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15.24.5 The liver in systemic disease 3169 with pain, sometimes in the back and rarely after cholecystectomy with jaundice and biliary obstruction. Spontaneous rupture has been associated with haemobilia and is a major medical emergency presenting with severe abdominal pain and shock followed by jaundice. Treatment is with either hepatic artery embolization or surgery. Portal vein thrombosis Spontaneous thrombosis of the portal vein, although often asymptomatic, may cause a range of serious medical complications. A thrombosis may develop in one or more of the intrahepatic portal vein branches, or within the main portal vein itself, and may involve the superior mesenteric or splenic veins which join to form the main trunk of the portal vein. Thrombosis may result from infection after birth arising in the umbilical vein, following acute pancreatitis (occasionally isolated to the splenic vein alone), surgery or abdominal trauma, as a complication of cirrhosis with or without an additional hepatocellular carcinoma, pancreatic and other intrabdominal malignancy, retroperitoneal fibrosis, and a number of thrombophilic states. These include polycythaemia rubra vera, any cause of thrombocytosis, factor V Leiden and factor II (G20210A) deficiency, antithrombin III, protein C and S deficiency, paroxysmal nocturnal haemoglobinuria, and the lupus anticoagulant. Septic thrombosis of the portal vein may also occur associated with another infective focus within the abdomen, such as acute appendicitis or diverticular disease. Often asymptomatic, portal vein thrombosis may present as haemorrhage from oesophageal or gastric varices, and rarely with biliary obstruction from choledochal varices. The diagnosis can be made at Doppler ultrasound examination of the liver, CT, or magnetic resonance angiography. Endoscopic therapy with variceal band ligation or injection sclerotherapy is required when portal vein thrombosis presents with variceal haemorrhage. Occasionally, surgical shunts can decompress the portal venous system, but this is often not possible due to the extensive nature of the thrombosis. Clot lysis is not possible as the thrombosis is usually longstanding. Anticoagulation, when given early after identification of an acute portal vein thrombosis, may improve long-term portal vein patency. In chronic portal vein thrombosis, it has been shown to reduce the risk of further thrombotic events in the splanchnic circulation and does not increase the risk of variceal haemorrhage. FURTHER READING Das CJ, et al. (2018). Role of radiological imaging and interventions in management of Budd-Chiari syndrome. Clin Radiol, 73, 610-24.

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15.24.5 The liver in systemic disease James Neuberger ESSENTIALS The liver is affected in many systemic diseases, with important examples being: Cardiovascular diseases—raised venous pressure (e.g. cardiac failure and constrictive pericarditis) can lead to hepatic congestion, which sometimes causes nausea, vomiting, right upper quadrant pain, and (rarely) jaundice. Hepatomegaly is frequent in moderately severe heart failure. Cardiac cirrhosis is a rare complication. Pulmonary diseases—conditions that involve the liver as well as the lungs include cystic fibrosis, sarcoidosis, and α 1-antitrypsin deficiency. Gastrointestinal diseases—inflammatory bowel disease is associated with a range of hepatic pathology including fatty change, pericholangitis, sclerosing cholangitis, autoimmune hepatitis, cirrhosis, and (rarely) amyloidosis. Hepatobiliary disease associated with total parenteral nutrition varies from a mild, asymptomatic disease to jaundice, cirrhosis, and liver failure. Coeliac disease may rarely present with abnormal liver tests. Obesity, especially in association with the metabolic syndrome, may be associated with nonalcoholic hepatitis and steatohepatitis. Endocrine diseases—autoimmune hepatitis and primary biliary cholangitis may be associated with autoimmune endocrine disorders. Both hypothyroidism and hyperthyroidism can cause abnormalities of liver function, which are usually mild. Haematological diseases—conditions associated with abnormal blood clotting, such as protein C or S deficiency and paroxysmal nocturnal haemoglobinuria, may lead to Budd-Chiari syndrome (hepatic vein thrombosis). The liver may be involved in both non-Hodgkin's lymphoma and leukaemia. Infectious diseases—agents that particularly affect the liver (e.g. viral hepatitis) are discussed in other chapters although many systemic infections also infect the liver. Abnormal liver function may occur during many systemic infections, but it is rare for patients with sepsis to present primarily with liver symptoms, although jaundice, abnormal liver function tests, or (very rarely) fulminant hepatic failure may be the principal presenting feature. Rheumatological diseases—hepatic disease may either be a consequence of treatment or occur in association with other autoimmune diseases.

Introduction The liver may be affected in many systemic diseases. It may be damaged by toxic, infectious, immunological, vascular, or hormonal factors, with the damage affecting hepatocytes, cholangiocytes, and/or vascular (often microvascular) structures. In most instances, disturbance of liver structure and/or function is a minor component of the disease, but in some cases, systemic disease may present as liver disease or disturbance of liver tests (although the so-called liver function tests are neither tests of liver function nor liver specific).

section 15 Gastroenterological disorders 3170 In this chapter, some of the abnormalities of liver function seen in systemic disease are discussed. Liver disease may also impact other organs, so distinguishing the prime lesion may be difficult: for example, cirrhosis may be associated with cirrhotic cardiomyopathy and, conversely, heart failure may lead to cirrhosis, Budd-Chiari-like syndrome or even acute liver failure. Both acute hepatitis and acute liver failure may be a presentation or major feature of such diverse conditions as heat stroke, acute heart failure, and chronic inflammatory conditions. Many infections can affect the liver: for example, jaundice may be a feature of systemic sepsis, pneumonia, or lymphoma, and many infections, for example, Q fever or influenza, may have an associated hepatitis. Drug-induced liver injury The possibility that drugs used to treat systemic disease may cause liver injury must always be borne in mind. The diagnosis

of drug-induced liver injury is usually one of exclusion and one agent may be associated with multiple patterns of liver damage. See Chapter 15.24.3 for further discussion.

Cardiovascular disease

Congestive cardiac failure Most patients with chronic congestive cardiac failure have few symptoms related to hepatic congestion, although nausea, vomiting, and right upper quadrant pain may occur occasionally. Hepatomegaly is present in most patients with moderately severe heart failure. Rarely, cardiac cirrhosis develops and may be associated with splenomegaly and ascites. With progressive failure, jaundice occurs in about one-quarter of patients. The standard liver tests may show a rise in serum bilirubin, which rarely exceeds 50 $\mu\text{mol/litre}$ and is usually predominantly unconjugated. The serum aminotransferases may also be elevated but rarely exceed twice the upper limit of normal although concentrations in excess of 1000 IU/litre may be found in severe acute heart failure. Serum alkaline phosphatase is rarely elevated. The prothrombin time is often prolonged by a few seconds. Ultrasonography may show widened hepatic veins. The liver is usually enlarged and a cut section shows the classical nutmeg appearance, with the pale periportal zones alternating with darker centrilobular zones. Microscopically there is congestion, with dilatation of the terminal hepatic venules and adjacent sinusoids, and areas of centrilobular necrosis. With chronic heart failure, there may be features of centrilobular necrosis and fibrosis. Jaundice and transaminitis may be present in acute heart failure, and in rare cases the patient may present with signs and symptoms of acute liver failure. Constrictive pericarditis

Hepatic complications of constrictive pericarditis occur late in the course of the illness. Cardiovascular features of constrictive pericarditis are described elsewhere (see Chapter 16.8). The liver is enlarged and there may be associated splenomegaly. Jaundice and ascites may develop. Ultrasonography of the liver will show enlargement with dilated hepatic veins.

Tricuspid incompetence Tricuspid incompetence most commonly occurs as a result of right heart failure but may also result from congenital or acquired disease of the tricuspid valve. The liver is enlarged and pulsatile.

Tumours of the heart Tumours of the right atrium, including myxoma and myosarcoma, may infiltrate the hepatic veins resulting in a Budd-Chiari syndrome (a syndrome of hepatic venous thrombosis, characterized by abdominal pain, progressive ascites, and diarrhoea). Cardiac myxoma may be associated with abnormalities of liver function tests, including increased serum bilirubin and alkaline phosphatase, and a reduction in serum albumin and total protein.

Hypoxia Hypoxic episodes, especially during surgery, may lead to an acute liver injury resulting from an ischaemic hepatitis. The clinical severity ranges from an asymptomatic elevation of serum aminotransferases to fulminant hepatic failure. The syndrome may be followed by a period of cholestasis. The aminotransferases may become greatly elevated (in excess of 10 000 IU/litre). Histologically there is hepatocellular necrosis in the absence of inflammation, most marked in acinar zone 3 (the perivenular area). Similar changes may be seen in patients with heat stroke.

Syndromes affecting both heart and liver Several conditions affect both heart and liver, including Alagille's syndrome (a multisystemic disorder, associated with JAG1 mutations and characterized by a paucity of intrahepatic bile ducts, leading to a biliary cirrhosis, and cardiac syndromes such as pulmonary stenosis and other cardiac abnormalities), biliary atresia (where up to 10% may have congenital heart disease), and cardiomyopathy, and may be associated with a variety of inherited and acquired diseases affecting both organs including alcohol excess, haemochromatosis, tyrosinaemia, and mitochondrial cytopathy. Drugs such as the immunosuppressive agent tacrolimus may also cause cardiomyopathy.

Pulmonary disease Cirrhosis Lung disease is not uncommon in patients with cirrhosis; the hepatopulmonary syndrome and portopulmonary hypertension may resolve after treatment of the underlying liver disease or after liver transplantation. In contrast, abnormalities of liver function in patients with pulmonary disease may

arise either as a consequence of that disease or of diseases affecting both lung and liver. In most patients with chronic lung disease, abnormalities of liver function are mild and may be manifest only by more functional tests of liver function such as abnormalities of bromosulphophthalein clearance. In more advanced disease, associated with hypoxia, there may be more widespread disturbances of liver function, with elevation of serum aminotransferase, bilirubin, alkaline phosphatase, and γ -glutamyl transferase. However, abnormality of liver function

15.24.5 The liver in systemic disease 3171 In patients with pulmonary disease is associated mainly with pulmonary hypertension rather than lung disease or hypoxia per se. Pneumonia Some patients with pneumococcal pneumonia may have jaundice. It usually manifests on the fourth or fifth day of the illness and is seen particularly in patients with consolidation of the right lower lobe. The serum bilirubin rarely exceeds 100 μ mol/litre, and abnormalities of other liver tests are unusual. The cause of the jaundice is not known: factors that have been implicated are glucose-6-phosphatase deficiency, associated acute haemolysis, hypoxia, fever, and direct toxicity. The increased amounts of inflammatory cytokines seen in such patients may also contribute to the jaundice. Abnormal liver function tests are also seen in patients with Legionnaires' disease and are characterized by elevation of aspartate aminotransferase and alkaline phosphatase. Jaundice is less common and tends to occur only in patients who are severely ill. Diseases that involve both lung and liver α 1-Antitrypsin deficiency The syndrome of α 1-antitrypsin deficiency arises as a consequence of a point mutation that leads to misfolding of the protein that renders it unable to follow the normal secretory pathway and leads to its accumulation in the endoplasmic reticulum of the hepatocyte, which may result in hepatitis, fibrosis, and cirrhosis. The clinical spectrum varies widely: it was initially described in relation to pulmonary emphysema but it subsequently became clear that the liver, kidney, and pancreas can also be involved. In children, liver disease often presents as neonatal hepatitis or jaundice, usually in the first 2 months of life: in one-third it resolves, one-third develop fibrosis, and the remainder develop progressive cirrhosis often requiring transplantation. In adults, the disease often presents with signs or symptoms of portal hypertension or cirrhosis or their complications; some adults will have had unexplained hepatitis as a neonate. The liver shows the characteristic histological features of periodic acid-Schiff-positive, diastase-resistant globules in the liver, but these globules are not diagnostic of the disease. Patients usually have the Pi ZZ phenotype. Whether the Pi MZ or other phenotypes are associated with liver disease is less clear. Liver disease is more severe in those with additional causes such as alcohol excess, diabetes mellitus, or obesity. The prognosis is unpredictable but many patients develop progressive disease, often requiring liver transplantation. There is no proven effective treatment. The onset of cholestasis often heralds liver failure. In cases where lung and liver disease coexist, the only effective therapy is with a triple transplant (heart, lung, and liver), but this is rarely done. Cystic fibrosis The increasing success in treating respiratory complications in children with cystic fibrosis has resulted in a greater number surviving to develop liver disease. Abnormal liver tests are found in up to half of the children, and in adults up to a quarter of patients with cystic fibrosis develop a biliary cirrhosis. Clinically, patients present with cholestasis and jaundice. The pathogenesis and aetiology of this cholestasis are poorly understood. In most cases, liver disease is characterized by the development of a focal biliary cirrhosis that increases with time. Early involvement of the liver is characterized by the presence of eosinophilic granular material in the portal ducts. There is proliferation of bile ducts and portal fibrosis. This progresses to a focal biliary cirrhosis, which then develops into a multilobular cirrhosis with onset of symptoms of cholestasis and jaundice. However, many patients have evidence of biliary obstruction shown by

imaging the biliary tree by magnetic resonance or endoscopic retrograde cholangiopancreatography. There is some evidence that infusion of N-acetylcysteine into the biliary tree may relieve the obstruction in the extrahepatic biliary tree. The onset of jaundice and ascites is associated with a poor prognosis. Standard liver tests may underestimate the severity of the liver disease. Treatment with ursodeoxycholic acid will improve the liver tests and may improve liver function. Other causes of cholestasis in patients with cystic fibrosis include gallstones and pancreatic insufficiency associated with increased loss of faecal bile salts, a consequent decrease in the size of the bile-salt pool, and the development of lithogenic bile. Treatment is uncertain. Open-label studies have suggested that ursodeoxycholic acid, 10 to 15 mg/kg per day, may result in biochemical improvement, weight gain, and improved nutrition. However, whether this agent has any long-term effect remains to be established. The effects (if any) of cystic fibrosis transmembrane conductance regulator modulators and potentiators on cystic fibrosis-related liver disease are not yet clear. Liver transplantation, sometimes with lung transplantation, may be required.

Sarcoidosis Sarcoidosis, a systemic granulomatous disease of unknown aetiology, involves the liver in up to 70% of cases, but symptoms and signs are relatively uncommon. Hepatomegaly and splenomegaly occur in about one-quarter of patients. While jaundice is rare, elevation of the serum alkaline phosphatase is not uncommon; abnormalities of liver tests occur in up to one-third of patients. Complications of granulomatous infiltration of the liver are unusual. There are cases where liver failure develops. More commonly, portal hypertension may occur, with bleeding varices or ascites and may be present in up to one in five patients; portal hypertension may occur in the absence of cirrhosis, usually as a consequence of presinusoidal or sinusoidal obstruction associated with the granulomas or biliary fibrosis. As with sarcoid elsewhere, the diagnosis is supported by an elevated concentration of serum angiotensin-converting enzyme but this lacks both sensitivity and specificity. Imaging using ultrasonography, especially if contrast-enhanced ultrasonography, CT, or MR may show multiple hypointense or hypoattenuated nodules within the liver. The diagnosis is usually made by the finding of noncaseating granulomas which, in the liver, are concentrated around the portal tracts. These granulomas are usually large and consist of multinuclear giant cells with lymphocytes and areas of epithelioid cells. Many patients respond to corticosteroids, although the portal hypertension may persist, possibly due to established presinusoidal fibrosis. Overlap with primary biliary cholangitis (formerly known as primary biliary cirrhosis) is well recognized, and cases have been described with typical sarcoid involvement of both lungs and liver in the presence of bile duct damage consistent with primary biliary cholangitis. These patients are antimitochondrial antibody positive. Other causes of granulomatous hepatitis are discussed later in this chapter.

section 15 Gastroenterological disorders 3172 Gastrointestinal tract disorders Inflammatory bowel disease The spectrum of liver abnormality associated with inflammatory bowel disease ranges from fatty change to pericholangitis, sclerosing cholangitis, autoimmune hepatitis, cirrhosis, and amyloidosis. The reported incidence of liver abnormalities in inflammatory bowel disease varies from 3 to 10%. In general, abnormalities of liver function tests correlate poorly with severity of liver disease determined histologically. Ulcerative colitis is more commonly associated with abnormality of liver function tests than is Crohn's disease. There is no clear-cut relation between the onset of symptoms of inflammatory bowel disease and of the liver abnormalities. In general, symptoms of ulcerative colitis precede changes in liver function tests by about 8 years but liver disease may precede by many years the onset of clinically apparent inflammatory bowel disease. Conversely, liver disease may become manifest several years after colectomy. Furthermore, there

is no clear-cut correlation between the severity of inflammatory bowel disease and the incidence or severity of liver disease. Indeed, in many patients with primary sclerosing cholangitis, the colitis tends to be a pancolitis but is often quiescent (Table 15.24.5.1). Fatty change is relatively common on histological examination of liver in patients with inflammatory bowel disease and probably multifactorial in origin, relating to the degree of ill health, poor nutrition, and use of corticosteroids. As a patient's condition improves, the fatty infiltration resolves. Primary sclerosing cholangitis is associated with inflammatory bowel disease in about 10% cases whereas nearly 90% of patients with primary sclerosing cholangitis have inflammatory bowel disease. Primary sclerosing cholangitis is a premalignant condition, associated with bile duct carcinoma in 5 to 20%. In patients with primary sclerosing cholangitis and ulcerative colitis, there is an increased risk of colon cancer. Cirrhosis occurs in up to 10% of patients dying with colitis. The cause of the cirrhosis is not known, but it may, in some cases, relate to alcohol, to chronic hepatitis C infection from drug transfusions, or to drug toxicity, rather than primary sclerosing cholangitis. Although autoimmune hepatitis in association with inflammatory bowel disease is rare, it is important to diagnose it because many cases have features similar to autoimmune hepatitis and respond well to corticosteroids. Other hepatic complications of inflammatory bowel disease include granulomatous hepatitis, amyloid infiltration of the liver, bile duct carcinoma, gallbladder cancer, and gallstones. Coeliac disease In patients with coeliac disease, there may be minor abnormalities of liver function tests, characterized by elevation of serum aminotransferases; they usually resolve with treatment. Coeliac disease may also be associated with autoimmune diseases affecting the liver, including primary biliary cholangitis, cryptogenic cirrhosis, sclerosing cholangitis, and autoimmune hepatitis. Up to 4% of patients with primary biliary cholangitis may have coeliac disease and up to 3% of patients with coeliac disease may have primary biliary cholangitis. Gastrointestinal bypass surgery Jejunioileal bypass surgery may be associated with a significant degree of liver impairment; the changes in the liver range from simple fatty infiltration to cirrhosis. In a few cases, there may be features identical to those of alcoholic hepatitis. In those in whom liver function tests are deranged, there is a likelihood of progression, and although treatment with metronidazole has been advocated, restoration of normal anatomy appears to be the only effective treatment. Total parenteral nutrition The association of hepatobiliary disorders with total parenteral nutrition (TPN) has been recognized over the last two decades. Although the pathogenesis remains obscure, most studies suggest that the incidence is falling to less than 5% of patients. Clinically, TPN-associated hepatobiliary disease varies from a mild, asymptomatic disease with acalculous cholecystitis, biliary sludge, or hepatomegaly, to jaundice, cirrhosis, and liver failure. Biochemically, the severity of abnormalities will reflect the severity of the disease but elevations of liver enzymes, such as aspartate and alanine transferases, lactate dehydrogenase, and alkaline phosphatase, and serum bilirubin are common. The histological features vary from a mild fatty infiltrate or cholestasis to a more severe picture resembling alcoholic fatty liver. In chronic cases, cirrhosis will develop. The mechanism is uncertain. Suggestions include hypoxic enterocytes, nutritional depletion, sepsis, toxicity of certain unidentified amino acids, and carnitine deficiency (Table 15.24.5.2). Once a patient develops abnormal liver function, and provided that other causes have been excluded, there is little alternative other than to reduce or stop parenteral nutrition and find other ways of providing adequate nutrition. Obesity and malnutrition Obesity is occasionally associated with abnormalities of liver tests, especially of the serum aminotransferases. Cutaneous manifestations of chronic liver disease may develop. The liver ultrasound examination will show a fatty liver, and liver histology a macrovesicular fatty infiltration. Rarely, a nonalcoholic steatohepatitis syndrome will develop. Nonalcoholic fatty liver disease is described in detail in

Chapter 15.24.2. The liver is also affected in malnutrition. In those with severe protein-calorie malnutrition (Kwashiorkor), fatty liver may be seen, possibly as a consequence of loss of peroxisomes and reduced β -oxidation of long-chain fatty acids. Table 15.24.5.1 Liver and biliary disorders associated with inflammatory bowel disease
 Parenchymal Granuloma Pericholangitis
 Autoimmune hepatitis Primary biliary cholangitis Liver abscess Amyloid Biliary Gallstones Primary sclerosing cholangitis IgG4 cholangitis/autoimmune cholangitis Cholangiocarcinoma

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 Autoimmune hepatitis may be associated with autoimmune endocrine disorders, such as thyroid disease and vitiligo. In addition to those conditions, such as haemochromatosis, where both liver and pancreas are affected, diabetes mellitus itself is associated with liver abnormalities. The liver may be enlarged due to excess stores of fat and glycogen. In severe cases, there may be a nonalcoholic steatohepatitis syndrome which can lead to hepatic fibrosis and cirrhosis. Liver abnormalities are seen much more commonly in type 2 diabetes (20–75%) compared with well-controlled type 1 diabetes (<1%). Hypothyroidism may be associated with a mild hyperbilirubinaemia and elevations of serum transaminases (which may be of muscle origin). Ascites occurs very rarely. Hyperthyroidism is also associated with mild abnormalities of liver function which resolve on treatment of the thyroid disorder. Henoch–Schönlein purpura is associated with jaundice and cholestasis. The liver in haematological diseases
 Procoagulant disorders Procoagulant disorders such as protein C or S deficiency and paroxysmal nocturnal haemoglobinuria may lead to a Budd–Chiari syndrome (thrombosis of the hepatic vein) or portal vein thrombosis. Haemolysis Jaundice may accompany haemolysis, usually through an increase in unconjugated bilirubin. In patients with underlying liver disease, there may be an elevation of both conjugated and unconjugated bilirubin out of proportion to the degree of haemolysis. Patients with chronic haemolytic anaemia are at risk of developing haemosiderosis. Iron is deposited initially in the Kupffer cells but spread to the parenchyma will subsequently occur. The identification of the genes for hereditary haemochromatosis (HFE) has greatly helped in the distinction between primary and secondary iron overload. The haemolytic anaemias are associated with an increased risk of pigment gallstones, which may lead to liver and biliary tract disease. Sickle cell disease Most of the abnormalities of liver function in sickle cell disease are due to haemolysis or infections transmitted by blood transfusion. Kupffer cell hyperplasia, haemosiderosis, fibrosis, or cirrhosis may be due to iron overload following multiple transfusions. Patients sometimes present with fever, severe right upper quadrant pain, and jaundice, with rapid enlargement of the liver as part of the hepatic sequestration syndrome (so-called sickle cell intrahepatic cholestasis). The liver histology may show clumps of sickled red cells in the sinusoids, erythrophagocytosis, sinusoidal dilatation, and bilirubinostasis. There is an increased risk of gallstones and their complications may result in jaundice. High serum ferritin and conjugated serum bilirubin levels are good predictors of poor prognosis. Thalassaemia As with sickle cell disease, there is an increase in haemolysis and the complications of blood transfusions. Gallstones are common Multiple transfusions Patients who are maintained with regular transfusion of blood or blood products (e.g. those with thalassaemia or haemophilia) are at risk of developing viral hepatitis B or C, or much less commonly hepatitis A and E. Although transfusion-associated transmission of blood-borne viruses is greatly reduced by current screening tests, because of the window period, such cases do still very occasionally occur. Haemophagocytic syndrome Features of the haemophagocytic syndrome include hepatomegaly. In addition to the coagulopathy, hypofibrinogenaemia, hyponatraemia, and hyperferritinaemia (which is often in excess of 10 000 $\mu\text{g/L}$), there may be jaundice and elevated levels of serum

aminotransferases. Liver histology shows haemophagocytosis, sinusoidal dilatation, and Kupffer cell hyperplasia. Lymphoreticular disease In patients with Hodgkin's disease, liver tests are of limited value in predicting liver involvement. Jaundice is a recognized feature, but may be due to several different causes. For example, haemolysis may complicate Hodgkin's disease, and occasionally there is a bland cholestasis in the absence of infiltration, which usually resolves when the disease is treated. In some cases, there is a vanishing bile duct syndrome. The clinical manifestations of liver involvement in Hodgkin's disease relate to the degree of infiltration. In rare cases, patients present with fulminant hepatic failure: the clue to infiltration is a large liver as most cases of viral or drug-related fulminant hepatic failure are associated with small livers. Liver biopsy may be diagnostic. Primary lymphoma of the liver has been described but is rare. The liver may be involved in both non-Hodgkin's lymphoma and leukaemia. The diagnosis is usually made by biopsy. Some patients with non-Hodgkin's lymphoma have a chronic hepatitis preceding diagnosis or treatment. A causal effect cannot be excluded. Both Hodgkin's disease and non-Hodgkin's lymphoma may be associated with obstructive jaundice due to hilar obstruction by nodes; this is more common in the latter and resolves with treatment.

Table 15.24.5.2 Factors contributing to liver dysfunction in patients receiving TPN

Underlying sepsis	Systemic	Local	Small-bowel colonization	Underlying disease	Duration of TPN	Pre-existing liver disease	Underlying condition	Nutritional factors	Excess nonprotein calories	Essential fatty acid deficiency	Amino acid toxicity	Carnitine deficiency	Bile acid abnormalities	Drug toxicity

section 15 Gastroenterological disorders 3174 The liver and infections Abnormal liver function may occur during systemic infections, both Gram positive and Gram negative, although it is unusual for patients with sepsis to present primarily with liver symptoms (Table 15.24.5.3). However, jaundice, abnormal liver tests, or even, occasionally, fulminant hepatic failure may be major presenting features of sepsis. The liver tests usually show a significant elevation of serum bilirubin (mainly conjugated); serum alkaline phosphatase and aminotransferase activity are usually less increased. The pathophysiology is becoming clearer; endotoxins induce sinusoidal endothelial cells and hepatocytes to produce inflammatory cytokines such as interleukins 2, 6, and 12 and tumour necrosis factor- α , which are thought to have a post-transcriptional effect on bile uptake and transporter receptors. There may also be haemolysis, drug-induced liver injury, and hepatic ischaemia. The treatment is of the underlying infection. Bacterial infections Pneumococcal infections are discussed in 'Pneumonia'. Meningococcal infections are occasionally associated with features suggestive of viral hepatitis. Jaundice may be associated with the toxic shock syndrome associated with *Staphylococcus aureus*. Gonococcal infection is a well-recognized cause of liver disease. The classical Fitzhugh-Curtis syndrome, perihepatitis, is characterized by sudden onset of severe pain in the right upper quadrant, occurring classically in a woman with a previous history of pelvic inflammatory disease. On examination there may be little to find, although tender hepatomegaly and a hepatic rub may be present. Where laparotomy has been performed in the mistaken diagnosis of cholecystitis, perihepatitis with adhesions and pus around the liver may give the clue to the diagnosis. In chronic infection, adhesions develop between the surface of the liver and the anterior abdominal wall. The condition usually resolves without treatment, although the use of penicillin causes a more rapid resolution. Abnormalities of liver function may occur in gonococcal bacteraemia, peritonitis, and endocarditis. Perihepatitis is also reported in association with syphilis and chlamydial infections. In childhood, some infections with *Escherichia coli* may be associated with hepatitis and jaundice. Jaundice is rare in older patients, although pregnant women seem more susceptible. Abnormalities of liver function occur in systemic streptococcal and

staphylococcal infection and in enteric fevers, paratyphoid, and typhoid. In typhoid infection, hepatomegaly is common and jaundice occurs in about 10% of patients, although up to a third have abnormal liver function tests, with increased levels of aminotransferase and normal values for alkaline phosphatase. The hepatomegaly rapidly responds with treatment. There may be an associated cholecystitis. In gas gangrene, deep jaundice may occur in up to a fifth of patients. The liver may be infected and a plain radiograph of the abdomen may show gas within the liver. Liver damage and jaundice are associated with *Listeria monocytogenes* and *Legionella pneumophila* infections. Brucellosis may also be associated with jaundice and abnormal liver function tests. All three forms of brucella have been associated with abnormal liver function. Characteristically, the liver biopsy shows a marked inflammatory infiltrate and fibrosis with multiple large or small granulomas scattered throughout the parenchyma. Although some reports have suggested granulomatous hepatitis due to brucella may progress to cirrhosis, the data are not convincing. The common causes of liver granulomas, including infections, are listed in Table 15.24.5.4. Actinomycosis israelii and bovis are commensals that rarely cause disease. Actinomycotic infection of the liver may occur, the patient presenting with abdominal pain, anorexia, and fever. In one case report, the liver was found to have small, multilocular abscesses. Tuberculosis may present with granulomatous hepatitis, biliary tuberculosis, a solitary tuberculoma, or tuberculosis of the biliary tract. The liver is involved in up to 85% of patients with tuberculosis, Table 15.24.5.3 Systemic infections affecting the liver

Bacterial	Actinomycosis
Brucellosis	Chlamydia
Clostridium welchii	Escherichia coli
Gonorrhoea	Granuloma inguinale
Listeriosis	Legionella pneumophila
Melioidosis	Meningococcus
Nocardia	Shigella
Streptococcus	Staphylococcus
Typhoid and paratyphoid	Tularaemia
Yersinia	Mycobacterial
Tuberculosis	Leprosy
Others	Protozoal
Giardiasis	Kala-azar
Malaria	Toxoplasmosis
Fungal	Aspergillosis
Blastomycosis	Candidosis
Cryptococcus	Coccidiomycosis
Histoplasmosis	Rickettsial
Q fever	Rocky Mountain spotted fever
Spirochaetes	Leptospirosis
Lyme disease	Relapsing fever
Syphilis	

15.24.5 The liver in systemic disease particularly those with miliary disease. The presence of multiple granulomas in the liver should raise the possibility of tuberculosis, although—as seen in Table 15.24.5.4—the differential diagnosis of granulomatous hepatitis is long. With the increasing incidence of atypical mycobacterial infections, lesions similar to tuberculosis can be found. In those infected with *Mycobacterium avium* intracellulare there are numerous acid-fast bacilli, often in the absence of granulomas. Rarely, tuberculosis may cause jaundice because of lymph node obstruction of the biliary tree. Acute leptospirosis is frequently accompanied by jaundice, although frank liver failure is uncommon. The jaundice is mainly cholestatic, although there may be liver cell damage. Syphilis may rarely be associated with hepatitis or jaundice. Rickettsial infection Liver involvement in Q fever (*Coxiella burnetii*) is recognized, although symptoms of liver disease are uncommon. Hepatomegaly is frequent and liver function tests may show an elevation of serum alkaline phosphatase and, rarely, a picture resembling viral hepatitis. Histologically, the liver has areas of focal necrosis, Kupffer cell proliferation, lipogranuloma formation, and mononuclear cell infiltration in the portal tracts. The characteristic histological feature of Q fever is eosinophilic fibrinoid necrosis but this is not specific. Treatment is with chloramphenicol or tetracycline. Liver involvement has a much greater incidence in Rocky Mountain spotted fever (*Rickettsia rickettsia*). Fungal infections The liver may be involved in fungal infection, often in patients with immunodeficiency such as with AIDS, following chemotherapy, and after organ transplantation. Histoplasmosis, cryptococcosis, aspergillosis, blastomycosis, and candidiasis are all causes of liver damage. The liver is usually involved in disseminated fungal infections. Cryptococcal infection has

also been associated with a primary biliary cholangitis-like condition. Protozoal infections Many protozoal infections involve the liver. In toxoplasmosis, while most patients are asymptomatic and liver involvement is mild, hepatitis may occur and on biopsy *Toxoplasma gondii* may be found in the liver. In malaria, due to either *Plasmodium falciparum* or *vivax*, abnormality of liver function may be observed. Hepatomegaly is common and often associated with jaundice. The jaundice is in part due to haemolysis but liver tests may show a picture suggestive of viral hepatitis. Histological examination may show characteristic features of Kupffer cell proliferation with black malarial pigment and mononuclear cell infiltrate. Frank hepatic failure is extremely rare. Schistosomiasis is one of the most common causes of liver disease worldwide. A heavy infection of fertile schistosomes in the portal system results in deposition of eggs that induce an immune response, leading to portal fibrosis and granuloma formation, portal hypertension with consequent splenomegaly, ascites, and variceal haemorrhage. Hepatocyte function is well preserved. There is a complex interaction between schistosomal eggs and the immune system; the degree of fibrosis is directly related to the number of eggs and the duration of infection. The diagnosis is made on stool examination or finding schistosomes in the liver. Successful treatment is associated with a significant but variable improvement in the degree of portal hypertension. Treatment of the portal hypertension is dependent on the medical facilities available. As parenchymal function is well preserved, these patients usually tolerate a portosystemic shunt. Coinfection of patients with schistosomiasis and hepatitis B or C virus is associated with aggressive progression. Viral infections Hepatitis may be a significant feature of viral infection other than the classical hepatitis viruses. Thus, infection with cytomegalovirus, Epstein-Barr virus, herpes viruses, measles, rubella, Coxsackie virus, adenoviruses, and ECHO viruses may all cause a significant hepatitis. Such viral infections (especially cytomegalovirus) are more common in immunosuppressed patients. Cytomegalovirus infection in the context of HIV or immunosuppression may cause a sclerosing cholangitis. The diagnosis is made serologically but in some cases, such as with cytomegalovirus, herpes, and adenoviral infections, the liver histology may show characteristic features. In the immunosuppressed, hepatitis viruses B and E are more likely to run a chronic course, resulting in chronic hepatitis, fibrosis, and cirrhosis. In many Western countries, there is an increase in infection with hepatitis E virus genotype 3; treatment is with ribavirin. Treatment of hepatitis B virus is discussed elsewhere. Some viruses, such as respiratory syncytial virus and influenza virus, may induce a hepatitis associated with cytokine-associated immune activation. Table 15.24.5.4

Common causes of hepatic granulomas

Infective	Bacterial: Mycobacteria
	Brucellosis Rickettsial
	Spirochaetal
Parasitic: Amoebiasis	Ascariasis Giardiasis
	Schistosomiasis Toxocariasis
Viral: Cytomegalovirus	Epstein-Barr virus
Fungal	Drugs
	Allopurinol Sulphonamides
	Phenylbutazone
Parenchymal disease	Primary biliary cholangitis
	Primary sclerosing cholangitis
	Malignancy
	Hodgkin's disease
Other	Sarcoid Systemic lupus erythematosus
	Whipple's disease Collagen disease
	Erythema nodosum Crohn's disease
Toxins:	beryllium and silicon

section 15 Gastroenterological disorders 3176 Other particular infective conditions Pyogenic liver abscess Pyogenic liver abscesses may occur as part of a systemic illness as a consequence of portal phlebitis, often associated with bowel sepsis, biliary tract disease, direct trauma, septicaemia, and in association with carcinoma of the colon or bacterial endocarditis. Most commonly they arise out of portal phlebitis, with the primary focus being the appendix, colon, diverticular disease, or in the pelvis (Table 15.24.5.5). Although abscesses may occur in patients with inflammatory bowel disease, this is relatively rare. The patient presents with abdominal pain, pyrexia, nausea, and weight loss, although fever is less common in children. Hepatomegaly may be

present and the liver is sometimes tender. The serum albumin is often reduced and alkaline phosphatase elevated. There is usually a marked neutrophil leucocytosis, but this is not invariable. The diagnosis is made on imaging of the liver. A chest radiograph may show elevation of the right hemidiaphragm with an associated pleural effusion or even lung consolidation. Ultrasonography, CT scanning, and MRI may define an hepatic abscess. Treatment of a solitary abscess is usually by percutaneous drainage in the first instance. Under ultrasonographic or CT guidance, a percutaneous drain should be established for single abscesses, and even in some cases of multiple abscesses. The abscesses should be drained to dryness and antibiotics given according to the sensitivities of the organisms isolated. Pathogens are usually anaerobic or aerobic gut coliforms, especially *Streptococcus milleri*, although *S. aureus* is common in children. The success rate of treatment with drainage and systemic antibiotics is 80 to 90%. Fatality is high in children and the elderly, in those with coexisting disease such as diabetes mellitus, and those with delayed diagnosis. Once the abscess has been drained, the primary source of infection must be sought and appropriate management instituted. Surgery may be required for patients with multiple abscesses or for those with abscesses that do not respond to simple drainage and antibiotic therapy. Liver abscess due to hydatid and amoeba are discussed elsewhere. HIV as a cause of liver disease

Liver disease in patients with HIV infection may be due to pre-existing hepatitis virus, opportunistic infections, or neoplasms, but in some cases the abnormality of liver function may be due to the virus itself. Such patients have nontender hepatomegaly with anorexia, weight loss, and low-grade fever. Liver function tests show a slight derangement with cholestasis. The liver biopsy shows nonspecific features including Kupffer cell hyperplasia, fat infiltration, noncaseating granulomas, and portal tract inflammation; occasionally, Mallory bodies may be present. Other causes of hepatobiliary abnormality in patients with HIV include primary hepatic infection due to viral hepatitis. Other causes of liver damage in AIDS

Many patients with AIDS are also at risk from hepatitis B, C, and D. As discussed elsewhere, these patients respond less well to interferon than those who are HIV negative. Other infections that are more common in these patients include cytomegalovirus, herpes virus, cryptosporidiosis, and mycobacteria including tuberculosis and *M. avium intracellulare*. Drug-induced liver damage must always be considered in HIV patients with abnormal liver tests, and it has been suggested that such patients are more susceptible to drug hepatotoxicity. Thus, many of the anticonvulsants, analgesics, and antimicrobials are associated with hepatocellular damage, and antibiotics may also be associated with cholestasis. Other abnormalities that may be of less significance clinically include peliosis hepatis and fatty infiltration. The biliary tree may also be affected in HIV infection inducing a syndrome superficially resembling primary sclerosing cholangitis. This is characterized by a rapid elevation of the serum alkaline phosphatase, which may be associated with pain in the right upper quadrant and, later, jaundice. Ultrasonography may be unhelpful, although dilated and thickened walls of the bile duct may be seen. Otherwise, endoscopic retrograde cholangiopancreatography will show the characteristic changes of sclerosing cholangitis with bleeding, dilatation, and stricture. Both cryptosporidial and cytomegaloviral infections have been associated with this form of sclerosing cholangitis. The liver may be involved in a number of other ways. There is an association between AIDS and lymphomas, be they Burkitt's, large cell, or immunoblastic. The liver and/or spleen may be the site of these tumours and hepatic involvement may be present in up to a third of those with gastrointestinal lymphomas. Tumours may be microscopic or macroscopic. The hepatic masses are often asymptomatic but if large may cause pain in the right upper quadrant, fever, jaundice, and abnormalities of liver function tests, especially of the serum alkaline phosphatase. Kaposi's sarcoma may affect the liver and biliary tree but is often asymptomatic. Autoimmune and

rheumatic conditions Liver abnormalities are not uncommon in patients with rheumatological disorders, although rarely prove a significant problem. Liver test abnormalities occur in around 50% of those with Sjögren's syndrome and 30% with systemic lupus erythematosus, and liver histology abnormalities are found in around 20% in both. More significant involvement may either be a consequence of treatment or occur in association with other autoimmune diseases. For example, those diseases assumed to have an autoimmune basis, such as autoimmune hepatitis or primary biliary cholangitis, may be associated with extrahepatic rheumatological diseases such as sicca syndrome. Rheumatoid arthritis Abnormalities of liver structure and function are uncommon in patients with rheumatoid arthritis, although minor abnormalities of liver function tests occur in 20 to 50%. Nodular regenerative hyperplasia may cause complications of portal hypertension. Felty's syndrome Felty's syndrome is characterized by the triad of splenomegaly, hypersplenism, and seropositive rheumatoid arthritis. Liver Table 15.24.5.5 Sources of a pyogenic abscess Source Percentage of cases Obstructive biliary tree 30–40 Intra-abdominal infection 15–25 Systemic infection 15–20

15.24.5 The liver in systemic disease 3177 function tests tend to be more commonly deranged than in uncomplicated rheumatoid arthritis. Anti-inflammatory therapy may contribute to the abnormal liver tests. Histological examination of the liver shows lymphocytic infiltration and, rarely, an established cirrhosis. Nodular regenerative hyperplasia has been described, as it has in rheumatoid arthritis. Although portal hypertension and variceal haemorrhage may occur, jaundice is unusual. Systemic lupus erythematosus Abnormalities of liver function in patients with systemic lupus erythematosus are usually minor, although spontaneous rupture of the liver has been described. The pattern of liver disease in patients with systemic lupus erythematosus varies from minimal change to chronic persistent hepatitis, chronic active hepatitis, and cirrhosis. In others, a granulomatous hepatitis has been described. Polyarteritis nodosa In contrast to rheumatoid arthritis, liver involvement in polyarteritis nodosa is relatively uncommon, although hepatic arteritis may occur, leading to aneurysm. Rupture of an aneurysm is rare and is characterized by fever, pain in the right upper quadrant, and jaundice. In most cases, abnormalities of liver function are due to an associated hepatitis C virus infection. Polymyalgia rheumatica Abnormalities of liver function are well recognized in patients with polymyalgia rheumatica. These abnormalities (elevation of serum alkaline phosphatase and aminotransferase activity) usually resolve with effective treatment. Histologically, the liver shows mild portal inflammation with occasional liver cell necrosis. Granulomas and steatosis may also be seen. Sjögren's syndrome Symptoms of sicca syndrome are common in patients with liver disease, particularly primary biliary cholangitis, and abnormalities of salivary gland function have been described in all patients in some series. Sicca syndrome is also found in patients with cryptogenic cirrhosis and autoimmune hepatitis. In patients with Sjögren's syndrome, there is often hepatomegaly and minor derangement of liver tests, particularly serum alkaline phosphatase, in 25%. The liver may show nonspecific inflammatory infiltration. Amyloid The liver may be involved in both primary and secondary amyloidosis; liver involvement is found in over 80% of patients with either form. In general, however, liver involvement has few significant clinical consequences, although jaundice, hepatitis, portal hypertension, and spontaneous rupture have been described. Clinically, the liver is enlarged. The serum alkaline phosphatase is usually greatly elevated; jaundice is uncommon. It is believed that liver biopsy may be particularly hazardous in patients with amyloid because there may be an increased risk of bleeding after biopsy. The liver histology is similar in both primary and secondary amyloid with protein deposition in the portal tracts, vessel walls, and space of Disse. Cryoglobulinaemia The reported incidence of liver disease in essential, mixed cryoglobulinaemia

varies greatly. In 20 to 50% of patients there is an association with hepatitis C viral infection. Up to half of patients have evidence of infection with hepatitis B virus, and up to 10% have chronic active hepatitis or cirrhosis with jaundice. Antiphospholipid syndrome Patients with antiphospholipid syndrome may develop liver abnormalities. Mostly this is reflected by vascular disease such as arterial, venous, or portal venous thrombosis, veno-occlusive disease, or, rarely, hepatic infarction. Some patients develop nodular regenerative hyperplasia. Other conditions Malignancy Although the liver may become infiltrated by metastatic cancer, abnormalities of liver tests can be seen in the absence of infiltration. This may be due to a systemic effect of tumour-derived cytokines, to the hepatotoxic effects of drugs, or the effects of irradiation, or the effects of malnutrition.

Paraneoplastic syndromes occur, for example, cholestasis may be seen with lymphoma, ovarian cancers, and renal cell carcinoma. In other cases, such as with nonseminomatous testicular tumours, 'liver' enzymes may be synthesized by the tumour cells so abnormal 'liver tests' may not indicate any form of liver damage. Stauffer syndrome (abnormal liver tests, sometimes with hepatomegaly) is a rare complication of renal cell carcinoma which resolves after resection of the primary; it is believed to be caused by tumour production of interleukin 6. The liver in the sick patient Abnormalities of liver tests are commonly seen in patients who are critically sick and are associated with a poor prognosis. There are many causes of abnormal liver tests in this situation (Box 15.24.5.1). 'Intensive therapy unit jaundice' occurs in up to 10% of intensive therapy unit patients, usually in the context of sepsis or abdominal trauma. Hepatomegaly is often present but the cutaneous features of chronic liver disease are absent. Encephalopathy is uncommon. The liver tests show a rise in serum bilirubin with a smaller and less consistent rise in serum alkaline phosphatase and aminotransferase levels. The clotting is only mildly deranged and blood sugar levels tend to be high rather than low. The cause of intensive therapy unit jaundice is unclear but factors such as ischaemia, hypoxia, and hepatocyte necrosis may occur. Treatment is of the underlying cause. Box 15.24.5.1 Abnormal liver tests in the critically ill patient • Sepsis • Underlying, pre-existing liver disease • Drug-induced liver injury • Trauma • Ischaemia • Haemolysis • Parenteral nutrition • Acalculous cholecystitis

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