11). Hepatitis B core IgM antibody is the best screening test for acute hepatitis B infection, as liver damage is due to the immunological response to the virus, which has often been eliminated, and the test for hepatitis B surface antigen (HBsAg) may be negative. The PT rapidly becomes prolonged as coagulation factor synthesis fails; this is the laboratory test of greatest prognostic value and should be carried out at least twice daily. Its prognostic importance emphasises the necessity of avoiding the use of fresh frozen plasma to correct raised PT in acute liver failure, except in the setting of frank bleeding. Factor V levels can be used instead of the PT to assess the degree of liver impairment. The plasma 22.13 Complications of acute liver failure • Encephalopathy and cerebral oedema • Hypoglycaemia • Metabolic acidosis • Infection (bacterial, fungal) • Renal failure • Multi-organ failure (hypotension and respiratory failure)

When abnormal LFTs are detected, a thorough history should be compiled to determine the patient’s alcohol consumption, drug use (prescribed drugs or otherwise), risk factors for viral hepatitis (e.g. blood transfusion, injection drug use, tattoos), the presence of autoimmune diseases, family history, neurological symptoms, and the presence of features of the metabolic syndrome (p. 730), including diabetes and/or obesity (see Box 22.5 and Fig. 19.5, p. 698). The

presence or absence of stigmata of 22.14 Common causes of elevated serum transaminases Minor elevation (< 100 U/L*) • Chronic hepatitis C • Chronic hepatitis B • Haemochromatosis • Fatty liver disease Moderate elevation (100–300 U/L*) As above plus: • Alcoholic hepatitis • Non-alcoholic steatohepatitis • Autoimmune hepatitis • Wilson's disease Major elevation (> 300 U/L*) • Drugs (e.g. paracetamol) • Acute viral hepatitis • Autoimmune liver disease • Ischaemic liver • Toxins (e.g. Amanita phalloides poisoning) • Flare of chronic hepatitis B *These ranges are indicative but do not rigidly discriminate between different aetiologies. for acute liver failure is improving and 1-year survival rates of about 60% can be expected. A number of artificial liver support systems have been developed and evaluated for use as a bridge to either transplantation or recovery. None, however, has entered routine clinical use. Abnormal liver function tests Frequently, LFTs are requested in patients who have no symptoms or signs of liver disease, as part of routine health checks, insurance medicals or drug monitoring. When abnormal results are found, it is important for the clinician to be able to interpret them and to investigate appropriately. Many patients with chronic liver disease are asymptomatic or have vague, non-specific symptoms. Apparently asymptomatic abnormal LFTs are therefore a common occurrence. When LFTs are measured routinely prior to elective surgery, 3.5% of patients are discovered to have mildly elevated transaminases. The prevalence of abnormal LFTs has been reported to be as high as 10% in some studies. The most common abnormalities are alcoholic (p. 880) or non-alcoholic fatty liver disease (p. 882). Since effective medical treatments are now available for many types of chronic liver disease, further evaluation is usually warranted to make sure the patient does not have a treatable condition. Although transient mild abnormalities in LFTs may not be clinically significant, the majority of individuals with persistently abnormal LFTs do have significant liver disease. Biochemical abnormalities in chronic liver disease often fluctuate over time; even mild abnormalities can therefore indicate significant underlying disease and so warrant follow-up and investigation. Fig. 22.14 Suggested management of abnormal liver function tests in asymptomatic patients. *No further investigation needed. (α1AT = alpha1 antitrypsin; BMI = body mass index; ERCP = endoscopic retrograde cholangiopancreatography; GGT = γ-glutamyl transferase; HBsAg = hepatitis B surface antigen; HCVAb = antibody to hepatitis C virus; MRCP = magnetic resonance cholangiopancreatography; NAFLD = non-alcoholic fatty liver disease) Action Clinical situation Management Liver screen, i.e. Full history Chronic liver disease screen (Box 22.4) Ultrasound abdomen HBsAg HCVAb α1-antitrypsin Autoimmune profile Ferritin Caeruloplasmin Immunoglobulins Dilated bile ducts Non-dilated bile ducts Cholangiography MRCP or ERCP Consider liver biopsy and treat underlying disorder Abnormal alkaline phosphatase or serum transaminases

> 2 × upper limit of normal Check GGT if raised alkaline phosphatase Recheck LFTs in 3–6 months Abnormal alkaline phosphatase or serum transaminases < 2 × upper limit of normal Persistently abnormal LFT Determine whether: NAFLD/increased BMI Enzyme induction from drugs Alcohol Increased GGT only Recheck with conjugated bilirubin, exclude haemolysis Increased bilirubin only Stage disease; lifestyle modification (diet and exercise) Alcohol abstinence Review current medication Reassure, as likely Gilbert's syndrome Alcohol abstinence Stop hepatotoxic drugs Advise weight loss if BMI > 25

860 • HEPATOLOGY In haemolysis, destruction of red blood cells or their marrow precursors causes increased bilirubin production. Jaundice due to haemolysis is usually mild because a healthy liver can excrete a bilirubin load six times greater than normal before unconjugated bilirubin accumulates in the plasma. This does not apply to newborns, who have less capacity to metabolise bilirubin. The most common form of non-haemolytic hyperbilirubinaemia is Gilbert's syndrome, an inherited disorder of bilirubin metabolism (Box 22.17). Other inherited disorders of bilirubin metabolism are very rare. Hepatocellular jaundice Hepatocellular jaundice results from an inability of the liver to transport bilirubin into the bile, occurring as a consequence of parenchymal disease. Bilirubin transport across the hepatocytes may be impaired at any point between uptake of unconjugated bilirubin into the cells and transport of conjugated bilirubin into the canaliculi. In addition, swelling of cells and oedema resulting from the disease itself may cause obstruction of the biliary canaliculi. In hepatocellular jaundice, the concentrations of both unconjugated and conjugated bilirubin in the blood increase. 22.16 Key history points in patients with jaundice Symptoms* • Itching preceding jaundice • Abdominal pain (suggests stones) • Weight loss (chronic liver disease and malignancy) • Dark urine and pale stools • Fever ± rigors • Dry eyes/dry mouth • Fatigue Recent drug history Other • Exposure to intravenous drug or blood transfusions • Travel history and country of birth • Metabolic syndrome (increased body mass index ± type 2 diabetes/ hypertension) • Autoimmune disease history • Alcohol history • Inflammatory bowel disease • Family history of liver disease, autoimmune disease or the metabolic syndrome *Symptoms may be absent and abnormal liver function tests detected incidentally. 22.17 Congenital non-haemolytic hyperbilirubinaemia Syndrome Inheritance Abnormality Clinical features Treatment Unconjugated hyperbilirubinaemia Gilbert's Can be autosomal recessive or dominant ↓Glucuronyl transferase Mild jaundice, especially with fasting None necessary ↓Bilirubin uptake Crigler–Najjar: Type I Autosomal recessive Absent glucuronyl transferase Rapid death in neonate (kernicterus) Type II Autosomal recessive ↓↓Glucuronyl transferase Presents in neonate Phenobarbital, phototherapy or liver transplant Conjugated hyperbilirubinaemia Dubin–Johnson Autosomal recessive ↓Canalicular excretion of organic anions, including bilirubin Mild jaundice None necessary Pigmentation of liver biopsy tissue Rotor's Autosomal recessive ↓Bilirubin uptake Mild jaundice None necessary ↓Intrahepatic binding 22.15 Causes of cholestatic jaundice Intrahepatic • Primary biliary cholangitis • Primary sclerosing cholangitis • Alcohol • Drugs • Hepatic infiltrations (lymphoma, granuloma, amyloid, metastases) • Cystic fibrosis • Severe bacterial infections • Pregnancy (p. 899) • Inherited cholestatic liver disease, e.g. benign recurrent intrahepatic cholestasis • Chronic right heart failure Extrahepatic • Carcinoma: Ampullary Pancreatic Bile duct (cholangiocarcinoma) Liver metastases • Choledocholithiasis • Parasitic infection • Traumatic biliary strictures • Chronic pancreatitis chronic liver disease does not reliably identify those individuals with significant disease and investigations are indicated, even in the absence of these signs. Both the pattern of LFT abnormality (hepatitic or obstructive) and the degree of elevation are helpful in determining the cause of underlying liver disease (Boxes 22.14 and 22.15). The investigations that make up a standard liver screen and additional or confirmatory tests are shown in Boxes 22.4 and 22.5. An algorithm for investigating abnormal LFTs is provided in Figure 22.14. Jaundice Jaundice is usually detectable clinically when the plasma bilirubin exceeds 40 µmol/L (~2.5 mg/dL). The causes of jaundice overlap with the causes of abnormal LFTs discussed above. In a patient with jaundice it is useful to consider whether the cause might be pre-hepatic, hepatic or post-hepatic, and there are often important clues in the history (Box 22.16). Pre-hepatic jaundice This is caused either by haemolysis or by congenital hyperbilirubinaemia, and is characterised by an isolated raised bilirubin level.

Hepatocellular jaundice can be due to acute or chronic injury (see Fig. 22.11), and clinical features of acute or chronic liver disease may be detected clinically (see Box 22.7). Characteristically, jaundice due to parenchymal liver disease is associated with increases in transaminases (AST, ALT), but increases in other LFTs, including cholestatic enzymes (GGT, ALP), may occur and suggest specific aetiologies (see below). Acute jaundice in the presence of an ALT of > 1000 U/L is highly suggestive of an infectious cause (e.g. hepatitis A or B), drugs (e.g. paracetamol) or hepatic ischaemia. Imaging is essential, in particular to identify features suggestive of cirrhosis, define the patency of the hepatic vasculature and obtain evidence of portal hypertension. Liver biopsy has an important role in defining the aetiology of hepatocellular jaundice and the extent of liver injury. Obstructive (cholestatic) jaundice Cholestatic jaundice may be caused by: • failure of hepatocytes to initiate bile flow • obstruction of the bile ducts or portal tracts • obstruction of bile flow in the extrahepatic bile ducts between the porta hepatis and the papilla of Vater. In the absence of treatment, cholestatic jaundice tends to become progressively more severe because conjugated bilirubin is unable to enter the bile canaliculi and passes back into the blood, and also because there is a failure of clearance of unconjugated bilirubin arriving at the liver cells. The causes of cholestatic jaundice are listed in Box 22.15. Cholestasis may result from defects at more than one of these levels. Those confined to 22.18 Clinical features and complications of cholestatic jaundice Cholestasis Early features • Jaundice • Dark urine • Pale stools • Pruritus Late features • Malabsorption (vitamins A, D, E and K): weight loss, steatorrhoea, osteomalacia, bleeding tendency • Xanthelasma and xanthomas Cholangitis • Fever • Rigors • Pain (if gallstones present) Fig. 22.15 Investigation of jaundice. (ERCP = endoscopic retrograde cholangiopancreatography; LFTs = liver function tests; MRCP = magnetic resonance cholangiopancreatography) History and examination Serum for biochemical liver tests (LFTs) Liver ultrasound Urine for bilirubin Isolated bilirubin rise (other LFTs normal) Normal ultrasound Urobilinogen present Pre-hepatic jaundice Unconjugated bilirubin rise Conjugated bilirubin rise Blood film/ reticulocyte count Dubin–Johnson/ Rotor’s syndrome (very rare) Gilbert’s syndrome Coombs test + Haemolysis work-up Raised conjugated bilirubin and other LFTs abnormal Evidence of biliary disease Raised conjugated bilirubin and other LFTs abnormal No evidence of biliary disease Biliary obstruction (i.e. dilated bile ducts) Obstructive jaundice Cholangiography (MRCP or ERCP) Hepatocellular jaundice Clotting Hepatitis/serology Immunoglobulins Autoantibodies Copper studies Iron studies the extrahepatic bile ducts may be amenable to surgical or endoscopic correction. Clinical features (Box 22.18) comprise those due to cholestasis itself, those due to secondary infection (cholangitis) and those of the underlying condition (Box 22.19). Obstruction of the bile duct drainage due to blockage of the extrahepatic biliary tree is characteristically associated with pale stools and dark urine. Pruritus may be a dominant feature and can be accompanied by skin excoriations. Peripheral stigmata of chronic liver disease are absent. If the gallbladder is palpable, the jaundice is unlikely to be caused by biliary obstruction due to gallstones, probably because a chronically inflamed, stone-containing gallbladder cannot readily dilate. This is Courvoisier’s Law, and suggests

 that jaundice is due to a malignant biliary obstruction (e.g. pancreatic cancer). Cholangitis is characterised by ‘Charcot’s triad’ of jaundice, right upper quadrant pain and fever. Cholestatic jaundice is characterised by a relatively greater elevation of ALP and GGT than the aminotransferases. Ultrasound is indicated to determine whether there is evidence of mechanical obstruction and dilatation of the biliary tree (Fig. 22.15). EUS provides an additional investigation

modality for investigation of lower common bile duct obstruction. Management of cholestatic jaundice depends on the underlying cause and is discussed in the relevant sections below. Hepatomegaly Hepatomegaly may occur as the result of a general enlargement of the liver or because of primary or secondary liver tumour 22.20 Causes of change in liver size Large liver (hepatomegaly) • Liver metastases • Multiple or large hepatic cysts • Cirrhosis (early): non-alcoholic fatty liver disease, alcohol, haemochromatosis • Hepatic vein outflow obstruction • Infiltration: amyloid Small liver • Cirrhosis (late) 22.21 Causes of ascites Low SAAG (exudative) High SAAG (transudative) Common causes Malignant disease: Hepatic Peritoneal Cardiac failure Hepatic cirrhosis Other causes Acute pancreatitis Lymphatic obstruction Infection: Tuberculosis Nephrotic syndrome Hypoproteinaemia: Protein-losing enteropathy Malnutrition Hepatic venous occlusion: Budd–Chiari syndrome Sinusoidal obstruction syndrome (Veno-occlusive disease) Rare causes Hypothyroidism Meigs' syndrome* Constrictive pericarditis *Meigs' syndrome is the association of a right pleural effusion with or without ascites and a benign ovarian tumour. The ascites resolves on removal of the tumour. (SAAG = serum ascites albumin gradient; see text) (Box 22.20). The most common liver tumour in Western countries is liver metastasis, whereas primary liver cancer complicating chronic viral hepatitis is more common in the Far East. Unlike carcinoma metastases, those from neuro-endocrine tumours typically cause massive hepatomegaly but without significant weight loss. Cirrhosis can be associated with either hepatomegaly or reduced liver size in advanced disease. Although all causes of cirrhosis can involve hepatomegaly, it is much more common in alcoholic liver disease and haemochromatosis. Hepatomegaly may resolve in patients with alcoholic cirrhosis when they stop drinking. Ascites Ascites is present when there is accumulation of free fluid in the peritoneal cavity. Small amounts of ascites are asymptomatic, but with larger accumulations of fluid (> 1 L) there is abdominal distension, fullness in the flanks, shifting dullness on percussion and, when the ascites is marked, a fluid thrill/fluid wave. Other features include eversion of the umbilicus, herniae, abdominal striae, divarication of the recti and scrotal oedema. Dilated superficial abdominal veins may be seen if the ascites is due to portal hypertension. Pathophysiology Ascites has numerous causes, the most common of which are malignant disease, cirrhosis and heart failure. Many primary disorders of the peritoneum and visceral organs can also cause ascites, and these need to be considered even in a patient with chronic liver disease (Box 22.21). Splanchnic vasodilatation is thought to be the main factor leading to ascites in cirrhosis. This is mediated by vasodilators (mainly nitric oxide) that are released when portal hypertension causes shunting of blood into the systemic circulation. Systemic arterial pressure falls due to pronounced splanchnic vasodilatation as cirrhosis advances. This leads to activation of the renin–angiotensin system with secondary aldosteronism, increased sympathetic nervous activity, increased atrial natriuretic hormone secretion and altered activity *Each of these diseases can give rise to almost any of the clinical features shown but the box indicates the most likely cause of the clinical features listed. 22.19 Clinical features suggesting an underlying cause of cholestatic jaundice* Clinical feature Causes Jaundice Static or increasing Carcinoma Primary biliary cholangitis Primary sclerosing cholangitis Fluctuating Choledocholithiasis Stricture Pancreatitis Choledochal cyst Primary sclerosing cholangitis Abdominal pain Choledocholithiasis Pancreatitis Choledochal cyst Cholangitis Stone Stricture Choledochal cyst Abdominal scar Stone Stricture Irregular hepatomegaly Hepatic carcinoma Palpable gallbladder Carcinoma below cystic duct (usually pancreas) Abdominal mass Carcinoma Pancreatitis (cyst) Choledochal cyst Occult blood in stools Ampullary tumour

indicated by an albumin gradient of > 11 g/L (1.1 g/dL) but, unlike in cirrhosis, the total protein content is usually > 25 g/L (2.5 g/dL). High protein ascites (‘exudate’; protein concentration > 25 g/L (2.5 g/dL) or a SAAG of < 11 g/L (1.1 g/dL) raises the possibility of infection (especially tuberculosis), malignancy, pancreatic ascites or, rarely, hypothyroidism. Ascites amylase activity of

> 1000 U/L identifies pancreatic ascites, whereas low ascites glucose concentrations suggest malignant disease or tuberculosis. Cytological examination may reveal malignant cells (one-third of cirrhotic patients with a bloody tap have a hepatocellular carcinoma). Polymorphonuclear leucocyte counts of > 250 × 106/L strongly suggest infection (spontaneous bacterial peritonitis; see below). Laparoscopy can be valuable in detecting peritoneal disease. The presence of triglyceride at a level > 1.1 g/L (110 mg/dL) is diagnostic of chylous ascites and suggests anatomical or functional abnormality of lymphatic drainage from the abdomen. The ascites in this context has a characteristic milky-white appearance. Management Successful treatment relieves discomfort but does not prolong life; if over-vigorous, it can produce serious disorders of fluid and electrolyte balance, and precipitate hepatic encephalopathy (p. 864). Treatment of transudative ascites is based on restricting sodium and water intake, promoting urine output with diuretics and, if necessary, removing ascites directly by paracentesis. Exudative ascites due to malignancy is treated with paracentesis but fluid replacement is generally not required. During management of ascites, the patient should be weighed regularly. Diuretics should be titrated to remove no more than 1 L of fluid daily, so body weight should not fall by more than 1 kg daily to avoid excessive fluid depletion. Sodium and water restriction Restriction of dietary sodium intake is essential to achieve negative sodium balance and a few patients can be managed satisfactorily by this alone. Restriction of sodium intake to 100 mmol/24 hrs (‘no added salt diet’) is usually adequate. Drugs containing relatively large amounts of sodium, and those promoting sodium retention, such as non-steroidal anti-inflammatory drugs (NSAIDs), must be avoided (Box 22.23). Restriction of water intake to 1.0–1.5 L/24 hrs is necessary only if the plasma sodium falls below 125 mmol/L. of the kallikrein–kinin system (Fig. 22.16). These systems tend to normalise arterial pressure but produce salt and water retention. In this setting, the combination of splanchnic arterial vasodilatation and portal hypertension alters intestinal capillary permeability, promoting accumulation of fluid within the peritoneum. Investigations Ultrasonography is the best means of detecting ascites, particularly in the obese and those with small volumes of fluid. Paracentesis (if necessary under ultrasonic guidance) can be used to obtain ascitic fluid for analysis. The appearance of ascitic fluid may point to the underlying cause (Box 22.22). Pleural effusions are found in about 10% of patients, usually on the right side (hepatic hydrothorax); most are small and identified only on chest X-ray, but occasionally a massive hydrothorax occurs. Pleural effusions, particularly those on the left side, should not be assumed to be due to the ascites. Measurement of the protein concentration

and the serum– ascites albumin gradient (SAAG) can be a useful tool to distinguish ascites of different aetiologies. Cirrhotic patients typically develop ascites with a low protein concentration ('transudate'; protein concentration < 25 g/L (2.5 g/dL)) and relatively few cells. In up to 30% of patients, however, the total protein concentration is > 30 g/L (3.0 g/dL). In these cases, it is useful to calculate the SAAG by subtracting the concentration of the ascites fluid albumin from the serum albumin. A gradient of > 11 g/L (1.1 g/dL) is 96% predictive that ascites is due to portal hypertension. Venous outflow obstruction due to cardiac failure or hepatic venous outflow obstruction can also cause a transudative ascites, as Fig. 22.16 Pathogenesis of ascites. Ascites Transudation of fluid ↓ Oncotic pressure Portal hypertension Reduced aldosterone metabolism Aldosterone Reduced renal blood flow Under-filling of circulation Activation of renin–angiotensin system Splanchnic vasodilatation Reduced albumin Salt and water retention Lymph formation exceeds lymph return Cirrhosis *To calculate the serum–ascites albumin gradient (SAAG). 22.22 Ascitic fluid: appearance and analysis Cause/appearance • Cirrhosis: clear, straw-coloured or light green • Malignant disease: bloody • Infection: cloudy • Biliary communication: heavy bile staining • Lymphatic obstruction: milky-white (chylous) Useful investigations • Total albumin (plus serum albumin) and protein* • Amylase • Neutrophil count • Cytology • Microscopy and culture

 1 month). There is usually no proteinuria, a urine sodium excretion of less than 10 mmol/24 hrs and a urine/plasma osmolarity ratio of more than 1.5. Other non-functional causes of renal failure must be excluded before the diagnosis is made. Treatment consists of albumin infusions in combination with terlipressin (or octreotide and midodrine where terlipressin is not approved for use) and is effective in about two-thirds of patients. Haemodialysis should not be used routinely because it does not improve the outcome. Patients who survive should be considered for liver transplantation, which, along with TIPSS, is an effective treatment in appropriate patients. Type 2 hepatorenal syndrome This usually occurs in patients with refractory ascites, is characterised by a moderate and stable increase in serum creatinine, and has a better prognosis. Spontaneous bacterial peritonitis Spontaneous bacterial peritonitis (SBP) may present with abdominal pain, rebound tenderness, absent bowel sounds and fever in a patient with obvious features of cirrhosis and ascites. Abdominal signs are mild or absent in about one-third of patients, and in these individuals hepatic encephalopathy and fever are the main features. Diagnostic paracentesis may show cloudy fluid, and an ascites neutrophil count of > 250 × 106/L almost invariably indicates infection. The source of infection cannot usually be determined, but most organisms isolated are of enteric origin and Escherichia coli is the most frequently found. Ascitic culture in blood culture bottles gives the highest yield of organisms. SBP needs to be differentiated from other intra-abdominal emergencies, and the finding of multiple organisms on culture should arouse suspicion of a perforated viscus. Treatment should be started immediately with broad-spectrum antibiotics, such as cefotaxime or piperacillin/tazobactam). Recurrence of SBP is common but may be reduced with prophylactic quinolones, such as norfloxacin or ciprofloxacin. Prophylactic antibiotics reduce the incidence of SBP and improve survival in cirrhotic patients with gastrointestinal bleeding. In patients with a previous episode of SBP and continued ascites,

norfloxacin (400 mg/day) prevents recurrence. Prognosis Only 10–20% of patients survive for 5 years from the first appearance of ascites due to cirrhosis. The outlook is not universally poor, however, and is best in those with well-maintained liver function and a good response to therapy. The prognosis is also better when a treatable cause for the underlying cirrhosis is present or when a precipitating cause for ascites, such as excess salt intake, is found. The mortality at 1 year is 50% following the first episode of bacterial peritonitis. Hepatic encephalopathy Hepatic encephalopathy is a neuropsychiatric syndrome caused by liver disease. As it progresses, delirium is followed by coma. Simple delirium needs to be differentiated from delirium tremens and Wernicke's encephalopathy, and coma from subdural haematoma, which can occur in alcoholics after a fall (Box 22.24). Features include changes of intellect, personality, emotions and consciousness, with or without neurological signs. The degree of encephalopathy can be graded from 1 to 4, depending on these features, and this is useful in assessing response to therapy (see Box 22.9). When an episode develops acutely, a precipitating factor may be found (Box 22.25). The earliest features are very Diuretics Most patients require diuretics in addition to sodium restriction. Spironolactone (100–400 mg/day) is the first-line drug because it is a powerful aldosterone antagonist; it can, however, cause painful gynaecomastia and hyperkalaemia, in which case amiloride (5–10 mg/day) can be substituted. Some patients also require loop diuretics, such as furosemide, but these can lead to fluid and electrolyte imbalance and renal dysfunction. Diuresis may be improved if patients are rested in bed, perhaps because renal blood flow increases in the horizontal position. Patients who do not respond to doses of 400 mg spironolactone and 160 mg furosemide, or who are unable to tolerate these doses due to hyponatraemia or renal impairment, are considered to have refractory or diuretic-resistant ascites and should be treated by other measures. Paracentesis First-line treatment of refractory ascites is large-volume paracentesis. Paracentesis to dryness is safe, provided the circulation is supported with an intravenous colloid such as human albumin (6–8 g per litre of ascites removed, usually as 100 mL of 20% or 25% human albumin solution (HAS) for every 1.5–2 L of ascites drained) or another plasma expander. Paracentesis can be used as an initial therapy or when other treatments fail. Transjugular intrahepatic portosystemic stent shunt A transjugular intrahepatic portosystemic stent shunt (TIPSS; p. 870) can relieve resistant ascites but does not prolong life; it may be an option where the only alternative is frequent, largevolume paracentesis. TIPSS can be used in patients awaiting liver transplantation or in those with reasonable liver function, but can aggravate encephalopathy in those with poor function. Complications Renal failure Renal failure can occur in patients with ascites. It can be pre-renal and due to vasodilatation from sepsis and/or diuretic therapy, or due to hepatorenal syndrome. Hepatorenal syndrome This occurs in 10% of patients with advanced cirrhosis complicated by ascites. There are two clinical types; both are mediated by renal vasoconstriction due to under-filling of the arterial circulation. Type 1 hepatorenal syndrome This is characterised by progressive oliguria, a rapid rise of the serum creatinine and a very poor prognosis (without treatment, median survival is less than 22.23 Some drugs containing relatively large amounts of sodium or causing sodium retention High sodium content • Alginates • Antacids • Antibiotics • Phenytoin • Effervescent preparations (e.g. aspirin, calcium, paracetamol) • Sodium valproate Sodium retention • Carbenoxolone • Glucocorticoids • Metoclopramide • Non-steroidal antiinflammatory drugs • Oestrogens

Some degree of liver failure is a key factor, as portosystemic shunting of blood alone hardly ever causes encephalopathy. The ‘neurotoxins’ causing encephalopathy are unknown but are thought to be mainly nitrogenous substances produced in the gut, at least in part by bacterial action. These substances are normally metabolised by the healthy liver and excluded from the systemic circulation. Ammonia has traditionally been considered an important factor. Recent interest has focused on γ-aminobutyric acid (GABA) as a mediator, along with octopamine, amino acids, mercaptans and fatty acids that can act as neurotransmitters. The brain in cirrhosis may also be sensitised to other factors, such as drugs that can precipitate hepatic encephalopathy (Box 22.25). Disruption of the function of the blood–brain barrier is a feature of acute hepatic failure and may lead to cerebral oedema. Investigations The diagnosis can usually be made clinically; when doubt exists, an electroencephalogram shows diffuse slowing of the normal alpha waves with eventual development of delta waves. The arterial ammonia is usually increased in patients with hepatic encephalopathy. Increased concentrations can, however, occur in the absence of clinical encephalopathy, rendering this investigation of little diagnostic value. Management The principles are to treat or remove precipitating causes (Box 22.25) and to suppress the production of neurotoxins by bacteria in the bowel. Dietary protein restriction is rarely needed and is no longer recommended as first-line treatment because it is unpalatable and can lead to a worsening nutritional state in already malnourished patients. Lactulose (15–30 mL 3 times daily) is increased gradually until the bowels are moving twice daily. It produces an osmotic laxative effect, reduces the pH of the colonic content, thereby limiting colonic ammonia absorption, and promotes the incorporation of nitrogen into bacteria. Rifaximin (400 mg 3 times daily) is a well-tolerated, non-absorbed antibiotic that acts by reducing the bacterial content of the bowel and has been shown to be effective. It can be used in addition, or as an alternative, to lactulose if diarrhoea becomes troublesome. Chronic or refractory encephalopathy is one of the main indications for liver transplantation. Variceal bleeding Acute upper gastrointestinal haemorrhage from gastro-oesophageal varices (Fig. 22.17) is common in chronic liver disease. Investigation mild and easily overlooked, but as the condition becomes more severe, apathy, inability to concentrate, delirium, disorientation, drowsiness, slurring of speech and eventually coma develop. Convulsions sometimes occur. Examination usually shows a flapping tremor (asterixis), inability to perform simple mental arithmetic tasks or to draw objects such as a star (constructional apraxia; p. 847), and, as the condition progresses, hyper-reflexia and bilateral extensor plantar responses. Hepatic encephalopathy rarely causes focal neurological signs; if these are present, other causes must be sought. Fetor hepaticus, a sweet musty odour to the breath, is usually present but is more a sign of liver failure and portosystemic shunting than of hepatic encephalopathy. Rarely, chronic hepatic encephalopathy (hepatocerebral degeneration) gives rise to variable combinations of cerebellar dysfunction, Parkinsonian syndromes, spastic paraplegia and dementia. Pathophysiology Hepatic encephalopathy is thought to be due to a disturbance of brain function provoked by circulating neurotoxins that are normally metabolised by the liver. Accordingly, most affected patients have evidence of liver failure and portosystemic shunting of blood, but the balance between these varies from individual to individual. Fig. 22.17 Varices: endoscopic views. A Oesophageal varices (arrows) at the lower end of the oesophagus. B Gastric varices (arrows). C Appearance of oesophageal varices following application of strangulating bands (band ligation, arrow). B A C 22.25 Factors precipitating hepatic encephalopathy • Drugs (especially sedatives, antidepressants) • Dehydration (including diuretics, paracentesis) • Portosystemic shunting • Infection • Hypokalaemia • Constipation • ↑Protein load (including gastrointestinal bleeding) 22.24 Differential diagnosis of hepatic encephalopathy • Intracranial bleed (subdural/extradural haematoma, p. 1133) • Drug or

alcohol intoxication (pp. 1194 and 1195) • Delirium tremens/alcohol withdrawal (p. 1194) • Wernicke’s encephalopathy (p. 1195) • Primary psychiatric disorders (p. 1191) • Hypoglycaemia (p. 738) • Neurological Wilson’s disease (p. 1115) • Post-ictal state

866 • HEPATOLOGY non-specific and include weakness, fatigue, muscle cramps, weight loss, anorexia, nausea, vomiting and upper abdominal discomfort (Box 22.27). Cirrhosis will occasionally present because of shortness of breath due to a large right pleural effusion, or with hepatopulmonary syndrome (p. 898). Hepatomegaly is common when the cirrhosis is due to alcoholic liver disease or haemochromatosis. Progressive hepatocyte destruction and fibrosis gradually reduce liver size as the disease progresses in other causes of cirrhosis. A reduction in liver size is especially common if the cause is viral hepatitis or autoimmune liver disease. The liver is often hard, irregular and non-tender. Jaundice is mild when it first appears and is due primarily to a failure to excrete bilirubin. Palmar erythema and management are discussed on page 780 and the specific management of variceal bleeding on page 869. Cirrhosis Cirrhosis is characterised by diffuse hepatic fibrosis and nodule formation. It can occur at any age, has significant morbidity and is an important cause of premature death. It is the most common cause of portal hypertension and its complications. Worldwide, the most common causes are chronic viral hepatitis, prolonged excessive alcohol consumption and NAFLD but any condition leading to persistent or recurrent hepatocyte death may lead to cirrhosis. The causes of cirrhosis are listed in Box 22.26. Cirrhosis may also occur in prolonged biliary damage or obstruction, as is found in primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and post-surgical biliary strictures. Persistent blockage of venous return from the liver, such as is found in sinusoidal obstruction syndrome (SOS; veno-occlusive disease) and Budd–Chiari syndrome, can also result in cirrhosis. Pathophysiology Following liver injury, stellate cells in the space of Disse (see Fig. 22.3, p. 849) are activated by cytokines produced by Kupffer cells and hepatocytes. This transforms the stellate cell into a myofibroblast-like cell, capable of producing collagen, pro-inflammatory cytokines and other mediators that promote hepatocyte damage and tissue fibrosis (see Fig. 22.4, p. 849). Cirrhosis is a histological diagnosis (Fig. 22.18). It evolves over years as progressive fibrosis and widespread hepatocyte loss lead to distortion of the normal liver architecture that disrupts the hepatic vasculature, causing portosystemic shunts. These changes usually affect the whole liver but in biliary cirrhosis (e.g. PBC) they can be patchy. Cirrhosis can be classified histologically into: • Micronodular cirrhosis, characterised by small nodules about 1 mm in diameter and typically seen in alcoholic cirrhosis. • Macronodular cirrhosis, characterised by larger nodules of various sizes. Areas of previous collapse of the liver architecture are evidenced by large fibrous scars. Clinical features The clinical presentation is highly variable. Some patients are asymptomatic and the diagnosis is made incidentally at ultrasound or at surgery. Others present with isolated hepatomegaly, splenomegaly, signs of portal hypertension (p. 868) or hepatic insufficiency. When symptoms are present, they are often Fig. 22.18 Histological features in normal liver, hepatic fibrosis and cirrhosis. A Normal liver. Columns of hepatocytes 1–2 cells thick radiate from the portal tracts (PT) to the central veins. The portal tract contains a normal intralobular bile duct branch of the hepatic artery and portal venous radical. B Bridging fibrosis (stained pink, arrows) spreading out around the hepatic vein and single liver cells (pericellular) and linking adjacent portal tracts and hepatic veins. C A cirrhotic liver. The liver architecture is disrupted. The normal arrangement of portal tracts and hepatic veins is now lost and nodules of proliferating hepatocytes are broken up by strands of pink-/orange-staining fibrous tissue (arrows) forming cirrhotic nodules (CN). PT PT PT CN A B C 22.26 Causes of cirrhosis • Alcohol • Chronic viral hepatitis (B or C) • Non-alcoholic fatty

liver disease • Immune: Primary sclerosing cholangitis Autoimmune liver disease • Biliary: Primary biliary cholangitis Secondary biliary cirrhosis Cystic fibrosis • Genetic: Haemochromatosis Wilson's disease α1-antitrypsin deficiency • Cryptogenic (unknown – 15%) • Chronic venous outflow obstruction • Any chronic liver disease

to screen for oesophageal varices (p. 869) and repeated every 2 years. As cirrhosis is associated with an increased risk of hepatocellular carcinoma, patients should be placed under regular surveillance for it (p. 890). Chronic liver failure due to cirrhosis can also be treated by liver transplantation. This currently accounts for about three-quarters of all liver transplants (p. 900).
Prognosis The overall prognosis is poor. Many patients present with advanced disease and/or serious complications that carry a high mortality. Overall, only 25% of patients survive 5 years from diagnosis, but where liver function is good, 50% survive for 5 years and 25% for up to 10 years. The prognosis is more favourable when the underlying cause can be corrected, as in alcohol misuse, haemochromatosis or Wilson's disease. Laboratory tests give only a rough guide to prognosis in individual patients. Deteriorating liver function, as evidenced by jaundice, ascites or encephalopathy, indicates a poor prognosis unless a treatable cause such as infection is found. Increasing bilirubin, falling albumin (or an albumin concentration of < 30 g/L (3.0 g/dL)), marked hyponatraemia (< 120 mmol/L) not due to diuretic therapy, and a prolonged PT are all bad prognostic features (Box 22.29 and Fig. 22.19). The Child–Pugh and MELD (Model for End-stage Liver Disease) scores can be used to assess prognosis. The MELD is more difficult to calculate at the bedside but, unlike the Child–Pugh score, includes renal function; if this is impaired, it is known to be a poor prognostic feature in end-stage disease (Box 22.30). Although these scores give a guide to prognosis, the course of cirrhosis can be unpredictable, as complications such as variceal bleeding may occur. can be seen early in the disease but is of limited diagnostic value, as it occurs in many other conditions associated with a hyper-dynamic circulation, including normal pregnancy, as well as being found in some healthy people. Spider telangiectasias occur and comprise a central arteriole (that occasionally raises the skin surface), from which small vessels radiate. They vary in size from 1 to 2 mm in diameter and are usually found only above the nipples. One or two small spider telangiectasias may be present in about 2% of healthy people and may occur transiently in greater numbers in the third trimester of pregnancy, but otherwise they are a strong indicator of liver disease. Florid spider telangiectasia, gynaecomastia and parotid enlargement are most common in alcoholic cirrhosis. Pigmentation is most striking in haemochromatosis and in any cirrhosis associated with prolonged cholestasis. Pulmonary arteriovenous shunts also develop, leading to hypoxaemia and eventually to central cyanosis, but this is a late feature. Endocrine changes are noticed more readily in men, who show loss of male hair distribution and testicular atrophy. Gynaecomastia is common and can be due to drugs such as spironolactone. Easy bruising becomes more frequent as cirrhosis advances. Splenomegaly and collateral vessel formation are features of portal hypertension, which occurs in more advanced disease (see below). Ascites also signifies advanced disease. Evidence of hepatic encephalopathy also becomes common with disease progression. Non-specific features of chronic liver disease include clubbing of the fingers and toes. Dupuytren's contracture is traditionally regarded as a complication of cirrhosis but the evidence for this is weak. Chronic liver failure develops when the metabolic capacity of the liver is exceeded. It is characterised by the presence of encephalopathy and/ or ascites. The term 'hepatic decompensation' or 'decompensated liver disease' is often used when chronic liver failure occurs.

Other clinical and laboratory features may be present (Box 22.28); these include peripheral oedema, renal failure, jaundice, and hypoalbuminaemia and coagulation abnormalities due to defective protein synthesis. Management This includes treatment of the underlying cause, maintenance of nutrition and treatment of complications, including ascites, hepatic encephalopathy, portal hypertension and varices. Once the diagnosis of cirrhosis is made, endoscopy should be performed 22.27 Clinical features of hepatic cirrhosis • Hepatomegaly (although liver may also be small) • Jaundice • Ascites • Circulatory changes: spider telangiectasia, palmar erythema, cyanosis • Endocrine changes: loss of libido, hair loss Men: gynaecomastia, testicular atrophy, impotence Women: breast atrophy, irregular menses, amenorrhoea • Haemorrhagic tendency: bruises, purpura, epistaxis • Portal hypertension: splenomegaly, collateral vessels, variceal bleeding • Hepatic (portosystemic) encephalopathy • Other features: pigmentation, digital clubbing, Dupuytren's contracture 22.29 Child–Pugh classification of prognosis in cirrhosis Score

Encephalopathy None Mild Marked Bilirubin (µmol/L (mg/dL))* Primary biliary cholangitis/sclerosing cholangitis < 68 (4) 68–170 (4–10)

> 170 (10) Other causes of cirrhosis < 34 (2) 34–50 (2–3) 50 (3) Albumin (g/L (g/dL)) 35 (3.5) 28–35 (2.8–3.5) < 28 (2.8) Prothrombin time (secs prolonged) < 4 4–6 6 Ascites None Mild Marked Add the individual scores: < 7 = Child's A, 7–9 = Child's B, > 9 = Child's C *To convert bilirubin in µmol/L to mg/dL, divide by 17. 22.28 Features of chronic liver failure • Worsening synthetic liver function: Prolonged prothrombin time Low albumin • Jaundice • Portal hypertension • Variceal bleeding • Hepatic encephalopathy • Ascites: Spontaneous bacterial peritonitis Hepatorenal failure

868 • HEPATOLOGY more than 5 cm below the left costal margin in adults but more marked splenomegaly can occur in childhood and adolescence. Collateral vessels may be visible on the anterior abdominal wall and occasionally several radiate from the umbilicus to form a 'caput medusae' (p. 846). Rarely, a large umbilical collateral vessel has a blood flow sufficient to give a venous hum on auscultation (Cruveilhier–Baumgarten syndrome). The most important collateral vessel formation occurs in the oesophagus and stomach, and this can be a source of severe bleeding. Rectal varices also cause bleeding and are often mistaken for haemorrhoids (which are no more common in portal hypertension than in the general population). Fetor hepaticus results from portosystemic shunting of blood, which allows mercaptans to pass directly to the lungs. Portal hypertension Portal hypertension frequently complicates cirrhosis but has other causes. The normal hepatic venous pressure gradient (difference between the wedged hepatic venous pressure (WHVP) and free hepatic venous pressure; see below) is 5–6 mmHg. Clinically significant portal hypertension is present when the gradient exceeds 10 mmHg and risk of variceal bleeding increases beyond a gradient of 12 mmHg. Increased vascular resistance is common. Causes are classified in accordance with the main sites of obstruction to blood flow in the portal venous system (Fig. 22.20). Extrahepatic portal vein obstruction is the usual source of portal hypertension in childhood and adolescence, while cirrhosis causes at least 90% of cases of portal hypertension in adults in developed countries. Schistosomiasis is the most common cause of portal hypertension

worldwide but is infrequent outside endemic areas, such as Egypt (p. 294). Clinical features The clinical features result principally from portal venous congestion and collateral vessel formation (Box 22.31). Splenomegaly is a cardinal finding and a diagnosis of portal hypertension is unusual when splenomegaly cannot be detected clinically or by ultrasonography. The spleen is rarely enlarged Fig. 22.20 Classification of portal hypertension according to site of vascular obstruction. *Most common cause. Note that splenic vein occlusion can also follow pancreatitis, leading to gastric varices. Post-hepatic post-sinusoidal Budd–Chiari syndrome

Intrahepatic post-sinusoidal Veno-occlusive disease

Sinusoidal Cirrhosis* Polycystic liver disease Nodular regenerative hyperplasia Metastatic malignant disease

Intrahepatic pre-sinusoidal Schistosomiasis* Congenital hepatic fibrosis Drugs Vinyl chloride Sarcoidosis

Pre-hepatic pre-sinusoidal Portal vein thrombosis due to sepsis (umbilical, portal pyaemia) or procoagulopathy or secondary to cirrhosis Abdominal trauma including surgery

Splenic vein Spleen Superior mesenteric vein Blood from gut Heart Inferior vena cava Hepatic vein Portal vein Blood flow Liver Blood flow Fig. 22.19 Survival in cirrhosis by Child–Pugh score.

(%)

A B C

1 year 5 years 10 years 22.30 One-year survival rate depending on MELD score MELD score 1-year survival (%) No complications Complications* < 9

10–19

20–29

30–39

MELD from SI units 10 × (0.378 [In serum bilirubin (μmol/L) + 1.12 [In INR] + 0.957 [In serum creatinine (μmol/L)] + 0.643) MELD from non-SI units 3.8 [In serum bilirubin (mg/dL)] + 11.2 [In INR] + 9.3 [In serum creatinine (mg/dL)] + 6.4 In = natural log. To calculate online, go to https://optn.transplant.hrsa .gov/resources/allocation-calculators/meld-calculator/ *‘Complications’ means the presence of ascites, encephalopathy or variceal bleeding. (INR = International Normalised Ratio; MELD = Model for End-stage Liver Disease) 22.31 Complications of portal hypertension • Variceal bleeding: oesophageal, gastric, other (rare) • Congestive gastropathy • Hypersplenism • Ascites • Iron deficiency anaemia • Renal failure • Hepatic encephalopathy

important to remember, though, that bleeding can also result from peptic ulceration, which is more common in patients with liver disease than in the general population. The investigation and management of gastrointestinal bleeding are dealt with in more detail on page 780. Primary prevention of variceal bleeding If non-bleeding varices are identified at endoscopy, β-adrenoceptor antagonist (β-blocker) therapy with propranolol (80–160 mg/ day) or nadolol (40–240 mg/day) is effective in reducing portal venous pressure. Administration of these drugs at doses that reduce the heart rate by 25% has been shown to be effective in the primary prevention of variceal bleeding. In patients with cirrhosis, treatment with propranolol reduces variceal bleeding by 47% (number needed to treat for benefit (NNTB) 10), death from bleeding by 45% (NNTB 25) and overall mortality by 22% (NNTB 16). The efficacy of β-blockers in primary prevention is similar to that of prophylactic banding, which may also be considered, particularly in patients who are unable to tolerate or adhere to β-blocker therapy. Carvedilol, a non-cardioselective vasodilating β-blocker, is also effective and may be better tolerated at doses of 6.25–12.5 mg/day). For these, dose should be titrated, as tolerated, to achieve a heart rate of 50–55 beats/min, if possible. Management of acute variceal bleeding The priority in acute bleeding is to restore the circulation with blood and plasma, not least because shock reduces liver blood flow and causes further deterioration of liver function. The source of bleeding should always be confirmed by endoscopy because about 20% of patients are bleeding from non-variceal lesions. Management of acute variceal bleeding is described in Box 22.32 and illustrated in Figure 22.21. All patients with cirrhosis and gastrointestinal bleeding should receive prophylactic broadspectrum antibiotics, such as oral ciprofloxacin or intravenous cephalosporin or piperacillin/tazobactam, because sepsis is common and treatment with antibiotics improves outcomes. The measures used to control acute variceal bleeding include vasoactive medications (e.g. terlipressin), endoscopic therapy (banding or sclerotherapy), balloon tamponade, TIPSS and, rarely, oesophageal transection. 22.32 Emergency management of bleeding Management Reason Intravenous fluids To replace extracellular volume Vasopressor (terlipressin)* To reduce portal pressure, acute bleeding and risk of early rebleeding Prophylactic antibiotics (cephalosporin IV) To reduce incidence of spontaneous bacterial peritonitis Emergency endoscopy To confirm variceal rather than ulcer bleed Variceal band ligation To stop bleeding Proton pump inhibitor To prevent peptic ulcers Phosphate enema and/or lactulose To prevent hepatic encephalopathy *Caution in patients with significant coronary artery, peripheral or other vascular disease. Ascites occurs as a result of renal sodium retention and portal hypertension that may be due, for example, to post-hepatic causes (hepatic outflow obstruction, p. 862) or cirrhosis. The most important consequence of portal hypertension is variceal bleeding, which commonly arises from oesophageal varices located within 3–5 cm of the gastro-oesophageal junction, or from gastric varices. The size of the varices, endoscopic variceal features such as red spots and stripes, high portal pressure and liver failure are all general factors that predispose to bleeding. Drugs capable of causing mucosal erosion, such as salicylates and NSAIDs, can also precipitate bleeding. Variceal bleeding is often severe, and recurrent if preventative treatment is not given. Pathophysiology Increased portal vascular resistance leads to a gradual reduction in the flow of portal blood to the liver and simultaneously to the development of collateral vessels, allowing portal blood to bypass the liver and enter the systemic circulation directly. Portosystemic shunting occurs, particularly in the gastrointestinal tract and especially the distal oesophagus, stomach and rectum, in the anterior abdominal wall, and in the renal, lumbar, ovarian and testicular vasculature. Stomal varices can also occur at the site of an ileostomy. As collateral vessel formation progresses, more than half of the portal blood flow may be shunted directly to the systemic circulation. Increased portal flow contributes to portal hypertension but is not the

dominant factor. Investigations The diagnosis is often made clinically. Portal venous pressure measurements are rarely needed for clinical assessment or routine management but can be used to confirm portal hypertension and to differentiate sinusoidal and pre-sinusoidal forms. Pressure measurements are made by using a balloon catheter inserted using the transjugular route (via the inferior vena cava into a hepatic vein and then hepatic venule) to measure the WHVP. This is an indirect measurement of portal vein pressure. Thrombocytopenia is common due to hypersplenism, and platelet counts are usually in the region of 100 × 109/L; values below 50 × 109/L are uncommon. Leucopenia occurs occasionally but anaemia is seldom attributed directly to hypersplenism; if anaemia is found, a source of bleeding should be sought. Endoscopy is the most useful investigation to determine whether gastro-oesophageal varices are present (see Fig. 22.17). Once the diagnosis of cirrhosis is made, endoscopy should be performed to screen for oesophageal varices (and repeated every 2 years). Ultrasonography often shows features of portal hypertension, such as splenomegaly and collateral vessels, and can sometimes indicate the cause, such as liver disease or portal vein thrombosis. CT and magnetic resonance angiography can identify the extent of portal vein clot and are used to identify hepatic vein patency. Management Acute upper gastrointestinal haemorrhage from gastrooesophageal varices is a common manifestation of chronic liver disease. In the presence of portal hypertension, the risk of a variceal bleed occurring within 2 years varies from 7% for small varices up to 30% for large varices. The mortality following a variceal bleed has improved to around 15% overall but is still about 45% in those with poor liver function (i.e. Child–Pugh C). The management of portal hypertension is largely focused on the prevention and/or control of variceal haemorrhage. It is

870 • HEPATOLOGY Regular follow-up endoscopy is required to identify and treat any recurrence of varices. Band ligation has fewer side-effects than sclerotherapy, a technique in which varices are injected with a sclerosing agent, and has largely replaced it. Banding is best suited to the treatment of oesophageal varices. It is associated with a lower risk of oesophageal perforation or stricturing than sclerotherapy. Prophylactic acid suppression with proton pump inhibitors reduces the risk of secondary bleeding from bandinginduced ulceration. In the case of gastric fundal varices, banding is less effective and so endoscopic therapy relies on injection of agents such as thrombin or cyanoacrylate glue directly into the varix to induce thrombosis. Although highly effective, cyanoacrylate injection treatment may be complicated by ‘glue embolism’ to the lungs. Active bleeding may make endoscopic therapy difficult. Protection of the patient’s airway with endotracheal intubation aids the endoscopist, facilitating therapy and significantly reducing the risk of pulmonary aspiration. Balloon tamponade This technique employs a Sengstaken– Blakemore tube, which consists of two balloons that exert pressure in the fundus of the stomach and in the lower oesophagus, respectively (Fig. 22.22). Additional lumens allow contents to be aspirated from the stomach and from the oesophagus above the oesophageal balloon. This technique may be used in the event of life-threatening haemorrhage if early endoscopic therapy is not available or is unsuccessful. Endotracheal intubation prior to tube insertion reduces the risk of pulmonary aspiration. The tube should be passed through the mouth and its presence in the stomach should be checked by auscultating the upper abdomen while injecting air and by confirming with radiology. The safest technique is Pharmacological reduction of portal venous pressure Terlipressin is a synthetic vasopressin analogue that, in contrast to vasopressin, can be given by intermittent injection rather than continuous infusion. It reduces portal blood flow and/or intrahepatic resistance and hence brings down portal pressure. It lowers mortality in the setting of acute variceal bleeding. The dose of terlipressin is 2 mg IV 4 times daily until bleeding stops, and then 1 mg 4 times daily

for up to 72 hours. Caution is needed in patients with severe ischaemic heart disease or peripheral vascular disease because of the drug's vasoconstrictor properties. In countries where terlipressin is not available, octreotide is a frequently used alternative. Variceal ligation ('banding') and sclerotherapy This is the most widely used initial treatment and is undertaken, if possible, at the time of diagnostic endoscopy (see Fig. 22.17C). It stops variceal bleeding in 80% of patients and can be repeated if bleeding recurs. Band ligation involves the varices being sucked into a cap placed on the end of the endoscope, allowing them to be occluded with a tight rubber band. The occluded varix subsequently sloughs with variceal obliteration. Banding is repeated every 2–4 weeks until all varices are obliterated. Fig. 22.22 Sengstaken–Blakemore tube. Oesophageal balloon Oesophageal aspirate Traction Gastric balloon (clamped) Gastric aspirate Gastric balloon (inflated with 200–250 mL of air) Oesophageal balloon (deflated) Fig. 22.21 Management of acute bleeding from oesophageal varices. (TIPSS = transjugular intrahepatic portosystemic stent shunt) Start IV terlipressin and antibiotic prophylaxis Suspected variceal haemorrhage Varices present? Urgent upper gastrointestinal endoscopy Yes Endoscopic therapy (variceal banding, sclerotherapy) Haemostasis? No Stop terlipressin (treat as for nonvariceal haemorrhage) Yes Continue terlipressin to 72 hrs Introduce β-blocker as secondary prophylaxis Enter patient into endoscopic banding programme to obliterate varices No Further endoscopic therapy or Balloon tamponade or Emergency TIPSS

Fig. 22.23 Transjugular intrahepatic portosystemic stent shunt (TIPSS). X-ray showing placement of a TIPSS within the portal vein (PV), allowing blood to flow from the portal vein into the hepatic vein (HV) and then the inferior vena cava (IVC). IVC HV PV Secondary prevention of variceal bleeding Beta-blockers are used as a secondary measure to prevent recurrent variceal bleeding. Following successful endoscopic therapy, patients should be entered into an oesophageal banding programme with repeated sessions of therapy at 12–24-week intervals until the varices are obliterated. In selected individuals, TIPSS may also be considered in this setting. Congestive 'portal hypertensive' gastropathy Long-standing portal hypertension causes chronic gastric congestion, which is recognisable at endoscopy as multiple areas of punctate erythema ('portal hypertensive gastropathy' or 'snakeskin gastropathy'). Rarely, similar lesions occur more distally in the gastrointestinal tract. These areas may become eroded, causing bleeding from multiple sites. Acute bleeding can occur but repeated minor bleeding causing iron deficiency anaemia is more common. Anaemia may be prevented by oral iron supplements but repeated blood transfusions can become necessary. Reduction of the portal pressure using propranolol (80–160 mg/day) is the best initial treatment. If this is ineffective, a TIPSS procedure can be undertaken. Infections and the liver The liver may be subject to a number of different infections. These include hepatotropic viral infections and bacterial and protozoal infections. Each has specific clinical features and requires targeted therapies. Viral hepatitis This must be considered in anyone presenting with hepatitic liver blood tests (high transaminases). The causes are listed in Box 22.33. All these viruses cause illnesses that have similar clinical and pathological features and are frequently anicteric or even asymptomatic. They differ in their tendency to cause acute and chronic infections. The features of the major hepatitis viruses are shown in Box 22.34. Therapeutic developments for viral hepatitis, in particular hepatitis C, are evolving very rapidly, with several new classes of drugs entering clinical practice. Clinical features of acute infection A non-specific prodromal illness characterised by headache, myalgia, arthralgia, nausea and anorexia usually precedes the development of jaundice

by a few days to 2 weeks. Vomiting and diarrhoea may follow and abdominal discomfort is common. to inflate the balloon in the stomach under direct endoscopic vision. Gentle traction is essential to maintain pressure on the varices. Initially, only the gastric balloon should be inflated, with 200–250 mL of air, as this will usually control bleeding. Inflation of the gastric balloon must be stopped if the patient experiences pain because inadvertent inflation in the oesophagus can cause oesophageal rupture. If the oesophageal balloon needs to be used because of continued bleeding, it should be deflated for about 10 minutes every 3 hours to avoid oesophageal mucosal damage. Pressure in the oesophageal balloon should be monitored with a sphygmomanometer and should not exceed 40 mmHg. Balloon tamponade will almost always stop oesophageal and gastric fundal variceal bleeding but is only a bridge to more definitive therapy. Self-expanding removable oesophageal stents are a new alternative in patients with bleeding oesophageal, but not gastric, varices. TIPSS This technique uses a stent placed between the portal vein and the hepatic vein within the liver to provide a portosystemic shunt and therefore reduce portal pressure (Fig. 22.23). It is carried out under radiological control via the internal jugular vein; prior patency of the portal vein must be determined angiographically, coagulation deficiencies may require correction with fresh frozen plasma, and antibiotic cover is provided. Successful shunt placement stops and prevents further variceal bleeding, and is an effective treatment for both oesophageal and gastric varices. Further bleeding necessitates investigation and treatment (e.g. angioplasty) because it is usually associated with shunt narrowing or occlusion. Hepatic encephalopathy may occur following TIPSS and is managed by reducing the shunt diameter. Although TIPSS is associated with less rebleeding than endoscopic therapy, survival is not improved. Portosystemic shunt surgery Surgery prevents recurrent bleeding but carries a high mortality and often leads to encephalopathy. In practice, portosystemic shunts are now reserved for when other treatments have not been successful and are offered only to patients with good liver function. Oesophageal transection Rarely, surgical transection of the varices may be performed as a last resort when bleeding cannot be controlled by other means but operative mortality is high. 22.33 Causes of viral hepatitis Common • Hepatitis A • Hepatitis B ± hepatitis D • Hepatitis C • Hepatitis E Less common • Cytomegalovirus • Epstein–Barr virus Rare • Herpes simplex • Yellow fever

872 • HEPATOLOGY Hepatitis A The hepatitis A virus (HAV) belongs to the picornavirus group of enteroviruses. HAV is highly infectious and is spread by the faecal–oral route. Infected individuals, who may be asymptomatic, excrete the virus in faeces for about 2–3 weeks before the onset of symptoms and then for a further 2 weeks or so. Infection is common in children but often asymptomatic, and so up to 30% of adults will have serological evidence of past infection but give no history of jaundice. Infection is also more common in areas of overcrowding and poor sanitation. In occasional outbreaks, water and shellfish have been the vehicles of transmission. In contrast to hepatitis B, a chronic carrier state does not occur. Investigations Only one HAV antigen has been found and infected people make an antibody to this antigen (anti-HAV). Anti-HAV is important in diagnosis, as HAV is present in the blood only transiently during the incubation period. Excretion in the stools occurs for only 7–14 days after the onset of the clinical illness and the virus cannot be grown readily. Anti-HAV of the IgM type, indicating a primary immune response, is already present in the blood at the onset of the clinical illness and is diagnostic of an acute HAV infection. Titres of this antibody fall to low levels within about 3 months of recovery. Anti-HAV of the IgG type is of no diagnostic value, as HAV infection is common and this antibody persists for years after infection, but it can be used as a marker of previous HAV infection. Its presence indicates immunity to HAV. Management Infection in the community is best prevented by improving social conditions,

especially overcrowding and poor sanitation. Individuals can be given substantial protection from infection by active immunisation with an inactivated virus vaccine. Immunisation should be considered for individuals with chronic hepatitis B or C infections. Immediate protection can be provided by immune serum globulin if this is given soon after exposure to the virus. The protective effect of immune serum globulin is attributed to its anti-HAV content. Immunisation should be Dark urine and pale stools may precede jaundice. There are usually few physical signs. The liver is often tender but only minimally enlarged. Occasionally, mild splenomegaly and cervical lymphadenopathy are seen. These features are more frequent in children or those with Epstein–Barr virus (EBV) infection. Symptoms rarely last longer than 3–6 weeks. Complications may occur but are rare (Box 22.35). Investigations A hepatitic pattern of LFTs develops, with serum transaminases typically between 200 and 2000 U/L in an acute infection (usually lower and fluctuating in chronic infections). The plasma bilirubin reflects the degree of liver damage. The ALP rarely exceeds twice the upper limit of normal. Prolongation of the PT indicates the severity of the hepatitis but rarely exceeds 25 seconds, except in rare cases of acute liver failure. The white cell count is usually normal with a relative lymphocytosis. Serological tests confirm the aetiology of the infection. Management Most individuals do not need hospital care. Drugs such as sedatives and narcotics, which are metabolised in the liver, should be avoided. No specific dietary modifications are required. Alcohol should not be taken during the acute illness. Elective surgery should be avoided in cases of acute viral hepatitis, as there is a risk of post-operative liver failure. Liver transplantation is very rarely indicated for acute viral hepatitis complicated by liver failure, but is commonly performed for complications of cirrhosis resulting from chronic hepatitis B and C infection. 22.34 Features of the main hepatitis viruses Hepatitis A Hepatitis B Hepatitis C Hepatitis D Hepatitis E Virus Group Enterovirus Hepadnavirus Flavivirus Incomplete virus Calicivirus Nucleic acid RNA DNA RNA RNA RNA Size (diameter) 27 nm 42 nm 30–38 nm 35 nm 27 nm Incubation (weeks) 2–4 4–20 2–26 6–9 3–8 Spread* Faeces Yes No No No Yes Blood Uncommon Yes Yes Yes No Saliva Yes Yes Yes Unknown Unknown Sexual Uncommon Yes Uncommon Yes Unknown Vertical No Yes Uncommon Yes No Chronic infection No Yes Yes Yes No (except immune- compromised) Prevention Active Vaccine Vaccine No Prevented by hepatitis B vaccination No Passive Immune serum globulin Hyperimmune serum globulin No No *All body fluids are potentially infectious, although some (e.g. urine) are less infectious than others. 22.35 Complications of acute viral hepatitis • Acute liver failure • Cholestatic hepatitis (hepatitis A) • Aplastic anaemia • Chronic liver disease and cirrhosis (hepatitis B and C) • Relapsing hepatitis

evident in the absence of a significant innate or inflammatory response. • Finally, very high loads of antigen may lead to so-called ‘exhaustion’ of cellular immune responses. The state of tolerance is not permanent, however, and may be reversed as a result of therapy, or through spontaneous changes in innate responses, such as interferon alpha (IFN-α) and NK cells, accompanied by host-mediated immunopathology. Chronic hepatitis can lead to cirrhosis or hepatocellular carcinoma, usually after decades of infection (Fig. 22.25). Chronic HBV infection is a dynamic process that can be divided into five phases (Box 22.37); these are not necessarily sequential, however, and not all patients will go through all phases. It is important to remember that the virus is not directly cytotoxic to cells; rather, it is an immune response to viral antigens displayed on infected hepatocytes that initiates liver injury. This explains why there may be very high levels of viral replication but little hepatocellular damage during the ‘immune-tolerant’ phase. Investigations

Serology HBV contains several antigens to which infected persons can make immune responses (Fig. 22.26); these antigens and their antibodies are important in identifying HBV infection (Boxes 22.37 and 22.38), although the widespread availability of polymerase chain reaction (PCR) techniques to measure viral DNA levels in peripheral blood means that longitudinal monitoring is now also frequently guided by direct assessment of viral load. Hepatitis B surface antigen Hepatitis B surface antigen (HBsAg) is an indicator of active infection, and a negative test for HBsAg makes HBV infection very unlikely. In acute liver failure from hepatitis B, the liver damage is mediated by viral clearance and so HBsAg is negative, with evidence of recent infection provided by the presence of hepatitis B core IgM. HBsAg appears in the blood late in the incubation period but before the prodromal phase of acute type B hepatitis; it may be present for a few days only, disappearing even before jaundice has developed, but usually lasts for 3–4 weeks and can persist for up to 5 months. The persistence of HBsAg for longer than 6 months indicates chronic infection. Antibody to HBsAg (anti-HBs) usually appears after about 3–6 months and persists for many years or perhaps permanently. Anti-HBs implies either a previous infection, in which case anti-HBc (see below) is usually also present, or previous vaccination, in which case anti-HBc is not present. Hepatitis B core antigen Hepatitis B core antigen (HBcAg) is not found in the blood, but antibody to it (anti-HBc) appears early considered for those at particular risk, such as close contacts of HAV-infected patients, the elderly, those with other major disease and perhaps pregnant women. Immune serum globulin can be effective in an outbreak of hepatitis, in a school or nursery, as injection of those at risk prevents secondary spread to families. People travelling to endemic areas are best protected by vaccination. Acute liver failure is rare in hepatitis A (0.1%) and chronic infection does not occur. Infection in patients with chronic liver disease, however, may cause serious or life-threatening disease. In adults, a cholestatic phase with elevated ALP levels may complicate infection. There is no role for antiviral drugs in the therapy of HAV infection. Hepatitis B The hepatitis B virus consists of a core containing DNA and a DNA polymerase enzyme needed for virus replication. The core of the virus is surrounded by surface protein (Fig. 22.24). The virus, also called a Dane particle, and an excess of its surface protein (known as hepatitis B surface antigen, HBsAg) circulate in the blood. Humans are the only source of infection. Hepatitis B is one of the most common causes of chronic liver disease and hepatocellular carcinoma worldwide. Approximately one-third of the world’s population have serological evidence of past or current infection with hepatitis B and approximately 350–400 million people are chronic HBsAg carriers. Hepatitis B may cause an acute viral hepatitis; however, acute infection is often asymptomatic, particularly when acquired at birth. Many individuals with chronic hepatitis B are also asymptomatic. The risk of progression to chronic liver disease depends on the source and timing of infection (Box 22.36). Vertical transmission from mother to child in the perinatal period is the most common cause of infection worldwide and carries the highest risk of ongoing chronic infection. In this setting, adaptive immune responses to HBV may be absent initially, with apparent immunological tolerance. Several mechanisms contribute towards this: • Firstly, the introduction of antigen in the neonatal period is tolerogenic. • Secondly, the presentation of such antigen within the liver, as described above, promotes tolerance; this is particularly Fig. 22.24 Schematic diagram of the hepatitis B virus. Hepatitis B surface antigen (HBsAg) is a protein that makes up part of the viral envelope. Hepatitis B core antigen (HBcAg) is a protein that makes up the capsid or core part of the virus (found in the liver but not in blood). Hepatitis B e antigen (HBeAg) is part of the HBcAg that can be found in the blood and indicates infectivity. HBV-DNA HBV-DNA polymerase HBsAg HBcAg HBeAg (blood) 22.36 Source of hepatitis B infection and risk of chronic infection Horizontal transmission (10%) • Injection drug use • Infected unscreened blood products •

Tattoos/acupuncture needles • Sexual transmission • Close living quarters/playground play as a toddler (may contribute to high rate of horizontal transmission in Africa) Vertical transmission (90%) • Hepatitis B surface antigen (HBsAg)-positive mother

874 • HEPATOLOGY Hepatitis B e antigen Hepatitis B e antigen (HBeAg) is an indicator of viral replication. In acute hepatitis B it may appear only transiently at the outset of the illness; its appearance is followed by the production of antibody (anti-HBe). The HBeAg reflects active replication of the virus in the liver. in the illness and rapidly reaches a high titre, which subsides gradually but then persists. Anti-HBc is initially of IgM type, with IgG antibody appearing later. Anti-HBc (IgM) can sometimes reveal an acute HBV infection when the HBsAg has disappeared and before anti-HBs has developed (see Fig. 22.26 and Box 22.38). Fig. 22.25 Natural history of chronic hepatitis B virus (HBV) infection. There is an initial immunotolerant phase with high levels of virus and normal liver biochemistry. An immunological response to the virus then occurs, with elevation in serum transaminases, which causes liver damage: chronic hepatitis. If this response is sustained over many years and viral clearance does not occur promptly, chronic hepatitis may result in cirrhosis. In individuals with a successful immunological response, viral load falls, HBe antibody (HBeAg) develops and there is no further liver damage. Some individuals may subsequently develop HBV-DNA mutants that escape from immune regulation, and viral load again rises with further chronic hepatitis. Mutations in the core protein result in the virus's inability to secrete HBe antigen despite high levels of viral replication; such individuals have HBeAg-negative chronic hepatitis. (ALT = alanine aminotransferase; AST = aspartate aminotransferase) HBeAg-positive HBeAg-negative Viral load HBV-tolerant HBV clearance Latent phase HBV mutant Liver transaminases ALT/AST Time (years) Chronic infection Liver histology Normal Chronic hepatitis Minimal inflammation Chronic hepatitis Cirrhosis Hepatocellular carcinoma 22.37 The five phases of chronic hepatitis B virus (HBV) infection Phase HBsAg HBeAg Anti-HBe Ab Viral load ALT Histology Notes 'Immune-tolerant' phase + + – +++ Normal/ low Normal/minimal necroinflammation Prolonged in perinatally infected individuals; may be short or absent if infected as an adult. High viral load and so very infectious 'Immune-reactive' HBeAg-positive chronic hepatitis phase + + – ++ Raised Moderate/severe necroinflammation May last weeks or years. High risk of cirrhosis or HCC if prolonged. Increased chance of spontaneous loss of HBeAg with seroconversion to anti-HBe antibody-positive state 'Inactive carrier' phase + – + –/+ Normal Normal/minimal necroinflammation Low risk of cirrhosis or HCC in majority HBeAg-negative chronic hepatitis phase + – + Fluctuating +/++ Raised/ fluctuating Moderate/severe necroinflammation May represent late immune reactivation or presence of 'pre-core mutant' HBV. High risk of cirrhosis or HCC HBsAg-negative phase – – + –/± Normal Normal Ultrasensitive techniques may detect low-level HBV even after HBsAg loss (HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma)

affected are classified as having e antigen-negative chronic hepatitis. They respond differently to antiviral drugs from those with classical e antigen-positive chronic hepatitis. Measurement of viral load is important in monitoring antiviral therapy and identifying patients with pre-core mutants. Specific HBV genotypes (A–H) can also be identified using PCR. In some settings, these may be useful in guiding therapy, as genotype A tends to respond better to pegylated interferon-alfa compared to genotypes C and D. Management of acute hepatitis B Treatment is supportive with

monitoring for acute liver failure, which occurs in less than 1% of cases. There is no definitive evidence that antiviral therapy reduces the severity or duration of acute hepatitis B. Full recovery occurs in 90–95% of adults following acute HBV infection. The remaining 5–10% develop a chronic hepatitis B infection that usually continues for life, although later recovery occasionally occurs. Infection passing from mother to child at birth leads to chronic infection in the child in 90% of cases and recovery is rare. Chronic infection is also common in immunodeficient individuals, such as those with Down's syndrome or human immunodeficiency virus (HIV) infection. Fulminant liver failure due to acute hepatitis B occurs in less than 1% of cases. Recovery from acute HBV infection occurs within 6 months and is characterised by the appearance of antibody to viral antigens. Persistence of HBeAg beyond this time indicates chronic infection. Combined HBV and hepatitis delta virus (HDV) infection causes more aggressive disease. Management of chronic hepatitis B Treatments are still limited, as no drug is consistently able to eradicate hepatitis B infection completely (i.e. render the Chronic HBV infection (see below) is marked by the presence of HBsAg and anti-HBc (IgG) in the blood. Usually, HBeAg or anti-HBe is also present; HBeAg indicates continued active replication of the virus in the liver. The absence of HBeAg usually implies low viral replication; the exception is HBeAg-negative chronic hepatitis B (also called 'pre-core mutant' infection, discussed below), in which high levels of viral replication, serum HBV-DNA and hepatic necroinflammation are seen, despite negative HBeAg. Viral load and genotype HBV-DNA can be measured by PCR in the blood. Viral loads are usually in excess of 105 copies/mL in the presence of active viral replication, as indicated by the presence of e antigen. In contrast, in individuals with low viral replication, who are HBsAg- and anti-HBe-positive, viral loads are less than 105 copies/mL. The exception is in patients who have a mutation in the pre-core protein, which means they cannot secrete e antigen into serum (Fig. 22.27). Such individuals will be anti-HBe-positive but have a high viral load and often evidence of chronic hepatitis. These mutations are common in the Far East, and those patients Fig. 22.26 Serological responses to hepatitis B virus infection. (anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to HBeAg; anti-HBs = antibody to HBsAg; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; IgM = immunoglobulin M)

Relative amount of product detectable Clinical illness HBeAg HBsAg Anti-HBe Anti-HBs Anti-HBc IgM anti-HBc Time after exposure (months) 22.38 How to interpret the serological tests of acute hepatitis B virus infection Interpretation HBsAg Anti-HBc IgM Anti-HBc IgG Anti-HBs Incubation period + + – – Acute hepatitis Early + + – – Established + + + – Established (occasional) – + + – Convalescence (3–6 months) – ± + ± (6–9 months) – – + + Post-infection – – + ± Immunisation without infection – – – +

- = positive; – = negative; ± = present at low titre or absent. (anti-HBc IgM/IgG = antibody to hepatitis B core antigen of immunoglobulin M/G type; anti-HBs = antibody to HBsAg; HBsAg = hepatitis B surface antigen) Fig. 22.27 The site of hepatitis B virus (HBV)-DNA mutations. HBV-DNA encodes four proteins: a DNA polymerase needed for viral replication (P), a surface protein (S), a core protein (C) and an X protein. The pre-C and C regions encode a core protein and an e antigen. Although mutations in the hepatitis B virus are frequent, certain mutations have important clinical consequences. Pre-C encodes a signal sequence needed for the C protein to be secreted from the liver cell into serum as e antigen. A mutation in the pre-core region leads to a failure of secretion of e antigen into serum, and so individuals have high levels of viral production but no detectable e antigen in the serum. Mutations can also occur in the surface protein and may lead to the failure

of vaccination to prevent infection, since surface antibodies are produced against the native S protein. Mutations also occur in the DNA polymerase during antiviral treatment with lamivudine. Mutations P X S C HBV-DNA pre-S1 pre-S2 pre-C Mutations Mutations

876 • HEPATOLOGY may cause a rise in serum transaminases and precipitate liver failure. Longer-acting pegylated interferons that can be given once weekly have been evaluated in both HBeAg-positive and HBeAg-negative chronic hepatitis. Side-effects are common and include fatigue, depression, irritability, bone marrow suppression and the triggering of autoimmune thyroid disease. Liver transplantation Historically, liver transplantation was contraindicated in hepatitis B because infection often recurred in the graft. The use of post- liver transplant prophylaxis with direct-acting antiviral agents and hepatitis B immunoglobulins has, however, reduced the reinfection rate to 10% and increased 5-year survival to 80%, making transplantation an acceptable treatment option. Prevention Individuals are most infectious when markers of continuing viral replication, such as HBeAg, and high levels of HBV-DNA are present in the blood. HBV-DNA can be found in saliva, urine, semen and vaginal secretions (although urine is not usually considered to be capable of transmitting infection). The virus is about ten times more infectious than hepatitis C, which in turn is about ten times more infectious than HIV. A recombinant hepatitis B vaccine containing HBsAg is available (Engerix) and is capable of producing active immunisation in 95% of normal individuals. The vaccine should be offered to those at special risk of infection who are not already immune, as evidenced by anti-HBs in the blood (Box 22.39). The vaccine is ineffective in those already infected by HBV. Infection can also be prevented or minimised by the intramuscular injection of specific hepatitis B immunoglobulin (HBIg) prepared from blood containing anti-HBs. This should be given within 48 hours, or at most a week, of exposure to infected blood in circumstances likely to cause infection (e.g. needlestick injury, contamination of cuts or mucous membranes). Vaccine can be given together with HBIg (active–passive immunisation). Neonates born to hepatitis B-infected mothers should be immunised at birth and given immunoglobulin. Hepatitis B serology should then be checked at 12 months of age. Co-infection with HIV Around 10% of the HIV-infected population has concurrent HBV and this figure may be as high as 25% in areas where both viruses are prevalent. Up to half of injection drug users with HIV are co-infected with HBV. Co-infection increases the morbidity and mortality compared to either infection alone: there are greater levels of HBV viraemia, faster progression to chronic infection and greater risk of cirrhosis and hepatocellular carcinoma than with HBV infection alone. The immunosuppression that is seen in HIV infection can lead to loss of anti-HBs antibodies, reactivation of infection and a poorer antibody response to HBV vaccination. patient HBsAg-negative). The goals of treatment are HBeAg seroconversion, reduction in HBV-DNA and normalisation of the LFTs. The indication for treatment is a high viral load in the presence of active hepatitis, as demonstrated by elevated serum transaminases and/or histological evidence of inflammation and fibrosis. The oral antiviral agents are more effective in reducing viral loads in patients with e antigen-negative chronic hepatitis B than in those with e antigen-positive chronic hepatitis B, as the pre-treatment viral loads are lower. Most patients with chronic hepatitis B are asymptomatic and develop complications, such as cirrhosis and hepatocellular carcinoma, only after many years (see Fig. 22.25). Cirrhosis develops in 15–20% of patients with chronic HBV over 5–20 years. This proportion is higher in those who are e antigen-positive. Two different types of drug are used to treat hepatitis B: direct-acting nucleoside/nucleotide analogues and pegylated interferon-alfa. Direct-acting nucleoside/nucleotide antiviral agents Orally administered nucleoside/nucleotide antiviral agents are the mainstay of therapy. These act by inhibiting the

reverse transcription of pre-genomic RNA to HBV-DNA by HBV-DNA polymerase but do not directly affect the covalently closed circular DNA (cccDNA) template for viral replication, and so relapse is common if treatment is withdrawn. One major concern is the selection of antiviral-resistant mutations with long-term treatment. This is particularly important with some of the older agents, such as lamivudine, as mutations induced by previous antiviral exposure may also induce resistance to newer agents. Entecavir and tenofovir (see below) are potent antivirals with a high barrier to genetic resistance and so are the most appropriate first-line agents. Lamivudine Although effective, long-term therapy is often complicated by the development of HBV-DNA polymerase mutants (e.g. the 'YMDD variant'), which lead to viral resistance. These occur after approximately 9 months and are characterised by a rise in viral load during treatment. Outside resource-limited settings, this agent is now seldom used for the treatment of HBV but may be used to prevent reactivation of HBV in previously infected, HBsAg-negative patients if they are undergoing chemotherapy. Entecavir and tenofovir Monotherapy with entecavir or tenofovir is substantially more effective than lamivudine in reducing viral load in HBeAg-positive and HBeAg-negative chronic hepatitis. Antiviral resistance mutations occur in only 1–2% after 3 years of entecavir drug exposure. Both drugs have anti-HIV action and so their use as monotherapy is contraindicated in HIV-positive patients, as it may lead to HIV antiviral drug resistance. Current European guidelines advise that the other nucleoside/nucleotide antivirals should not be used as first-line monotherapy due to the induction of viral mutations, unless more potent drugs with a high barrier to resistance are not available or appropriate. Interferon-alfa This is most effective in patients with a low viral load and serum transaminases greater than twice the upper limit of normal, in whom it acts by augmenting a native immune response. In HBeAg-positive chronic hepatitis, 33% lose e antigen after 4–6 months of treatment, compared to 12% of controls. Response rates are lower in HBeAg-negative chronic hepatitis, even when patients are given longer courses of treatment. Interferon is contraindicated in the presence of cirrhosis, as it 22.39 At-risk groups meriting hepatitis B vaccination in low-endemic areas • Parenteral drug users • Men who have sex with men • Close contacts of infected individuals: Newborn of infected mothers Regular sexual partners • Patients on chronic haemodialysis • Patients with chronic liver disease • Medical, nursing and laboratory personnel

Hepatitis C infection is usually identified in asymptomatic individuals screened because they have risk factors for infection, such as previous injecting drug use (Box 22.40), or have incidentally been found to have abnormal liver blood tests. Although most people remain asymptomatic until progression to cirrhosis occurs, fatigue can complicate chronic infection and is unrelated to the degree of liver damage. Hepatitis C is the most common cause of what used to be known as 'non-A, non-B hepatitis'. If hepatitis C infection is left untreated, progression from chronic hepatitis to cirrhosis occurs over 20–40 years. Risk factors for progression include male gender, immunosuppression (such as co-infection with HIV), prothrombotic states and heavy alcohol misuse. Not everyone with hepatitis C infection will necessarily develop cirrhosis but approximately 20% do so within 20 years. Once cirrhosis has developed, the 5- and 10-year survival rates are 95% and 81%, respectively. One-quarter of people with cirrhosis will develop complications within 10 years and, once complications such as ascites develop, the 5-year survival is around 50%. Once cirrhosis is present, 2–5% per year will develop primary hepatocellular carcinoma. Investigations Serology and virology The HCV genome encodes a large polypeptide precursor that is modified

post-translationally to at least ten proteins, including several antigens that give rise to antibodies in an infected person; these are used in diagnosis. It may take 6–12 weeks for antibodies to appear in the blood following acute infection, such as a needlestick injury. In these cases, hepatitis C RNA can be identified in the blood as early as 2–4 weeks after infection. Active infection is confirmed by the presence of serum hepatitis C RNA in anyone who is antibody-positive. Anti-HCV antibodies persist in serum even after viral clearance, whether spontaneous or post-treatment. Molecular analysis There are six common viral genotypes, the distribution of which varies worldwide. Genotype has no effect on progression of liver disease but does affect response to treatment. Genotype 1 is most common in northern Europe and was less easy to eradicate than genotypes 2 and 3 with traditional pegylated interferon alfa-/ribavirin-based treatments. Knowledge of viral genotype still remains relevant in guiding selection of drugs to treat HCV. Liver function tests LFTs may be normal or show fluctuating serum transaminases between 50 and 200 U/L. Jaundice is rare and only usually appears in end-stage cirrhosis. Pregnancy poses particular problems in co-infected patients, with increased risk of perinatal transmission of HBV to the child. Treatment can also be problematic. Several nucleoside analogues have dual antiviral activity and some regimens have been associated with emergence of drug resistance. Co-infection is also associated with diminished response to interferons and increased resistance to lamivudine in some patients. Co-infection should be managed by specialists with expertise in this area and combinations of antiviral agents need to be thought through carefully. Antiviral therapy should be considered for co-infected pregnant women, using drugs with dual activity, e.g. tenofovir with emtricitabine or lamivudine. Globally, there is a need to identify co-infected patients earlier, especially in endemic areas, as well as a need for early effective interventions, particularly in pregnant women, to reduce perinatal transmission. Hepatitis D (Delta virus) The hepatitis D virus (HDV) is an RNA-defective virus that has no independent existence; it requires HBV for replication and has the same sources and modes of spread. It can infect individuals simultaneously with HBV or can superinfect those who are already chronic carriers of HBV. Simultaneous infections give rise to acute hepatitis, which is often severe but is limited by recovery from the HBV infection. Infections in individuals who are chronic carriers of HBV can cause acute hepatitis with spontaneous recovery, and occasionally there is simultaneous cessation of the chronic HBV infection. Chronic infection with HBV and HDV can also occur, and this frequently causes rapidly progressive chronic hepatitis and eventually cirrhosis. HDV has a worldwide distribution. It is endemic in parts of the Mediterranean basin, Africa and South America, where transmission is mainly by close personal contact and occasionally by vertical transmission from mothers who also carry HBV. In non-endemic areas, transmission is mainly a consequence of parenteral drug misuse. Investigations HDV contains a single antigen to which infected individuals make an antibody (anti-HDV). Delta antigen appears in the blood only transiently, and in practice diagnosis depends on detecting anti-HDV. Simultaneous infection with HBV and HDV, followed by full recovery, is associated with the appearance of low titres of anti-HDV of IgM type within a few days of the onset of the illness. This antibody generally disappears within 2 months but persists in a few patients. Super-infection of patients with chronic HBV infection leads to the production of high titres of anti-HDV, initially IgM and later IgG. Such patients may then develop chronic infection with both viruses, in which case anti-HDV titres plateau at high levels. Management Effective management of hepatitis B prevents hepatitis D. Hepatitis C This is caused by an RNA flavivirus. Acute symptomatic infection with hepatitis C is rare. Most individuals are unaware of when they became infected and are identified only when they develop chronic liver disease. Eighty per cent of individuals exposed to the virus become chronically infected and late spontaneous viral clearance is rare. There is no active or passive protection against hepatitis C

virus (HCV). 22.40 Risk factors for the acquisition of chronic hepatitis C infection • Intravenous drug misuse (95% of new cases in the UK) • Unscreened blood products • Vertical transmission (3% risk) • Needlestick injury (3% risk) • Iatrogenic parenteral transmission (e.g. contaminated vaccination needles) • Sharing toothbrushes/razors

878 • HEPATOLOGY Since 2011, new classes of direct-acting antiviral agents (DAAs) have been developed. There are four main classes of DAA, which are defined according to their mechanism of action and therapeutic target (Box 22.41). These compounds are targeted to specific steps in the hepatitis C viral life cycle to disrupt viral replication (Fig. 22.28). Initially, DAAs were added to interferon-/ ribavirin-based regimens; more recently, however, combinations of DAAs have increasingly been used in 'interferon-free' regimens. This maximises treatment efficacy by directly interfering with replication at multiple points in the viral life cycle without exposing patients to the side-effect profile of interferon-alfa therapy. For example, 12 weeks of treatment with oral sofosbuvir plus ledipasvir plus ribavirin can achieve a 99% SVR in treatment-naïve genotype 1 patients. Sofosbuvir plus velpatasvir achieves similar results and is pan-genotypic. Although not without side-effects, DAAs are often orally administered, efficacious and, in general, well tolerated. Liver transplantation should be considered when complications of cirrhosis occur, such as diuretic-resistant ascites. Unfortunately, if the virus is not cleared, hepatitis C will infect the transplanted liver and up to 15% of patients then develop cirrhosis in the liver graft within 5 years of transplantation. This should no longer happen, as modern antiviral therapy post-transplant achieves excellent results. Hepatitis E Hepatitis E is caused by an RNA virus that is endemic in India and the Middle East. Prevalence is now increasing across Asia and Europe, especially south-west France, so it is important to note that infection is no longer seen only in travellers from an endemic area. The clinical presentation and management of hepatitis E are similar to those of hepatitis A. Disease is spread via the faecal–oral route or through contaminated food; the virus is commonly present in uncooked game and pig-liver sausage in southern France, and this may be a route of infection. In most cases, it presents as a self-limiting acute hepatitis and does not usually cause chronic liver disease. There is increasing recognition that hepatitis E may develop into chronic infection, usually in immunocompromised patients and especially in organ-transplant recipients, although this remains uncommon. If treatment is required for chronic infection, agents such as ribavirin may be used. Blood donations are now routinely screened for hepatitis E. Hepatitis E differs from hepatitis A in that infection during pregnancy is associated with the development of acute liver failure, which has a high mortality. In acute infection, IgM antibodies to hepatitis E virus (HEV) are positive. Other forms of viral hepatitis Non-A, non-B, non-C (NANBNC) or non-A–E hepatitis is the term used to describe hepatitis thought to be due to a virus that is not HAV, HBV, HCV or HEV. Other viruses that affect the liver probably exist but the viruses described above now account for the majority of hepatitis infections. Cytomegalovirus and EBV infection causes abnormal LFTs in most patients and occasionally jaundice occurs. Herpes simplex is a rare cause of hepatitis in adults, most of whom are immunocompromised. Herpes simplex virus hepatitis can be very severe in pregnancy. Abnormal LFTs are also common in chickenpox, measles, rubella and acute HIV infection. Liver histology Serum transaminase levels in hepatitis C are a poor predictor of the degree of liver fibrosis and so a liver biopsy may be required to stage the extent of liver damage. The degree of inflammation and fibrosis can be scored histologically. The most common way of doing this in hepatitis C is the Metavir system, which scores fibrosis from 1 to 4, the latter equating to cirrhosis. Recently, non-invasive markers and fibrosis scoring systems have been used routinely, with biopsy being reserved for cases where these give conflicting results. Management

The aim of treatment is to eradicate infection. In recent years, there have been substantial advances, so much so that rates of viral clearance achieved 6 months after finishing treatment (termed sustained virological response, SVR) have risen from less than 40% a decade ago to levels approaching 100% with some of the newer direct-acting antivirals. The infection is cured in more than 99% of patients who achieve an SVR. These newer drugs are extremely expensive, however, and so their use is placing substantial strain on the finite health-care resources of developed countries and has severely limited their availability in resource-poor settings. Until 2011, the treatment of choice was dual therapy with pegylated interferon-alfa, given as a weekly subcutaneous injection, together with oral ribavirin, a synthetic nucleotide analogue. Treatment was long – up to 12 months for genotype 1 infection, and both agents had significant side-effects that limited tolerability: ribavirin induces haemolytic anaemia and is teratogenic, while interferon induces influenza-like symptoms, irritability and depression, all of which can affect quality of life. As already mentioned, efficacy of these agents was poor (12 months' treatment for genotype 1 resulted in only a 40% SVR, rising to an SVR of over 70% for genotypes 2 or 3 after 6 months' treatment). 22.41 Direct-acting antiviral agents for hepatitis C Drug class Therapeutic target Selected drugs Protease inhibitors (PIs) Non-structural viral protein NS3/4A (protease that cleaves the HCV polyprotein) Telaprevir Boceprevir Simeprevir Paritaprevir Grazoprevir Nucleoside polymerase inhibitors (NPIs) Non-structural viral protein NS5B (RNA-dependent RNA polymerase needed for viral replication) Sofosbuvir Non-nucleoside polymerase inhibitors (NNPIs) Non-structural viral protein NS5B (RNA-dependent RNA polymerase needed for viral replication) Dasabuvir NS5A replication complex inhibitors Non-structural viral protein NS5A (assembly of viral replication complex) Daclatasvir Velpatasvir Ledipasvir Ombitasvir Elbasvir Host-targeting antiviral drugs (HTAs) Cyclophilin (pharmacological inhibitor targets host cell functions involved in the HCV life cycle) Alisporivir (HCV = hepatitis C virus)

Liver abscess Liver abscesses are classified as pyogenic, hydatid or amoebic. Pyogenic liver abscess Pyogenic liver abscesses are uncommon but important because they are potentially curable, carry significant morbidity and mortality if untreated, and are easily overlooked. The mortality of liver abscesses is 20–40%; failure to make the diagnosis is the most common cause of death. Older patients and those with multiple abscesses have a higher mortality. Pathophysiology Infection can reach the liver in several ways (Box 22.43). Pyogenic abscesses are most common in older patients and usually result from ascending infection due to biliary obstruction (cholangitis) or contiguous spread from an empyema of the gallbladder. They can also complicate dental sepsis or colonic pathology, e.g. cancer, diverticulitis or inflammatory bowel disease causing portal pyaemia. HIV infection and the liver Several causes of abnormal LFTs occur in HIV infection, as shown in Box 22.42. This topic is discussed in more detail on page 317. Co-infection with HIV and HBV is discussed on page 876. Fig. 22.28 Direct-acting antiviral agents. These compounds are targeted to specific steps in the hepatitis C viral life cycle to disrupt replication. (5′NTR = 5′ non-translated region; HCV = hepatitis C virus; IFN = interferon) 1 Receptor binding and endocytosis 2 Hepatocyte entry 3 Fusion and RNA coating 5 Polyprotein cleaved into functional proteins by protease 6 RNA replication by encoded polymerase 7 Lipoviral particle assembly 8 Transport and release 4 Translation of RNA into protein Endoplasmic reticulum Nucleus Golgi apparatus Metalloprotease Serine protease RNA helicase Transmembrane protein Region encoding polyprotein precursor Non-structural proteins Structural proteins p22 C gp35 E1 gp70 E2 p7 NS1 p8 NS 4A p23 NS2 p27 NS4B

p56/58 NS5A p68 NS5B p70 NS3 5′ NTR 5′ NTR HCV-RNA IFN-resistance protein RNA polymerase Co-factors Envelope glycoproteins Nucleocapsid NS5A inhibitors NS3/4A protease inhibitors NS5B polymerase inhibitors 22.42 Causes of abnormal liver blood tests in HIV infection Hepatitic blood tests • Chronic hepatitis C • Chronic hepatitis B • Antiretroviral drugs • Cytomegalovirus Cholestatic blood tests • Tuberculosis • Atypical mycobacterium • Sclerosing cholangitis due to cryptosporidia

880 • HEPATOLOGY Alcoholic liver disease Alcohol is one of the most common causes of chronic liver disease worldwide, with consumption continuing to increase in many countries. Patients with alcoholic liver disease (ALD) may also have risk factors for other liver diseases (e.g. coexisting NAFLD or chronic viral hepatitis infection), and these may interact to increase disease severity. In the UK, a unit of alcohol contains 8 g of ethanol (Box 22.44). An upper threshold of 14 units/week in women and 21 units/week in men is generally considered safe. Recently, however, Public Health England advice has adopted a more conservative threshold of 14 units/week for both men and women. The risk threshold for developing ALD is variable but begins at 30 g/day of ethanol. There is no clear linear relationship between dose and liver damage, however. For many, consumption of more than 80 g/day, for more than 5 years, is required to confer significant risk of advanced liver disease. The average alcohol consumption of a man with cirrhosis is 160 g/day for over 8 years. Some of the risk factors for ALD are: • Drinking pattern. ALD and alcohol dependence are not synonymous; many of those who develop ALD are not alcohol-dependent and most dependent drinkers have normal liver function. Liver damage is more likely to occur in continuous rather than intermittent or ‘binge’ drinkers, as this pattern gives the liver a chance to recover. It is therefore recommended that people should have at least two alcohol-free days each week. The type of beverage does not affect risk. • Gender. The incidence of ALD is increasing in women, who have higher blood ethanol levels than men after consuming the same amount of alcohol. This may be related to the reduced volume of distribution of alcohol. • Genetics. Alcoholism is more concordant in monozygotic than dizygotic twins. While polymorphisms in the genes involved in alcohol metabolism, such as aldehyde dehydrogenase, may alter drinking behaviour, they have not been linked to ALD. The patatin-like phospholipase domain-containing 3 (PNPLA3) gene, also known as adiponutrin, has been implicated in the pathogenesis of both ALD and NAFLD (p. 883). • Nutrition. Obesity increases the incidence of liver-related mortality by over fivefold in heavy drinkers. Ethanol itself produces 7 kcal/g (29.3 kJ/g) and many alcoholic drinks also contain sugar, which further increases the calorific Abscesses complicating suppurative appendicitis used to be common in young adults but are now rare. Immunocompromised patients are particularly likely to develop liver abscesses. Single lesions are more common in the right liver; multiple abscesses are usually due to infection secondary to biliary obstruction. Escherichia coli and various streptococci, particularly Strep. milleri, are the most common organisms; anaerobes, including streptococci and Bacteroides, can often be found when infection has been transmitted from large bowel pathology via the portal vein, and multiple organisms are present in one-third of patients. Clinical features Patients are generally ill with fever and sometimes rigors and weight loss. Abdominal pain is the most common symptom and is usually in the right upper quadrant, sometimes with radiation to the right shoulder. The pain may be pleuritic in nature. Tender hepatomegaly is found in more than 50% of patients. Mild jaundice may be present, becoming severe if large abscesses cause biliary obstruction. Atypical presentations are common and explain the frequency with which the diagnosis is made only at autopsy. This is a particular problem in patients with gradually developing illnesses or pyrexia of unknown origin without localising features. Necrotic colorectal metastases can be

misdiagnosed as hepatic abscess. Investigations Liver imaging is the most revealing investigation and shows 90% or more of symptomatic abscesses. Needle aspiration under ultrasound guidance confirms the diagnosis and provides pus for culture. A leucocytosis is frequently found, plasma ALP activity is usually increased, and the serum albumin is often low. The chest X-ray may show a raised right diaphragm and lung collapse, or an effusion at the base of the right lung. Blood cultures are positive in 50–80%. Abscesses caused by gut-derived organisms require active exclusion of significant colonic pathology, such as a colonoscopy to exclude colorectal carcinoma. Management Pending the results of culture of blood and pus from the abscess, treatment should be commenced with a combination of antibiotics, such as ampicillin, gentamicin and metronidazole. Aspiration or drainage with a catheter placed in the abscess under ultrasound guidance is required if the abscess is large or if it does not respond to antibiotics. Any associated biliary obstruction and cholangitis require biliary drainage (preferably endoscopically). Surgical abscess drainage is rarely undertaken, although hepatic resection may be indicated for a chronic persistent abscess or ‘pseudotumour’. Hydatid cysts and amoebic liver abscesses These are described on pages 299 and 287. Leptospirosis This is described on page 257. 22.44 Amount of alcohol in an average drink Alcohol type % Alcohol by volume Amount Units* Beer 3.5 568 mL (1 pint)

568 mL (1 pint)

Wine

125 mL

750 mL

‘Alcopops’

330 mL

Sherry 17.5 750 mL

Vodka/rum/gin 37.5 25 mL

Whisky/brandy

700 mL

*1 unit = 8 g. 22.43 Causes of pyogenic liver abscesses • Biliary obstruction (cholangitis) • Haematogenous: Portal vein (intra-abdominal infections) Hepatic artery (bacteraemia) • Direct extension • Trauma: Penetrating or non-penetrating • Infection of liver tumour or cyst

The pathological features of ALD are shown in Box 22.45. In about 80% of patients with severe alcoholic hepatitis, cirrhosis will coexist at presentation. Iron deposition is common and does not necessarily indicate haemochromatosis. Figure 22.30A below shows the histological features of alcoholic liver disease, which are identical to those of non-alcoholic steatohepatitis. Clinical

features ALD has a wide clinical spectrum, ranging from mild abnormalities of LFTs on biochemical testing to advanced cirrhosis. The liver is often enlarged in ALD, even in the presence of cirrhosis. Stigmata of chronic liver disease, such as palmar erythema, are more common in alcoholic cirrhosis than in cirrhosis of other aetiologies. Alcohol misuse may also cause damage of other organs and this should be specifically looked for (see Box 28.22, p. 1194). Three types of ALD are recognised (Box 22.46) but these overlap considerably, as do the pathological changes seen in the liver. Alcoholic fatty liver disease Alcoholic fatty liver disease (AFLD) usually presents with elevated transaminases in the absence of hepatomegaly. It has a good prognosis and steatosis usually disappears after 3 months of abstinence. Alcoholic hepatitis This presents with jaundice and hepatomegaly; complications of portal hypertension may also be present. It has a significantly worse prognosis than AFLD. About one-third of patients die in the acute episode, particularly those with hepatic encephalopathy or a prolonged PT. Cirrhosis often coexists; if not present, it is the likely outcome if drinking continues. Patients with acute alcoholic hepatitis often deteriorate during the first 1–3 weeks in hospital. Even if they abstain, it may take up to 6 months for jaundice to resolve. In patients presenting with jaundice who subsequently abstain, the 3- and 5-year survival is 70%. In contrast, those who continue to drink have 3- and 5-year survival rates of 60% and 34%, respectively. value and may contribute to weight gain. Excess alcohol consumption is frequently associated with nutritional deficiencies that contribute to morbidity. Pathophysiology Alcohol reaches peak blood concentrations after about 20 minutes, although this may be influenced by stomach contents. It is metabolised almost exclusively by the liver via one of two pathways (Fig. 22.29). Approximately 80% of alcohol is metabolised to acetaldehyde by the mitochondrial enzyme, alcohol dehydrogenase. Acetaldehyde is then metabolised to acetyl-CoA and acetate by aldehyde dehydrogenase. This generates NADH from NAD (nicotinamide adenine dinucleotide), which changes the redox potential of the cell. Acetaldehyde forms adducts with cellular proteins in hepatocytes that activate the immune system, contributing to cell injury. The remaining 20% of alcohol is metabolised by the microsomal ethanol-oxidising system (MEOS) pathway. Cytochrome CYP2E1 is an enzyme that oxidises ethanol to acetate. It is induced by alcohol, and during metabolism of ethanol it releases oxygen free radicals, leading to lipid peroxidation and mitochondrial damage. The CYP2E1 enzyme also metabolises acetaminophen, and hence chronic alcoholics are more susceptible to hepatotoxicity from low doses of paracetamol. It is thought that pro-inflammatory cytokines may also be involved in inducing hepatic damage in alcoholic hepatitis, since endotoxin is released into the blood because of increased gut permeability, leading to release of tumour necrosis factor alpha (TNF-α) and interleukin 1 (IL-1), IL-2 and IL-8 from immune cells. All of these cytokines have been implicated in the pathogenesis of liver fibrosis (see Fig. 22.4, p. 849). Fig. 22.29 Factors involved in the pathogenesis of alcoholic liver disease. Alcohol Genetic susceptibility Alcoholic liver disease Acetaldehyde Adducts Gut permeability CYP2E1 Immune system Endotoxin Kupffer cells Inflammation Coexistent disorders, e.g. viral hepatitis haemochromatosis Tumour necrosis factor alpha Interleukin-6 ↑Oxidative stress • Lipid peroxidation • Low glutathione 22.45 Pathological features of alcoholic liver disease • Alcoholic hepatitis: Lipogranuloma Neutrophil infiltration Mallory’s hyaline Pericellular fibrosis • Macrovesicular steatosis • Fibrosis and cirrhosis • Central hyaline sclerosis 22.46 Clinical syndromes of alcoholic liver disease Fatty liver • Asymptomatic abnormal liver biochemistry • Normal/large liver Alcoholic hepatitis • Jaundice • Malnutrition • Hepatomegaly • Features of portal hypertension (e.g. ascites, encephalopathy) Cirrhosis • Stigmata of chronic liver disease • Ascites/varices/ encephalopathy • Large, normal or small liver • Hepatocellular carcinoma

Score

Age < 50

> 50 White cell count (× 109/L) < 15 15 Urea (mmol/L (BUN mg/dl)) < 5 (14) 5 (14) PT ratio < 1.5 1.5–2.0 2.0 Bilirubin (µmol/L (mg/dL)) < 125 (7.4) 125–250 (7.4–14.8) 250 (14.8) A score of ≥ 9 is associated with a 40% 28-day survival, compared to 80% for patients with a score of < 9. (BUN = blood urea nitrogen; PT = prothrombin time) Alcoholic cirrhosis Alcoholic cirrhosis often presents with a serious complication, such as variceal haemorrhage or ascites, and only half of such patients will survive for 5 years from presentation. However, most who survive the initial illness and who become abstinent will survive beyond 5 years. Investigations Investigations aim to establish alcohol misuse, exclude alternative or additional coexistent causes of liver disease, and assess the severity of liver damage. The clinical history from patient, relatives and friends is important to establish alcohol misuse duration and severity. Biological markers, particularly macrocytosis in the absence of anaemia, may suggest and support a history of alcohol misuse. A raised GGT is not specific for alcohol misuse and may also be elevated in the presence of other conditions, including NAFLD. The level may therefore not return to normal with abstinence if chronic liver disease is present, and GGT should not be relied on as an indicator of ongoing alcohol consumption. The presence of jaundice may suggest alcoholic hepatitis. Determining the extent of liver damage often requires a liver biopsy. In alcoholic hepatitis, PT and bilirubin are used to calculate a ‘discriminant function’ (DF), also known as the Maddrey score, which enables the clinician to assess prognosis (PT = prothrombin time; serum bilirubin in µmol/L is divided by 17 to convert to mg/dL): DF Increase in PT Bilirubin mg/dL = ×

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[. (sec)] ( ) 4 6 A value over 32 implies severe liver disease with a poor prognosis and is used to guide treatment decisions (see below). A second scoring system, the Glasgow score, uses the age, white cell count and renal function, in addition to PT and bilirubin, to assess prognosis and has a cut-off of 9 (Box 22.47). Management Cessation of alcohol consumption is the single most important treatment and prognostic factor. Life-long abstinence is the best advice. General health and life expectancy are improved when this occurs, irrespective of the stage of liver disease. Abstinence is even effective at preventing progression, hepatic decompensation and death once cirrhosis is present. Treatment of alcohol dependency is discussed on page 1195. In the acute presentation of ALD it is important to identify and anticipate alcohol withdrawal and Wernicke’s encephalopathy, which need treating in parallel with the liver disease and any complications of cirrhosis. Nutrition Good nutrition is very important, and enteral feeding via a fine-bore nasogastric tube may be needed in severely ill patients. Drug therapy The optimum treatment of severe alcoholic hepatitis (Maddrey’s discriminative score > 32) has been debated for some time. The STOPAH study was a large, multicentre, double-blind, randomised trial to evaluate the relative

merits of glucocorticoids and/or a weak anti-TNF agent (pentoxifylline), alone or in combination. In a cohort of 1103 patients, no significant benefit from pentoxifylline treatment was identified but treatment with prednisolone (40 mg daily for 28 days) led to a modest reduction in short-term mortality, from 17% in placebo-treated patients to 14% in the prednisolone group. These findings were consistent with earlier studies where an improvement in 28-day survival from 52% to 78% is seen when glucocorticoids are given to those with a Glasgow score of more than 9. Neither glucocorticoids nor pentoxifylline improved survival at 90 days or 1 year, however. Sepsis is the main side-effect of glucocorticoids, and existing sepsis and variceal haemorrhage are the main contraindications to their use. If the bilirubin has not fallen 7 days after starting glucocorticoids, the drugs are unlikely to reduce mortality and should be stopped. Liver transplantation The role of liver transplantation in the management of ALD remains controversial. In many centres, ALD is a common indication for liver transplantation. The challenge is to identify patients with an unacceptable risk of returning to harmful alcohol consumption. Many programmes require a 6-month period of abstinence from alcohol before a patient is considered for transplantation. Although this relates poorly to the incidence of alcohol relapse after transplantation, liver function may improve to the extent that transplantation is no longer necessary. The outcome of transplantation for ALD is good and if the patient remains abstinent there is no risk of disease recurrence. Transplantation for alcoholic hepatitis has been thought to have a poorer outcome and is seldom performed due to concerns about recidivism; studies to quantify this are ongoing. Non-alcoholic fatty liver disease Increasingly sedentary lifestyles and changing dietary patterns mean that the prevalence of obesity and insulin resistance has increased worldwide, and so fat accumulation in the liver is a common finding during abdominal imaging studies and on liver biopsy. In the absence of high alcohol consumption (typically, a threshold of < 20 g/day for women and < 30 g/day for men is adopted), this is called non-alcoholic fatty liver disease (NAFLD). NAFLD includes a spectrum of progressive liver disease ranging from fatty infiltration alone (steatosis) to fatty infiltration with inflammation (non-alcoholic steatohepatitis, NASH) and may progress to cirrhosis and primary liver cancer (Fig. 22.30B). NAFLD is considered by many to be the hepatic manifestation of the ‘metabolic syndrome’ (p. 730), as it is strongly associated with obesity, dyslipidaemia, type 2 diabetes and hypertension. Estimates vary between populations, although one large European study found NAFLD to be present in 94% of obese patients

Fig. 22.30 Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). A Features. Rate of progression is determined by environmental (dietary) and genetic factors. B The spectrum of NAFLD. (FA = fatty acid; TGF-β = transforming growth factor beta; TNF-α = tumour necrosis factor alpha; VLDL = very low-density lipoprotein) Fat infiltration > 5% with or without mild inflammation Steatosis + necroinflammation (ballooning, Mallory bodies, megamitochondria) Increasing fibrosis, eventually leading to cirrhosis Steatosis NASH Cirrhosis TNF-α Oxidant stress Endotoxin Immune factors TGF-β Stellate cell activation ↑FA influx ↓FA oxidation ↑FA synthesis ↓VLDL assembly Insulin resistance Metabolic syndrome NAFLD/steatosis NASH A B the liver leads to the development of steatosis. This may be an adaptive response through which hepatocytes store potentially toxic lipids as relatively inert triglyceride. A ‘two-hit’ hypothesis has been proposed to describe the pathogenesis of NAFLD, the ‘first hit’ causing steatosis that then progresses to NASH if a ‘second hit’ occurs. In reality, progression probably follows hepatocellular injury caused by a combination of several different ‘hits’, including: • oxidative stress due to free

radicals produced during fatty acid oxidation • direct lipotoxicity from fatty acids and other metabolites in the liver • endoplasmic reticulum stress • gut-derived endotoxin • cytokine release (TNF-α etc.) and immune-mediated hepatocellular injury. Cellular damage triggers cell death and inflammation, which leads to stellate cell activation and development of hepatic fibrosis that culminates in cirrhosis (Fig. 22.30A). As with many other liver diseases, subtle inter-patient genetic variations and environmental factors interact to determine disease progression. Several genetic modifiers of disease severity have been identified, with PNPLA3 and its product, adiponutrin, being the best validated. This should not be confused with acute fatty liver, which can occur in hepatic mitochondrial cytopathies, e.g. acute fatty liver of pregnancy (p. 1283), or in other situations, e.g. Reye's syndrome (p. 241) or drug toxicity (sodium valproate, tetracyclines), or with bacterial toxins (e.g. Bacillus cereus). In these, defective mitochondrial beta-oxidation of lipids leads to fat droplet accumulation in hepatocytes and microvesicular steatosis. (body mass index (BMI) > 30 kg/m2), 67% of overweight patients (BMI > 25 kg/m2) and 25% of normal-weight patients. The overall prevalence of NAFLD in patients with type 2 diabetes ranges from 40% to 70%. Histological NASH has been found in 3–16% of apparently healthy potential living liver donors in Europe and 6–15% in the USA. Overall, NAFLD is estimated to affect 20–30% of the general population in Western countries and 5–18% in Asia, with about 1 in 10 NAFLD cases exhibiting NASH. The frequency of steatosis varies with ethnicity (45% in Hispanics, 33% in whites and 24% in blacks) and gender (42% white males versus 24% white females) but only a minority of patients will progress to cirrhosis and end-stage liver disease. However, because obesity is common and the prevalence of NAFLD is rising, this still represents a large number of patients, placing a substantial burden on health-care resources. Over a median 12-year follow-up period in a cohort of 619 NAFLD patients, an overall 33.2% risk of death or liver transplantation was observed, with liver-related mortality being the third most common cause of death after cardiovascular disease and extra-hepatic malignancy. NAFLD is the leading cause of liver dysfunction in the non-alcoholic, viral hepatitis-negative population in Europe and North America, and is predicted to become the main aetiology in patients undergoing liver transplantation during the next 5 years. Pathophysiology The initiating events in NAFLD are based on the development of obesity and insulin resistance, leading to increased hepatic free fatty acid flux. This imbalance between the rate of import/ synthesis and the rate of export/catabolism of fatty acids in

 fibrosis in many NAFLD patients. This allows care to focus on those most likely to have advanced disease. Imaging Ultrasound is most often used and provides a qualitative assessment of hepatic fat content, as the liver appears 'bright' due to increased echogenicity; sensitivity is limited when fewer than 33% of hepatocytes are steatotic, however. CT, MRI or MR spectroscopy offer greater sensitivity for detecting lesser degrees of steatosis, but these are resource-intensive and not widely used. No routine imaging modality can distinguish simple steatosis from steatohepatitis or accurately quantify hepatic fibrosis short of cirrhosis. Liver biopsy Liver biopsy remains the 'gold standard' investigation for diagnosis and assessment of degree of inflammation and extent of liver fibrosis. The histological definition of NASH is based on a combination of three lesions (steatosis, hepatocellular injury and inflammation; see Fig. 22.30A) with a mainly centrilobular, acinar zone 3 distribution. Specific features include hepatocyte ballooning degeneration with or without acidophil bodies or spotty necrosis and a mild, mixed inflammatory infiltrate. These may be accompanied by Mallory–Denk bodies (also known as Mallory's hyaline). Perisinusoidal fibrosis is a characteristic feature of NASH. Histological scoring systems are widely used to assess disease severity semi-quantitatively. It is important to note that

hepatic fat content tends to diminish as cirrhosis develops and so NASH is likely to be under-diagnosed in the setting of advanced liver disease, where it is thought to be the underlying cause of 30–75% of cases in which no specific aetiology is readily identified (so-called ‘cryptogenic cirrhosis’). Management As it is a marker of the metabolic syndrome, identification of NAFLD should prompt screening for and treatment of cardiovascular risk factors in all patients. It is also necessary to assess whether patients have progressive disease and advanced fibrosis so that liver-targeted treatment can be focused particularly on those patients. While liver biopsy is best able to do this, it is invasive and unsuitable for widespread use outside the specialist care setting. An example of an algorithm for the assessment and risk stratification of patients with NAFLD is provided in Figure 22.31. Non-pharmacological treatment Current treatment comprises lifestyle interventions to promote weight loss and improve insulin sensitivity through dietary changes Clinical features NAFLD is frequently asymptomatic, although it may be associated with fatigue and mild right upper quadrant discomfort. It is commonly identified as an incidental biochemical abnormality during routine blood tests or as a fatty liver during an ultrasound or CT scan of the abdomen. Alternatively, patients with progressive NASH may present late in the natural history of the disease with complications of cirrhosis and portal hypertension, such as variceal haemorrhage, or with hepatocellular carcinoma. The average age of NASH patients is 40–50 years (50–60 years for NASH–cirrhosis); however, the emerging epidemic of childhood obesity means that NASH is present in increasing numbers of younger patients. Recognised independent risk factors for disease progression are age over 45 years, presence of diabetes (or severity of insulin resistance), obesity (BMI > 30 kg/m2) and hypertension. These factors help with identification of ‘high-risk’ patient groups. NAFLD is also associated with polycystic ovary syndrome, obstructive sleep apnoea and small-bowel bacterial overgrowth. Investigations Investigation of patients with suspected NAFLD should be directed first towards exclusion of excess alcohol consumption and other liver diseases (including viral, autoimmune and other metabolic causes) and then at confirming the presence of NAFLD, discriminating simple steatosis from NASH and determining the extent of any hepatic fibrosis that is present. Biochemical tests There is no single diagnostic blood test for NAFLD. Elevations of serum ALT and AST are modest, and usually less than twice the upper limit of normal. ALT levels fall as hepatic fibrosis increases and the characteristic AST : ALT ratio of < 1 seen in NASH reverses (AST : ALT > 1) as disease progresses towards cirrhosis, meaning that steatohepatitis with advanced disease may be present even in those with normal-range ALT levels. Other laboratory abnormalities that may be present include non-specific elevations of GGT, low-titre antinuclear antibody (ANA) in 20–30% of patients and elevated ferritin levels. Although routine blood tests are unable to determine the degree of liver fibrosis/cirrhosis accurately, calculated scores, such as the NAFLD Fibrosis Score and FIB-4 Score, which are based on the results of routinely available blood tests and anthropometrics, have a high negative predictive value for advanced fibrosis/ cirrhosis (Box 22.48) and so can be used to rule out advanced 22.48 Simple non-invasive scores for non-alcoholic fatty liver disease (NAFLD)/fibrosis* Test Formula Thresholds Age < 65 years Age > 65 years NAFLD Fibrosis Score (NFS) −1.675 + 0.037 × Age (years) + 0.094 × BMI (kg/m2) + 1.13 × IFG or diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet count (× 109/L) − 0.66 × albumin (g/dL) High risk (NFS > 0.676) Indeterminate risk (NFS −1.455–0.676) Low risk (NFS < −1.455) High risk (NFS > 0.676) Indeterminate risk (NFS 0.12–0.676) Low risk (NFS < 0.12) FIB-4 Score Age (years) × AST (IU/L)/platelet count (× 109/L) × ¥ALT (IU/L) High risk (FIB-4 > 2.67) Indeterminate risk (FIB-4 1.30–2.67) Low risk (FIB-4 < 1.30) High risk (FIB-4 > 2.67) Indeterminate risk (2.00–2.67) Low risk (FIB-4 < 2.00) (ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; IFG = impaired

fasting glucose) *Predict advanced fibrosis and cirrhosis (F3–4). Simple scores like NFS and FIB-4 are based on the results of routinely available blood tests and anthropometrics. Online calculators for these are widely available.

evidence that high doses may be associated with an increased risk of prostate cancer and all-cause mortality, which has limited its use. Several new medicines are currently in late-phase clinical trials and so liver-targeted pharmacological treatments are likely to be available within the next few years. Autoimmune liver and biliary disease The liver is an important target for autoimmune injury. The clinical picture is dictated by the nature of the autoimmune process and, in particular, the target cell for immune injury. The disease patterns are quite distinctive for primary hepatocellular injury (in the context of autoimmune hepatitis) and biliary epithelial cell injury (primary biliary cholangitis and primary sclerosing cholangitis). and physical exercise. Sustained weight reduction of 7–10% is associated with significant improvement in histological and biochemical NASH severity. Pharmacological treatment No pharmacological agents are currently licensed specifically for NASH therapy. Treatment directed at coexisting metabolic disorders, such as dyslipidaemia and hypertension, should be given. Although use of HMG-CoA reductase inhibitors (statins) does not ameliorate NAFLD, there does not appear to be any increased risk of hepatotoxicity or other side-effects from these agents, and so they may be used to treat dyslipidaemia. Specific insulin-sensitising agents, in particular glitazones, may help selected patients, while recent results with bezafibrate, a lipid-lowering fibrate, have been encouraging. Positive results with high-dose vitamin E (800 U/day) have been tempered by Fig. 22.31 Assessment and risk stratification of patients with non-alcoholic fatty liver disease (NAFLD). (HCC = hepatocellular carcinoma; M probe = medium probe; XL = large probe) Suspected NAFLD Features of the metabolic syndrome, radiological evidence of steatosis and/or abnormal liver biochemistry, alternative diagnoses excluded Calculate NAFLD fibrosis score (NFS) Refer to liver specialist care Transient elastography (fibroscan) Age <65: -1.455 to 0.676 Age >65: 0.12 to 0.676 NFS >0.676 Age <65: NFS <-1.455 Age >65: NFS <0.12 Low risk Indeterminate High risk Consider liver biopsy M probe 7.9–9.6 kPa XL probe 7.2–9.3 kPa M probe <7.9 kPa XL probe <7.2 kPa M probe >9.6 kPa XL probe >9.3 kPa Advanced [F3–4] fibrosis excluded Advanced [F3–4] fibrosis likely Indeterminate Fibrosis F2–3 Fibrosis F0–1 Recalculate NFS in 3–5 years or if patient develops type 2 diabetes Cirrhosis F4 Lifestyle advice Address cardiovascular risks NAFLD-directed therapy Manage in primary care Lifestyle advice Address cardiovascular risks Recalculate NFS in 3– 5 years Lifestyle advice Address cardiovascular risks NAFLD-directed therapy HCC and variceal surveillance

 typically adult patients, often with aggressive disease and usually lacking autoantibodies of other specificities. Clinical features The onset is usually insidious, with fatigue, anorexia and eventually jaundice. The non-specific nature of the early features can lead to the diagnosis being missed in the early disease stages. In about one-quarter of patients the onset is acute, resembling viral hepatitis, but resolution does not occur. This acute presentation can lead to extensive liver necrosis and liver failure. Other features include fever, arthralgia, vitiligo and epistaxis. Amenorrhoea can occur. Jaundice is mild to moderate or occasionally absent, but signs of chronic liver disease, especially spider naevi and hepatosplenomegaly, can be present. Associated autoimmune disease, such as Hashimoto’s thyroiditis or rheumatoid arthritis, is often present and can modulate the clinical presentation. Investigations Serological tests for autoantibodies are often

positive (Box 22.50), but low titres of these antibodies occur in some healthy people and in patients with other inflammatory liver diseases. ANA also occur in connective tissue diseases and other autoimmune diseases (with an identical pattern of homogenous nuclear staining) while anti-smooth muscle antibody has been reported in infectious mononucleosis and a variety of malignant diseases. Anti-microsomal antibodies (anti-LKM) occur particularly in children and adolescents. Elevated serum IgG levels are an important diagnostic and treatment response feature if present, but the diagnosis is still possible in the presence of normal IgG levels. If the diagnosis of autoimmune hepatitis is suspected, liver biopsy should be performed. It typically shows interface hepatitis, with or without cirrhosis. Scoring systems, such as the International Autoimmune Hepatitis Group (IAIHG) criteria, are useful for epidemiological study and for assessing trial eligibility but are complex for normal clinical practice. Management Treatment with glucocorticoids is life-saving in autoimmune hepatitis, particularly during exacerbations of active and symptomatic disease. Initially, prednisolone (40 mg/day) is given orally; the dose is then gradually reduced as the patient and LFTs improve. Maintenance therapy should only be instituted once LFTs are normal (as well as IgG if elevated). Approaches to maintenance include reduced-dose prednisolone (ideally, below 5–10 mg/day), usually in the context of azathioprine (1.0–1.5 mg/kg/day). Azathioprine can also be used as the sole maintenance immunosuppressive agent in patients with low-activity disease. Newer agents, such as mycophenolate mofetil (MMF), are increasingly being used but formal evidence to inform practice in this area is lacking. Patients should be monitored for acute exacerbations (LFT and IgG screening with patients alerted Autoimmune hepatitis Autoimmune hepatitis is a disease of immune-mediated liver injury characterised by the presence of serum antibodies and peripheral blood T lymphocytes reactive with self-proteins, a strong association with other autoimmune diseases (Box 22.49), and high levels of serum immunoglobulins – in particular, elevation of IgG. Although most commonly seen in women, particularly in the second and third decades of life, it can develop in either sex at any age. The reasons for the breakdown in immune tolerance in autoimmune hepatitis remain unclear, although cross-reactivity with viruses such as HAV and EBV in immunogenetically susceptible individuals (typically those with human leucocyte antigen (HLA)-DR3 and DR4, particularly HLA-DRB3*0101 and HLA-DRB1*0401) has been suggested as a mechanism. Pathophysiology Several subtypes of this disorder have been proposed that have differing immunological markers. Although the different patterns can be associated with variation in disease aspects, such as response to immunosuppressive therapy, histological patterns are similar in the different settings and the basic approach to treatment (complete control of liver injury using immunosuppressive drugs and maintained with appropriate therapy) is the same. The formal classification into disease types has fallen out of favour in recent years. The most frequently seen autoantibody pattern is high titre of antinuclear and anti-smooth muscle antibodies, typically associated with IgG hyperglobulinaemia (type I autoimmune hepatitis in the old classification), frequently seen in young adult females. Disease characterised by the presence of anti-liver–kidney microsomal (LKM) antibodies, recognising cytochrome P450-IID6 expressed on the hepatocyte membrane, is typically seen in paediatric populations and can be more resistant to treatment than ANA-positive disease. Adult onset of anti-LKM can be seen in chronic HCV infection. This was classified as type II disease in the old system. More recently, a pattern of antibody reactivity with anti-soluble liver antigen (anti-SLA) has been described in 22.49 Conditions associated with autoimmune hepatitis • Migrating polyarthritis • Urticarial rashes • Lymphadenopathy • Hashimoto’s thyroiditis • Thyrotoxicosis • Myxoedema • Pleurisy • Coombs-positive haemolytic anaemia • Transient pulmonary infiltrates • Ulcerative colitis • Glomerulonephritis • Nephrotic syndrome 22.50 Frequency of autoantibodies in

chronic non-viral liver diseases and in healthy people Disease Antinuclear antibody (%) Anti-smooth muscle antibody (%) Antimitochondrial antibody* Healthy controls

1.5 0.01 Autoimmune hepatitis

Primary biliary cholangitis

Cryptogenic cirrhosis

*Patients with antimitochondrial antibody frequently have cholestatic liver function tests and may have primary biliary cholangitis (see text).

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patients with severe pruritus. Jaundice is prominent only late in the disease and can become intense. Xanthomatous deposits occur in a minority, especially around the eyes. Mild hepatomegaly is common and splenomegaly becomes increasingly common as portal hypertension develops. Liver failure may supervene. Associated diseases Autoimmune and connective tissue diseases occur with increased frequency in PBC, particularly the sicca syndrome (p. 1038), systemic sclerosis, coeliac disease (p. 805) and thyroid diseases. Hypothyroidism should always be considered in patients with fatigue. Diagnosis and investigations The LFTs show a pattern of cholestasis (see Box 22.2, p. 853). Hypercholesterolaemia is common and worsens as disease progresses but appears not to be associated with increased cardiac risk. AMA is present in over 95% of patients; when it is absent, the diagnosis should not be made without obtaining histological evidence and considering cholangiography (typically, MRCP) to exclude other biliary disease. ANA and anti-smooth muscle antibodies are present in around 15% of patients (see Box 22.50); autoantibodies found in associated diseases may also be present. Ultrasound examination shows no sign of biliary obstruction. Liver biopsy is necessary only if there is diagnostic uncertainty. The histological features of PBC correlate poorly with to the possible symptoms) and such exacerbations should be treated with glucocorticoids. Although treatment can significantly reduce the rate of progression to cirrhosis, end-stage disease can be seen in patients despite treatment. Primary biliary cholangitis Primary biliary cholangitis (PBC, known as primary biliary cirrhosis until 2015, when the name was changed to reflect more accurately the disease seen in the modern era) is a chronic, progressive cholestatic liver disease that predominantly affects women aged 30 and over. It is strongly associated with the presence of antimitochondrial antibodies (AMA), which are diagnostic, and is characterised by a granulomatous inflammation of the portal tracts, leading to progressive damage and eventually loss of the small and middle-sized bile ducts. This, in turn, leads to fibrosis and cirrhosis of the liver. The condition can present with an insidious onset of itching and/or tiredness; it may also frequently be found incidentally as the result of routine blood tests. Epidemiology The prevalence of PBC varies across the world. It is relatively common in northern Europe and North America but is rare in Africa and Asia. There is a strong female-to-male predominance of 9 : 1; it is also more common among cigarette smokers. Clustering of cases has been reported, suggesting an environmental trigger in susceptible individuals. Pathophysiology Immune mechanisms are clearly involved. The condition is closely associated with other autoimmune non-hepatic diseases, such as thyroid disease, and there is a genetic association with HLA-DR8, together with polymorphisms in a number of other genes regulating the nature of the

immune response (e.g. IL-12 and its receptor). AMA is directed at pyruvate dehydrogenase complex, a mitochondrial enzyme complex that plays a key role in cellular energy generation. PBC-specific ANAs (such as those directed at the nuclear pore antigen gp210) have a characteristic staining pattern in immunofluorescence assays (selectively binding to the nuclear rim or nuclear dots), which means that they should not be mistaken for the homogenously staining ANA seen in autoimmune hepatitis. Increases in serum immunoglobulin levels are frequent but, unlike in autoimmune hepatitis, it is typically IgM that is elevated. Pathologically, chronic granulomatous inflammation destroys the interlobular bile ducts; progressive lymphocyte-mediated inflammatory damage causes fibrosis, which spreads from the portal tracts to the liver parenchyma and eventually leads to cirrhosis. A model of the natural history of the disease process is shown in Figure 22.32. Clinical features Systemic symptoms such as fatigue are common and may precede diagnosis by years. Pruritus, which can be a feature of any cholestatic disease, is a common presenting complaint and may precede jaundice by months or years. Jaundice is rarely a presenting feature. The itching is usually worse on the limbs. Although there may be right upper abdominal discomfort, fever and rigors do not occur. Bone pain or fractures can rarely result from osteomalacia (fat-soluble vitamin malabsorption) or, more commonly, from osteoporosis (hepatic osteodystrophy). Initially, patients are well nourished but weight loss can occur as the disease progresses. Scratch marks may be found in Fig. 22.32 Natural history of primary biliary cholangitis. (AMA = antimitochondrial antibody; LFTs = liver function tests) Genetic susceptibility Latent disease (antimitochondrial Ab-positive, normal LFTs) Environmental trigger factor(s) Early disease AMA-positive (abnormal LFTs) Late disease (liver scarring/cirrhosis) Liver decompensation Genetic factors Genetic factors Death Liver transplant 30% disease recurrence

 Bone disease Osteopenia and osteoporosis are common and normal post-menopausal bone loss is accelerated. Baseline bone density should be measured (p. 989) and treatment started with replacement calcium and vitamin D3. Bisphosphonates should be used if there is evidence of osteoporosis. Osteomalacia is rare. Overlap syndromes AMA-negative PBC (‘autoimmune cholangitis’) A few patients demonstrate the clinical, biochemical and histological features of PBC but do not have detectable AMA in the serum. Serum transaminases, serum immunoglobulin levels and titres of ANA tend to be higher than in AMA-positive PBC. The clinical course mirrors classical PBC, however, and these patients should be considered as having a variant of PBC. PBC/autoimmune hepatitis overlap A few patients with AMA and cholestatic LFTs have elevated transaminases, high serum immunoglobulins and interface hepatitis on liver histology. In such individuals, a trial of glucocorticoid therapy may be beneficial. Primary sclerosing cholangitis Primary sclerosing cholangitis (PSC) is a cholestatic liver disease caused by diffuse inflammation and fibrosis; it can involve the entire biliary tree and leads to the gradual obliteration of intrahepatic and extrahepatic bile ducts, and ultimately biliary cirrhosis, portal hypertension and hepatic failure. Although considered as an autoimmune disease, evidence for an autoimmune pathophysiology is weaker than is the case for PBC and autoimmune hepatitis. The incidence is about 6.3/100 000 in Caucasians. Cholangiocarcinoma develops in about 10–30% of patients during the course of the disease. PSC is twice as common in young men. Most patients present at age 25–40 years, although the condition may be diagnosed at any age and is an important cause of chronic liver disease in children. The generally accepted diagnostic criteria are: • generalised beading and stenosis of the biliary system on cholangiography (Fig. 22.33) • absence of choledocholithiasis (or history of bile duct surgery) • exclusion of bile duct cancer, by prolonged follow-up. The term ‘secondary sclerosing cholangitis’ is used to describe the typical changes

described above when a clear predisposing factor for duct fibrosis can be identified. The causes of secondary sclerosing cholangitis are shown in Box 22.51. Pathophysiology The cause of PSC is unknown but there is a close association with inflammatory bowel disease, particularly ulcerative colitis (Box 22.52). About two-thirds of patients have coexisting ulcerative colitis, and PSC is the most common form of chronic liver disease in ulcerative colitis. Between 3% and 10% of patients with ulcerative colitis develop PSC, particularly those with extensive colitis or pancolitis. The prevalence of PSC is lower in patients with Crohn's colitis (about 1%). Patients with PSC and ulcerative colitis are at greater risk of colorectal neoplasia than those with ulcerative colitis alone, and individuals who develop colorectal neoplasia are at greater risk of cholangiocarcinoma. It is currently believed that PSC is an immunologically mediated disease, triggered in genetically susceptible individuals by toxic the clinical features; portal hypertension can develop before the histological onset of cirrhosis. Management The hydrophilic bile acid ursodeoxycholic acid (UDCA), at a dose of 13–15 mg/kg/day, improves bile flow, replaces toxic hydrophobic bile acids in the bile acid pool, and reduces apoptosis of the biliary epithelium. Clinically, UDCA improves LFTs, may slow down histological progression and has few side-effects; it is therefore widely used in the treatment of PBC and should be regarded as the optimal first-line treatment. Its use is recommended in all clinical guidelines. A significant minority of patients either fail to normalise their LFTs with UDCA or show an inadequate response, and such individuals have an increased risk of developing end-stage liver disease compared to those showing a full response. Obeticholic acid (OCA) is a second-generation bile acid therapeutic that acts as an agonist for the nuclear farnesoid X receptor. It reduces hepatocyte synthesis of bile acids and was approved in 2016 for use in patients showing an inadequate response to UDCA. Immunosuppressants, such as glucocorticoids, azathioprine, penicillamine and ciclosporin, have all been trialled in PBC. None shows overall benefit when given to unselected patients. It is unclear whether these drugs offer benefit to the specific subgroup of patients who do not respond to UDCA and require second-line approaches to treatment. Liver transplantation should be considered once liver failure has developed and may be indicated in patients with intractable pruritus. Serum bilirubin remains the most reliable marker of declining liver function. Transplantation is associated with an excellent 5-year survival of over 80%, although the disease will recur in over one-third of patients at 10 years. Pruritus This is the main symptom requiring treatment. The cause is unknown, but up-regulation of opioid receptors and increased levels of endogenous opioids may play a role. First-line treatment is with the anion-binding resin colestyramine, which probably acts by binding potential pruritogens in the intestine and increasing their excretion in the stool. A dose of 4–16 g/day orally is used. The powder is mixed in orange juice and the main dose (8 g) taken before and after breakfast, when maximal duodenal bile acid concentrations occur. Colestyramine may bind other drugs in the gut (most obviously UDCA) and adequate spacing should be used between drugs. Colestyramine is sometimes ineffective, especially in complete biliary obstruction, and can be difficult for some patients to tolerate. Alternative treatments include rifampicin (150 mg/day, titrated up to a maximum of 600 mg/day as required and contingent on there being no deterioration in LFTs), naltrexone (an opioid antagonist; 25 mg/day initially, increasing up to 300 mg/day), plasmapheresis and a liver support device (e.g. a molecular adsorbent recirculating system, MARS). Fatigue Fatigue affects about one-third of patients with PBC. The cause is unknown but it may reflect intracerebral changes due to cholestasis. Unfortunately, once depression, hypothyroidism and coeliac disease have been excluded, there is currently no specific treatment. The impact on patients' lives can be substantial. Malabsorption Prolonged cholestasis is associated with steatorrhoea and malabsorption of fat-soluble vitamins, which should be replaced as necessary. Coeliac disease should be excluded since

its incidence is increased in PBC.

Clinical features The diagnosis is often made incidentally when persistently raised serum ALP is discovered in an individual with ulcerative colitis. Common symptoms include fatigue, intermittent jaundice, weight loss, right upper quadrant abdominal pain and pruritus. Attacks of acute cholangitis are uncommon and usually follow biliary instrumentation. Physical examination is abnormal in about 50% of symptomatic patients; the most common findings are jaundice and hepatomegaly/splenomegaly. The condition may be associated with many other diseases (Box 22.52). Investigations Biochemical screening usually reveals a cholestatic pattern of LFTs but ALP and bilirubin levels may vary widely in individual patients during the course of the disease. For example, ALP and bilirubin values increase during acute cholangitis, decrease after therapy, and sometimes fluctuate for no apparent reason. Modest elevations in serum transaminases are usually seen, whereas hypoalbuminaemia and clotting abnormalities are found at a late stage only. In addition to ANCA, low titres of serum ANA and anti-smooth muscle antibodies may be found in PSC but have no diagnostic significance; serum AMA is absent. The key investigation is now MRCP, which is usually diagnostic and reveals multiple irregular stricturing and dilatation (Fig. 22.33). ERCP should be reserved for when therapeutic intervention is likely to be necessary and should follow MRCP. On liver biopsy, the characteristic early features of PSC are periductal ‘onion skin’ fibrosis and inflammation, with portal oedema and bile ductular proliferation resulting in expansion of the portal tracts (Fig. 22.34). Later, fibrosis spreads, progressing inevitably to biliary cirrhosis; obliterative cholangitis leads to the so-called ‘vanishing bile duct syndrome’. Management There is no cure for PSC but management of cholestasis and its complications and specific treatment of the disease process are indicated. UDCA is widely used, although the evidence to support this is limited. UDCA may have benefit in terms of reducing colon carcinoma risk. The course of PSC is variable. In symptomatic patients, median survival from presentation to death or liver transplantation is about 12 years. About 75% of asymptomatic patients survive 15 years or more. Most patients die from liver failure, about 30% die from bile duct carcinoma, and the remainder die from colonic cancer or complications of colitis. Immunosuppressive agents, including or infectious agents, which may gain access to the biliary tract through a leaky, diseased colon. A close link with HLA haplotype A1-B8-DR3-DRW52A has been identified. This haplotype is commonly found in association with other organ-specific autoimmune diseases (e.g. autoimmune hepatitis). The importance of immunological factors has been emphasised by reports showing humoral and cellular abnormalities in PSC. Perinuclear antineutrophil cytoplasmic antibodies (ANCA) have been detected in the sera of 60–80% of patients with PSC with or without ulcerative colitis, and in 30–40% of patients with ulcerative colitis alone. The antibody is not specific for PSC and is found in other chronic liver diseases (e.g. 50% of patients with autoimmune hepatitis). Fig. 22.33 Magnetic resonance cholangiopancreatogram showing typical changes of primary sclerosing cholangitis. There is intrahepatic bile duct beading, stricturing and dilatation. The extrahepatic bile duct is also diffusely strictured. Courtesy of Dr Dilip Patel, Royal Infirmary of Edinburgh. 22.51 Causes of secondary sclerosing cholangitis • Previous bile duct surgery with stricturing and cholangitis • Bile duct stones causing cholangitis • Intrahepatic infusion of 5-fluorodeoxyuridine • Insertion of formalin into hepatic hydatid cysts • Insertion of alcohol into hepatic tumours • Parasitic infections (e.g. Clonorchis) • Autoimmune pancreatitis/immunoglobulin G4-associated cholangitis • Acquired immunodeficiency syndrome (AIDS; probably infective as a result of cytomegalovirus or

Cryptosporidium) 22.52 Diseases associated with primary sclerosing cholangitis • Ulcerative colitis • Crohn’s colitis • Chronic pancreatitis • Retroperitoneal fibrosis • Riedel’s thyroiditis • Retro-orbital tumours • Immune deficiency states • Sjögren’s syndrome • Angio-immunoblastic lymphoma • Histiocytosis X • Autoimmune haemolytic anaemia • Autoimmune pancreatitis/ immunoglobulin G4-associated cholangitis Fig. 22.34 Primary sclerosing cholangitis. Note onion skin scarring (arrows) surrounding a bile duct.

890 • HEPATOLOGY Primary malignant tumours Hepatocellular carcinoma Hepatocellular carcinoma (HCC) is the most common primary liver tumour, and the sixth most frequent cause of cancer worldwide. Cirrhosis is present in 75–90% of individuals with HCC and is an important risk factor for the disease. The risk is between 1% and 5% in cirrhosis caused by hepatitis B and C. There is also an increased risk in cirrhosis due to haemochromatosis, alcohol, NASH and α1-antitrypsin deficiency. In northern Europe, 90% of those with HCC have underlying cirrhosis, compared with 30% in Taiwan, where hepatitis B is the main risk factor. The age-adjusted incidence rates vary from 28 per 100 000 in South-east Asia (reflecting the prevalence of hepatitis B) to 10 per 100 000 in southern Europe and 5 per 100 000 in northern Europe. Chronic hepatitis B infection increases the risk of HCC 100-fold and is the major risk factor worldwide. The risk of HCC is 0.4% per year in the absence of cirrhosis and 2–6% in cirrhosis. The risk is four times higher in HBeAg-positive individuals than in those who are HBeAg-negative. Hepatitis B vaccination has led to a fall in HCC in countries with a high prevalence of hepatitis B. The incidence in Europe and North America has risen recently, probably related to the increased prevalence of hepatitis C and NASH cirrhosis. The risk is higher in men and rises with age. Macroscopically, the tumour usually appears as a single mass in the absence of cirrhosis, or as a single nodule or multiple nodules in the presence of cirrhosis. It takes its blood supply from the hepatic artery and tends to spread by invasion into the portal vein and its radicals. Lymph node metastases are common, while lung and bone metastases are rare. Well-differentiated tumours can resemble normal hepatocytes and can be difficult to distinguish from normal liver. Clinical features Patients typically present with HCC in one of two ways. Commonly, liver function deteriorates in those with underlying cirrhosis, with worsening ascites and/or jaundice or variceal haemorrhage. Other characteristic symptoms can include weight loss, anorexia and abdominal pain. This often-rapid deterioration can, however, be the event that leads to previously occult cirrhosis becoming clinically apparent, meaning that absence of an established diagnosis of cirrhosis does not preclude a diagnosis of HCC complicating cirrhosis. Examination may reveal hepatomegaly or a right hypochondrial mass. Tumour vascularity can lead to an abdominal bruit, and hepatic rupture with intra-abdominal bleeding may occur. The advanced nature of disease that presents in this way makes curative therapy unlikely. The second presentation is through screening of patients at risk of HCC. The disease is typically detected much earlier in its natural history, significantly increasing the treatment options. Investigations Serum markers Alpha-fetoprotein (AFP) is produced by 60% of HCCs. Levels increase with the size of the tumour and are often normal or only minimally elevated in small tumours detected by ultrasound screening. Serum AFP can also rise in the presence of active hepatitis B and C viral replication; very high levels are seen in acute hepatic necrosis, such as that following paracetamol toxicity. AFP is used in conjunction with ultrasound in screening but, in view of low sensitivity and specificity, levels need to prednisolone, azathioprine, methotrexate and ciclosporin, have been tried; results have generally been disappointing. Symptomatic patients often have pruritus. Management is as for PBC. Fatigue appears to be less prominent than in PBC, although it is still present in some patients. Management of complications Broad-spectrum antibiotics (e.g. ciprofloxacin) should be

given for acute attacks of cholangitis but have no proven value in preventing attacks. If cholangiography shows a well-defined obstruction to the extrahepatic bile ducts (‘dominant stricture’), mechanical relief can be obtained by placement of a stent or by balloon dilatation performed at ERCP. It is important, in this situation, to give active consideration to the possibility of cholangiocarcinoma (the differential diagnosis for a dominant extrahepatic stricture). Fat-soluble vitamin replacement is necessary in jaundiced patients. Metabolic bone disease (usually osteoporosis) is a common complication that requires treatment (p. 1044). Surgical treatment Surgical resection of the extrahepatic bile duct and biliary reconstruction have a limited role in the management of noncirrhotic patients with dominant extrahepatic disease. Orthotopic transplantation is the only surgical option in patients with advanced liver disease; 5-year survival is 80–90% in most centres. Unfortunately, the condition may recur in the graft and there are no identified therapies able to prevent this. Cholangiocarcinoma is a contraindication to transplantation. Colon carcinoma risk can be increased in patients following transplantation because of the effects of immune suppression, and enhanced surveillance should be instituted. IgG4-associated cholangitis This disease (as well as its nomenclature) is closely related to autoimmune pancreatitis (which is present in more than 90% of the patients; p. 841). IgG4-associated cholangitis (IAC) often presents with obstructive jaundice (due to either hilar stricturing/intrahepatic sclerosing cholangitis or a low bile duct stricture), and cholangiographic appearances suggest PSC with or without hilar cholangiocarcinoma. The serum IgG4 is often raised and liver biopsy shows a lymphoplasmacytic infiltrate, with IgG4-positive plasma cells. An important observation is that, compared to PSC, IAC appears to respond well to glucocorticoid therapy. Liver tumours and other focal liver lesions Identification of a hepatic mass lesion is common, both in patients with known pre-existing liver disease and as a primary presentation. Although primary and secondary malignant tumours are important potential diagnoses, benign disease is frequent. The finding of a liver mass, with its association in the minds of patients with metastatic malignant disease, creates a high level of anxiety, a factor that should always be borne in mind. The critical steps to be taken in diagnosing hepatic mass lesions are: • determining the presence, nature and severity of any underlying chronic liver disease, as the differential diagnosis is very different in patients with and those without chronic liver disease • using optimal (usually multiple) imaging modalities.

Screening may also be indicated in those with chronic hepatitis B (who carry an increased risk of HCC, even in the absence of cirrhosis). Although no randomised controlled studies of outcome have been undertaken, screening identifies smaller tumours, often less than 3 cm in size, which are more likely to be cured by surgical resection, local ablative therapy or transplantation. The role of screening in other forms of chronic liver disease, such as autoimmune hepatitis and PBC, is unclear. This is compounded by the fact that disease staging by biopsy is no longer standard practice in conditions such as PBC, so formal documentation of the presence of cirrhosis, which might be the trigger for commencement of HCC screening, rarely takes place. Management This is different for patients with cirrhosis and those without. In the presence of cirrhosis, tumour size, multicentricity, extent of liver disease (Child–Pugh score) and performance status dictate therapy. An algorithm for managing those with cirrhosis is shown in Figure 22.36. Prognosis depends on tumour size, the presence of vascular invasion, and liver function in those with cirrhosis. Screening has improved the outlook through early detection. Hepatic resection This is the treatment of choice

for non-cirrhotic patients. The 5-year survival in this group is about 50%. There is a 50% recurrence rate at 5 years, however, which may be due to a second de novo tumour or recurrence of the original tumour. Few patients with cirrhosis are suitable for hepatic resection because of the high risk of hepatic failure; nevertheless, surgery is offered, particularly in the Far East, to some cirrhotic patients with small tumours and good liver function (Child–Pugh A with no portal hypertension). Liver transplantation Transplantation has the benefit of curing underlying cirrhosis and removing the risk of a second, de novo tumour in an at-risk patient. The requirement for immunosuppression creates its own risks of reactivation, however, if residual or metastatic disease is present, and assessment of patients for suitability for liver transplantation focuses on the exclusion of extrahepatic disease and vascular invasion. The 5-year survival following liver transplantation is 75% for patients with single tumours of less than 5 cm in size or three tumours smaller than 3 cm (the Milan criteria). Unfortunately, the underlying liver disease, in particular hepatitis C, may recur in the transplanted liver and can result in recurrent cirrhosis that gives rise to a de novo HCC risk, now complicated by the presence of immunosuppression. Percutaneous therapy Percutaneous ethanol injection into the tumour under ultrasound guidance is efficacious (80% cure rate) for tumours of 3 cm or less. Recurrence rates (50% at 3 years) are similar to those following surgical resection. Radiofrequency ablation, using a single electrode inserted into the tumour under radiological guidance, is an alternative that takes longer to perform but may cause more complete tumour necrosis. Improvements in percutaneous therapy, with the combination of low patient impact, relative efficacy and capacity for repeat treatment, are making these approaches attractive, particularly when major surgery would be inappropriate. Their role in primary therapy as an alternative to curative resection or transplantation is yet to be established. be interpreted with caution. Nevertheless, in the absence of a marked hepatic flare of disease, a progressively rising AFP, or AFP of > 400 ng/mL (330 IU/mL; normal is < 10 ng/mL (8 IU/mL), warrants an aggressive search for HCC. In HCC patients with elevated AFP levels, serial measurements can be a useful biomarker of disease progression or response to treatment. Imaging Ultrasound will detect focal liver lesions as small as 2–3 cm. The use of ultrasound contrast agents has increased sensitivity and specificity but is highly user-dependent. Ultrasound may also show evidence of portal vein involvement and features of coexistent cirrhosis. Multidetector row CT, following intravenous contrast, identifies HCC by its classical hypervascular appearance (Fig. 22.35). Small lesions of less than 2 cm can be difficult to differentiate from hyperplastic nodules in cirrhosis. MRI can be used instead. Angiography is now seldom performed and has been superseded by the above techniques. A combination of imaging modalities more accurately diagnoses and stages the extent of disease, and use of at least two modalities (typically, CT or MRI following initial screening ultrasound identification of a mass lesion) is recommended. Liver biopsy Histological confirmation is advisable in patients with large tumours who do not have cirrhosis or hepatitis B, in order to confirm the diagnosis and exclude metastatic tumour. Biopsy should be avoided in patients who may be eligible for transplantation or surgical resection because there is a small (< 2%) risk of tumour seeding along the needle tract. In all cases of potential HCC where biopsy is being considered, the impact that a confirmed diagnosis will have on therapy must be weighed against the risks of bleeding. If biopsy will not change management, then its appropriateness should be considered carefully. Role of screening Screening for HCC, by ultrasound scanning and AFP measurements at 6-month intervals, is indicated in high-risk patients who would be suitable for therapy if diagnosed with HCC. These include individuals with cirrhosis caused by hepatitis B and C, haemochromatosis, alcohol, NASH and α1-antitrypsin deficiency. Fig. 22.35 Computed tomogram showing a large hepatocellular carcinoma (arrows). Courtesy of Dr D. Redhead, Royal Infirmary of Edinburgh.

892 • HEPATOLOGY malignant hepatocytes surrounded by a dense fibrous stroma. The treatment of choice is surgical resection. This variant of HCC has a better prognosis following surgery than an equivalent-sized HCC, two-thirds of patients surviving beyond 5 years. Other primary malignant tumours These are rare but include haemangio-endothelial sarcomas. Cholangiocarcinoma (bile duct cancer) typically presents with bile duct obstruction rather than as a hepatic mass lesion, although the latter occasionally occurs. Secondary malignant tumours These are common and usually originate from carcinomas in the lung, breast, abdomen or pelvis. They may be single or multiple. Peritoneal dissemination frequently results in ascites. Clinical features The primary neoplasm is asymptomatic in 50% of patients, being detected on either radiological, endoscopic or blood biochemistry screening. There is liver enlargement and weight loss; jaundice may be present. Investigations A raised ALP activity is the most common biochemical abnormality but LFTs may be normal. Ascitic fluid, if present, has a high protein content and may be blood-stained; cytology sometimes reveals malignant cells. Imaging shows filling defects (Fig. 22.37); laparoscopy may reveal the tumour and facilitates liver biopsy. Trans-arterial chemo-embolisation Hepatocellular cancers are not radiosensitive and the response rate to chemotherapy with drugs, such as doxorubicin, is only around 30%. In contrast, hepatic artery embolisation with absorbable gelatin powder (Gelfoam) and doxorubicin is more effective, with survival rates of 60% in cirrhotic patients with unresectable HCC and good liver function (compared with 20% in untreated patients) at 2 years. Unfortunately, any survival benefit is lost at 4 years. Trans-arterial chemo-embolisation (TACE) is contraindicated in decompensated cirrhosis and multifocal HCC. TACE is now most frequently used as a holding first intervention while the tumour is being assessed and the definitive management plan is being developed. Chemotherapy Sorafenib improves survival from 7.9 to 10.7 months in cirrhotic patients. The drug is a multikinase inhibitor with activity against Raf, vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) signalling, and is the first systemic therapy to prolong survival in HCC. The ultimate role of sorafenib in HCC – in particular, when and how best to use it – is yet to be established. Fibrolamellar hepatocellular carcinoma This rare variant differs from HCC in that it occurs in young adults, equally in males and females, in the absence of hepatitis B infection and cirrhosis. The tumours are often large at presentation and the AFP is usually normal. Histology of the tumour reveals Fig. 22.36 Management of hepatocellular carcinoma complicating cirrhosis. Performance status (PST; see Box 33.3, p. 1322): 0 = fully active, no symptoms; > 2 = limited self-care, confined to bed or chair for 50% of waking hours. Child–Pugh score: see Box 22.29, p. 867. N1, M1: lymph node involvement and metastases (for TNM classification, see Box 33.4, p. 1322) (OS = overall survival; PEI = percutaneous ethanol injection; RFA = radiofrequency ablation; TACE = trans-arterial chemo-embolisation). Based on European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL–EORTC clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 2012; 56:908–943. Intermediate stage Multinodular; PST 0 PST 0–2, Child–Pugh A–B PST 0, Child–Pugh A Single Portal pressure Normal Resection RFA/PEI Liver transplantation Curative treatment (30–40%) Median OS: > 60 months 5-year survival: 40–70% Target: 20% OS: 20 months (14–45 months) Target: 40% OS: 11 months (6–14 months) Target: 10% OS: < 3 months Sorafenib Best supportive care TACE No Yes Increased Associated diseases 3 nodules < 3 cm PST > 2, Child–Pugh C Hepatocellular carcinoma Advanced stage Portal vein invasion; N1, M1; PST 1–2 Very early stage Single < 2 cm Early stage Single < 5 cm Terminal stage

consist of nodular regeneration of hepatocytes without fibrosis. They may be multiple but only rarely need resection. Cystic liver disease and liver abscess Isolated or multiple simple cysts are common in the liver and are a relatively frequent finding on ultrasound screening. They can be associated with polycystic renal disease (Fig. 22.39). They are intrinsically benign and require no therapy, other than in rare cases where the mass effect of very large or multiple cysts causes abdominal discomfort. In such cases, percutaneous or surgical debulking can be attempted but recurrence is typical. Liver abscesses are discussed on page 879. Drugs and the liver The liver is the primary site of drug metabolism and an important target for drug-induced injury. Pre-existing liver disease may affect the capacity of the liver to metabolise drugs and unexpected toxicity may occur when patients with liver disease are given drugs in normal doses (p. 32). Box 22.53 also shows drugs that should be avoided in patients with cirrhosis, as they can exacerbate known complications of cirrhosis. The possibility of undiagnosed underlying liver injury should always be considered in patients exhibiting unexpected effects following drug exposure. Management Hepatic resection can improve survival for slow-growing tumours, such as colonic carcinomas, and is an approach that should be actively explored in patients who are fit for liver resection and have had the primary tumour resected once extrahepatic disease has been excluded. Patients with neuro-endocrine tumours, such as gastrinomas, insulinomas and glucagonomas, and those with lymphomas may benefit from surgery, hormonal treatment or chemotherapy. Unfortunately, palliative treatment to relieve pain is all that is available for most patients; this may include arterial embolisation of the tumour masses. Benign tumours The increasing use of ultrasound scanning has led to more frequent identification of incidental benign focal liver lesions. Hepatic adenomas These are rare vascular tumours that may present as an abdominal mass, or with abdominal pain or intraperitoneal bleeding. They are more common in women and may be caused by oral contraceptives, androgens and anabolic glucocorticoids. Resection is indicated for the relief of symptoms. Hepatic adenomas can increase in size during pregnancy. Large or rapidly growing adenomas can rarely rupture, causing intraperitoneal bleeding. Haemangiomas These are the most common benign liver tumours and are present in 1–20% of the population. Most are smaller than 5 cm and rarely cause symptoms (Fig. 22.38). The diagnosis is usually made by ultrasound but CT may show a low-density lesion with delayed arterial filling. Surgery is needed only for very large symptomatic lesions or where the diagnosis is in doubt. Focal nodular hyperplasia Focal nodular hyperplasia is common in women under the age of 40. The lesions are usually asymptomatic but can be up to 10 cm in diameter; they can be differentiated from adenoma by a focal central scar seen on CT or MRI. Histologically, they Fig. 22.37 Computed tomogram showing multiple liver metastases (arrows). Fig. 22.38 Magnetic resonance image showing a haemangioma (arrows) in the liver. Courtesy of Dr D. Redhead, Royal Infirmary of Edinburgh. Fig. 22.39 Computed tomogram showing multiple cysts in the liver and kidneys in polycystic disease.

 cases (e.g. NSAIDs and cyclo-oxygenase 2 (COX-2) inhibitors), there is overlap with acute hepatocellular injury. Hepatocyte necrosis Many drugs cause an acute hepatocellular necrosis with high serum transaminase concentrations; paracetamol is the best known. Inflammation is not always present but does accompany necrosis in liver injury due to diclofenac (an NSAID) and isoniazid (an anti-tuberculous drug). Granulomas may be seen in liver injury following the use of allopurinol. Acute hepatocellular necrosis has also been described following the use of several herbal remedies, including germander, comfrey and jin bu huan. Recreational drugs, including cocaine and ecstasy, can also cause severe acute hepatitis. Steatosis Microvesicular hepatocyte fat deposition, due to direct effects on mitochondrial beta-oxidation, can follow

exposure to tetracyclines and sodium valproate. Macrovesicular hepatocyte fat deposition has been described with tamoxifen, and amiodarone toxicity can produce a similar histological picture to NASH. Vascular/sinusoidal lesions Drugs such as the alkylating agents used in oncology can damage the vascular endothelium and lead to hepatic venous Drug-induced liver injury Drug toxicity should always be considered in the differential diagnosis of patients presenting with acute liver failure, jaundice or abnormal liver biochemistry. Some typical patterns of drug toxicity are listed in Box 22.54; the most common picture is a mixed cholestatic hepatitis. The presence of jaundice indicates more severe liver damage. Although acute liver failure can occur, most drug reactions are self-limiting and chronic liver damage is rare. Abnormal LFTs often take weeks to normalise following a drug-induced hepatitis, and it may be months before they normalise after a cholestatic hepatitis. Occasionally, permanent bile duct loss (ductopenia) follows a cholestatic drug reaction, such as that due to co-amoxiclav, resulting in chronic cholestasis with persistent symptoms such as itching. The key to diagnosing acute drug-induced liver disease is to take a detailed drug history (Box 22.55), looking for temporal relationships between drug exposure and onset of liver abnormality (bearing in mind the fact that liver injury can frequently take weeks or even months to develop following exposure). A liver biopsy should be considered if there is suspicion of pre-existing liver disease or if blood tests fail to improve when the suspect drug is withdrawn. Where drug-induced liver injury is suspected or cannot be excluded, the potential culprit drug should be discontinued unless it is impossible to do so safely. Types of liver injury Different histological patterns of liver injury may occur with drug injury. Cholestasis Pure cholestasis (selective interference with bile flow in the absence of liver injury) can occur with oestrogens; this was common when high concentrations of oestrogens (50 µg/day) were used as contraceptives. Both the current oral contraceptive pill and hormone replacement therapy can be safely used in chronic liver disease. Chlorpromazine and antibiotics such as flucloxacillin are examples of drugs that cause cholestatic hepatitis, which is characterised by inflammation and canalicular injury. Co-amoxiclav is the most common antibiotic to cause abnormal LFTs but, unlike other antibiotics, it may not produce symptoms until 10–42 days after it is stopped. Anabolic glucocorticoids used by body-builders may also cause a cholestatic hepatitis. In some 22.55 Diagnosing acute drug-induced liver disease • Tabulate the drugs taken: Prescribed and self-administered • Establish whether hepatotoxicity is reported in the literature • Relate the time the drugs were taken to the onset of illness: 4 days to 8 weeks (usual) • Establish the effect of stopping the drugs on normalisation of liver biochemistry: Hepatitic liver function tests (2 months) Cholestatic/mixed liver function tests (6 months) N.B. Challenge tests with drugs should be avoided • Exclude other causes: Viral hepatitis Biliary disease • Consider liver biopsy 22.54 Examples of common causes of drug-induced hepatotoxicity Pattern Drug Cholestasis Chlorpromazine High-dose oestrogens Cholestatic hepatitis Non-steroidal anti-inflammatory drugs Co-amoxiclav Statins Acute hepatitis Rifampicin Isoniazid Non-alcoholic steatohepatitis Amiodarone Venous outflow obstruction Busulfan Azathioprine Fibrosis Methotrexate 22.53 Drugs to be avoided in cirrhosis Drug Problem Toxicity Non-steroidal anti-inflammatory drugs Reduced renal blood flow Mucosal ulceration Hepatorenal failure Bleeding varices Angiotensinconverting enzyme inhibitors Reduced renal blood flow Hepatorenal failure Codeine Constipation Hepatic encephalopathy Narcotics Constipation, drug accumulation Hepatic encephalopathy Anxiolytics Drug accumulation Hepatic encephalopathy

Pathophysiology The disease is caused by increased absorption of dietary iron and is inherited as an autosomal recessive trait. Approximately 90% of patients are homozygous for a single point mutation resulting in a cysteine to tyrosine substitution at position 282 (C282Y) in the HFE protein, which has structural and functional similarity to the HLA proteins. The mechanisms by which HFE regulates iron absorption are unclear. It is believed, however, that HFE normally interacts with the transferrin receptor in the basolateral membrane of intestinal epithelial cells. In HHC, it is thought that the lack of functional HFE causes a defect in uptake of transferrin-associated iron, leading to up-regulation of enterocyte iron-specific divalent metal transporters and excessive iron absorption. A histidine-to-aspartic acid mutation at position 63 (H63D) in HFE causes a less severe form of haemochromatosis that is most commonly found in patients who are compound heterozygotes also carrying a C282Y mutated allele. Fewer than 50% of C282Y homozygotes will develop clinical features of haemochromatosis; therefore other factors must also be important. HHC may promote accelerated liver disease in patients with alcohol excess or hepatitis C infection. Iron loss in menstruation and pregnancy can delay the onset of HHC in females. Clinical features Symptomatic disease usually presents in men over 40 years of age with features of liver disease (often with hepatomegaly), type 2 diabetes or heart failure. Fatigue and arthropathy are early symptoms but are frequently absent. Leaden-grey skin pigmentation due to excess melanin occurs, especially in exposed parts, axillae, groins and genitalia: hence the term ‘bronzed diabetes’. Once again, absence of this feature does not preclude the diagnosis. Impotence, loss of libido and testicular atrophy are recognised complications, as are early-onset osteoarthritis targeting unusual sites such as the metacarpophalangeal joints, chondrocalcinosis and pseudogout. Cardiac failure or cardiac dysrhythmia may occur due to iron deposition in the heart. Investigations Serum iron studies show a greatly increased ferritin, a raised plasma iron and saturated plasma iron-binding capacity. Transferrin saturation of more than 45% is suggestive of iron overload. Significant liver disease is unusual in patients with ferritin lower than 1000 µg/L (100 µg/dL). The differential diagnoses for elevated ferritin are inflammatory disease or excess ethanol consumption for modest elevations (< 1000 µg/L (100 µg/dL)). Very significant ferritin elevation can be seen in adult Still’s disease. In terms of imaging techniques, MRI has high specificity for iron overload but poor sensitivity. Liver biopsy allows assessment of fibrosis and distribution of iron (hepatocyte iron characteristic of haemochromatosis). The Hepatic Iron Index (HII) provides quantification of liver iron (µmol of iron per g dry weight of liver/age in years). An HII of more than 1.9 suggests genetic haemochromatosis (Fig. 22.40). Both the C282Y and the H63D mutations can be identified by genetic testing, which is now in routine clinical use. Management Treatment consists of weekly venesection of 500 mL blood (250 mg iron) until the serum iron is normal; this may take 2 years or more. The aim is to reduce ferritin to under 50 µg/L (5 µg/dL). Thereafter, venesection is continued as required to keep the serum ferritin normal. Liver and cardiac problems 22.56 Causes of haemochromatosis Primary haemochromatosis • Hereditary haemochromatosis • Congenital acaeruloplasminaemia • Congenital atransferrinaemia Secondary iron overload • Parenteral iron loading (e.g. repeated blood transfusion) • Iron-loading anaemia (thalassaemia, sideroblastic anaemia, pyruvate kinase deficiency) • Liver disease Complex iron overload • Juvenile haemochromatosis • Neonatal haemochromatosis • Alcoholic liver disease • Porphyria cutanea tarda • African iron overload (Bantu siderosis) outflow obstruction. Chronic overdose of vitamin A can damage the sinusoids and trigger local fibrosis that can result in portal hypertension. Hepatic fibrosis Most drugs cause reversible liver injury and hepatic fibrosis is very uncommon. Methotrexate, however, as well as causing acute liver injury when it is started, can lead to cirrhosis when used in high doses over a long period of time. Risk factors for drug-induced hepatic fibrosis include pre-existing liver disease

and a high alcohol intake. Inherited liver diseases The inherited diseases are an important and probably underdiagnosed group of liver diseases. In addition to the ‘classical’ conditions, such as haemochromatosis and Wilson’s disease, the important role played by the liver in the expression of the inborn errors of metabolism should be remembered, as should the potential for genetic underpinning for intrahepatic cholestasis. Haemochromatosis Haemochromatosis is a condition in which the amount of total body iron is increased; the excess iron is deposited in, and causes damage to, several organs, including the liver. It may be primary or secondary to other diseases (Box 22.56). Hereditary haemochromatosis In hereditary haemochromatosis (HHC), iron is deposited throughout the body and total body iron may reach 20–60 g (normally 4 g). The important organs involved are the liver, pancreatic islets, endocrine glands, joints and heart. In the liver, iron deposition occurs first in the periportal hepatocytes, extending later to all hepatocytes. The gradual development of fibrous septa leads to the formation of irregular nodules, and finally regeneration results in macronodular cirrhosis. An excess of liver iron can occur in alcoholic cirrhosis but this is mild in comparison with haemochromatosis.

 Pathophysiology Normally, dietary copper is absorbed from the stomach and proximal small intestine and is rapidly taken into the liver, where it is stored and incorporated into caeruloplasmin, which is secreted into the blood. The accumulation of excessive copper in the body is ultimately prevented by its excretion, the most important route being via bile. In Wilson’s disease, there is almost always a failure of synthesis of caeruloplasmin; however, some 5% of patients have a normal circulating caeruloplasmin concentration and this is not the primary pathogenic defect. The amount of copper in the body at birth is normal but thereafter it increases steadily; the organs most affected are the liver, basal ganglia of the brain, eyes, kidneys and skeleton. The ATP7B gene encodes a member of the copper-transporting P-type adenosine triphosphatase family, which functions to export copper from various cell types. At least 200 different mutations have been described. Most cases are compound heterozygotes with two different mutations in ATP7B. Attempts to correlate the genotype with the mode of presentation and clinical course have not shown any consistent patterns. The large number of culprit mutations means that, in contrast to haemochromatosis, genetic diagnosis is not routine in Wilson’s disease, although it may have a role in screening families following identification of the genotype in an index patient. Clinical features Symptoms usually arise between the ages of 5 and 45 years. Hepatic disease occurs predominantly in childhood and early adolescence, although it can present in adults in their fifties. Neurological damage causes basal ganglion syndromes and dementia, which tends to present in later adolescence. These features can occur alone or simultaneously. Other manifestations include renal tubular damage and osteoporosis, but these are rarely presenting features. Liver disease Episodes of acute hepatitis, sometimes recurrent, can occur, especially in children, and may progress to fulminant liver failure. The latter is characterised by the liberation of free copper into the blood stream, causing massive haemolysis and renal tubulopathy. Chronic hepatitis can also develop insidiously and eventually present with established cirrhosis; liver failure and portal hypertension may supervene. The possibility of Wilson’s disease should be considered in any patient under the age of 40 presenting with recurrent acute hepatitis or chronic liver disease of unknown cause, especially when this is accompanied by haemolysis. Neurological disease Clinical features include a variety of extrapyramidal features, particularly tremor, choreoathetosis, dystonia, parkinsonism and dementia (Ch. 25). Unusual clumsiness for age may be an early symptom. Neurological disease typically develops after the onset of liver disease and can be prevented by effective treatment started following diagnosis in the liver disease phase. This

increases the importance of diagnosis in the liver phase beyond just allowing effective management of liver disease. Kayser–Fleischer rings These constitute the most important single clinical clue to the diagnosis and can be seen in 60% of adults with Wilson's disease (less often in children but almost always in neurological improve after iron removal, but joint pain is less predictable and can improve or worsen after iron removal. Type 2 diabetes does not resolve after venesection. Other therapy includes that for cirrhosis and diabetes. First-degree family members should be investigated, preferably by genetic screening and also by checking the plasma ferritin and iron-binding saturation. Liver biopsy is indicated in asymptomatic relatives only if the LFTs are abnormal and/or the serum ferritin is greater than 1000 μg/L (100 μg/dL) because these features are associated with significant fibrosis or cirrhosis. Asymptomatic disease should also be treated by venesection until the serum ferritin is normal. Pre-cirrhotic patients with HHC have a normal life expectancy, and even cirrhotic patients have a good prognosis compared with other forms of cirrhosis (three-quarters of patients are alive 5 years after diagnosis). This is probably because liver function is well preserved at diagnosis and improves with therapy. Screening for hepatocellular carcinoma (p. 890) is mandatory because this is the main cause of death, affecting one-third of patients with cirrhosis, irrespective of therapy. Venesection reduces but does not abolish the risk of hepatocellular carcinoma in the presence of cirrhosis. Secondary haemochromatosis Many conditions, including chronic haemolytic disorders, sideroblastic anaemia, other conditions requiring multiple blood transfusion (generally over 50 L), porphyria cutanea tarda, dietary iron overload and occasionally alcoholic cirrhosis, are associated with widespread secondary siderosis. The features are similar to those of primary haemochromatosis but the history and clinical findings point to the true diagnosis. Some patients are heterozygotes for the HFE gene and this may contribute to the development of iron overload. Wilson's disease Wilson's disease (hepatolenticular degeneration) is a rare but important autosomal recessive disorder of copper metabolism caused by a variety of mutations in the ATP7B gene on chromosome 13. Total body copper is increased, with excess copper deposited in, and causing damage to, several organs. Fig. 22.40 Liver histology: haemochromatosis. This Perls stain shows accumulating iron within hepatocytes, which is stained blue. There is also accumulation of large fat globules in some hepatocytes (macrovesicular steatosis). Iron also accumulates in Kupffer cells and biliary epithelial cells.

but this is not necessary to make the diagnosis. Occasionally, patients with liver disease and minor reductions of plasma α1-AT concentrations have α1-AT variants other than PiZZ, but the relationship of these to liver disease is uncertain. There is no specific treatment. The risk of severe and earlyonset emphysema means that all patients should be advised to stop smoking. Gilbert's syndrome Gilbert's syndrome is by far the most common inherited disorder of bilirubin metabolism (see Box 22.17, p. 860). It is an autosomal recessive trait when caused by a mutation in the promoter region of the gene for UDP-glucuronyl transferase enzyme (UGT1A1), which leads to reduced enzyme expression. It can be inherited in a dominant fashion when there is a missense mutation in the gene. This results in decreased conjugation of bilirubin, which accumulates as unconjugated bilirubin in the blood. The levels of unconjugated bilirubin increase during fasting, as fasting reduces levels of UDP-glucuronyl transferase. Clinical features The typical presentation is with isolated elevation of bilirubin, typically, although not exclusively, in the setting of physical stress or illness. There are no stigmata of chronic liver disease other than jaundice. Increased excretion of bilirubin and hence stercobilinogen leads to normal-coloured or dark stools, and

increased urobilinogen excretion causes the urine to turn dark on standing as urobilin is formed. In the presence of haemolysis, pallor due to anaemia and splenomegaly due to excessive reticulo-endothelial activity are usually present. Investigations The plasma bilirubin is usually less than 100 μmol/L (~6 mg/ dL) and the LFTs are otherwise normal. There is no bilirubinuria because the hyperbilirubinaemia is predominantly unconjugated. Hepatic histology is normal and liver biopsy is not recommended for the investigation of patients with possible Gilbert's syndrome. The condition is not associated with liver injury and thus has an excellent prognosis, needs no treatment, and is clinically important only because it may be mistaken for more serious liver disease. Wilson's disease), albeit sometimes only by slit-lamp examination. Kayser–Fleischer rings are characterised by greenish-brown discoloration of the corneal margin appearing first at the upper periphery (p. 846). They disappear with treatment. Investigations A low serum caeruloplasmin is the best single laboratory clue to the diagnosis. Advanced liver failure from any cause can, however, reduce the serum caeruloplasmin and occasionally it is normal in Wilson's disease. Other features of disordered copper metabolism should therefore be sought; these include a high free serum copper concentration, a high urine copper excretion of greater than 0.6 μmol/24 hrs (38 μg/24 hrs) and a very high hepatic copper content. Measuring 24-hour urinary copper excretion while giving D-penicillamine is a useful confirmatory test; more than 25 μmol/24 hrs is considered diagnostic of Wilson's disease. Management The copper-binding agent penicillamine is the drug of choice. The dose given must be sufficient to produce cupriuresis and most patients require 1.5 μg/day (range 1–4 μg). The dose can be reduced once the disease is in remission but treatment must continue for life, even through pregnancy. Care must be taken to ensure that re-accumulation of copper does not occur. Abrupt discontinuation of treatment must be avoided because this may precipitate acute liver failure. Toxic effects occur in one-third of patients and include rashes, protein-losing nephropathy, lupus-like syndrome and bone marrow depression. If these do arise, trientine dihydrochloride (1.2–2.4 μg/day) and zinc (50 mg 3 times daily) are potential alternatives. Liver transplantation is indicated for fulminant liver failure or for advanced cirrhosis with liver failure. The value of liver transplantation in severe neurological Wilson's disease is unclear. Prognosis is excellent, provided treatment is started before there is irreversible damage. Siblings and children of patients with Wilson's disease must be investigated and treatment should be given to all affected individuals, even if they are asymptomatic. Alpha1-antitrypsin deficiency Alpha1-antitrypsin (α1-AT) is a serine protease inhibitor (Pi) produced by the liver. One of its main anti-protease functions is the breakdown of neutrophil elastase. The mutated form of α1-AT (PiZ) cannot be secreted into the blood by liver cells because it is retained within the endoplasmic reticulum of the hepatocyte. Homozygous individuals (PiZZ) have low plasma α1-AT concentrations, although globules containing α1-AT are found in the liver, and these people may develop hepatic and pulmonary disease. Liver manifestations include cholestatic jaundice in the neonatal period (neonatal hepatitis), which can resolve spontaneously; chronic hepatitis and cirrhosis in adults; and, in the long term, HCC. Alpha1-AT deficiency is a not uncommon exacerbating factor for liver disease of other aetiologies, and the possibility of dual pathology should be considered when severity of disease, such as ALD, appears disproportionate to the level of underlying insult. There are no clinical features that distinguish liver disease due to α1-AT deficiency from liver disease due to other causes, and the diagnosis is made from the low plasma α1-AT concentration and genotyping for the presence of the mutation. Alpha1-ATcontaining globules can be demonstrated in the liver (Fig. 22.41) Fig. 22.41 Liver histology in α1-antitrypsin deficiency. Accumulation of periodic acid–Schiff-positive granules (arrows) within individual hepatocytes is shown in this section from a patient with α1-AT deficiency.

898 • HEPATOLOGY Portal vein thrombosis Portal venous thrombosis as a primary event is rare but can occur in any condition predisposing to thrombosis. It may also complicate intra-abdominal inflammatory or neoplastic disease and is a recognised cause of portal hypertension. Acute portal venous thrombosis causes abdominal pain and diarrhoea, and may rarely lead to bowel infarction, requiring surgery. Treatment is otherwise based on anticoagulation, although there are no randomised data that demonstrate efficacy. An underlying thrombophilia needs to be excluded. Subacute thrombosis can be asymptomatic but may subsequently lead to extrahepatic portal hypertension (p. 868). Ascites is unusual in non-cirrhotic portal hypertension, unless the albumin is particularly low. Portal vein thrombosis can arise as a secondary event in patients with cirrhosis and portal hypertension, and is a recognised cause of decompensation in patients with previously stable cirrhosis. In individuals showing such decompensation, portal vein patency should be assessed by ultrasound with Doppler flow studies. Chronic portal vein thrombosis can be a cause of portal hypertension. Hepatopulmonary syndrome This condition is characterised by resistant hypoxaemia ($PaO_2 < 9.3$ kPa (70 mmHg)), intrapulmonary vascular dilatation in patients with cirrhosis, and portal hypertension. Clinical features include finger clubbing, cyanosis, spider naevi and a characteristic reduction in arterial oxygen saturation on standing. The hypoxia is due to intrapulmonary shunting through direct arteriovenous communications. Nitric oxide (NO) over-production may be important in pathogenesis. The hepatopulmonary syndrome can be treated by liver transplantation but, if severe ($PaO_2 < 6.7$ kPa (50 mmHg)), is associated with an increased operative risk. Portopulmonary hypertension This unusual complication of portal hypertension is similar to ‘primary pulmonary hypertension’ (p. 621). It is defined as pulmonary hypertension with increased pulmonary vascular resistance and a normal pulmonary artery wedge pressure in a patient with portal hypertension. The condition is caused by vasoconstriction and obliteration of the pulmonary arterial system and leads to breathlessness and fatigue. Hepatic venous disease Obstruction to hepatic venous blood flow can occur in the small central hepatic veins, the large hepatic veins, the inferior vena cava or the heart (see Fig. 22.20, p. 868). The clinical features depend on the cause and on the speed with which obstruction develops, and can mimic many other forms of chronic liver disease, sometimes leading to delayed diagnosis. Congestive hepatomegaly and ascites are, however, the most consistent features. The possibility of hepatic venous obstruction should always be considered in patients with an atypical liver presentation. Budd–Chiari syndrome This uncommon condition is caused by thrombosis of the larger hepatic veins and sometimes the inferior vena cava. Many patients have haematological disorders such as myelofibrosis, primary proliferative polycythaemia, paroxysmal nocturnal haemoglobinuria, Vascular liver disease Metabolically, the liver is highly active and has large oxygen requirements. This places it at risk of ischaemic injury in settings of impaired perfusion. The risk is mitigated, however, by the dual perfusion of the liver (via the portal vein as well as hepatic artery), with the former representing a low-pressure perfusion system that offers protection against the potential effects of arterial hypotension. The single outflow through the hepatic vein and the low-pressure perfusion system of the portal vein make the liver vulnerable to venous thrombotic ischaemia in the context of Budd–Chiari syndrome and portal vein thrombosis, respectively. Hepatic arterial disease Liver ischaemia Liver ischaemic injury is relatively common during hypotensive or hypoxic events and is under-diagnosed. The characteristic pattern is one of rising transaminase values in the days following such an event (e.g. prolonged seizures). Liver synthetic dysfunction and encephalopathy are uncommon but can occur. Liver failure is very rare. Diagnosis typically rests on clinical suspicion and exclusion of other potential aetiologies. Treatment is aimed at optimising liver perfusion and oxygen delivery. Outcome is dictated by the morbidity and mortality associated

with the underlying disease, given that liver ischaemia frequently occurs in the context of other organ ischaemia in high-risk patients. Liver arterial disease Hepatic arterial disease is rare outside the setting of liver transplantation and is difficult to diagnose. It can cause significant liver damage. Hepatic artery occlusion may result from inadvertent injury during biliary surgery or may be caused by emboli, neoplasms, polyarteritis nodosa, blunt trauma or radiation. It usually causes severe upper abdominal pain with or without signs of circulatory shock. LFTs show raised transaminases (AST or ALT usually > 1000 U/L), as in other causes of acute liver damage. Patients usually survive if the liver and portal blood supply are otherwise normal. Hepatic artery aneurysms are extrahepatic in three-quarters of cases and intrahepatic in one-quarter. Atheroma, vasculitis, bacterial endocarditis and surgical or biopsy trauma are the main causes. They usually lead to bleeding into the biliary tree, peritoneum or intestine and are best diagnosed by angiography. Treatment is radiological or surgical. Any of the vasculitides can affect the hepatic artery but this rarely causes symptoms. Hepatic artery thrombosis is a recognised complication of liver transplantation and typically occurs in the early post-transplant period. Clinical features are often related to bile duct rather than liver ischaemia because of the dominant role of the hepatic artery in extrahepatic bile duct perfusion. Manifestations can include bile duct anastomotic failure with bile leak or the development of late bile duct strictures. Diagnosis and initial intervention are radiological in the first instance, with ERCP and biliary stenting being the principal approaches to the treatment of bile duct injury. Portal venous disease Portal hypertension See page 868.

by widespread occlusion of the small central hepatic veins. Pyrrolizidine alkaloids in Senecio and Heliotropium plants used to make teas, as well as cytotoxic drugs and hepatic irradiation, are all recognised causes. SOS may develop in 10–20% of patients following haematopoietic stem cell transplantation (usually within the first 20 days) and carries a 90% mortality in severe cases. Pathogenesis involves obliteration and fibrosis of terminal hepatic venules due to deposition of red cells, haemosiderin-laden macrophages and coagulation factors. In this setting, SOS is thought to relate to pre-conditioning therapy with irradiation and cytotoxic chemotherapy. The clinical features are similar to those of the Budd–Chiari syndrome (see above). Investigations show evidence of venous outflow obstruction histologically but, in contrast to Budd–Chiari, the large hepatic veins appear patent radiologically. Transjugular liver biopsy (with portal pressure measurements) may facilitate the diagnosis. Traditionally, treatment has been supportive but defibrotide shows promise (the drug binds to vascular endothelial cells, promoting fibrinolysis and suppressing coagulation). Cardiac disease Hepatic damage, due primarily to congestion, may develop in all forms of right heart failure (p. 461); usually, the clinical features are predominantly cardiac. Very rarely, long-standing cardiac failure and hepatic congestion give rise to cardiac cirrhosis. Severe left ventricular dysfunction is a cause of ischaemic hepatitis. Cardiac causes of acute and chronic liver disease are typically under-diagnosed. Treatment is principally that of the underlying heart disease with supportive treatment for the liver component. Nodular regenerative hyperplasia of the liver This is the most common cause of non-cirrhotic portal hypertension in developed countries; it is characterised by small hepatocyte nodules throughout the liver without fibrosis, which can result in sinusoidal compression. It is believed to be due to damage to small hepatic arterioles and portal venules. It occurs in older people and is associated with many conditions, including connective tissue disease, haematological diseases and immunosuppressive drugs, such as azathioprine. The condition is usually asymptomatic but occasionally presents with

portal hypertension or with an abdominal mass. The diagnosis is made by liver biopsy, which, in contrast to cirrhosis, shows nodule formation in the absence of fibrous septa. Liver function is good and the prognosis is very favourable. Management is based on treatment of the portal hypertension. Pregnancy and the liver The inter-relationship between liver disease and pregnancy can be a complex one and a source of real anxiety for both patient and clinician. Three possibilities need to be borne in mind when treating a pregnant woman with a liver abnormality: • This represents a worsening of pre-existing chronic liver or biliary disease (although pregnancy may be the first time a woman's liver biochemistry has been tested, so this may not have previously been diagnosed). • This represents a genuine first presentation of liver disease that is not intrinsically related to pregnancy. • This represents a genuine pregnancy-associated liver injury process. or antithrombin III, protein C or protein S deficiencies (Ch. 23). Pregnancy and oral contraceptive use, obstruction due to tumours (particularly carcinomas of the liver, kidneys or adrenals), congenital venous webs and occasionally inferior vena caval stenosis are the other main causes. The underlying cause cannot be found in about 50% of patients, although this percentage is falling as molecular diagnostic tools (such as the JAK2 mutation in myelofibrosis) increase our capacity to diagnose underlying haematological disorders. Hepatic congestion affecting the centrilobular areas is followed by centrilobular fibrosis, and eventually cirrhosis supervenes in those who survive long enough. Clinical features Acute venous occlusion causes rapid development of upper abdominal pain, marked ascites and occasionally acute liver failure. More gradual occlusion causes gross ascites and, often, upper abdominal discomfort. Hepatomegaly, frequently with tenderness over the liver, is almost always present. Peripheral oedema occurs only when there is inferior vena cava obstruction. Features of cirrhosis and portal hypertension develop in those who survive the acute event. Investigations The LFTs vary considerably, depending on the presentation, and can show the features of acute hepatitis. Ascitic fluid analysis shows a protein concentration above 25 g/L (2.5 g/dL) (exudate) in the early stages; this often falls later in the disease, however. Doppler ultrasound may reveal obliteration of the hepatic veins and reversed flow or associated thrombosis in the portal vein. CT may show enlargement of the caudate lobe, as this often has a separate venous drainage system that is not involved in the disease. CT and MRI may also demonstrate occlusion of the hepatic veins and inferior vena cava. Liver biopsy demonstrates centrilobular congestion with fibrosis, depending on the duration of the illness. Venography is needed only if CT and MRI are unable to demonstrate the hepatic venous anatomy clearly. Management Predisposing causes should be treated as far as possible; where recent thrombosis is suspected, thrombolysis with streptokinase, followed by heparin and oral anticoagulation, should be considered. Ascites is initially treated medically but often with only limited success. Short hepatic venous strictures can be treated with angioplasty. In the case of more extensive hepatic vein occlusion, many patients can be managed successfully by insertion of a covered TIPSS, followed by anticoagulation. Surgical shunts, such as portacaval shunts, are less commonly performed now that TIPSS is available. Occasionally, a web can be resected or an inferior vena caval stenosis dilated. Progressive liver failure is an indication for liver transplantation and life-long anticoagulation. Prognosis without transplantation or shunting is poor, particularly following an acute presentation with liver failure. A 3-year survival of 50% is reported in those who survive the initial event. The 1- and 10-year survival following liver transplantation is 85% and 69%, respectively, and this compares with a 5- and 10-year survival of 87% and 37%, respectively, following surgical shunting. Sinusoidal obstruction syndrome (veno-occlusive disease) Sinusoidal obstruction syndrome (SOS; previously known as veno-occlusive disease) is a rare condition characterised

900 • HEPATOLOGY LFTs in pregnancy, which include pregnancy-associated liver disease, are shown in Box 22.57. Liver transplantation The outcome following liver transplantation has improved significantly over the last decade so that elective transplantation in low-risk individuals now has a 1-year survival rate of more than 90% and is an effective treatment for end-stage liver disease. The number of procedures is limited by cadaveric donor availability and in many parts of the world this has led to living donor transplant programmes. Despite this, 10% of those listed for liver transplantation will die while awaiting a donor liver. The main complications of liver transplantation relate to rejection, complications of long-term immunosuppression and disease recurrence in the liver graft. Indications and contraindications Currently, around 9500 liver transplants are undertaken in Europe and the USA annually. About 10% are performed for acute liver failure, 6% for metabolic diseases, 71% for cirrhosis and 11% for hepatocellular carcinoma. Most patients are under 60 years of age and only 10% are aged between 60 and 70 years. Indications for elective transplant assessment are listed in Box 22.58. In North America, the most common indication is hepatitis C cirrhosis, about 10–20% of transplants being for alcoholic cirrhosis (Fig. 22.42). Patients with alcoholic liver disease need to show a capacity for abstinence. The main contraindications to transplantation are sepsis, extrahepatic malignancy, active alcohol or other substance misuse, and marked cardiorespiratory dysfunction. Patients are matched for ABO blood group and size but do not require HLA matching with donors, as the liver is a relatively immune-privileged organ compared with the heart or kidneys. In many parts of the world, the MELD score (see Box 22.30, p. 868) is used to identify and prioritise patients for transplantation. In the UK, a similar system that also incorporates serum sodium, the United Kingdom End-stage Liver Disease (UKELD) score, is used to guide recipient selection. To be listed for elective (non-super-urgent) transplantation in the UK, patients must have a greater than 50% projected post-transplant 5-year survival and must fall into one of three categories: • Category 1: estimated 1-year mortality without transplantation of more than 9% (equivalent to a UKELD score of more than 49 points) It is critical to obtain information relating to liver disease risk factors and pre-pregnancy liver status to establish whether any abnormality was present before pregnancy. In general, the earlier in pregnancy that liver abnormality presents, the more likely it is to represent either pre-existing liver disease or non-pregnancy-related acute liver disease. Equally, the best outcome for both mother and baby results from optimising the physical condition of the mother, and in situations of deteriorating liver function (which can be steep in late pregnancy) consideration should always be given to early delivery if the fetus is viable. Joint management between hepatologists and obstetricians is essential. Intercurrent and pre-existing liver disease Acute hepatitis A can occur during pregnancy but has no effect on the fetus. Chronic hepatitis B requires identification in pregnancy because of long-term health implications for the mother and the effectiveness of perinatal vaccination (with or without pre-delivery maternal antiviral therapy) in reducing neonatal acquisition of chronic hepatitis B. Maternal transmission of hepatitis C occurs in 1% of cases and there is no convincing evidence that the mode of delivery affects this. Hepatitis E is reported to progress to acute liver failure much more commonly in pregnancy, with a 20% maternal mortality. Pregnancy may be associated with either worsening or improvement of autoimmune hepatitis, although improvement during pregnancy and rebound post-partum is the most common pattern seen. Complications of portal hypertension may be a particular issue in the second and third trimesters. Gallstones (p. 903) are more common during pregnancy and may present with cholecystitis or biliary obstruction. The diagnosis can usually be made with ultrasound. In biliary obstruction due to gallstones, therapeutic ERCP can be safely performed but lead protection for the fetus is essential and X-ray screening must be kept to a minimum. Pregnancy-associated liver disease Several conditions occur

only during pregnancy, may recur in subsequent pregnancies and resolve after delivery of the baby, and these are discussed on page 1283. The causes of abnormal 22.57 Abnormal liver function tests in pregnancy • Liver function tests: alkaline phosphatase (ALP) levels and albumin normally fall in pregnancy. ALP levels can rise due to the contribution of placental ALP. • Pre-existing liver disease: pregnancy is uncommon in cirrhosis because cirrhosis causes relative infertility. Varices can enlarge in pregnancy, and ascites should be treated with amiloride rather than spironolactone. Penicillamine for Wilson's disease and azathioprine for autoimmune liver disease should be continued during pregnancy. Autoimmune liver disease can flare up post-partum. • Incidental: viral, autoimmune and drug-induced hepatitis must be excluded in the presence of an elevated alanine aminotransferase (ALT). Immunoglobulin/vaccination given to the fetus at birth prevents transmission of hepatitis B to the fetus if the mother is infected. Gallstones are more common in pregnancy and post-partum, and are a cause of a raised ALP level. Biliary imaging with ultrasound and magnetic resonance cholangiopancreatography is safe. Endoscopic retrograde cholangiopancreatography to remove stones can be performed safely with shielding of the fetus from radiation. • Pregnancy-related liver diseases: occur predominantly in the third trimester and resolve post-partum. Maternal and fetal mortality and morbidity are reduced by expediting delivery. 22.58 Indications for liver transplant assessment for cirrhosis Complications • First episode of bacterial peritonitis • Diuretic-resistant ascites • Recurrent variceal haemorrhage • Hepatocellular carcinoma < 5 cm • Persistent hepatic encephalopathy Poor liver function • Bilirubin > 100 µmol/L (5.8 mg/dL) in primary biliary cholangitis • MELD score > 12 (Box 22.30, p. 868) • Child–Pugh grade C (Box 22.29, p. 867) (MELD = Model for End-stage Liver Disease)

Technical complications These include hepatic artery thrombosis, which may necessitate re-transplantation. Anastomotic biliary strictures can also occur; these may respond to endoscopic balloon dilatation and stenting, or require surgical reconstruction. Portal vein thrombosis is rare. Rejection Less immunosuppression is needed following liver transplantation than with kidney or heart/lung grafting. Initial immunosuppression is usually with tacrolimus or ciclosporin, prednisolone and azathioprine or mycophenolate. Some patients can eventually be maintained on a single agent. Acute cellular rejection occurs in 60–80% of patients, commonly at 5–10 days post-transplant and usually within the first 6 weeks, but can arise at any point. This normally responds to 3 days of high-dose intravenous methylprednisolone. Infections Bacterial infections, such as pneumonia and wound infections, can occur in the first few weeks after transplantation. Cytomegalovirus (primary infection or reactivation) is a common infection in the 3 months after transplantation and can cause hepatitis. Patients who have never had cytomegalovirus infection but who receive a liver from a donor who has been exposed are at greatest risk of infection and are usually given prophylactic antiviral therapy, such as valganciclovir. Herpes simplex virus reactivation or, rarely, primary infection may occur. Prophylaxis is given to recipients who have had previous exposure to tuberculosis for the first 6 months after transplantation to prevent reactivation. Late complications These include recurrence of the initial disease in the graft and complications due to the immunosuppressive therapy, such as renal impairment from ciclosporin. Metabolic syndrome (p. 730) is common, being described in about 50% of transplant recipients within 6 months in the USA. Chronic vascular rejection is rare, occurring in only 5% of cases. Prognosis The outcome following transplantation for acute liver failure is worse than that for chronic liver disease because most patients have multi-organ failure at the time of transplantation.

The 1-year survival is 65% and falls only a little to 59% at 5 years. The 1-year survival for patients with cirrhosis is over 90%, falling to 70–75% at 5 years. • Category 2: HCC diagnosed radiologically by two concordant modalities; based on CT, a single lesion of less than 5 cm maximum diameter, or fewer than three lesions each less than 3 cm in diameter, without macrovascular invasion or metastases. • Category 3: 'variant syndromes', including diuretic-resistant ascites, hepatopulmonary syndrome, chronic hepatic encephalopathy, intractable pruritus, familial amyloidosis, primary hyperlipidaemia, polycystic liver disease and recurrent cholangitis. Super-urgent listing is reserved for patients with acute liver failure, according to specific criteria. Two types of transplant are increasingly used because of insufficient cadaveric donors: • Split liver transplantation. A cadaveric donor liver can be split into two, with the larger right lobe used in an adult and the smaller left lobe used in a child. This practice has led to an increase in procedures despite a shortage of donor organs. • Living donor transplantation. This is normally performed using the left lateral segment or the right lobe. The donor mortality is significant at 0.5–1%. Pre-operative assessment includes looking at donor liver size and psychological status. Complications Early complications Primary graft non-function This is a state of hepatocellular dysfunction arising as a consequence of liver paresis, which results from ischaemia following removal from the donor and prior to reperfusion in the recipient. Factors that increase the likelihood of primary non-function include increasing donor age, degree of steatosis in the liver and the length of ischaemia. Treatment is supportive until recovery of function. Occasionally, recovery is not seen and re-transplantation is necessary. Fig. 22.42 Indications for elective adult liver transplantation in the UK, 2016. Hepatitis C Hepatocellular carcinoma Alcohol Hepatitis B Primary biliary cholangitis Primary sclerosing cholangitis Autoimmune liver disease Cryptogenic Other 24% 6% 6% 26% 2% 11% 9% 5% 11% 22.59 Liver disease in old age • Alcoholic liver disease: 10% of cases present over the age of 70 years, when disease is more likely to be severe and has a worse prognosis. • Hepatitis A: causes more severe illness and runs a more protracted course. • Primary biliary cholangitis: one-third of cases are over 65 years. • Liver abscess: more than 50% of all cases in the UK are over 60 years. • Hepatocellular carcinoma: approximately 50% of cases in the UK present over the age of 65 years. • Surgery: older people are less likely to survive liver surgery (including transplantation) because comorbidity is more prevalent.

 Caroli's disease This very rare disease is characterised by segmental saccular dilatations of the intrahepatic biliary tree. The whole liver is usually affected and extrahepatic biliary dilatation occurs in about one-quarter of patients. Recurrent attacks of cholangitis (see Box 22.18, p. 861) may cause hepatic abscesses. Complications include biliary stones and cholangiocarcinoma. Antibiotics are required for episodes of cholangitis. Occasionally, localised disease can be treated by segmental liver resection, and liver transplantation may sometimes be required. Congenital hepatic fibrosis This is characterised by broad bands of fibrous tissue linking the portal tracts in the liver, abnormalities of the interlobular bile ducts and sometimes a lack of portal venules. The renal tubules may show cystic dilatation (medullary sponge kidney; p. 433), and eventually renal cysts may develop. The condition can be inherited as an autosomal recessive trait. Liver involvement causes portal hypertension with splenomegaly and bleeding from oesophageal varices that usually presents in adolescence or in early adult life. The prognosis is good because liver function is preserved. Treatment may be required for variceal bleeding and occasionally cholangitis. Patients can present during childhood with renal failure if the kidneys are severely affected. Cystic fibrosis Cystic fibrosis (p. 580) is associated with biliary cirrhosis in about 5% of individuals. Splenomegaly and an elevated ALP are characteristic. Complications do not

normally arise until late adolescence or early adulthood, when bleeding due to variceal haemorrhage may occur. UDCA improves liver blood tests but it is not known whether the drug can prevent progression of liver disease. Deficiency of fat-soluble vitamins (A, D, E and K) may need to be treated in view of both biliary and pancreatic disease. Extrahepatic biliary disease Diseases of the extrahepatic biliary tree typically present with the clinical features of impaired bile flow (obstructive jaundice and fat Cholestatic and biliary disease The concepts of biliary and cholestatic disease, and the important distinctions between them, can be a source of confusion. ‘Cholestasis’ relates to a biochemical abnormality (typically, elevation of ALP and elevation in serum bile acid levels and bilirubin) that results from an abnormality in bile flow. The cause can range from inherited or acquired dysfunction of transporter molecules responsible for the production of canalicular bile to physical obstruction of the extrahepatic bile duct. ‘Biliary disease’ relates to pathology at any level from the small intrahepatic bile ducts to the sphincter of Oddi. Although there is very significant overlap between cholestatic and biliary disease, there are scenarios where cholestasis can exist without biliary disease (transporter disease or pure drug-induced cholestasis) and where biliary disease can exist without cholestasis (when disease of the bile duct does not impact on bile flow). These anomalies should always be borne in mind and cholestasis and biliary disease always effectively distinguished. Chemical cholestasis Pure cholestasis can occur as an inherited condition (p. 895), as a consequence of cholestatic drug reactions (p. 894) or as acute cholestasis of pregnancy (p. 1284). A more frequent, but less recognised, acquired biochemical cholestasis occurs in sepsis (‘cholangitis lente’). This biochemical phenomenon is one of the causes of LFT abnormality in sepsis, does not require specific treatment, and has a prognostic significance conferred by the underlying septic process. Mutations in the biliary transporter proteins on the hepatocyte canalicular membrane (familial intrahepatic cholestasis 1, FIC1), illustrated in Figure 22.7 (p. 851), have been shown to cause an inherited intrahepatic biliary disease in childhood, characterised by raised ALP levels and progression to a biliary cirrhosis. It is also becoming increasingly clear that these proteins contribute to intrahepatic biliary disease in adulthood. Benign recurrent intrahepatic cholestasis This rare condition usually presents in adolescence and is characterised by recurrent episodes of cholestasis, lasting 1–6 months. It is now known to be mediated by mutations in the ATP8B1 gene, which lies on chromosome 18 and encodes FIC1. Episodes start with pruritus, while painless jaundice develops later. LFTs show a cholestatic pattern. Liver biopsy shows cholestasis during an episode but is normal between episodes. Treatment is required to relieve the symptoms of cholestasis, such as pruritus, and the long-term prognosis is good. Intrahepatic biliary disease Inflammatory and immune disease The small intrahepatic bile ducts appear to be specifically vulnerable to immune injury, and ductopenic injury (‘vanishing bile duct syndrome’) can be a feature of a number of chronic conditions, including graft-versus-host disease (GVHD), sarcoidosis and, in the setting of liver transplantation, ductopenic rejection. Intrahepatic small bile duct injury occurs most frequently in primary biliary cholangitis, an autoimmune cholestatic disease, and less frequently in primary sclerosing cholangitis (Box 22.60). 22.60 Comparison of primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) PBC PSC Gender (F : M) 10 : 1 1 : 3 Age Older: median age 50–55 years Younger: median age 20–40 years Disease associations Non-organ-specific autoimmune disease (e.g. Sjögren’s syndrome) and autoimmune thyroid disease Ulcerative colitis Autoantibody profile 90% AMA +ve 65–85% pANCA +ve (but this is non-specific and not diagnostic) Predominant bile-duct injury Intrahepatic Extrahepatic > intrahepatic (AMA = antimitochondrial antibody; pANCA = perinuclear antineutrophil cytoplasmic antibody)

cholesterol, fat, total calories and refined carbohydrate or lack of dietary fibre has been implicated. Pathophysiology Gallstones are conventionally classified into cholesterol or pigment stones, although the majority are of mixed composition. Gallstones contain varying quantities of calcium salts, including calcium bilirubinate, carbonate, phosphate and palmitate, which are radio-opaque. Gallstone formation is multifactorial and the factors involved are related to the type of gallstone (Boxes 22.61 and 22.62). Cholesterol gallstones Cholesterol is held in solution in bile by its association with bile acids and phospholipids in the form of micelles and vesicles. Biliary lipoproteins may also have a role in solubilising cholesterol. In gallstone disease, the liver produces bile that contains an excess of cholesterol because there is either a relative deficiency of bile salts or a relative excess of cholesterol ('lithogenic' bile). Abnormalities of bile salt synthesis and circulation, cholesterol secretion and gallbladder function may make production of lithogenic bile more likely. Pigment stones Brown, crumbly pigment stones are almost always the consequence of bacterial or parasitic biliary infection. They are common in the Far East, where infection allows bacterial β-glucuronidase to hydrolyse conjugated bilirubin to its free form, malabsorption). Obstructive disease is frequently a consequence of stricturing following gallstone passage and associated infection and inflammation or post-surgical intervention. PSC frequently involves the extrahepatic biliary tree and its differential, IgG4 disease, is an important and potentially treatable cause of disease (p. 890). Malignant diseases (cholangiocarcinoma or carcinoma of the head of pancreas) should be considered in all patients with extrahepatic biliary obstruction). Choledochal cysts This term applies to cysts anywhere in the biliary tree (Fig. 22.43). The great majority cause diffuse dilatation of the common bile duct (type I) but others take the form of biliary diverticula (type II), dilatation of the intraduodenal bile duct (type III) and multiple biliary cysts (type IV). The last type merges with Caroli's disease (see above). In the neonate, they may present with jaundice or biliary peritonitis. Recurrent jaundice, abdominal pain and cholangitis may arise in the adult. Liver abscess and biliary cirrhosis may develop and there is an increased incidence of cholangiocarcinoma. Excision of the cyst with hepatico-jejunostomy is the treatment of choice. Secondary biliary cirrhosis Secondary biliary cirrhosis develops after prolonged large duct biliary obstruction due to gallstones, benign bile duct strictures or sclerosing cholangitis (see below). Carcinomas rarely cause secondary biliary cirrhosis because few patients survive long enough. The clinical features are those of chronic cholestasis with episodes of ascending cholangitis or even liver abscess (p. 879). Cirrhosis, ascites and portal hypertension are late features. Relief of biliary obstruction may require endoscopic or surgical intervention. Cholangitis dictates treatment with antibiotics, which can be given continuously if attacks recur frequently. Gallstones Gallstone formation is the most common disorder of the biliary tree and it is unusual for the gallbladder to be diseased in the absence of gallstones. In developed countries, gallstones occur in 7% of males and 15% of females aged 18–65 years, with an overall prevalence of 11%. In individuals under 40 years there is a 3 : 1 female preponderance, whereas in the elderly the sex ratio is about equal. Gallstones are less frequent in India, the Far East and Africa. There has been much debate over the role of diet in cholesterol gallstone disease; an increase in dietary Fig. 22.43 Classification and frequency of choledochal cysts. From Shearman DC, Finlayson NDC. Diseases of the gastrointestinal tract and liver, 2nd edn. Edinburgh: Churchill Livingstone, Elsevier Ltd; 1989. Type I (87%) Type II (7%) Type III (3%) Type IV (3%) 22.62 Composition of and risk factors for pigment stones Black Brown Composition Polymerised calcium bilirubinates* Calcium bilirubinate crystals* Mucin glycoprotein Mucin glycoprotein Calcium phosphate Cholesterol Calcium carbonate Calcium

palmitate/stearate Cholesterol Risk factors Haemolysis Infected bile Age Stasis Hepatic cirrhosis Ileal resection/disease *Major component. 22.61 Risk factors and mechanisms for cholesterol gallstones ↑Cholesterol secretion • Old age • Female gender • Pregnancy • Obesity • Rapid weight loss Impaired gallbladder emptying • Pregnancy • Gallbladder stasis • Fasting • Total parenteral nutrition • Spinal cord injury ↓Bile salt secretion • Pregnancy

 15% of patients and cause biliary colic. Rarely, fistulae develop between the gallbladder and the duodenum, colon or stomach. If this occurs, air will be seen in the biliary tree on plain abdominal X-rays. If a stone larger than 2.5 cm in diameter has migrated into the gut, it may impact either at the terminal ileum or occasionally in the duodenum or sigmoid colon. The resultant intestinal obstruction may be followed by ‘gallstone ileus’. Gallstones impacted in the cystic duct may cause stricturing of the common hepatic duct and the clinical picture of extrahepatic biliary diseases (‘Mirizzi’s syndrome’, with its important differential of malignant bile duct stricture). The more common cause of jaundice due to gallstones is a stone passing from the cystic duct into the common bile duct (choledocholithiasis), which may also result in cholangitis or acute pancreatitis. It is usually very small stones that precipitate acute pancreatitis, due (it is thought) to oedema at the ampulla as the stone passes into the duodenum (no stone is seen within the bile duct in 80% of cases of presumed gallstone pancreatitis, suggesting stone passage). Previous stone passage is also the likely cause of most cases of benign papillary fibrosis, which is most commonly seen in patients with previous or present gallstone disease (it may present with jaundice, obstructive LFTs with biliary dilatation, post-cholecystectomy pain or acute pancreatitis). Cancer of the gallbladder is growing in frequency (p. 907) but in over 95% of cases is associated with the presence of gallstones. Previously, the diagnosis was typically made as an incidental histological finding following cholecystectomy for gallstone disease. Increasing awareness of the risk of gallbladder carcinoma and of the role played by polyps in the natural history has led to an increase in screening activity and prospective diagnosis. Investigations Ultrasound is the investigation of choice for diagnosing gallstones. Most stones are diagnosed by transabdominal ultrasound, which has more than 92% sensitivity and 99% specificity for gallbladder stones (see Fig. 22.8, p. 854). CT, MRCP (Fig. 22.44) and, increasingly, EUS are excellent modalities for detecting complications of gallstones (distal bile duct stone or gallbladder empyema) but are inferior to ultrasound in defining which then precipitates as calcium bilirubinate. The mechanism of black pigment gallstone formation in developed countries is not satisfactorily explained. Haemolysis is important as a contributing factor for the development of black pigment stones that occur in chronic haemolytic disease. Biliary sludge This describes gelatinous bile that contains numerous microspheroliths of calcium bilirubinate granules and cholesterol crystals, as well as glycoproteins; it is an important precursor to the formation of gallstones in the majority of patients. Biliary sludge is frequently formed under normal conditions but then either dissolves or is cleared by the gallbladder; only in about 15% of patients does it persist to form cholesterol stones. Fasting, parenteral nutrition and pregnancy are also associated with sludge formation. Clinical features Only 10% of individuals with gallstones develop clinical evidence of gallstone disease. Symptomatic stones within the gallbladder (Box 22.63) manifest as either biliary pain (‘biliary colic’) or cholecystitis (see below). If a gallstone becomes acutely impacted in the cystic duct, the patient will experience pain. The term ‘biliary colic’ is a misnomer because the pain does not rhythmically increase and decrease in intensity like other forms of colic. Typically, the pain occurs suddenly and persists for about 2 hours; if it continues for more than 6 hours, a complication such as cholecystitis or pancreatitis may be present. Pain is usually felt in the epigastrium (70% of patients)

or right upper quadrant (20%) and radiates to the interscapular region or the tip of the right scapula, but other sites include the left upper quadrant and the lower chest. The pain can mimic intrathoracic disease, oesophagitis, myocardial infarction or dissecting aortic aneurysm. Combinations of fatty food intolerance, dyspepsia and flatulence not attributable to other causes have been referred to as ‘gallstone dyspepsia’. These symptoms are not now recognised as being caused by gallstones and are best regarded as functional dyspepsia (p. 779). Acute and chronic cholecystitis is described below. A mucocele may develop if there is slow distension of the gallbladder from continuous secretion of mucus; if this material becomes infected, an empyema supervenes. Calcium may be secreted into the lumen of the hydropic gallbladder, causing ‘limey’ bile, and if calcium salts are precipitated in the gallbladder wall, the radiological appearance of ‘porcelain’ gallbladder results. Gallstones in the gallbladder (cholecystolithiasis) migrate to the common bile duct (choledocholithiasis; p. 906) in approximately 22.63 Clinical features and complications of gallstones Clinical features • Asymptomatic (80%) • Biliary colic • Acute cholecystitis • Chronic cholecystitis Complications • Empyema of the gallbladder • Porcelain gallbladder • Choledocholithiasis • Acute pancreatitis • Fistulae from gallbladder to duodenum/colon • Pressure on/inflammation of the common hepatic duct by a gallstone in the cystic duct (Mirizzi’s syndrome) • Gallstone ileus • Cancer of the gallbladder Fig. 22.44 Magnetic resonance cholangiopancreatogram showing multiple stones in the gallbladder (long arrow) and also within the distal common bile duct (inset, arrow).

Investigations Peripheral blood leucocytosis is common, except in the elderly patient, in whom the signs of inflammation may be minimal. Minor increases of transaminases and amylase may be encountered. Amylase should be measured to detect acute pancreatitis (p. 837), which may be a potentially serious complication of gallstones. Only when the amylase is higher than 1000 U/L can pain be confidently attributed to acute pancreatitis, since moderately elevated levels of amylase can occur with many other causes of abdominal pain. Plain X-rays of the abdomen and chest may show radio-opaque gallstones, and rarely intrabiliary gas due to fistulation of a gallstone into the intestine; they are important in excluding lower lobe pneumonia and a perforated viscus. Ultrasonography detects gallstones and gallbladder thickening due to cholecystitis but gallbladder empyema or perforation is best assessed by CT. Management Medical Medical management consists of bed rest, pain relief, antibiotics and intravenous fluids. Moderate pain can be treated with NSAIDs but more severe pain should be managed with opiates. A cephalosporin (such as cefuroxime) or piperacillin/tazobactam is the usual antibiotic of choice, but metronidazole is normally added in severely ill patients and local prescribing practice may vary. Nasogastric aspiration is needed only for persistent vomiting. Cholecystitis usually resolves with medical treatment but the inflammation may progress to an empyema or perforation and peritonitis. Surgical Urgent surgery is the optimal treatment when cholecystitis progresses in spite of medical therapy and when complications such as empyema or perforation develop. Operation should be carried out within 5 days of the onset of symptoms. Delayed surgery after 2–3 months is no longer favoured. When cholecystectomy may be difficult due to extensive inflammatory change, percutaneous gallbladder drainage can be performed, with subsequent cholecystectomy 4–6 weeks later. Recurrent biliary colic or cholecystitis is frequent if the gallbladder is not removed. Chronic cholecystitis Chronic inflammation of the gallbladder is almost invariably associated with gallstones. The usual symptoms are those of recurrent attacks of upper abdominal pain, often at

night and following a heavy meal. The clinical features are similar to those of acute calculous cholecystitis but milder. Patients may recover spontaneously or following analgesia and antibiotics. They are usually advised to undergo elective laparoscopic cholecystectomy. Acute cholangitis Acute cholangitis is caused by bacterial infection of bile ducts and occurs in patients with other biliary problems, such as choledocholithiasis (see below), biliary strictures or tumours, or after ERCP. Jaundice, fever (with or without rigors) and right upper quadrant pain are the main presenting features ('Charcot's triad'). Treatment is with antibiotics, relief of biliary obstruction and removal (if possible) of the underlying cause. 22.64 Treatment of gallstones Gallbladder stones • Cholecystectomy: laparoscopic or open • Oral bile acids: chenodeoxycholic or ursodeoxycholic (low rate of stone dissolution) Bile duct stones • Lithotripsy (endoscopic or extracorporeal shock wave, ESWL) • Endoscopic sphincterotomy and stone extraction • Surgical bile duct exploration their presence in the gallbladder. When recurrent attacks of otherwise unexplained acute pancreatitis occur, they may result from 'microlithiasis' in the gallbladder or common bile duct and are best assessed by EUS. Management Asymptomatic gallstones found incidentally should not be treated because the majority will never cause symptoms. Symptomatic gallstones are best treated surgically by laparoscopic cholecystectomy; the severity of symptoms should be balanced against the individual patient surgical risk in order to decide whether surgery is warranted. Various techniques can be used to treat common bile duct stones (Box 22.64). Cholecystitis Acute cholecystitis Pathophysiology Acute cholecystitis is almost always associated with obstruction of the gallbladder neck or cystic duct by a gallstone. Occasionally, obstruction may be by mucus, parasitic worms or a biliary tumour, or may follow endoscopic bile duct stenting. The pathogenesis is unclear but the initial inflammation is possibly chemically induced. This leads to gallbladder mucosal damage, which releases phospholipase, converting biliary lecithin to lysolecithin, a recognised mucosal toxin. At the time of surgery, approximately 50% of cultures of the gallbladder contents are sterile. Infection occurs eventually, and in elderly patients or those with diabetes mellitus a severe infection with gas-forming organisms can cause emphysematous cholecystitis. Acalculous cholecystitis can occur in the intensive care setting and in association with parenteral nutrition, sickle cell disease and diabetes mellitus. Clinical features The cardinal feature is pain in the right upper quadrant but also in the epigastrium, the right shoulder tip or the interscapular region. Differentiation between biliary colic (p. 904) and acute cholecystitis may be difficult; features suggesting cholecystitis include severe and prolonged pain, fever and leucocytosis. Examination shows right hypochondrial tenderness, rigidity worse on inspiration (Murphy's sign) and occasionally a gallbladder mass (30% of cases). Fever is present but rigors are unusual. Jaundice occurs in less than 10% of patients and is usually due to passage of stones into the common bile duct, or to compression or even stricturing of the common bile duct following stone impaction in the cystic duct (Mirizzi's syndrome). Gallbladder perforation occurs in 10–15% of cases and gallbladder empyema may arise.

 cause of the obstruction in the common bile duct; 50% of bile duct stones are missed on ultrasound, particularly those in the distal common bile duct. EUS is extremely accurate at identifying bile duct stones. MRCP is non-invasive and is indicated when intervention is not necessarily mandatory (e.g. the patient with possible bile duct stones but no jaundice or sepsis). Management Cholangitis should be treated with analgesia, intravenous fluids and broad-spectrum antibiotics, such as cefuroxime and metronidazole (local prescribing practice may vary). Blood cultures should be taken before the antibiotics are administered. Patients also require urgent decompression of the biliary tree and stone removal. ERCP with biliary sphincterotomy and stone

extraction is the treatment of choice and is successful in about 90% of patients. If ERCP fails, other approaches include percutaneous transhepatic drainage and combined (‘rendezvous’) endoscopic procedures, extracorporeal shock wave lithotripsy (ESWL) and surgery. Surgical treatment of choledocholithiasis is performed less frequently than ERCP, and before the common bile duct is explored the diagnosis of choledocholithiasis should be confirmed by intraoperative cholangiography. If gallstones are found, the bile duct is explored, either via the cystic duct or by opening it, all stones are removed, clearance is checked by cholangiography or choledochoscopy, and then primary closure of the duct is performed if possible. External drainage of the common bile duct by T-tube is rarely required nowadays. It is now possible to achieve these goals laparoscopically in specialist centres. Recurrent pyogenic cholangitis This disease occurs predominantly in South-east Asia. Biliary sludge, calcium bilirubinate concretions and stones accumulate in the intrahepatic bile ducts, with secondary bacterial infection. Patients present with recurrent attacks of upper abdominal pain, fever and cholestatic jaundice. Investigation of the biliary tree demonstrates that both the intrahepatic and the extrahepatic portions are filled with soft biliary mud. Eventually, the liver becomes scarred and liver abscesses and secondary biliary cirrhosis develop. The condition is difficult to manage and requires Choledocholithiasis Stones in the common bile duct (choledocholithiasis) occur in 10–15% of patients with gallstones (Fig. 22.45), which have usually migrated from the gallbladder. Primary bile duct stones are rare but can develop within the common bile duct many years after a cholecystectomy, and are sometimes related to biliary sludge arising from dysfunction of the sphincter of Oddi. In Far Eastern countries, primary common bile duct stones are thought to follow bacterial infection secondary to parasitic infections with Clonorchis sinensis, Ascaris lumbricoides or Fasciola hepatica (pp. 297 and 289). Common bile duct stones can cause bile duct obstruction and may be complicated by cholangitis due to secondary bacterial infection, sepsis, liver abscess and biliary stricture. Clinical features Choledocholithiasis may be asymptomatic, may be found incidentally by operative cholangiography at cholecystectomy, or may manifest as recurrent abdominal pain with or without jaundice. The pain is usually in the right upper quadrant, and fever, pruritus and dark urine may be present. Rigors may be a feature; jaundice is common and usually associated with pain. Physical examination may show the scar of a previous cholecystectomy; if the gallbladder is present, it is usually small, fibrotic and impalpable. Investigations The LFTs show a cholestatic pattern and there is bilirubinuria. If cholangitis is present, the patient usually has a leucocytosis. The most convenient method of demonstrating obstruction to the common bile duct is transabdominal ultrasound. This shows dilated extrahepatic and intrahepatic bile ducts, together with gallbladder stones (Fig. 22.46), but does not always reveal the Fig. 22.45 Endoscopic retrograde cholangiopancreatogram showing common duct stones (arrows). Fig. 22.46 Endoscopic ultrasound image in a patient with cholangitis. The dilated common bile duct (CBD) contains a small stone (arrow), which causes acoustic shadowing. CBD

tumour is associated with gallstones, primary and secondary sclerosing cholangitis, Caroli’s disease and choledochal cysts (see Fig. 22.43). In the Far East, particularly northern Thailand, chronic liver fluke infection (Clonorchis sinensis) is a major risk factor for the development of CCA in men. Primary sclerosing cholangitis carries a lifetime risk of CCA of approximately 20%, although only 5% of CCAs relate to primary sclerosing cholangitis. Chronic biliary inflammation appears to be a common factor in the development of biliary dysplasia and cancer that is shared by all the

predisposing causes. Tumours typically invade the lymphatics and adjacent vessels, with a predilection for spread within perineural sheaths. The presentation is usually with obstructive jaundice. About 50% of patients also have upper abdominal pain and weight loss. The diagnosis is made using a combination of CT and MRI (see Fig. 22.10, p. 855) but can be difficult to confirm in patients with sclerosing cholangitis. Serum levels of the tumour marker CA19-9 are elevated in up to 80% of cases, although this may occur in biliary obstruction of any cause. In the setting of biliary obstruction, ERCP may result in positive biliary cytology. Endoscopic ultrasound–fine needle aspiration (EUS-FNA) of bile duct masses is sometimes possible, and in specialist centres single-operator cholangioscopy with biopsy is now established. CCAs can be treated surgically in about 20% of patients, which improves 5-year survival from less than 5% to 20–40%. Surgery involves excision of the extrahepatic biliary tree with or without a liver resection and a Roux loop reconstruction. However, most patients are treated by stent insertion across the malignant biliary stricture, using endoscopic or percutaneous transhepatic techniques (Fig. 22.47). Combination chemotherapy is increasingly used and palliation with endoscopic photodynamic therapy has provided encouraging results. Carcinoma at the ampulla of Vater Nearly 40% of all adenocarcinomas of the small intestine arise in relationship to the ampulla of Vater and present with pain, anaemia, vomiting and weight loss. Jaundice may be intermittent or persistent. The diagnosis is made by duodenal endoscopy and biopsy of the tumour but staging by CT/MRI and EUS is essential. Ampullary carcinoma must be differentiated from carcinoma of drainage of the biliary tract with extraction of stones, antibiotics and, in certain patients, partial resection of damaged areas of the liver. Tumours of the gallbladder and bile duct Carcinoma of the gallbladder This is an uncommon tumour, occurring more often in females and usually in those over the age of 70 years. More than 90% are adenocarcinomas; the remainder are anaplastic or, rarely, squamous tumours. Gallstones are present in 70–80% of cases and are thought to be important in the aetiology of the tumour. Individuals with a calcified gallbladder (‘porcelain gallbladder’; p. 904) are at high risk of malignant change, and gallbladder polyps over 1 cm in size are associated with increased risk of malignancy; preventative cholecystectomy should be considered in such patients. Chronic infection with Salmonella, especially in areas where typhoid is endemic, is also a risk factor. Carcinoma of the gallbladder may be diagnosed incidentally and is found in 1–3% of gallbladders removed at cholecystectomy for gallstone disease. It may manifest as repeated attacks of biliary pain and, later, persistent jaundice and weight loss. A gallbladder mass may be palpable in the right hypochondrium. LFTs show cholestasis, and porcelain gallbladder may be found on X-ray. The tumour can be diagnosed by ultrasonography and staged by CT. The treatment is surgical excision but local extension of the tumour beyond the wall of the gallbladder into the liver, lymph nodes and surrounding tissues is invariable and palliative management is usually all that can be offered. Survival is generally short, death typically occurring within 1 year in patients presenting with symptoms. Cholangiocarcinoma Cholangiocarcinoma (CCA) is an uncommon tumour that can arise anywhere in the biliary tree, from the intrahepatic bile ducts (20–25% of cases) and the confluence of the right and left hepatic ducts at the liver hilum (50–60%) to the distal common bile duct (20%). It accounts for only 1.5% of all cancers but the incidence is increasing. The cause is unknown but the Fig. 22.47 Cholangiocarcinoma. A Endoscopic retrograde cholangiopancreatogram showing a malignant distal biliary stricture (arrow) and dilated duct above this. B A self-expanding metallic stent (SEMS) has been placed across the stricture to relieve jaundice (arrow). B A

 Functional biliary sphincter disorders (‘sphincter of Oddi dysfunction’) The sphincter of Oddi is a small smooth-muscle sphincter situated at the junction of the bile duct and

pancreatic duct in the duodenum. It has been believed that sphincter of Oddi dysfunction (SOD) was characterised by an increase in contractility that produces a benign non-calculous obstruction to the flow of bile or pancreatic juice. This may cause pancreaticobiliary pain, deranged LFTs or recurrent pancreatitis. Classification systems, based on clinical history, laboratory results, findings on investigation and response to interventions, are difficult because of the fluctuating nature of symptoms and the well-recognised placebo effect of interventions. SOD was previously classified into types I–III but these have been replaced by newer terminology (Boxes 22.66 and 22.67). Clinical features Patients with functional biliary sphincter disorders, who are predominantly female, present with symptoms and signs suggestive of either biliary or pancreatic disease: • Patients with biliary sphincter disorders experience recurrent, episodic biliary-type pain. They have often had a cholecystectomy but the gallbladder may be intact. • Patients with pancreatic sphincter disorders usually present with unexplained recurrent attacks of pancreatitis. Investigations The diagnosis is established by excluding gallstones, including microlithiasis, and by demonstrating a dilated or slowly draining bile duct. The gold standard for diagnosis is sphincter of Oddi manometry. This is not widely available, however, and is associated with a high rate of procedure-related pancreatitis. Hepatobiliary scintigraphy (e.g. hepatobiliary iminodiacetic acid) may have value in the second-line investigation of post-cholecystectomy syndrome. the head of the pancreas and a CCA because these last two conditions both have a worse prognosis. Imaging may show a ‘double duct sign’ with stricturing of both the common bile duct and pancreatic duct at the ampulla and upstream dilatation of the ducts. EUS is the most sensitive method of assessing and staging ampullary or periampullary tumours. Curative surgical treatment can be undertaken by pancreaticoduodenectomy and the 5-year survival may be as high as 50%. If resection is impossible, palliative surgical bypass or stenting may be necessary. Benign gallbladder tumours These are uncommon, often asymptomatic and usually found incidentally at operation or postmortem. Cholesterol polyps, sometimes associated with cholesterolosis, papillomas and adenomas, are the main types. Miscellaneous biliary disorders Post-cholecystectomy syndrome Dyspeptic symptoms following cholecystectomy (postcholecystectomy syndrome) occur in about 30% of patients, depending on how the condition is defined, how actively symptoms are sought and what the original indication for cholecystectomy was. The syndrome occurs most frequently in women, in patients who have had symptoms for more than 5 years before cholecystectomy, and in cases when the operation was undertaken for non-calculous gallbladder disease. An increase in bowel habit resulting from bile acid diarrhoea occurs in about 5–10% of patients after cholecystectomy and often responds to colestyramine (4–8 g daily). Severe post-cholecystectomy syndrome occurs in only 2–5% of patients. The main causes are listed in Box 22.65. The usual symptoms include right upper quadrant pain, flatulence, fatty food intolerance and occasionally jaundice and cholangitis. The LFTs may be abnormal and sometimes show cholestasis. Ultrasonography is used to detect biliary obstruction, and EUS or MRCP to seek common bile duct stones. If retained bile duct stones are excluded, sphincter of Oddi dysfunction should be considered (see below). Other investigations that may be required include upper gastrointestinal endoscopy, small bowel radiology and pancreatic function tests. The possibility of a functional illness should also be considered. 22.65 Causes of post-cholecystectomy symptoms Immediate post-surgical • Bleeding • Biliary peritonitis • Abscess • Bile duct trauma/transection • Fistula Biliary • Common bile duct stones • Benign stricture • Tumour • Cystic duct stump syndrome • Disorders of the ampulla of Vater (e.g. benign papillary fibrosis; sphincter of Oddi dysfunction) Extrabiliary • Functional dyspepsia • Peptic ulcer • Pancreatic disease • Gastro-oesophageal reflux • Irritable bowel syndrome • Functional abdominal pain 22.67 Criteria for pancreatic sphincter of

Oddi dysfunction • Recurrent attacks of acute pancreatitis – pancreatic-type pain with amylase or lipase 3 times normal and/or imaging evidence of acute pancreatitis • Other aetiologies of acute pancreatitis excluded • Normal pancreas at endoscopic ultrasound • Abnormal sphincter manometry 22.66 Classification of biliary sphincter of Oddi dysfunction (SOD) Organic stenosis (formerly SOD type I) • Biliary-type pain • Abnormal liver enzymes (ALT/AST > twice normal on two or more occasions) • Dilated common bile duct (> 12 mm diameter) • Delayed drainage of ERCP contrast beyond 45 mins Functional sphincter of Oddi disorder (formerly SOD type II) • Biliary-type pain with one or two of the above criteria Functional biliary-type pain (formerly SOD type III) • Biliary-type pain with no other abnormalities

Adenomyomatosis of the gallbladder In this condition, there is hyperplasia of the muscle and mucosa of the gallbladder. The projection of pouches of mucous membrane through weak points in the muscle coat produces Rokitansky– Aschoff sinuses. There is much disagreement over whether adenomyomatosis is a cause of right upper quadrant pain or other gastrointestinal symptoms. It may be diagnosed by oral cholecystography, when a halo or ring of opacified diverticula can be seen around the gallbladder. Other appearances include deformity of the body of the gallbladder or marked irregularity of the outline. Localised adenomyomatosis in the region of the gallbladder fundus causes the appearance of a ‘Phrygian cap’. Most patients are treated by cholecystectomy but only after other diseases in the upper gastrointestinal tract have been excluded. IgG4-associated cholangitis This recently reported disease often presents with obstructive jaundice and is described on page 890. Further information Books and journal articles Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol 2013; 10:330–344. EASL Clinical practice guidelines: Autoimmune hepatitis. J Hepatol 2015; 63:971–1004. EASL Clinical practice guidelines: Liver transplantation. J Hepatol 2016; 64:433–485. EASL Recommendations on treatment of hepatitis C 2015. J Hepatol 2015; 63:199–236. EASL-EASD-EASO Clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016; 64:1388–1402. Neuberger J, Gimson A, Davies M, et al. Selection of patients for liver transplantation and allocation of donated livers in the UK. Gut 2008; 57:252–257. Williams R, Aspinall R, Bellis M, et al. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. Lancet 2014; 384:1953–1997. Websites aasld.org American Association for the Study of Liver Diseases (guidelines available). bsg.org.uk British Society of Gastroenterology (guidelines available). easl.eu European Association for the Study of the Liver (guidelines available). eltr.org European Liver Transplant Registry. unos.org United Network for Organ Sharing: US transplant register. Management All patients with organic stenosis are treated with endoscopic sphincterotomy. The results are good but patients should be warned that there is a high risk of complications, particularly acute pancreatitis. Manometry should ideally be performed in all suspected functional sphincter of Oddi disorder patients (‘type II’), and results of sphincterotomy in those with high pressures are good, but this should be avoided in patients with functional biliary-type pain (‘type III’), as it is of no benefit. Medical therapy with nifedipine and/or low-dose amitriptyline may be tried. Pancreatic SOD can be treated with biliary sphincterotomy, carried out in specialist centres, but this should be undertaken with caution and careful consideration. Routine prophylactic pancreatic duct stenting in patients undergoing ERCP for sphincter of Oddi disorders is no longer encouraged. Prophylactic administration of rectal

NSAIDs (e.g. diclofenac 100 mg) is recommended instead because this significantly reduces the risk of procedure-related acute pancreatitis. Cholesterolosis of the gallbladder In this condition, lipid deposits in the submucosa and epithelium appear as multiple yellow spots on the pink mucosa, giving rise to the description ‘strawberry gallbladder’. Cholesterolosis of the gallbladder is usually asymptomatic but may occasionally present with right upper quadrant pain. Small, fixed filling defects may be visible on ultrasonography; the radiologist can usually differentiate between gallstones and cholesterolosis. The condition is usually diagnosed at cholecystectomy; if the diagnosis is made radiologically, cholecystectomy may be indicated, depending on symptoms. 22.68 Gallbladder disease in old age • Gallstones: by the age of 70 years, prevalence is around 30% in women and 19% in men. • Acute cholecystitis: tends to be severe, may have few localising signs and is associated with a high frequency of empyema and perforation. If such complications supervene, mortality may reach 20%. • Cholecystectomy: mortality after urgent cholecystectomy for acute uncomplicated cholecystitis is not significantly higher than in younger patients. • Endoscopic sphincterotomy and removal of common duct stones: well tolerated by older patients, with lower mortality than surgical common bile duct exploration. • Cancer of the gallbladder: a disease of old age, with a 1-year survival of 10%.

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