7
The Liver

1. On physical examination, the normal *span of the liver* as measured by percussion in the right midclavicular line is 12–15 cm. It is the largest organ in the body.

2. *Riedel's lobe* is a common anatomical abnormality. This downward tonguelike projection of the right lobe is more common in women than in men. It does not cause symptoms, and treatment is not required.

3. *Liver cells (hepatocytes)* comprise about 60% of the liver mass. Their life-span is about 150 days.

4. The *excretory system* of the liver begins with the bile canaliculi, which drain into thin-walled terminal bile ducts (known also as ductules, cholangioles, or canals of Hering); these terminate in larger (interlobular) bile ducts in the portal spaces.

5. The following types of cells are found in the sinusoidal wall: (a) endothelial cells; (b) Kupffer cells; (c) lipocytes (Ito cells), which probably represent undifferentiated mesenchymal cells or resting fibroblasts; and (d) Pit cells, which contain granules and may have an endocrine function.

6. A palpable or audible *friction rub* over the liver is usually attributable to a tumor, a recent biopsy, or perihepatitis.

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7. A *venous hum* may be heard between the umbilicus and the xiphisternum in portal hypertension.

8. An *arterial murmur* over the liver may indicate a primary liver cancer or acute alcoholic hepatitis.

9. An increase of *urobilinogen in the urine* is found when hepatocellular function is inadequate to reexcrete all the bilirubin absorbed from the intestine. Thus, urinary urobilinogen is an index of hepatocellular dysfunction.

10. *Cholesterol* is synthesized in the liver, small intestine,and other tissues, from acetate. Hepatic synthesis is inhibited by cholesterol feeding and by fasting. Synthesis is increased by a biliary fistula, bile duct ligation, or an intestinal lymph fistula. The rate-limiting step is the conversion of hydroxymethylglutaryl–CoA(hMG-CoA) to mevalonate. Esterification is carried out in plasma by the enzyme lecithin cholesterol acyltransferase (LCAT), which is synthesized in the liver.

11. *Cholesterol, phospholipids,* and *triglycerides* are synthesized in the liver but are insoluble in water and cannot exist in plasma in free solution. Lipoproteins are involved in lipid transport. Four groups of lipoproteins are recognized: (a) high-density lipoproteins (HDL): migrate with alpha$_1$-globulin on electrophoresis; (b) low-density lipoproteins (LDL): migrate with beta-globulins; (c) very-low-density lipoproteins (VLDL); and (d) chylomicrons (large, triglyceride-rich particles originating in the gut and appearing in plasma after ingestion of a fatty meal).

12. *Bile salts* (a) take part in emulsification of dietary fat; (b) probably have some role in the mucosal phase of absorption; (c) assist in pancreatic lipolysis; (d) release GI hormones; (e) may contribute to the pruritus of cholestasis when levels are elevated in the serum; and (f) are responsible for the secretion of conjugated bilirubin in the urine.

13. *Serum bile acid levels* reflect the fraction reabsorbed from the

intestine that escaped extraction during its first passage through the liver. Both hepatocellular and cholestatic jaundice may be associated with elevated serum bile acid levels.

14. Some of the *amino acids* derived from the diet and from tissue breakdown are transaminated or deaminated in the liver to ketoacids, which are metabolized by many pathways. Others are metabolized to ammonia and urea.

15. In liver failure, *aromatic amino acids* (tyrosine, phenylalanine, tryptophan) increase in the serum due to failure of deamination. *Branched-chain aminoacids (BCAAs)* are decreased due to increased catabolism in skeletal muscle.

16. Liver disease is associated with failure to maintain *serum albumin* values, whereas immunoglobulins tend to increase. The reason is that the former is synthesized by liver cells, while the latter is synthesized by immunocytes.

17. *Alkaline phosphatase* synthesis is increased in any disorder that interferes with bile flow, whether intrahepatic or extrahepatic. With a serum half-life of 7 days, it tends to remain elevated after the serum bilirubin has returned to normal. In cholestatic jaundice, levels are usually four times the upper limit of normal, while in hepatocellular jaundice, they are less. Values may be increased (up to 50% above the upper limit of the norm) after the fifth decade of life.

18. *Serum 5-nucleotidase* level is normal in bone disease and raised in hepatobiliary conditions, especially cholestatic jaundice.

19. *Gamma-glutamyl transpeptidase* is an enzyme found in many tissues. It does not reflect one specific hepatic function, and serum values are increased in both cholestasis and hepatocellular disease. It is used to confirm whether a raised serum alkaline phosphatase is of hepatobiliary origin. It is also used to screen for alcohol abuse when serum levels are raised.

20. *Glutamic oxaloacetic transaminase (GOT), or aspartate transaminase,*

is a mitochondrial enzyme; its serum levels may rise to very high values in hepatocellular necrosis. *Glutamic pyruvic transaminase (GPT), or alanine transaminase* is a cytosol enzyme. Its increase in the serum is more specific for liver damage than is SGOT. The absolute values of SGOT and SGPT do not correlate with the degree of liver damage in *viral hepatitis.* Very high levels may be seen, not only in acute viral hepatitis but in early stages of acute choledocholithiasis as well. Values of these enzymes in cirrhosis vary from low to very high, being particularly high in *chronic active hepatitis.* A ratio of SGOT to SGPT greater than 2 is useful in diagnosing *alcoholic hepatitis* and *alcoholic cirrhosis.*

21. *Lactic dehydrogenase (LDH)* is a relatively insensitive index of hepatocellular injury.

22. Recent studies reported on other *liver enzymes* that may be of possible diagnostic value: (a) aldolase B for hepatocellular necrosis; (b) fructose 1,6-diphosphatase for piecemeal necrosis; (c) creatine phosphokinase for biliary obstruction; and (d) alpha$_2$-macroglobin serum levels—high in mechanical biliary obstruction but not in cholestatic hepatitis. All these reports are preliminary and need further investigation.

23. One recent study has reported on *indocyanine green* clearance as an early indicator of hepatic dysfunction following trauma (Gottlieb ME et al, Arch Surg 119:264, 1984).

24. *Percutaneous needle biopsy of the liver* is a procedure with low incidence of complications but should always be regarded as potentially risky. Most biopsy-induced hematomas probably go undetected. The incidence of hematomas detectable by radionuclide scanning or ultrasonography is 2.3%. They may cause fever, rises in SGOT and SGPT, and right upper quadrant tenderness. Other complications include pleuritis, perihepatitis, pneumothorax, intraperitoneal hemorrhage (extremely rare in nonjaundiced, most common in severe hepatocellular disease, uncommon in cholestatic

jaundice after vitamin K therapy), biliary peritonitis (may seal spontaneously or require surgical drainage; biopsy should be avoided when dilated intrahepatic ducts are identified by ultrasonography), hemobilia, and transient septicemia. In a review of more than 23,000 needle biopsies performed during the late 1960s, mortality was found to be 0.017%. It is probably even lower today with elaboration of the needle and technique and with better definition of indications and contraindications (see Nos. 25 and 26).

25. Prothrombin time and platelet count should always be done before needle *biopsy of the liver.* Biopsy should not be performed if prothrombin time is more than 3 sec increased over control, and platelet count should exceed 80,000. Vitamin K (10 mg IM) should be administered for a period of 2 days to jaundiced patients. Tense ascites, hydatid cyst, suspected hemangioma, right empyema, right subphrenic abscess, and deep hepatocellular jaundice are *contraindications to percutaneous liver biopsy.*

26. *Indications for needle liver biopsy* include: (a) jaundice, when the diagnosis is difficult; (b) cirrhosis and portal hypertension; (c) alcoholic liver injury; (d) chronic hepatitis; (e) suspected drug-related liver disease; (f) unexplained hepatomegaly or unexplained abnormalities of liver function; (g) infective and other systemic diseases (a portion of the biopsy should be cultured when biopsy is done for a suspected infective process); (h) storage diseases; and (i) screening of relatives of patients with familial diseases.

27. *Guided-needle liver biopsy* under control of sonography or CT facilitates the diagnosis of focal lesions, such as primary tumors of the liver, metastatic tumors of the liver, and simple cysts of the liver.

28. Lebrec and associates recently reported on 1000 *transjugular liver biopsies* in patients in whom percutaneous biopsies were contraindicated mainly because of bleeding tendency. Eight hundred

biopsy specimens were satisfactory, one fatal perforation of the liver occurred (Lebrec D et al, Gastroenterology 83:338, 1982).

29. *Causes of anemia in chronic liver disease* are (a) increased plasma volume (especially in portal hypertension with cirrhosis); (b) GI bleeding from varices; (c) bleeding from disturbed blood coagulation; (d) hypersplenism; (e) extrasplenic hemolysis in patients with alcoholic liver disease who also have hypercholesterolemia (Zieve's syndrome); and (f) rarely, a Coomb's positive hemolytic anemia seen in chronic active hepatitis and in primary biliary cirrhosis.

30. *Splenectomy* is not recommended in hypersplenism of chronic liver disease because the response of the RBCs is disappointing and mortality is high; also, in patients with portal hypertension it may be followed by splenic and portal vein thrombosis. Splenectomy should be performed only when clinical suffering from leukopenia or thrombocytopenia occurs.

31. *Bleeding in hepatocellular failure* is caused by (a) defective synthesis of vitamin K-dependent clotting factors II, VII, IX, and X and factor V, which is also synthesized in the liver (vitamin K is not absorbed due to insufficient bile salt secretion); (b) cell necrosis, which may lead to activation of hemostasis and disseminated intravascular coagulation (DIC) with fibrinolysis (consumptive coagulopathy can follow); and (c) defective clearance of activated factors, which may lead to DIC as well.

32. The *prothrombin time (PT)* and/or *partial thromboplastin time (PTT)* before and after administration of 10 mg vitamin K IM are the most satisfactory tests for a coagulation defect in patients with hepatobiliary disease. PT is also a most sensitive indication of the presence of hepatocellular necrosis and of prognosis.

33. In *hemolysis*, the healthy liver has a large capacity to handle the bilirubin load; even in massive hemolysis, serum bilirubin rises only to about 2–3 mg/dl. If in patients with hemolysis serum bili-

rubin values are greater than 4–5 mg/dl, there is probably an additional factor of hepatocellular dysfunction.

34. In *Hodgkin's disease,* hepatic involvement occurs in about 70% of cases. A multitude of parenchymal lesions have been described on biopsy, ranging from lymphocytic infiltration to focal necrosis. It is unusual for a needle biopsy of the liver to demonstrate Hodgkin's tissue if a radionuclide scan is normal.

35. In *myeloproliferative disorders,* portal hypertension may occur as a result of (a) thrombosis of the portal vein, splenic vein, or hepatic artery; (b) infiltrative lesions in the portal tracts or sinusoids; and (c) increased portal blood flow through the enlarged spleen.

36. *Plain films of the abdomen* for diagnosis of hepatobiliary disorders have been ignored in recent years. However, they may reveal gallstones, a calcified gallbladder wall, or emphysematous cholecystitis. *Gas in the biliary tree* may be due to (a) a spontaneous or postoperative biliary fistula; (b) incompetent sphincter of Oddi (as a result of gallstones or sphincterotomy); or (c) gas-gangrene infection (emphysematous cholecystitis).

37. *Oral cholecystography (OCG)* can be used to diagnose radiolucent gallstones and to evaluate gallbladder function, but it has chiefly been replaced by ultrasonography, which is now the initial diagnostic procedure for suspected gallstone disease. When there is a strong clinical suspicion of cholelithiasis or cholecystitis and the sonogram is normal, OCG can still be useful to exclude an isolated calculus in the cystic duct, which may be missed by sonography.

38. *Intravenous cholangiography (IVC)* has been largely replaced by ultrasonography and radionuclide studies for evaluation of acute cholecystitis, since the biliary system does not opacify adequately and tomography is necessary in a large number of patients. In addition, there is a false-negative rate of 17–45% in detecting chronic cholecystitis and cholelithiasis. An IVC that suggests partial ob-

struction by reason of delayed opacification generally requires further confirmation by direct cholangiography (PTC or ERCP) (see Nos. 43 and 44 and Chapter 5).

39. *Ultrasonography* is mainly used to detect focal lesions in the liver or to confirm suspected biliary tract disease. It is possible to distinguish among solid tumors, cysts, and abscesses, but false-positive and false-negative findings do occur. Because of its ease of application, sonography has become the preferred screening technique for suspected space-occupying lesions of the liver and for detecting biliary tract pathology. Endoscopic ultrasound probes, which facilitate the study of small lesions in the biliary tree (such as retained bile duct stones), are in the process of development.

40. *Radionuclide scintigraphy* in hepatobiliary disease is useful in (a) delineating size, location, and contour of the liver as well as uniformity of colloid distribution and the presence of "cold" lesions in the liver (^{99m}Tc); (b) determining the presence of hepatocellular disease by inhomogeneity of colloid distribution and by relatively increased activity in the spleen and bone marrow; (c) evaluating space-occupying lesions as small as 1–2 cm; (d) assessing cystic duct patency in suspected acute cholecystitis (by radiotracers that undergo hepatobiliary excretion, such as labeled N-substituted aminodiacetates, IDA group); (e) evaluating the biliary system after surgery or trauma, e.g., in suspected bile leak or fistula (IDA); (f) evaluating congenital biliary anomalies such as biliary atresia or choledochal cyst (IDA); and (g) evaluating a liver transplant (see No. 218).

41. *Cholescintigraphy (IDA)* as a means of detecting cystic duct obstruction is the preferred diagnostic technique in *suspected acute cholecystitis.*

42. *Computed tomography (CT)* of the liver and biliary tract has its main application in the diagnosis of focal lesions, such as tumors

or abscesses, but it can also provide information on the nature of diffuse liver disease (hemochromatosis, glycogenosis, diffuse steatosis). CT imaging is improved when performed with contrast media. Intravenous injection of an emulsion of ethiodized oil has recently been shown to permit the detection of lesions as small as 1 cm in diameter.

43. *Endoscopic retrograde cholangiopancreatography (ERCP)* is probably the most sensitive technique for detecting stones and tumors of the common duct. It is an excellent technique for evaluating patients with (a) either intrahepatic or extrahepatic jaundice, when the latter is suspected; (b) symptoms without jaundice after biliary tract surgery; (c) other abnormal tests suggesting biliary tract disease (such as common bile duct dilatation suggested by ultrasonography); and (d) known or suspected choledocholithiasis who are potential candidates for endoscopic sphincterotomy. (For the use of ERCP in pancreatic disease, see Chapter 5.)

44. *Percutaneous transhepatic cholangiography (PTC)* is a relatively simple and safe procedure. It permits direct visualization of the biliary tract in order to detect the site and nature of obstruction in patients with suspected obstructive jaundice. As opposed to ERCP, which outlines the distal portion of an obstruction, PTC can define the proximal extent of the blockage. PTC is also indicated when there is a need for delineation of the anatomy of the biliary tract after surgery, particularly after choledochojejunal anastomosis. It is also useful in determining the patency of the ductal system in sclerosing cholangitis. By providing access to the obstructed biliary system, PTC permits external or internal drainage of bile, which is usually performed either for decompression before surgery or as a substitute for surgical decompression of a biliary tract obstruction by an inoperable tumor.

45. *Nuclear magnetic resonance (NMR)* imaging of the liver is still in

a developmental stage, but preliminary observations seem promising, especially for demonstrating hepatomas and other tumors and for differentiating among various parenchymal diseases.

46. In *acute hepatocellular failure* due to such causes as viral hepatitis, jaundice parallels the extent of liver cell damage. But in chronic hepatic failure (e.g., cirrhosis) jaundice may be absent or mild; when present, it indicates active parenchymal disease and carries a poor prognosis.

47. In *hepatocellular failure,* hyperkinetic circulation (from an unknown cause) is manifested by flushed extremities, bounding pulse, capillary pulsation, increased skin and splenic blood flow, and increased cardiac output.

48. In *hepatocellular failure,* reduced oxygen saturation and cyanosis are common. This is probably due to intrapulmonary shunting through microscopic arteriovenous fistulas. The most profound cyanosis and clubbing are associated with chronic active hepatitis and long-standing cirrhosis.

49. In *active advanced cirrhosis,* about one-third of patients show a continuous low-grade fever. It is more frequent in alcoholics.

50. The *failing liver* is unable to convert ammonia to urea, but the reserve capacity of synthesis is great and blood urea levels fall only in a very advanced state or in fulminant hepatitis.

51. *Serum albumin* level falls in proportion to the degree and duration of *hepatocellular failure.* The same is true for other proteins such as prothrombin (prolonged PT is not restored to normal by vitamin K therapy) and other blood factors.

52. *Skin changes in chronic liver failure* include (a) spider angiomas, which may disappear with improving hepatic function or when blood pressure falls; (b) white spots on arms and buttocks on cooling the skin; (c) palmar erythema (also seen in rheumatoid arthritis,

pregnancy, chronic febrile disease, chronic leukemia, thyrotoxicosis); and (d) white nails.

53. *Endocrine changes in chronic hepatocellular failure* include (a) diminished libido and potency; (b) sterility (in advanced cirrhosis); (c) loss of secondary sexual hair; (d) testicular atrophy; (e) erratic, diminished, or absent menstruation; (f) atrophy of breasts and uterus; and (g) gynecomastia and other features of feminization (more common in alcoholic liver disease).

54. *Management of chronic hepatocellular failure* consists of the following symptomatic measures: (a) continued bed rest while improvement is maintained; (b) diet containing 80–100 g protein and 2500 cal; (c) abstention from alcohol (one glass of wine or beer daily is allowed in nonalcoholic chronic liver disease); (d) Hb level kept above 10 g/dl; and (e) avoidance of sedatives. If the need arises, oxazepam, which has a normal disposition in hepatic failure, may be the drug of choice.

55. The three types of *hepatic encephalopathy* are (a) *chronic portal sytemic encephalopathy (PSE)* with an etiology of portal-systemic shunting or increased dietary protein intake (survival rate: 100%, with proper treatment); (b) *cirrhosis with encephalopathy* precipitated by diuretics, hemorrhage, diarrhea and vomiting, paracentesis, surgery, infection, sedatives, or alcohol excess (survival rate: 70–80%); and (c) *encephalopathy in acute liver failure*, caused by acute viral hepatitis, alcoholic hepatitis, or drug overdose (survival rate: about 20%).

56. *Symptoms of PSE* are (a) inversion of sleep pattern; (b) apathy and slowness; (c) personality changes (childishness, irritability); (d) intellectual deterioration ranging from slight impairment of organic mental function to gross confusion; (e) slurred and slow speech; and (f) stupor and coma, which represent advanced stage of encephalopathy.

57. *Flapping tremor (asterixis)* is the most characteristic neurological abnormality in PSE. It is caused by impaired inflow of joint and other afferent information to the brainstem.

58. *Electroencephalographic (EEG) changes in PSE* appear early but are nonspecific. These include slowing of the frequency from the normal alpha range of 8–13 cycles/sec to the delta range of less than 4 cycles/sec.

59. *Ammonium* is derived from the nitrogenous contents of the intestine by bacterial action and is present in high concentration in portal blood. It is metabolized by the liver to urea. The question of whether a raised blood ammonium level in hepatic coma represents a toxic causative factor or is merely a nonspecific indicator of disturbed brain metabolism remains unresolved.

60. *Blood ammonia levels* usually corelate with either severity of encephalopathy or depth of coma, but in 10% of patients values are in the normal range regardless of depth of coma. After portocaval shunts, levels may be raised when no signs of encephalopathy are present. The level does not correlate with prognosis.

61. Recent studies indicate that levels of *ammonia in erythrocytes* are a better index of PSE than are blood ammonia levels.

62. *Cerebrospinal fluid (CSF) glutamine level* is a sensitive index of PSE.

63. *Alkalosis* is common in *PSE* due to the following: (a) toxic stimulation of the respiratory center by ammonia; (b) administration of alkali such as citrate in transfusions; and (c) hypokalemia precipitated by treatment with diuretics. Alkalosis increases ammonium toxicity by increased transfer of ionized ammonia across cell membranes.

64. *Hypoglycemia* is rare in chronic liver disease but may complicate fulminant hepatitis (see No. 72). The failing liver fails to metabolize insulin and glucagon adequately.

65. *GI bleeding triggers PSE* through the large protein contents in the intestine, the depression of hepatocellular function by anemia, and the reduction in liver blood flow.

66. *Surgical procedures* are poorly tolerated by patients with advanced liver failure, since remaining hepatic function is depressed by blood loss, anesthesia, and shock.

67. A large *protein meal* or *severe constipation* may precipitate coma in advanced liver disease.

68. *Prognosis in PSE* depends on the extent of liver cell failure. In cirrhosis, such findings as ascites, jaundice, and low serum albumin are indicators of poor prognosis, as they all represent liver failure.

69. *Child's classification* of prognosis in hepatocellular disease is based on the following parameters: the presence of ascites and encephalopathy, nutritional status, serum bilirubin and albumin levels, and PT. One-year survival is around 70% for patients in grade A or B and 30% in grade C.

70. *Management of PSE* includes (a) identification and elimination of precipitating factors; (b) limitation of dietary protein to 40 g; (c) avoidance of nitrogen-containing drugs (e.g., ammonium chloride, urea); (d) 1–2 semisolid bowel movements daily ensured by lactulose 10–30 ml tid; (e) maintenance of caloric and fluid and electrolyte balance; and (f) neomycin 1–1.5 g qid, recommended especially in acute hepatic coma; metronidazole 0.2 g qid has been shown to have an additive effect. Experimental therapeutic modalities that may be employed when symptoms worsen despite the above regimen include BCAAs, bromocriptine 15 mg/day, and liver transplantation (see No. 218).

71. The mechanism of action of *lactulose in PSE* is uncertain. It is broken down by bacteria in the cecum to lactic acid and acetic acid. Fecal pH drops. Changes in conditions are created that favor the growth of lactose-fermenting organisms over ammonia formers,

but clinical improvement after the administration of lactulose precedes these changes in bacterial flora. The decreased pH value reduces the ionization of NH_4 (unabsorbed) to NH_3 (absorbed), but fecal ammonia is not increased by lactulose.

72. *Acute (fulminant) hepatic failure* is a clinical syndrome resulting from massive necrosis of liver cells or from sudden and severe impairment of liver function. There should be no evidence of preceding liver disease. Possible etiologies include viral hepatitis, i.e., A, B, non-A–non-B (NANB); drugs, e.g., paracetamol and halothane; and the fatty liver of pregnancy. Survival is 12–20% if deep coma is reached. Advanced age and the coexistence of other diseases worsen the prognosis. Those who survive seldom develop chronic liver disease. Causes of death are bleeding, respiratory and circulatory failure, cerebral edema, renal failure, infection, hypoglycemia, and pancreatitis (see also No. 136).

73. *Cerebral edema* is a major factor in the mortality of acute hepatic failure. Mannitol has been shown to have a significant therapeutic value. Steroids have no proven value.

74. There is no well-founded scientific evidence showing therapeutic benefits of *BCAAs, extracorporal assists* (e.g., hemodialysis or charcoal hemoperfusion), or hepatocyte transplantation in *acute (fulminant) hepatic failure.*

75. *Ascites in portal hypertension* results from the following contributing factors: (a) both elevated portal venous pressure and hypoalbuminemia (leading to decreased colloid osmotic pressure); (b) most likely increased hepatic lymph production; and (c) sodium retention (either as a primary renal defect or secondary to low effective intravascular volume).

76. *Pleural effusion* is common among cirrhotic patients with ascites; it is caused by defects in the diaphragm permitting ascites to pass into the pleural cavity. It is right-sided in about two-thirds of cases.

77. *Peripheral edema* commonly follows the ascites in portal hyper-

tension; it is the result of hypoproteinemia and of functional inferior vena cava block by ascitic fluid.

78. The *fluid in ascites of portal hypertension is a transudate.* Protein concentration exceeding 2 g/dl suggests infection, obstruction to the hepatic veins (Budd–Chiari syndrome), or pancreatic ascites.

79. *Spontaneous bacterial peritonitis (SBP)* (a) develops in about 8% of cirrhotic patients with ascites, more commonly in decompensated cirrhosis and in alcoholics; (b) should be suspected if the condition of a patient with a known cirrhosis shows sudden deterioration, particularly encephalopathy; (c) may be associated with fever, local abdominal pain, and tenderness and leukocytosis; (d) is not conclusively established by an ascites WBC count exceeding 500/mm^3 of which at least 75% are polymorphs, but this finding is sufficiently alarming to merit antibiotic therapy; (e) is indicated with high specifity (100%) by a low ascitic fluid pH (below 7.32), but this measure has a low sensitivity (25%) as an indicator of bacterial peritonitis; (f) is most commonly caused by *Escherichia coli*, but streptococci and mixed infections do occur; (g) is treated by systemic administration of antimicrobial agents according to the sensitivity of the organism cultured from the ascitic fluid; and (h) carries a poor prognosis when accociated with acute alcoholic hepatitis, serum bilirubin above 8 mg/dl, and serum creatinine above 2.1 mg/dl.

80. *Dr. Sheila Sherlock's protocol for the management of ascites in portal hypertension* includes (a) bed rest; (b) a low-sodium diet (22 mEq/day); (c) restriction of fluid intake to 1 liter/day; (d) daily weight and frequent measurement of serum electrolytes; (e) daily intake of 100 mEq KCl; (f) spironolactone 100 mg or amiloride 10 mg/day started with reduction of KCl intake to 50 mEq/day, if after 4 days under the above regimen weight loss is less than 1 kg; (g) addition, 1 day later, of furosemide 80 mg after checking serum electrolytes; (h) doubling of daily dosage of spironolactone or amiloride if weight loss is less than 2 kg after 4 more days; and (i) increased furosemide

to 120 mg if necessary. Diuretics should be stopped if flapping tremor, hypolakemia, azotemia, or alkalosis develop.

81. *Management of refractory ascites* includes several techniques: (a) plasma expansion by salt-poor albumin or by ascites ultrafiltration and reinfusion: limited by risk of infection, development of heart failure, precipitation of variceal hemorrhage, and high cost; (b) *peritoneovenous shunt*: complications are multiple, frequent, and severe—fever, leakage of peritoneal fluid, occlusion of the shunt, local and systemic infections (including bacterial endocarditis), and severe DIC (lesser degrees of DIC always occur)—reserving its use for patients in whom conservative forms of treatment have failed; and (c) portocaval anastomosis to relieve ascites: carries high mortality and the development of PSE postoperatively is common.

82. *Prognosis of patients with advanced liver disease who have ascites* is grave. Even with adequate treatment, only 40% of patients will survive 2 years after the onset of ascites. Prognosis is better when ascites have accumulated rapidly and if there is a well-defined precipitating factor (such as GI hemorrhage); prognosis is worse if liver cell failure, as evidenced by jaundice and PSE, is severe.

83. *Hepatorenal syndrome* is a functional renal failure arising either spontaneously or in response to changes in blood volume or to shifts of fluid within body compartments. The diagnosis of the syndrome rests on (a) the presence of chronic liver disease with ascites; (b) slow-onset azotemia; (c) preserved tubular function (i.e., urine to plasma osmolality ratio >1.0, urine to plasma creatinine ratio >30, urine sodium concentration <10 mEq/dl); and (d) no sustained benefit by expansion of intravascular volume. Prognosis is extremely grave.

84. *Prevention of hepatorenal syndrome* consists of (a) avoidance of diuretic overdose; (b) slow treatment of ascites; and (c) early recognition and prompt treatment of electrolyte imbalance, hemorrhage, or infection.

85. *Management of the hepatorenal syndrome* is supportive and includes restriction of fluids, sodium, potassium, and protein and withdrawal of potentially nephrotoxic drugs, such as neomycin. Renal dialysis does not improve survival.

86. *Portal blood flow* in man is about 1000–1200 ml/min. The portal vein contributes 72% of the total oxygen supply to the liver. The *normal portal pressure* is about 7 mm Hg.

87. In *cirrhosis with portal hypertension,* only 13% of the portal vein blood flow can be recovered from the hepatic veins. The remainder is drained into the systemic circulation through the following groups of collateral channels: (a) short gastric veins and the left gastric vein (coronary vein) of the portal system, which anastomose with the intercostal, diaphragmoesophageal, and azygos minor veins of the caval system at the cardia of the stomach; (b) the superior hemorrhoidal vein of the portal system, which anastomoses with the middle and inferior hemorrhoidal veins of the caval system at the anus; (c) anastomoses in the falciparum ligament through paraumbilical veins; (d) anastomoses between veins draining abdominal viscera and veins draining retroperitoneal tissues at sites where the two are in contact (e.g., liver and diaphragm, omentum, and lienorenal ligament); and (e) portal venous blood carried to the left renal vein (directly from the splenic or via diaphragmatic, pancreatic, left adrenal, or gastric veins).

88. A recent study from Yale has shown that measurement of *azygos venous blood flow* by a continuous thermal dilution technique is an index of blood flow through gastroesophageal collaterals in cirrhosis (Bosch J & Groszman RJ, Hepatology 4:424, 1984).

89. *Hepatic cirrhosis* is the most common cause of portal hypertension. *Extrahepatic portal block* may be caused by previous recurrent abdominal inflammation or by chronic pancreatitis with obstruction of the splenic vein. *Oral contraceptives* may lead to portal and hepatic venous thrombosis.

90. In *portal hypertension,* the spleen size does not correlate with portal pressure, but an enlarged spleen is the single most important diagnostic sign of portal hypertension; the diagnosis should be questioned if the spleen is of normal size.

91. *Hematemesis* is the most common presentation of portal hypertension.

92. In *portal hypertension,* varices are most often seen in the lower third of the esophagus, but they may spread upward. Esophageal varices are nearly always accompanied by gastric varices in the fundus, but the latter may be difficult to distinguish from mucosal folds on barium meal. Esophageal and gastric varices may be visualized on endoscopy as blue, rounded projections.

93. *Methods of visualizing the portal venous system* include (a) ultrasonic measurement of venous flow velocity with the pulsed Doppler flowmeter: a recently developed noninvasive technique, the results of which compare well with cineangiographic measurements; (b) percutaneous transsplenic portal venography: gives the best definition of portal venous system and estimation of portal pressure but carries the risk of intraperitoneal hemorrhage; (c) scintiphotosplenoportography: a radiotracer is injected into the spleen and serial scans are made using a gamma camera (flow patterns defined, particularly as to whether portal vein flow is hepatofugal or hepatopetal); (d) transhepatic portography: technically difficult; and (e) selective splanchnic arteriography: the hepatic arterial system is demonstrated very clearly, but the portal venous system is not and pressure cannot be measured.

94. *Wedged hepatic venous pressure (WHVP)* recorded through a catheter introduced transhepatically into an hepatic venous radicle until it can go no further represents the sinusoidal venous pressure. Pressure in the hepatic vein is measured by withdrawing the catheter about 5 cm, to the free position. Normal WHVP is 5–6 mm Hg, whereas values of about 20 mm Hg are found in patients with portal hypertension.

95. *Hepatic blood flow* can be measured by infusion of bromsulphalein (BSP) or indocyanine green and catheterization of the hepatic vein or by an analysis of the disappearance curve of indocyanine green in a peripheral artery and hepatic vein.

96. *Portal hypertension* is classified into two types: (a) *presinusoidal*: (i) *extrahepatic*: block of portal or splenic vein by infection, thrombosis, congenital anomalies, malignant tumors (of pancreas, stomach, colon, or adjacent lymph glands), acute and chronic pancreatitis, or pancreatic pseudocysts and hypercoagulable states including the use of oral contraceptives), or (ii) *intrahepatic*: the obstruction is usually in the portal tracts, e.g., schistosomiasis, congenital hepatic fibrosis, and portal zone infiltration; and (b) *sinusoidal intrahepatic*: caused by all forms of cirrhosis, as a result of distortion of the portal vascular bed and mechanical obstruction of the portal blood flow by the regenerating nodules.

97. In *presinusoidal portal hypertension*, hepatocellular function is relatively preserved; patients can better tolerate variceal hemorrhage and usually do not develop liver failure. In *intrahepatic portal hypertension*, hepatocellular disease is commonly associated, and hemorrhage frequently leads to liver failure.

98. *Idiopathic (primary) portal hypertension* has been described in which no obvious obstruction to the portal venous system can be demonstrated. This entity is common in Japan and India, but its etiology is still not established. A portal venopathy is suggested by the occlusion of intrahepatic portal radicles by portal and periportal fibrosis as well as by irregular parenchymal atrophy. A reaction to an unidentified chemical or plant toxin has been suggested.

99. *Bleeding from variceal hemorrhage* in patients with portal hypertension may follow upper respiratory infections in children and the use of nonsteroid antiinflammatory agents.

100. *Emergency endoscopy* in upper GI bleeding is indicated even in patients with documented esophageal varices, as up to 50% may

bleed from other lesions, such as peptic ulcer disease, erosive gastritis, or Mallory–Weiss tears. A recent study has shown, however, that when multiple potential bleeding lesions are present and none of them is actively bleeding during endoscopy, esophageal varices are the most likely offenders; failure to prove this at endoscopy is usually attributable to delay in performing the procedure (Mitchell KJ et al, Scand J Gastroenterol 17:965, 1982).

101. The *degree of portal hypertension* correlates with the size of esophageal varices and with the chance for bleeding, but in the individual patient prediction of the chance for bleeding is inaccurate.

102. *Management of active variceal bleeding* includes (a) hospitalization with close monitoring and supportive measures (blood, plasma, vitamin K, platelets if needed, H_2-blockers because stress-induced acute mucosal ulcers are common, measures to prevent encephalopathy); (b) emergency endoscopy; (c) administration of *vasopressin*, 0.4–0.6 units/min in continuous intravenous infusion, if active variceal bleeding is seen; (d) insertion of a *Sengstaken–Blakemore* tube or one of its modifications, if bleeding continues; (e) an attempt at variceal sclerosis (see No. 103), if control of hemorrhage was achieved by one of the above measures; and (f) avoidance of emergency surgery whenever possible, but if control has not been achieved by any of the above measures a *portocaval* or *mesocaval shunt procedure* or *esophageal transection* should be done. Mortality rate is very high when shunts are done on an emergency basis. *Transhepatic variceal sclerosis* is another last-resort option in management of variceal bleeding that does not respond to a more conservative approach. Potential complications of this procedure are hemorrhage from the liver and biliary peritonitis.

103. Long-term management of variceal bleeding: (a) *Endoscopic sclerotherapy* has gained popularity in patients who have had one episode of variceal bleeding. There are only limited data from well-controlled trials to show its long-term effectiveness. A recent large study from Copenhagen supports a beneficial effect of sclerother-

apy on the incidence of rebleeding and on survival (The Copenhagen Esophageal Varices Sclerotherapy Project, N Engl J Med 311:1594, 1984). Many authorities recommend sclerotherapy as first-line therapy for variceal bleeding. Possible complications include disturbances in lower esophageal motility and ulcers that have the potential to cause perforation at the injection site. Adult respiratory distress syndrome (ARDS) and other acute and chronic pulmonary complications have been reported but are rare. (b) *Propranolol* in a dose that reduces the pulse rate by 25% has been shown by Lebrec and associates to have a beneficial effect on rebleeding rates and survival in patients with well-compensated cirrhosis (Lebrec D et al, N Engl J Med 305:1371, 1981). Other investigators have been unable to reproduce these results, and no effect of this medication has been demonstrated in patients with more advanced cirrhosis. The place of beta-blockers in the management and prevention of variceal bleeding is still under investigation. (c) *Portosystemic shunt surgery* to divert portal flow can reduce the incidence of rebleeding from varices but does not improve survival. Liver failure and encephalopathy are common among patients who have undergone portosystemic shunt surgery and the *selective distal splenorenal shunt*, which preserves portal blood flow to the liver, seems safer in this respect. The performance of distal splenorenal shunt requires great surgical expertise and is associated with postoperative development of ascites.

104. Controlled trials on *prophylactic treatment of esophageal varices* (before variceal bleeding has occurred) are being conducted, but the effectiveness of neither prophylactic sclerotherapy nor shunt surgery in preventing bleeding or prolonging survival in patients with portal hypertension and varices has been demonstrated to date.

105. *Gilbert's syndrome* affects 2–5% of the population. It is characterized by familial mild unconjugated hyperbilirubinemia, decreased plasma bilirubin clearance, and reduced hepatic UDP glu-

curonyltransferase activity. An exaggerated hyperbilirubinemia occurs after fasting and in response to administration of nicotinic acid. Liver histology and liver function tests are normal. Prognosis is excellent, with normal life expectancy.

106. *Crigler–Najjar syndrome* is characterized by a familial jaundice associated with very high serum unconjugated bilirubin levels. Deficiency of conjugating enzymes in the liver is well documented. In type I, no bilirubin-conjugating enzymes can be detected, and patients die with kernicterus during infancy. In type II, there is a deficiency in bilirubin-conjugating enzymes, but phenobarbital lowers bilirubin levels and patients survive into adulthood.

107. *Dubin–Johnson and Rotor syndromes* are characterized by familial accumulation of conjugated bilirubin in serum. Patients are mostly asymptomatic, and the condition may present as jaundice during pregnancy or after taking oral contraceptives. Defective canalicular excretion of unknown cause is thought to be the cause of the hyperbilirubinemia. The BSP test shows a diagnostic pattern—values of serum BSP after 2 hr exceed those seen after 45 min. Rotor type differs from Dubin–Johnson type in respect to pigmentation of liver (found only in Dubin–Johnson) and genetic inheritance. Both types carry an excellent prognosis.

108. *Bile acids* are metabolites of cholesterol. Synthesis is in the hepatocyte. Bile acids are secreted as glycine or taurine conjugates (3:1).

109. *Primary bile acids: cholic and chenodeoxycholic.* Intestinal flora metabolize cholic to *deoxycholic* and chenodeoxycholic to *lithocholic acids.*

110. *Lithocholic acid* is a hepatotoxin; it has a detergent effect and is minimally absorbed in the enterohepatic circulation.

111. *Bile* contains water, electrolytes, bile acids, cholesterol, phospholipids, bilirubin, and organic solutes.

112. *Total bile flow* consists of (a) bile-acid-dependent canalicular secretion (200 ml/day); (b) bile-acid-independent canalicular secretion (225 ml/day); and (c) ductular secretion (180 ml/day).

113. *Secretin, CCK,* and *gastrin* stimulate bile flow.

114. The concentration of *bile in the duodenum* is 5–10 mM in the basal state and 13–46 mM after contraction of the gallbladder.

115. *Bile salt pool*: 5–10 mM (1–4 g). *Enterohepatic circulation*: 3–12 times daily.

116. *Cholestasis* involves impaired bile formation. The lack of carrier for bilirubin excretion causes hyperbilirubinemia.

117. *Important histological characteristics of cholestasis* include (a) accumulation of bile in centrizonal areas, Kupffer cells, and canaliculi; (b) feathery degeneration of centrizonal hepatocytes; and (c) late portal zone fibrosis.

118. *Xanthomata* will develop in prolonged cholestasis, mainly when serum total lipids exceed 1800 mg/dl or serum cholesterol exceeds 450 mg/dl for more than 3 months.

119. *Osteomalacia* from failure to absorb calcium and vitamin D in chronic cholestasis will not manifest earlier than 2 years after the onset of cholestasis and cannot be predicted from serum calcium and phosphate levels.

120. *Copper* accumulates in the liver in cholestasis.

121. *Portal hypertension* and *hepatocellular failure* in cholestasis develop later than in other processes leading to cirrhosis.

122. *Management of chronic cholestasis* includes less than 40 g dietary fat; medium-chain triglycerides (MCT); vitamins A, D, and K; calcium; cholestyramine; and phenobarbital.

123. *Cholestyramine* is effective only in partial biliary obstruction, should be administered before meals, and relieves pruritus within 4–7 days.

124. *Cholestasis* (even severe) is not a contraindication for liver biopsy as long as PT is not over 3 sec off control after vitamin K and as long as platelets are over 80,000/mm^3.

125. *Hepatic bile* contains Na 150 mEq/liter, K 4 mEq/liter, Cl 95 mEq/liter, HCO_3 10 mEq/liter. Thus, in external biliary fistula, the primary loss is of Na and K.

126. *Hepatic histology in extrahepatic cholestasis* is characterized by (a) multiple tortuous bile ducts in the portal zone; (b) polymorphonuclear leukocytes around bile ducts if ascending cholangitis is caused by the obstruction; (c) focal necrosis of heptocytes starting in the middle of the lobe and spreading to the portal triads; (d) "bile lakes" (ruptured interlobular bile ducts); and (e) portal fibrosis as a late result.

127. *Hepatic histology in intrahepatic cholestasis* is different from histology in extrahepatic cholestasis; cholangitis is absent, bile ducts within the liver are not dilated, and bile duct multiplication and biliary necrosis are not seen.

128. *Intrahepatic cholestasis* may be classified according to the site of involvement on the biliary tree: (a) *hepatocellular*: viral hepatitis, alcoholic hepatitis, postnecrotic cirrhosis, drugs, and Dubin–Johnson–Rotor; (b) *canalicular*: sex hormones and pregnancy; and (c) *biliary*: chlorpromazine, benign recurrent cholestasis, primary biliary cirrhosis, biliary atresia, sclerosing cholangitis, and cholangiocarcinoma.

129. *Primary biliary cirrhosis (PBC)* (a) is a chronic inflammatory disease involving the small interlobular bile ducts that progresses to cirrhosis and may lead to liver failure and/or portal hypertension; (b) has an unknown etiology, but there seems to be familial clustering and there is an increase in the incidence of serological antibodies in healthy relatives of patients; (c) may be tested with *antimitochondrial antibodies* as the best immunological marker, being positive in 90% of patients, but they are not specific and may be

found in patients with chronic active or drug-induced hepatitis; (d) has clinical features including 90% incidence in females, usually between the ages of 40 and 59, presenting with pruritus; jaundice may be concomitant or follows a few months to years after the onset of pruritus, pigmentation, steatorrhea, and skin xanthomas; severe bone changes occur when jaundice is deep; (e) has a variable course—patients may be asymptomatic, and survival for this group has recently been reported to be no different from that in a control population for at least 12 years after diagnosis; the average length of survival from the onset of symptoms in symptomatic patients is about 12 years; (f) is commonly associated with extrahepatic diseases, including systemic lupus erythematosus (SLE), scleroderma (with or without Sjogren's syndrome), rheumatoid arthritis, dermatomyositis, celiac disease, and membranous glomerulonephritis; cholelithiasis has been reported in about 40% of cases; (g) exhibits biochemical findings including increased levels of serum bilirubin, alkaline phosphatase, and IgM; (h) displays histological findings that may be divided into four stages: stage 1 (damaged bile ducts surrounded by an infiltrate of lymphocytes, epithelioid cells, and plasma cells, and granulomas may be present), stage 2 (ductular proliferation, fibrosis, acute and chronic inflammatory infiltration, and lymphoid aggregates, and Mallory hyaline may be seen in liver cells), stage 3 (scarring with acellular septa extending from the portal tracts), and stage 4 (cirrhosis); (i) carries a better prognosis in association with portal fibrosis limited to the portal triad, onset at young age, normal-size liver, and normal serum bilirubin; and (j) is treated symptomatically as for other chronic cholestatic states; steroids are contraindicated due to increased bone damage, and other immunosuppressive agents as well as D-penicillamine did not improve liver function tests or prognosis. Primary biliary cirrhosis has been considered by many authorities to be one of the prime indications for liver transplantation.

130. *Primary sclerosing cholangitis* (a) is a chronic fibrosing inflam-

matory process involving all parts of the biliary tract; (b) shows the walls of the bile ducts (extrahepatic and intrahepatic) and gallbladder to be infiltrated with lymphocytes, plasma cells, and eosinophils with fibrosis; (c) in about 75% of cases is associated with *ulcerative colitis*, which preceded sclerosing cholangitis; (d) is associated with Riedel's struma, pancreatitis, retroperitoneal fibrosis, immune-deficiency syndromes, and rarely cholangiocarcinoma; (e) has clinical features including male-to-female ratio of 2:1 and a common presentation with jaundice, pruritus, weight loss, RUQ pain, and acute cholangitis, with possible manifestations of portal hypertension, and occasional lack of symptomatology; (f) is detected by the preferred diagnostic technique of ERCP, which shows irregular stricturing and dilatation (beading) of the intrahepatic and extrahepatic bile ducts; (g) has complications including recurrent cholangitis and portal hypertension; (h) has a mean survival from onset of symptoms of about 7 years, but patients can remain asymptomatic for many years; (i) shows a disappointing response to treatment, which includes surgery in complete main duct obstruction and, for removal of stones, endoprostheses when strictures are not amenable to surgical correction and antimicrobial agents for episodes of acute cholangitis; removal of diseased colon does not affect the course of biliary tract disease; and (j) has been surgically treated with liver transplantation, performed successfully.

131. The basic histological picture of *acute viral hepatitis* (A, B, or NANB) includes (a) hepatic cell necrosis, which is more prominent in the center of the lobules, and cellular infiltration, which is more prominent in the portal tracts; (b) hyperplasia of Kupffer cells, neutrophils, and eosinophils; (c) acidophilic bodies; (d) centrizonal cholestasis; and (e) commonly bile duct proliferation.

132. *Aplastic anemia* may occur in all three forms of hepatitis.

133. *The three types of viral hepatitis*—A, B, and NANB—run essentially the same clinical course, but type B tends to be more severe.

134. In *viral hepatitis,* the prodromal period lasts a few days to 3 weeks and consists of anorexia, nausea, abdominal pain, fever, loss of desire to smoke or to drink alcohol, malaise, and fatigue. Headache may be severe, but this is uncommon.

135. A *cholestatic variant of viral hepatitis* occurs and should be differentiated from extrahepatic obstruction by the acute onset of the latter.

136. In *fulminant hepatitis,* clinical deterioration develops rapidly and mortality rate is high. Repeated vomiting, fetor hepaticus, confusion, and drowsiness are grave prognostic signs. The clinical and laboratory features are those of acute liver failure (see No. 72). Prognosis is unrelated to bilirubin and enzyme levels, but PT correlates with prognosis. Survival is about 33% in fulminant hepatitis caused by hepatitis B virus (HBV) and 13% for fulminant-type NANB.

137. In *hepatitis A* (a) the cause is an RNA virus, a picornavirus in the genus *Enterovirus;* (b) the virus is excreted in the stool from about 2 weeks before until 1 week after the onset of jaundice; (c) serum IgM antibody to hepatitis A virus (HAV) is indicative of a recent infection, persisting in the serum for 2–6 months, while IgG anti-HAV is detectable for many years and probably confers immunity for life; (d) chronic carriers have not been identified; (e) rapid progress is being made for production of attenuated live vaccine but it is still unavailable; (f) in urban areas, most of the adult population (60–70%) show circulating anti-HAV; and (g) the course is usually clinically mild, frequently unicteric, and rarely fulminant. Long-term prognosis is excellent.

138. In *hepatitis B* (a) the cause is a DNA virus, the virion of which is composed of a core containing DNA polymerase, double-stranded DNA, core antigen (HBcAg), an e antigen (HBeAg), and a surface consisting of a surface antigen (HBsAg); (b) HBsAg appears in the blood about 6 weeks after infection and disappears by 3 months;

in early acute hepatitis (when HBsAg is still not demonstrable), diagnosis can be proved by IgM anti-HBc (mainly the 19 S IgM antibody, while the 7 S IgM antibody indicates a chronic disease); (c) persistence of HBsAg for more than 6 months implies a carrier state; anti-HBs appears about 3 months after the onset of illness and appears to confer immunity; 10–15% of patients with acute hepatitis B never develop anti-HBs; (d) HBeAg appears after about 1 week of illness and usually disappears by 2 weeks; persistence implies ongoing disease; the appearance of anti-HBe follows the disappearance of HBeAg and it is present for many months; (e) IgG anti-HBc appears early in the course and persists for many months; (f) HBeAg and DNA polymerase imply ongoing infectivity; and (g) in carriers and in chronic hepatitis B, hepatocytes may be stained orange with orcein.

139. In *hepatitis B* (a) spread is largely by whole blood and its products; health personnel and homosexuals are at high risk; (b) the carrier rate of HBsAg varies from 0.1 to 0.2% in Western developed countries to 15% in certain areas of the Far East; (c) subclinical episodes are common; (d) clinical features are similar to those of hepatitis A but tend to be more severe; and (e) serum-sickness-like syndrome may be part of the prodrome and includes fever, urticaria, and arthropathy of small joints.

140. *Endoscopy does not cause transmission of hepatitis B,* as shown by several studies.

141. In *hepatitis B* (a) a carrier state occurs in about 10% of patients suffering from acute hepatitis B and is manifested by persistence of HBsAg for more than 6 months; (b) carriers seldom revert to a negative HBsAg state, but conversion may occur after many years; (c) the extent of infectivity of a carrier has not been established but is probably small; (d) histological changes on liver biopsy are common even in carriers of HBsAg who appear to be healthy; (e) positive serum HBeAg or IgM anti-HBc indicates infectivity due to

ongoing disease; (f) the likelihood of a persistent HBsAg carrier state is greater if hepatitis B occurs before 3 years of age than if it is acquired later in childhood; and (g) a recent 10-year prospective cohort study of carriers over 40 years of age confirmed the high risk of hepatocellular carcinoma in these patients (Beasley RP et al, Lancet 2:1129, 1981) (see No. 212).

142. *Conditions associated with circulating immune complexes containing HBsAg* include (a) polyarteritis; (b) glomerulonephritis (a rare association exists between membranous or membranoproliferative glomerulonephritis and chronic hepatitis B infection); and (c) essential mixed cryoglobulinemia (the exact relationship with hepatitis B has not been determined).

143. *NANB hepatitis* (a) probably accounts for about 75% of post-transfusion hepatitis and 15–20% of sporadic hepatitis; (b) still awaits a suitable diagnostic test or a serological marker; (c) is largely blood spread; (d) has an average incubation period of 7 weeks, with clinical and laboratory features similar to those of hepatitis A or B, but serum enzyme levels tend to wax and wane for months; (e) is uncommonly associated with fulminant hepatitis; (f) commonly leads to the development of chronic hepatitis, in about 25% of cases, is usually mild, and improves with time, but cirrhosis may ensue.

144. *Delta agent*: (a) The agent is a defective RNA virus that requires the helper function of HBV for its multiplication; (b) it has been shown to be present in epidemics of acute hepatitis B in areas with a high HBV carrier rate, and the delta marker rate was recently found to be 34% in fulminant hepatitis in Los Angeles (Govindarajan S et al, Gastroenterology 86:1417, 1984); (c) it is common among drug addicts; (d) it causes a particularly progressive chronic hepatitis (now called hepatitis D) and is usually but not necessarily HBeAg negative; and (d) a sensitive enzyme immunoassay for D Ag and anti-D has recently been developed.

145. *Prevention and treatment of viral hepatitis* include (a) immune

globulin, 0.02 ml/kg body weight IM within 2 weeks after exposure, to modify hepatitis A infection to a subclinical form, indicated for household contacts of an index case; (b) passive immunization with hepatitis B immune globulin, indicated in the neonate of the HBsAg-positive mother (0.5 ml at birth and at 3 and 6 months), for sexual contacts of a patient with acute hepatitis B (3–5 ml and repeated after 1 month), and for accidental needle stick or mucous membrane exposure (same dose as for sexual contacts); (c) active immunization with the HBsAg vaccine, indicated postexposure for the three groups mentioned in (b) and as prophylaxis for health-care workers, hemodialysis patients, and other immunosuppressed persons (a second dose is given at 1 month and a third at 6 months) (the efficacy of passive immunization with immune globulin to prevent NANB hepatitis has not been determined and active immunization is still unavailable); (d) general measures such as a high-calorie fluid-rich diet, intravenous fluids if nausea and vomiting are severe, avoidance of tranquilizers, alcohol, and any medications that are not essential, and restriction of strenuous physical activity; corticosteroids should not be used; enteric precautions seem appropriate for hepatitis A and blood precautions for hepatitis B and NANB; and (e) follow-up evaluation of patients until resolution of abnormalities in liver function tests.

146. In *fulminant hepatitis*, no treatment is known to speed resolution or to increase survival rate, but emphasis should be given to vigorous maintenance of vital functions and prompt recognition and treatment of life-threatening complications. Such measures include close monitoring of vital signs, serum electrolytes, creatinine, glucose, and coagulation profile. Encephalopathy is common and should be treated promptly; the same is true for fluid and electrolyte imbalance, respiratory failure, cerebral edema, and GI bleeding from erosive gastritis. Artificial hepatic support devices are still under development, but successful liver transplantation has been reported in a few patients (see No. 218).

147. In *hepatitis B*, a general rule is that the more severe the acute attack, the less likely the chronic sequelae. Patients who survive an attack of fulminant hepatitis usually recover completely without the development of chronic disease.

148. *Chronic hepatitis* is a chronic inflammatory reaction in the liver that does not improve for at least 6 months. It is divided into three types: (a) *chronic persistent hepatitis (CPH)*: the mononuclear infiltrate and fibrosis expand the portal zone, but the limiting plate is intact, and piecemeal necrosis is not seen (CPH does not progress to cirrhosis); (b) *chronic lobular hepatitis*: histological features are similar to changes in acute viral hepatitis (intralobular inflammation and necrosis but no piecemeal or bridging necrosis), but duration is longer than 3 months (chronic lobular hepatitis does not progress to cirrhosis); and (c) *chronic active hepatitis (CAH)*: the inflammatory infiltrate expands the portal areas and extends into the lobules, eroding the limiting plate and leading to piecemeal necrosis; in its severe form, CAH often progresses to cirrhosis; bridging necrosis (portal–central or portal–portal) is considered prognostically significant in predicting the progression of CAH to cirrhosis.

149. *Chronic persistent hepatitis (CPH)* (a) may follow viral hepatitis B, NANB, and alcoholic hepatitis or complicate long-standing inflammatory bowel disease; (b) is asymptomatic in most patients but some patients may complain of mild fatigue and anorexia; physical examination is normal; (c) may show slightly to moderately disturbed liver function tests; (d) is treated with reassurance—steroids or immunosuppressive agents should not be given, and no dietary limitations are indicated; and (e) carries a favorable prognosis and no progression to cirrhosis occurs.

150. *Chronic lobular hepatitis* (a) is rare; (b) is characterized by a course of remissions and relapses marked by elevated transaminases; (c) may display positive anti-smooth-muscle antibodies and antimitochondrial antibodies; and (d) carries a favorable prognosis;

clinical or biochemical exacerbations respond to corticosteroids; cirrhosis does not develop.

151. *Chronic active hepatitis* has the following characteristics: (a) It may follow viral hepatitis B, NANB, or other viral infections such as rubella or cytomegalovirus or may represent the hepatic involvement of alpha$_1$-antitrypsin deficiency, alcoholic liver disease, drug-induced liver damage, and Wilson's disease. Another form of CAH is the autoimmune type, also called "lupoid" hepatitis or idiopathic CAH. (b) CAH that follows hepatitis B is more common in males, serum HBsAg is present, associated autoimmune disorders are rare, serum gammaglobulins may increase moderately, the presence of smooth muscle antibodies or LE cells is rare, and the risk of the development of primary liver cancer is high. Clinical presentation is variable: patients may be asymptomatic with only biochemical evidence of activity or may present with jaundice or signs of portal hypertension. Response to corticosteroids is unpredictable, and a few studies have shown that steroid therapy in HBsAg-positive CAH may increase mortality. Most authorities recommend a therapeutic trial with prednisolone, 20 mg/day, in symptomatic patients demonstrating "histological activity" (bridging necrosis or multilobular necrosis). If after 6 months of therapy there is no clinical, biochemical, or histological improvement, the drug should be discontinued. Antiviral therapy with interferon and adenine arabinoside (ara-a) or immunostimulation with transfer factor and levamisol have not proved efficacious. (c) CAH commonly follows posttransfusion NANB hepatitis and is characterized by waxing and waning of clinical and laboratory features. The rate of progression to cirrhosis is unknown and, as for CAH of hepatitis B, corticosteroids have not proved of great benefit and an effective specific therapy has not been established. (d) CAH of the autoimmune type ("lupoid") is more common in women under 30 years of age (with a female to male ratio of 3:1); HBsAg is absent in the serum, elevated IgG levels are common, smooth muscle antibody

is detected in the blood of about 70% of patients; antinuclear antibodies, rheumatoid factor, and LE cells may also be present. Association with other autoimmune disorders such as thyroiditis, glomerulonephritis, pernicious anemia, Coombs-positive hemolytic anemia, and Sjögren syndrome may occur. The risk of the development of primary liver cancer is low, and response to corticosteroid therapy is good (40 mg prednisolone should be given daily with gradual tapering to maintenance dose of 15–20 mg over 4–6 weeks). After 6 months, clinical and biochemical evidence of activity disappears in a large percentage of patients, and steroids can be discontinued. When relapse occurs, reinstitution of the same regimen usually suppresses activity of the disease. The overwhelming majority of patients progress to cirrhosis.

152. *Drug-induced liver disease*: (a) Drugs can induce an acute or chronic disease of the liver. Acute injury may lead to *necrosis, steatosis,* or *cholestasis.* Chronic injury may be manifested in the form of *chronic active hepatitis, fatty liver, phospholipidosis, vascular lesion, granulomas, cholestasis, cirrhosis, portal hypertension,* or *neoplasms.* (b) Mechanisms of drug hepatotoxicity include (i) a direct action on the liver cell (rare); (ii) combination of a metabolic product of the drug with essential cell proteins, causing necrosis (after exhaustion of glutathione stores), a dose-dependent reaction with a microscopic appearance characterized by centrizonal necrosis, fatty change, some inflammatory reaction, and periportal fibrosis (acetaminophen toxicity is an example); and (iii) an immunological reaction that is not dose dependent; only a small percentage of those receiving the drug are affected; diagnosis can be proved by rechallenge, which is not always ethically justified (halothane hepatotoxicity is an example).

153. In *acetaminophen (paracetamol) hepatotoxicity,* (a) doses over 10–15 g lead to hepatic necrosis that becomes overt after 24–48 hr; (b) myocardial and renal damage and hypoglycemia may be prominent; (c) serum transaminase levels and PT are excessively in-

creased; (d) if 4 hr after ingestion blood levels exceed 300 μg/ml there is 100% incidence of hepatic toxicity; if after 12 hr level is less than 50 μg/ml prognosis is good; (e) treatment includes *N-acetylcysteine (Mucomist)*, 140 mg/kg PO, followed by 70 mg/kg at 4-hr intervals for 72 hr; if the IV route is used, 150 mg/kg should be administered in 200 ml dextrose in 5% water over a 15-min period, followed by 50 mg/kg over the next 4 hr, 100 mg/kg over the next 16 hr; (f) patients arriving after more than 24 hr who have toxic blood levels should be managed as for fulminant hepatic failure, since *N*-acetylcysteine will be of no use; and (g) *charcoal column hemoperfusion* may be helpful when hepatic failure develops.

154. *Carbontetrachloride (CCl_4)* and other chlorinated hydrocarbons (e.g., trichlorethylene) may induce hepatic necrosis, acute renal failure (ARF), and drowsiness. Acute poisoning should be treated with a high-calorie, high-carbohydrate diet, the usual regimen for hepatic failure and hemodialysis when renal failure ensues.

155. *Methotrexate* is commonly used in the treatment of psoriasis. Prolonged therapy may result in hepatic fibrosis and subsequently cirrhosis. Liver cell carcinoma can develop. Periodic liver biopsies in patients on long-term methotrexate therapy should be done to detect fibrosis at an early stage.

156. *Azathioprine (Imuran)* may lead to *cholestasis, venoocclusive disease,* or *peliosis hepatis.*

157. *Cyclosporin A,* which is commonly given to patients undergoing liver or kidney transplants, has been reported to induce raised transaminase levels, but it generally does not result in clinical illness.

158. *Salicylates* and other *nonsteroidal antiinflammatory drugs* can all cause liver damage, usually of a mixed cholestatic–hepatitic type. Both acute hepatic injury and chronic active hepatitis have been reported.

159. *Amiodarone,* an antiarrhythmic agent with an unusually long

half-life, may produce features of alcoholic liver disease including Mallory bodies, as well as phospholipidotic small droplets.

160. *Isoniazid* can lead to transient elevation of SGOT in about 20% of patients. Alcohol consumption and advanced age are associated with increased risk. Rapid acetylators are at increased risk of developing liver damage, and combination with an enzyme inducer such as rifampicin further increases the risk and may even lead to fulminant hepatitis. In most cases, SGOT levels are transiently elevated with no resulting symptoms and with subsidance despite continued therapy, but when elevation is prolonged and medication is not stopped, hepatitis with jaundice may ensue. The hepatitis usually resolves on stopping the drug, but continued administration may lead to *CAH* and even *cirrhosis.*

161. *Methyldopa* may lead to asymptomatic elevation of serum transaminase in 5% of users. It usually subsides despite continued drug administration, but more severe liver damage with bridging and multilobular necrosis has been reported to occur uncommonly.

162. *Halothane* hepatotoxicity occurs in about 1/10,000 anesthesias in adults; it is very rare in children. A specific halothane-related antibody has been found, indicating sensitization to halothane-altered liver cell membrane components. Fever occurs about 7 days after exposure and jaundice appears 2–3 days later, but hepatitis is more common after multiple exposure; obese elderly female patients seem particularly at risk. Early onset of jaundice is a grave prognostic sign. In one large series, mortality was 46%, but in those who recover, chronic liver disease does not develop.

163. *Chlorpromazine* causes cholestatic jaundice in 1–2% of patients. The reaction is not dose dependent and usually occurs during the first 4 weeks. Pruritus may precede the cholestatic jaundice, and complete recovery is the rule if the drug is discontinued, although prolonged cholestatic jaundice with steatorrhea is occasionally seen.

164. *Oral contraceptives* may affect the hepatobiliary system in var-

ious ways: (a) cholestatic jaundice may appear during one of the first three cycles of administration, a rare complication; centrizonal necrosis is seen on biopsy, and prognosis is excellent if the medication is discontinued; (b) women on longterm oral contraceptives have a twofold increase in incidence of gallstones over incidence in controls; (c) the Budd–Chiari syndrome is associated with the use of oral contraceptives of the estrogen–progesterone type; and (d) a rare association of oral contraceptives with *hepatic adenomas*, *focal nodular hyperplasia*, and *peliosis hepatis* is well documented; very rarely, an association with *hepatocellular carcinoma* and with *cholangiocarcinoma* has been reported.

165. *Postoperative jaundice* may occur as a result of (a) bilirubin load from blood transfusions; (b) hepatic hypoperfusion caused by anesthetics and/or shock; or (c) halothane and other hepatotoxic drugs used for induction of anesthesia. A cholestatic jaundice of unknown mechanism may occur on the first or second postoperative day, reaching its height between the fourth and tenth days, and disappearing within approximately 15 days.

166. In *acute heart failure* or *shock*, congested central areas with local hemorrhage are seen on light microscopy. If shock is prolonged (longer than 24 hr), hepatic necrosis may occur.

167. In the *Budd–Chiari syndrome* (a) the cause is obstruction of hepatic veins at any site from the efferent vein of the lobule to the entry of the inferior vena cava into the right atrium; (b) etiological factors include intrahepatic venoocclusive disease (e.g., azathioprine-induced liver damage, acute alcoholic hepatitis), congenital webs, tumors occluding the hepatic vein or inferior vena cava, oral contraceptives, constrictive pericarditis, and hypercoagulable states such as polycythemia; (c) clinical features include hepatomegaly, abdominal pain, and ascites; (d) hepatic histology shows centrizonal sinusoidal distention and pooling; (e) the most frequent complications are thrombosis of the portal vein and pulmonary embolism; and (f) treatment consists of controlling ascites by conservative

measures, taking care of the etiological factor where possible (e.g., resection of webs, venesection in polycythemia) and side-to-side portocaval shunt if the portal vein and inferior vena cava are patent, or mesoatrial shunt if the inferior vena cava is obstructed; anticoagulants or fibrinolysins are of no benefit.

168. *Hepatic cirrhosis* is a diffuse process with fibrosis and nodule formation. It is the common end result of many liver diseases. The most common causes in Western countries are viral hepatitis, alcohol, and chronic active hepatitis. In about 25% of patients, the etiology is unknown and the term used is *cryptogenic cirrhosis*. Cirrhosis may result in *hepatocellular failure*, with jaundice, encephalopathy, hypoalbuminemia, ascites, high transaminase levels, and prothrombin deficiency, and/or in *portal hypertension*, with splenomegaly, esophageal varices, and ascites.

169. *Liver cirrhosis* may be associated with (a) esophageal and gastric varices and PUD; (b) splenomegaly and abdominal wall venous collaterals; (c) steatorrhea (due to chronic pancreatitis of alcoholism or reduced bile salt secretion); (d) abdominal hernia (due to ascites); (e) primary liver cancer (except in biliary and cardiac cirrhosis); (f) gallstones (mainly pigment stones); (g) digital clubbing (mainly in biliary cirrhosis); (h) Dupuytrens' contracture (mainly in alcoholic cirrhosis); (i) infection (frequent septicemia, spontaneous bacterial peritonitis); and (j) a continuous low-grade fever in one-third of patients with active advanced cirrhosis; it is more common in alcoholics.

170. In *hepatic cirrhosis*, elevation of serum globulin is common, mainly gamma-globulin (failure of the sick liver to clear intestinal antigens?).

171. In *hepatic cirrhosis*, needle biopsy should always be done unless a coagulation defect or significant ascites are present. The histological appearance may give a clue to etiology and activity, and serial biopsies help assess progression. A sampling error is common

due to the tendency of the commonly used needles to aspirate the soft parenchyma and leave fibrous tissue behind.

172. *Prognosis in hepatic cirrhosis* (a) depends on etiology (alcoholics who abstain do better than "cryptogenic" cirrhotics); (b) is improved when a precipitating factor of decompensation can be identified (e.g., hemorrhage, infection); (c) is poor when there are signs of jaundice, ascites, encephalopathy developing in the course of hepatocellular failure, hypoalbuminemia (<2.5 g/dl), hyponatremia unrelated to diuretic therapy, and persistent hypoprothrombinemia; and (d) is not correlated with serum transaminase and globulin levels.

173. *The management of hepatic cirrhosis* consists of a well-balanced diet (no limitation in fat consumption is necessary) in well-compensated cirrhosis, early detection of signs indicating hepatocellular failure, and treatment of complications of the latter (ascites, encephalopathy, portal hypertension). Therapeutic modalities aimed at preventing collagen synthesis or progressive fibrosis are still unavailable.

174. *Alcoholic liver disease* is related to the amount of alcohol consumed. Most alcoholics with cirrhosis have consumed about 190 g alcohol daily for 10 years, but individual variations exist. A "safe" limit may be the consumption of not more than 60 g alcohol daily for men and 20 g for women. There may be a genetic predisposition for liver damage from alcohol, as only 25% of alcoholics show severe liver damage and 50% show milder damage.

175. *The pathogenesis of alcoholic liver injury* invovles (a) stimulation of fibrogenesis and collagen synthesis; (b)immunological stimulation leading to progressive destruction of liver cells (hyaline may be the antigen); (c) increased hepatic oxygen consumption, with centrizonal areas the last to receive oxygen, and these regions suffer most; and (d) decreased consumption of dietary protein leading to decreased capacity of the liver to metabolize alcohol and to synthesize the lipoprotein necessary for transport of fat from the liver.

176. *The histopathology of alcoholic liver disease* is characterized by (a) fatty infiltration; (b) Mallory hyaline (particularly in centrizonal areas); (c) Kupffer cell proliferation; (d) cholestasis; (e) polymorphs surrounding necrotic cells characteristic of the "acute" phase; (f) in very advanced stages, a shrinking liver, disappearance of the fatty infiltration, and development of a fibrotic process (perivenular and perisinusoidal) leading to micronodular cirrhosis; and (g) megamitochondria seen on electron microscopy.

177. A *histological picture similar to alcoholic liver disease* may be seen in *severe obesity, Wilson's disease, diabetes mellitus, after jejunoileal bypass,* and in *Indian childhood cirrhosis.*

178. *Delirium tremens (DT)* can be differentiated from hepatic precoma by the following features: (a) in DT, patients are alert and hyperactive while in hepatic precoma drowsiness is the rule; and (b) the tremor is fine in DT and flapping in hepatic precoma.

179. *Alcoholic cirrhosis* is not always preceded by episodes of acute alcoholic hepatitis. It may present as any end-stage liver disease, and only the history of alcohol abuse suggests the diagnosis.

180. In *alcoholic cirrhosis,* portal hypertension may be caused by (a) regeneration nodules; (b) pressure exerted on portal venous drainage by fatty infiltration; and (c) sclerosing hyaline necrosis which may add a postsinusoidal component.

181. *Prognosis of patients with established alcoholic cirrhosis* depends on the presence of portal hypertension and on drinking habits. Before the onset of portal hypertension, survival may be significantly improved by abstinence.

182. *Mortality rate in acute alcoholic hepatitis* is 2–8%. Prolonged PT (especially if unresponsive to vitamin K), severe hyperbilirubinemia, and hypoalbuminemia are poor prognostic signs.

183. *Liver biopsy* is indicated in patients with alcoholic liver disease when abnormal liver function tests persist for 3–6 months, as, according to recent studies, *perivenular fibrosis* at the fatty liver stage

is an early sign of impending cirrhosis. These changes are still reversible in most cases, provided strict abstinence from alcohol is practiced.

184. *Treatment of acute alcoholic hepatitis* includes (a) complete alcohol withdrawal; (b) high-calorie diet—sometimes anorexia is severe and parenteral alimentation is needed, including daily infusion of 70–90 g amino acids (a mixture rich in BCAAs and poor in aromatic amino acids is advocated to minimize the risk of encephalopathy); (c) steroids—as a last-resort option in severe unresponsive cases although they are not recommended on a routine basis and may even have deleterious effects; and (d) propylthiouracil, colchicine, D-penicillamine, and the infusion of glucagon and insulin, which have been reported in a few studies to have a beneficial effect, but further studies are needed to confirm these initial observations.

185. Despite *vitamin A deficiency* in chronic liver disease, excess intake of this vitamin has been reported to cause *hepatic fibrosis* with *portal hypertension.* In replenishment of vitamin A, it is recommended that the daily dose not exceed 2000 IU.

186. Excess *iron* deposits in hepatocytes may lead to cellular damage resulting in the development of cirrhosis. Ferritin, hemosiderin, and lipofuscin may be found in the liver when iron overload occurs.

187. In *idiopathic hemochromatosis,* (a) the etiology is a rare genetically determined (autosomal recessive) metabolic disorder with increased iron absorption over many years; (b) portal zone fibrosis in hemochromatosis may develop into macronodular cirrhosis; fibrosis of the pancreas is common, and the spleen, heart, and intestine are also involved; (c) common manifestations include arthritis (67% of patients, involves metacarpophalangeal joints, knees, and hips, and chondrocalcinosis is seen in articular cartilage), bronze skin pigmentation, hepatosplenomegaly, weakness, loss of libido,

testicular atrophy, loss of body hair, diabetes mellitus, and cardiomyopathy with dysrhythmia; (d) diagnosis is made by liver biopsy showing increased iron stores in hepatocytes and Kupffer cells and varying degrees of hepatic fibrosis or cirrhosis; liver CT scan may help assess liver iron stores; serum ferritin and transferrin saturation are the best screening tests but patients with early disease may have normal values; (e) HLA types A3, B7, and B14 are particularly common when compared with the general population, and screening of relatives should be done as relatives homozygous with the proband are at high risk of developing the disease; (e) treatment consists of frequent phlebotomies; as body iron stores in these patients may be increased up to 100 – fold over normal, some patients require weekly or biweekly phlebotomies for 1–2 years; Hct levels should be followed and serum ferritin, iron saturation, reticulocyte count, and RBC indices are helpful in assessing whether an iron – deficient state has been reached; and (f) the above treatment improves liver function tests and probably prolongs survival, but about 15% of patients show the development of *hepatocellular carcinoma*, and its incidence is not reduced by therapy.

188. In *beta-(homozygous) thalassemia*, increased iron stores result from frequent blood transfusion and iron absorption rates disproportionate to the body stores. Treatment consists of low-iron diet and chelation therapy with desferrioxamine. Hepatic fibrosis may be impeded by this therapy.

189. In *cirrhosis*, especially *alcoholic cirrhosis*, increased hepatic iron stores result from increased iron absorption and the high iron content of wine. A distinction from idiopathic hemochromatosis is made on the basis of family history and liver biopsy. Treatment should be of the primary disorder, as removal of iron has not been found to improve morbidity or survival.

190. In *Wilson's disease* (a) the etiology is an inherited (autosomal recessive) disease characterized by cirrhosis of the liver, degener-

ation of basal ganglia in the brain, a pigmented ring in the periphery of the cornea (Kayser–Fleischer ring), and renal tubular lesions; (b) increased copper deposition is considered responsible for the lesions; (c) symptoms commonly appear in childhood or in youth; (d) liver histology is variable and may show *periportal fibrosis*, an *alcoholic-hepatitis-like picture* or *macronodular cirrhosis*; cirrhosis in the young should always arouse suspicion of Wilson's disease; (e) clinical presentation is also variable and includes fulminant hepatitis, chronic active hepatitis, cirrhosis with portal hypertension, and neurological symptoms (the latter are more common in patients presenting after age 20); (f) the diagnosis is made by demonstrating corneal Kayser–Fleischer rings, hepatic copper concentration of more than 250 μg/g dry tissue, and urinary copper of more than 100 μg/24 hr; serum ceruloplasmin is usually below 20 mg/dl; (g) treatment consists of D-penicillamine (should be given even to asymptomatic patients), 250 mg qid (adult dose) before meals; the dose should be increased to 2–3 g/day if improvement is not observed within 3–6 months; pyridoxine, 25 mg/day, should be supplemented; response to treatment is manifested by the disappearance of the corneal rings and by improvement in neurological symptoms; the liver disease may beocme inactive with improvement in liver function; (h) few reports on successful *liver transplantation* in patients with advanced liver failure caused by Wilson's disease have been published; and (i) prognosis is good when treatment is started early in the course, before the onset of neurological symptoms or advanced liver disease; acute neurological symptoms, dystonia, and early acute liver failure carry a poor prognosis.

191. In *obese patients*, fatty infiltration of the liver is common, but the fatty changes do not lead to cirrhosis.

192. *Total parenteral nutrition (TPN)* may be complicated by cholestasis. In infants, prolonged TPN has been reported to result in liver failure.

193. In *diabetes mellitus,* hepatomegaly with increased glycogen contents occurs uncommonly in patients with the insulin-sensitive type, mainly in uncontrolled patients and in diabetic ketoacidosis. Fatty liver, probably related to obesity, may be seen in patients with insulin-insensitive diabetes.

194. In *alpha$_1$-antitrypsin deficiency* (a) the etiology is an inherited disorder with decreased serum alpha$_1$-antitrypsin levels; (b) the alpha$_1$-globulin is an inhibitor of trypsin and other proteases *in vitro* that may have a protective function in various tissues; (c) clinical features include hepatitic–cholestatic jaundice during the neonatal period, cirrhosis in childhood or early adulthood, and pulmonary emphysema; pulmonary and hepatic disease rarely occur in the same patient; (d) diagnosis should be suspected with neonatal jaundice and confirmed by low or absent serum alpha$_1$-antitrypsin. Methods for prenatal diagnosis of homozygotes have been recently developed; and (e) there is no specific treatment, although *liver transplantation* has been performed successfully in a few patients to date.

195. Proliferation of *giant cells* is the common reaction of the neonatal liver to various insults. It may be induced by viruses (HBV, CMV, herpes, rubella, coxsackie), bacteria, metabolic disorders (e.g., alpha$_1$-antitrypsin deficiency, galactosemia), TPN, or biliary atresia, or may be "idiopathic."

196. *Viral hepatitis in the neonatal period* leads to a high incidence of chronic hepatitis and cirrhosis.

197. *Hepatitis B* may be transmitted from an HBeAg-positive mother (or rarely, from a mother who is an asymptomatic carrier) to the newborn through breast milk or transplacentally, but transmission is more common from the mother's blood during delivery or during contact while caring for the baby.

198. *Idiopathic neonatal hepatitis* (a) comprises about 75% of neonatal

hepatitis; (b) is a familial disorder of autosomal recessive inheritance; (c) includes such histological features as the presence of giant cells, focal necrosis, hemosiderosis, cholestasis, and loss of normal zonal architecture; (d) may cause stillbirth or death during the neonatal period or fluctuating jaundice during the first few months of life; (e) has a mortality rate of about 25–30%, with cirrhosis developing in about 20%; and (f) is treated symptomatically.

199. *Biliary atresia* (a) is defined as a congenital failure of development (atresia or hypoplasia) of a portion or all of the intrahepatic and/or extrahepatic systems; (b) has as its dominating clinical feature cholestatic jaundice starting shortly after birth and persisting thereafter; xanthomas may occur and biliary cirrhosis with signs of portal hypertension develops within a few months; (c) is difficult to distinguish from neonatal hepatitis—giant cells on liver histology may be present in both; (d) is diagnosed with the help of liver and biliary tract radionuclide scans (HIDA) that determine patency and flow through the ducts; ultrasonography, which demonstrates the absence of dilated ducts or the presence of abnormalities in their size; and liver biopsy, which helps distinguish neonatal hepatitis from biliary atresia; and (e) is managed depending on the distribution of the defect; in most cases, extrahepatic ducts are obliterated and Kasai operation (hepatic portoenterostomy) should be performed during the first months of life; rarely, the proximal bile ducts are patent and surgical correction by Roux-en-Y jejunal anastomosis is possible; biliary atresia is one of the commonest indications for liver transplantation.

200. In *choledochal cyst* (a) the etiology is a congenital cystic dilatation of the common bile duct associated with narrowing at its terminal portion; (b) most patients are asymptomatic, but others may present with RUQ pain, obstructive jaundice, a RUQ mass, or bile peritonitis as a result of rupture; (c) *cholangiocarcinoma* occurs in about 3%; and (d) management is surgical, with most surgeons removing the cystic dilatation and reconstructing the biliary tree.

201. *Caroli's disease* is a rare congenital malformation characterized by cystic dilatation of the intrahepatic bile ducts. Recurrent cholangitis is common and stones tend to accumulate in the dilated ducts. Treatment consists of antimicrobial agents for cholangitis and drainage of the common bile ducts to remove calculi.

202. *Congenital hepatic fibrosis* is an inherited (autosomal recessive) disorder characterized by dense fibrous bands containing bile ducts that surround normal liver lobules. Portal hypertension and associated renal defects (tubular ectasia and polycystic kidneys) are common. *Cholangiocarcinoma* or *hepatocellular carcinoma* are uncommon complications.

203. In *adult polycystic disease,* inheritance is dominant. Patients may be asymptomatic or may complain of abdominal pain, swelling, and pressure sensation, presenting during the fourth or fifth decade. Associated multiple renal cysts are very common (>50%), and the disease carries an excellent prognosis.

204. *Arteriohepatic dysplasia (Alagille syndrome)* is an autosomal dominant disorder characterized by chronic intrahepatic cholestasis presenting in the neonatal period and decreasing with age. Pulmonary stenosis, skeletal changes, and posterior embryotoxon are associated. Survival to adulthood is common but with physical and mental impairment.

205. *Reye's syndrome* is characterized by rapidly progressive encephalopathy with cerebral edema and fatty liver that develop a few days after a viral infection. Hyperammonemia, elevated SGOT levels, and hypoglycemia are common. An association with salicylate therapy has been suggested. Treatment is aimed at the relief of cerebral edema.

206. *Acute fatty liver of pregnancy* is an uncommon potentially fatal disorder characterized by acute liver failure occurring toward the end of a normal or "toxemic" pregnancy or shortly before or after delivery of a stillborn fetus. An association exists with IV admin-

istration of tetracyclines during pregnancy. Renal failure commonly accompanies liver failure. Mortality rate is around 75%, but the long-term prognosis of survivors is good.

207. *Hepatic granulomas* may be found on liver biopsy in sarcoidosis, tuberculosis, brucellosis, infectious mononucleosis, Hodgkin's disease, primary biliary cirrhosis, hypogammaglobulinemia and in a severe prolonged febrile syndrome of unknown etiology described by Simon and Wolff in 1973 (Simon WB & Wolff SM, Medicine (Baltimore) 52:1, 1973).

208. *Pyogenic liver abscess* may be caused (a) by obstruction of bile flow (by stones, tumor, sclerosing cholangitis, strictures); (b) by spread through portal blood flow (acute appendicitis, empyema of gallbladder, diverticulitis, perforated ulcer, pancreatitis); (c) by direct spread (trauma, perinephric abscess); or (d) idiopathically.

209. *Management of pyogenic liver abscess* includes antimicrobial agents (cefoxitin with an aminoglycoside or clindamycin with an aminoglycoside) combined with needle aspiration (the latter should be performed for large abscesses only). Surgical drainage is reserved for those patients who do not respond to these measures.

210. *Amebic abscess* (a) is usually solitary in the right lobe; (b) rarely has a history of amebic dysentery; (c) has as its main clinical features RUQ pain aggravated by change of posture and alcohol, with or without fever; (d) is diagnosed by the demonstration of a filling defect on radionuclide scan or ultrasonography, a positive amebic hemagglutination test, and the demonstration of amebic pus on needle aspiration; and (e) is treated with metronidazole, given orally 750 mg tid or intravenously 500 mg qid for 7–10 days; emetine, given intramuscularly in a dose of 1 mg/kg per day, is an alternative to metronidazole and is combined with the latter for 2–3 days in seriously ill or complicated cases.

211. In *schistosomiasis (bilharziasis)* (a) the liver may be infected by ova of *S. mansoni* or *S. japonicum* delivered from the intestine via

the mesenteric veins; (b) the prevalence is high in the Far East, Africa, and parts of South America; (c) clinical features include hepatosplenomegaly followed by portal hypertension resulting from extensive liver fibrosis; hepatocellular function is relatively preserved, and the portal hypertension is presinusoidal; (d) treatment includes oxaminiquine or praziquantel; prevention is by avoidance of infected water; and (e) *hepatocellular carcinoma* is an occasional late complication.

212. *Etiological factors in primary hepatocellular carcinoma (HCC)* include (a) the mycotoxin aflatoxin (well documented), whose estimated ingestion (through contaminated food) parallels HCC incidence; (b) HBV, especially when infection occurs at an early age; HBsAg is produced by cell lines derived from human HCC; (c) alcohol (incriminated since HCC is more common in patients with alcoholic liver disease); (d) smoking (recently listed as a risk factor); and (e) rather frequently, advanced hemochromatosis.

213. *Clinical features of HCC* include (a) M:F ratio of 5:1; (b) associated cirrhosis (common); HCC should be excluded in any deterioration in the clinical course of a patient with cirrhosis; (c) RUQ pain and low-grade fever (common); (d) bleeding into the gut or intraperitoneally as a result of blood vessel erosion; (e) an arterial murmur due to increased vascularity or a friction rub due to perihepatitis (may occasionally be heard over the liver); (f) ascites (common), which may be aggravated by portal vein and/or hepatic vein thrombosis; and (g) hypercalcemia, hypoglycemia, hyperlipidemia, and polycythemia, probably reflecting ectopic hormonal production by the tumor.

214. *Alpha-fetoprotein* is commonly present in the serum of patients with HCC but is also found in the serum of patients with embryonic tumors of ovary and testis, hepatoblastoma, and liver metastases from carcinomas of the GI tract. Levels of 500 ng/ml are suggestive of HCC.

215. *Diagnosis of HCC* is suggested by the clinical features and elevated levels of alpha-fetoprotein. The tumor can be demonstrated by radionuclide scans, ultrasonography, and CT scan. There is a typical angiographic appearance.

216. In the *treatment of HCC* (a) if disease is confined to one lobe, resection is recommended; the presence of cirrhosis is a contraindication to an extensive resection; (b) chemotherapy (mainly adriamycin or combination chemotherapy) occasionally leads to symptomatic improvement or somewhat prolonged survival; (c) ligation of hepatic artery has been reported to have very limited success; (d) regional hepatic chemotherapy using an implantable drug infusion pump has met with limited success and many side effects; (e) radiotherapy is used for palliation of pain; and (f) results of liver transplantation for HCC are very disappointing, with tumor recurring after surgery; the only exceptions were small tumors discovered incidentally or HCC of the fibrolamellar type.

217. *Liver metastases* may be characterized as follows: (a) common (in 35–50% of all cancers); (b) common sites of the primary tumor are the organs with portal venous drainage, stomach, breast, and lung; (c) hepatomegaly is a common physical finding, and fever, pleuritic pain, and a friction rub over the liver may be present; (d) liver function studies (mainly alkaline phosphatase, bilirubin, and SGOT) may be abnormal, but normal values do not exclude the diagnosis; (e) ultrasonography and CT scan can demonstrate metastases, and needle liver biopsy will detect metastases, especially when they are distributed diffusely, with CT- or ultrasonography-guided biopsies increasing the yield; and (f) hepatic lobectomy for solitary metastasis is recommeded by many authorities but a definite prolongation of survival has yet to be documented.

218. *Liver transplantation* (a) is performed at many medical centers all over the world and is no longer an experimental procedure; (b) has as its potential candidate a patient with advanced irreversible

liver disease who has become hospital bound; (c) is contraindicated in patients with psychiatric disorders, ongoing alcohol abuse, cardiopulmonary disease, extrahepatic malignancy, deep hepatic coma, and the presence of HBeAg in the serum; (d) has been indicated to date for nonalcoholic cirrhosis or CAH, biliary atresia in children, inborn errors of metabolism ($alpha_1$-antitrypsin deficiency, Wilson's disease, tyrosinosis, glycogen storage disease), hepatic malignancies, alcoholic cirrhosis (when prolonged abstinence was well documented), primary biliary cirrhosis, sclerosing cholangitis, and Budd–Chiari syndrome; limited experience has been accumulated in liver transplantation in acute liver failure (fulminant hepatitis and toxic hepatitis); (e) has shown improved survival when cyclosporin A was introduced as a part of antirejection therapy; overall 1-year survival is around 75% and is still improving each year; (f) demonstrates the best results in children with biliary atresia and in adults with relatively preserved hepatocellular function; (g) is associated with intra- and perioperative deaths due to hemorrhage and bile leakage, and these complications become uncommon as experience is gained; (h) has not been associated with hyperacute rejection to date, and acute rejection occurs mainly when immunosuppressive therapy is reduced or discontinued; chronic rejection manifests as chronic liver failure; rejection is diagnosed by repeated liver biopsies whenever a clinical or laboratory deterioration is observed and is treated by a course of high-dose antirejection chemotherapy; and (i) has become a promising therapeutic modality for end-stage liver disease.