First Principles of Gastroenterology

The Basis of Disease and an Approach to Management

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Fifth Edition
The Liver

1. LIVER STRUCTURE AND FUNCTION / E.A. Shaffer and R.P. Myers

1.1 Liver Morphology

The liver is the largest and most metabolically complex organ in humans. It occupies the right upper quadrant, extending from the fifth intercostal space in the midclavicular line down to the right costal margin. Anatomically, it consists of two main lobes, right and left, separated by the falciform ligament anteriorly and the lesser omentum and umbilical fissure posteriorly. Functionally, the liver is divided into eight segments based on the distribution of the vessels and ducts within the liver (so-called Couinaud’s segments). Each segment contains a pedicle of portal vessels and ducts and is drained by hepatic veins situated in the planes between the segments. The segments have no surface markers to allow their accurate identification. However, surgical dissection along the planes is relatively bloodless. Therefore, knowledge of their locations is vital for the planning of surgical resections. The caudate lobe (segment 1) differs from other segments in that it receives blood from both the right and left branches of the portal vein and drains directly into the inferior vena cava.

At a microscopic level, the liver consists of myriads of individual functional units, traditionally termed lobules. Each lobule is bounded by four to six portal triads (supplied from the portal vein and hepatic artery) and has a central terminal hepatic venule (central vein). A more physiologically sound concept...
is the unit termed the acinus. At the center of the acinus is the portal triad, while the terminal hepatic venules are at the periphery. The acinus is divided into three zones based upon their proximity from the feeding vessels (Figure 1).

The liver receives a dual blood supply. The portal vein drains the splanchnic circulation and provides 75% of the total blood flow (1,500 mL/min). The hepatic artery provides the remaining 25%. Small branches of each blood vessel (the terminal portal venule and hepatic arteriole) enter the acinus at the portal triad (zone 1). Blood then flows through sinusoids between plates of hepatocytes toward the terminal hepatic venule (zone 3), where blood from several adjacent acini merges. The sinusoidal lining is fenestrated; this porosity allows nutrients to gain access to the intervening space of Disse and from it to the hepatocyte. The terminal hepatic venules coalesce to form the hepatic vein, which carries all efferent blood to the inferior vena cava. A rich supply of lymphatic vessels also drains the liver.

Hepatocytes make up the bulk of the organ. They are arranged in plates, one cell in thickness, that radiate out from each portal triad toward adjacent terminal hepatic venules. Those hepatocytes surrounding the portal tract form an

**Figure 1.** Normal liver. This liver biopsy shows the orderly arrangement of the liver cell plates, terminal hepatic venules (or central veins; arrowheads) and portal tracts (P). A hepatic lobule is outlined. (Reticulin stain, original magnification x 370)
interface between the connective tissues of the portal tract and the hepatic parenchyma, termed the limiting plate.

The bile canaliculus is formed by grooves on the contact surfaces of adjacent hepatocytes, which are bound together by tight junctions. In these canaliculi, bile forms and then progressively flows into ductules, interlobular bile ducts and then larger hepatic ducts. Outside the porta hepatitis, the common hepatic duct joins the cystic duct from the gallbladder to form the common bile duct, which drains into the duodenum via the ampulla of Vater. The biliary portion of the sphincter of Oddi protects the biliary tract from reflux of duodenal contents, while the pancreatic portion guards the pancreatic duct.

Sinusoidal lining cells comprise at least four distinct populations: endothelial cells, Kupffer cells, stellate cells, and pit cells. Endothelial cells differ from the vascular endothelium elsewhere in the body in that they lack a basement membrane and contain numerous fenestrae that permit hepatocytes to have ready access to nutrients and macromolecules in plasma. Endothelial cells are also responsible for endocytosis of molecules and particles, and play a role in lipoprotein metabolism. Spindle-shaped Kupffer cells are tissue macrophages residing in the sinusoids and anchored to subendothelial structures via pseudopodia. They form an important part of the body’s reticuloendothelial system. Their major functions include phagocytosis of foreign particles, removal of endotoxins and other noxious substances, and modulation of the immune response through the release of mediators and cytotoxic agents. Stellate cells (previously known as lipocytes, fat-storing cells, perisinusoidal cells, or Ito cells) store vitamin A. When activated by certain cytokines in the setting of hepatic injury, they lose their fat droplets and transform into proliferative, fibrogenic and contractile “myofibroblasts.”

These activated stellate cells are integral to hepatic fibrogenesis and potential targets for anti-fibrotic therapies. Finally, pit cells are sinusoidal lymphocytes containing cytoplasmic granules. These granules contain perforin, a protein that injures cell membranes. Pit cells have a role in killing tumour cells and virus-infected cells.

The extracellular matrix of the liver includes its reticulin framework and several molecular forms of collagen, laminin, fibronectin and other extracellular glycoproteins.

1.2.1 Hepatobiliary Function

The liver plays a central role in carbohydrate, protein and fat metabolism. It stabilizes glucose levels by taking up and storing glucose as glycogen (glycogenesis), and when needed, breaking this down to glucose (glycogenolysis)
and forming glucose from non-carbohydrate sources such as amino acids (gluconeogenesis). Hypoglycemia occurs only late in the course of severe liver disease because the liver has a large functional reserve; glucose homeostasis can be maintained with only 20% of the liver functioning. The liver synthesizes the majority of circulating plasma proteins, including albumin and most of the globulins other than gamma globulins. Albumin provides most of the oncotic pressure of plasma and is a carrier for drugs and endogenous hydrophobic compounds such as unconjugated bilirubin. Globulins include the coagulation factors: fibrinogen, prothrombin (factor II), and factors V, VII, IX and X. Factors II, VII, IX and X are vitamin K-dependent. Availability of vitamin K, a fat-soluble vitamin, requires adequate bile salts for the vitamin’s absorption. These factors decrease with fat malabsorption (e.g., prolonged cholestasis with depressed bile secretion and hence fat solubilization and absorption) and with the reduced synthetic function of hepatocellular disease. In the latter case, deficiency of these coagulation factors is not corrected by parenteral vitamin K administration. The liver is also the site of most amino acid interconversions and catabolism. Amino acids are catabolized to urea. During this process, ammonia, a product of nitrogen metabolism (and a possible neurotoxin), is consumed and therefore detoxified. Fatty acids are taken up by the liver and esterified to triglycerides. The liver packages triglycerides with cholesterol, phospholipids and an apoprotein into a lipoprotein. The lipoprotein enters blood for utilization or storage in adipocytes. Most cholesterol synthesis takes place in the liver. Bile salts are the major product of cholesterol catabolism.

1.2.2 **DRUG DISPOSITION**

The liver’s rich enzyme system allows the metabolism of many drugs and xenobiotic agents, including alcohol. The liver detoxifies noxious substances arriving from the splanchnic circulation, preventing them from entering the systemic circulation. This makes the liver particularly susceptible to drug-induced injury. The liver converts some lipophilic compounds into more water-soluble agents, which are then easily excreted in the urine or bile. Others are metabolized to less active agents. Drug metabolizing pathways include: 1) oxidation, reduction, and hydrolytic (phase 1) reactions that produce substances that can be readily conjugated or excreted without further modification; and 2) conjugation reactions, in which a sugar, sulphate or amino acid molecule is added (phase 2 reactions). The cytochrome P450 enzyme system is the major drug metabolizing system involved in phase 1 reactions.

1.2.3 **BILE FORMATION**

Bile is primarily an aqueous solution, iso-osmotic with respect to plasma, with less than 5% solids. The major organic solutes are bile salts whose transport
The liver secretes molecules (mainly organic solutes like bile salts) into the canalicular lumen, creating an osmotic gradient that drives fluid formation. Bile provides the main excretory pathway for toxic metabolites, cholesterol, and lipid waste products. Bile is also necessary for the efficient digestion and absorption of dietary fats and fat-soluble vitamins (e.g., vitamins A, D, E, and K). Bile salts are synthesized exclusively in the liver from cholesterol and are the driving force behind bile formation. Their active transport into the canaliculi creates an osmotic gradient across the hepatocyte, causing a translocation of solutes and water into bile in order to maintain iso-osmolarity. Following secretion by the liver, bile is stored and concentrated some tenfold in the gallbladder during the enterohepatic circulation of bile salts. Conjugated bile salts (with taurine or glycine) are secreted from the liver, stored during fasting in the gallbladder where they are concentrated 5-10 fold, evacuated with meals into the duodenum, traverse the small intestine to the terminal ileum where they are actively transported (absorbed) into the portal vein. A small quantity is passively reabsorbed in the small intestine and colon. Returned to the liver by the rapidly flowing portal vein, bile salts are efficiently taken up and re-secreted. The mass of bile salts returning from the intestine via the portal vein regulates bile salt synthesis from cholesterol in the liver. Hence, the enterohepatic circulation between the intestine and the liver is governed by: two active transport sites (the liver and the terminal ileum) and two mechanical pumps (the gallbladder and small intestinal transit). The efficiency of the enterohepatic circulation is such that only about 5% of bile salts are lost to the colon with each circuit. It cycles about 10-15 times a day.
periods of fasting. Eating releases cholecystokinin (CCK) from the small intestine (via fatty acid and amino acid stimulation) and produces a cholinergic discharge. This causes the gallbladder to contract and the sphincter of Oddi to relax, evacuating bile into the duodenum. Here, bile aids fat absorption by acting as a biologic detergent. Bile salts are then reabsorbed predominantly in the ileum (by active transport). They return via the portal vein to the liver, where they are actively taken up and secreted once again into the duodenum. This cycling is termed the enterohepatic (intestine-to-liver) circulation (Figure 2).

The liver in humans secretes over 500 mL of bile each day, ridding the body of potentially noxious products and providing the biological detergents


**Figure 3A.** Basolateral membrane transport system. Transporters are represented as spheres with arrows showing the direction of transport. The sodium pump (Na\(^+/K^+\)-ATPase) provides the inwardly directed sodium gradient to secondarily drive the sodium-dependent sodium taurocholate co-transport polypeptide (NTCP), the major means of bile salt uptake. The potassium channel creates a necessary membrane potential (-35mK). The organic ion transport protein (OATP) takes up BS\(^-\), independent of sodium and organic ions (OA\(^-\)), while exporting glutathione (GSH) for later systemic use. The basolateral membrane also contains a sodium-hydrogen (Na\(^+/H^+\)) exchanger that extrudes protons and therefore maintains the intracellular pH. The sodium-bicarbonate symport (Na\(^+\)/HCO\(_3^-\)) takes up these two ions, allowing bicarbonate entry.
necessary for fat solubilization and digestion. The membrane surface of the hepatocyte is functionally divided into the following two regions:

1. Basolateral (sinusoidal) surface, which consists of 85% of the total surface area and has its basal portion facing the blood-filled sinusoidal space, while the lateral surfaces appose the adjacent hepatocytes (Figure 3A);

2. A smaller apical (canalicular) surface, which comprises about 15% of the surface area, and consists of groove-like clefts between adjacent liver cells. Functional complexes (tight junctions) separate the canaliculus from the basolateral hepatocyte membrane, thus preventing a free exchange of ions, organic solutes, and water with the extracellular space (of Disse) (Figure 3B).

Such an anatomical arrangement causes the hepatocytes to be polarized, necessitating the vectorial transport of solutes from blood in the sinusoid to bile to the canaliculus. Uptake transports exist on the basolateral surface next to the portal blood vessels, whereas export transporters reside on the canalicular surface where bile forms. Solute's must either cross the hepatocyte (transcellular pathway) or move through the junctional complexes between the cells (paracellular pathway) to reach the canaliculus.

Bile salts, bilirubin and most organic solutes follow the transcellular route, and are concentrated in the canalicular bile 100-fold greater than in serum. Such active transport requires energy, which is generated by ATP hydrolysis and involves the coupling of cellular transport to the movement of other ions ("secondary active transport"). The transport of bile salts and their counter ions, sodium (Na⁺) creates an osmotic gradient across the sinusoidal (basal) membrane of the hepatocyte. Once in the canalicular membrane, bile salts, reduced glutathione (GSH) and other negatively charged organic ions cannot diffuse back across the “tight” junctional complexes between the adjacent cells or back into the liver cell. Under normal conditions, there is no going back. Water and some electrolytes (through solvent drag) diffuse down this osmotic gradient using the paracellular route between cells. Thus, active transport systems located at the basolateral and canalicular membrane produce osmotic gradients down which water and electrolytes passively flow. The resultant canalicular bile is nearly isotonic with plasma.

Canalicular bile formation consists of two components: 1) the active transport of bile salts (termed “bile salt-dependent bile flow”), which represents a major portion plus GSH; 2) the canalicular secretion of bicarbonate without the involvement of bile salts (termed “bile salt-independent bile flow”); and 3) a ductular component (ductular flow) formed in the bile channels (bile ducts), largely regulated by hormones such as secretin and neuropeptides. Finally, the gallbladder concentrates bile 5-10 fold.
Basolateral Membrane Transport (Figure 3A) — the sodium pump Na⁺/K⁺-ATPase provides the energy that maintains the ion gradient across the basolateral plasma membrane. It expels three Na⁺ ions for every two potassium (K⁺) ions that move into the cell, yielding excess Na⁺ outside the cell and more K⁺ inside. This concentration gradient, assisted by the potassium channel, generates an intracellular negative potential of about –35 mV. Such chemical gradients and electrical potentials maintain the intracellular homeostasis of ion concentrations, its pH and volume. They drive proton (H⁺)
extrusion via the Na\(^+\)-H\(^+\) exchanger and promote bicarbonate (HCO\(_3^-\)) entry via sodium Na\(^+\)-HCO\(_3^-\) symport. (An “exchanger” moves one ion out and another in, whereas a “symport” promotes unidirectional movement of both ions, here Na\(^+\) and HCO\(_3^-\), together into the cell.) The sodium-taurocholate cotransporting polypeptide (NTCP) is the symport that brings about the uptake of sodium and taurocholate into the hepatocyte. Conversely, sodium-independent systems transport some conjugated and unconjugated bile salts along with a large number of organic ions such as hormones (e.g., estrogens), inflammatory mediators and various xenobiotics. This family of transporters’ wide substrate preferences are known as organic transporting polypeptides (OATPs), commonly exchanging with such organic ions as GSH.

Intracellular Transport — involves the diffusion of bile salts across the hepatocyte to the canalicular membrane, likely in complexes bound to one or more carrier proteins.

Canalicular Secretion Bile — salt secretion into the canaliculus is the rate-limiting step in bile formation. Two transport systems are responsible. The major one consists of “export” pumps that require energy drive from the hydrolysis of ATP. Other transport systems are ATP-independent and consist of an electrogenic system that is energized by the membrane potential and appear localized to a subcanalicular microsomal component.

The ATP-dependent transport systems are members of the ATP-binding cassette (ABC) superfamily of transport proteins. For each of the main bile constituents, transporters have now been identified, located in the canalicular membrane:

1. The bile salt export pump (BSEP) is responsible for bile salt secretion into the canaliculus. Mutation in its responsible gene results in markedly decreased bile salt secretion and a hereditary form of intrahepatic cholestasis (Progressive Familial Intrahepatic Cholestasis [PFIC-2] – familial cholestasis with low GGT levels).

2. The phospholipid export pump (MDR3) functions as a “flipase” in that it translocates (i.e., flips) the phospholipid, lecithin, from the inner to the outer leaflet of the canalicular membrane. Bile salts then complete the extraction of lecithin into the canalicular membrane. Within the lumen, lecithin forms unilamellar vesicles with cholesterol and mixed micelles with bile salts and cholesterol (see Chapter 12). Mutations of the gene responsible for this phospholipid transporter (MRD3) can cause familial cholestasis with high GGT (PFIC-3). Heterogeneous defects lead to cholestasis of pregnancy and cholesterol gallstone disease.

3. MDR1 (Multidrug Resistance Protein 1) transports lipophilic cations including drugs. It may protect the liver from toxic effects of xenobiotics and ingested toxins by excreting these agents into bile.
4. ABCG5 and ABCG8, together appear to act as the functional sterol pump, exporting cholesterol and plant sterols like sitosterol. It may act to flip cholesterol from the inner to the outer side of the membrane bilayer. Overexpression of these ABCG5/G8 genes encoding the canalicular cholesterol transporter might lead to cholesterol gallstone formation.

5. The MRP (Multidrug Resistance associated Protein family or ABC subfamily C) consists of six members. These mediate the ATP-dependent excretion of organic ion compounds into the systemic circulation when located on the basolateral membrane, or into bile when located on the canalicular membrane. The first identified, MRP1, in a cancer cell line was resistant to multiple drugs—hence its name. MRP2, located in the canalicular membrane, is an export pump for compounds that are conjugated in the liver, mediating the excretion of a broad range of organic ions, mostly conjugates with glutathione (GSH) (e.g., bilirubin, estrogen and leukotrienes) and sulfates. MRCP2 functions as a multispecific organic ion transporter. Mutation of its gene leads to impaired excretion for bilirubin conjugates, resulting in the Dubin-Johnson syndrome.

The canalicular membrane also contains transport processes that are not energy dependent and thus do not require ATP (ATP-independent transport). For example, the chloride/bicarbonate ion exchanger (AE2) secretes bicarbonate and promotes bile flow. The fluoride channel derives its exchanger but is distinct from the cystic fibrosis transmembrane regulator (CFTR).

Bile duct transports exist in the ductular system. Cholangiocytes possess both the AE2 Cl-/HCO₃⁻ exchanger and the CFTR chloride channel. The ileum sodium-dependent bile salt transporter is also present on the apical surface of large cholangiocytes. It appears to be involved in the reabsorption of bile salts which then pass via the peribiliary plexus into the portal vein and are again extracted by the liver. This pathway, first identified for ursodeoxycholic acid, is known as the “cholehepatic shunt.”

2. APPROACH TO THE PATIENT WITH LIVER DISEASE / J.B. Simon

Because of the liver’s complexity, liver disease is often reflected by abnormalities of different hepatic “systems”—i.e., hepatocytes (hepatocellular dysfunction), the biliary excretory apparatus (cholestasis) and the vascular system (portal hypertension). In addition, the liver often is involved in systemic disease by virtue of its rich metabolic and reticuloendothelial activity and its large blood supply.

Patterns of disproportionate involvement often provide an important clue to the underlying disorder. For example, viral hepatitis characteristically
produces predominantly hepatocellular dysfunction; primary biliary cirrhosis, predominantly cholestasis; cryptogenic cirrhosis, predominantly portal hypertension; and alcoholic liver disease, variable dysfunction of any of these three systems. The clinician can often take advantage of these general patterns to help establish a diagnosis, though overlap and exceptions are frequent.

2.1 Clinical Features of Liver Disease
Table 1 lists the most important clinical manifestations of liver disease. Most can be seen in both acute and chronic hepatic disorders. Features denoting chronicity are denoted by an asterisk and can be of diagnostic value at the bedside. For example, a clinical diagnosis of acute hepatitis should be reconsidered if physical examination reveals spider nevi and palmar erythema.

2.1.1 SYSTEMIC FEATURES
Nondescript anorexia, malaise and fatigue are common manifestations of both acute and chronic liver disease. An abrupt onset often reflects acute viral or drug-induced hepatitis, whereas an insidious development typifies alcoholic liver disease, autoimmune hepatitis and other chronic disorders.

Fever is another non-specific feature of some liver conditions, especially the prodromal phase of acute viral hepatitis, severe alcoholic hepatitis and occasionally malignancy. However, frank rigors and chills are rare in these conditions, and instead strongly suggest acute cholangitis, usually secondary to common duct stone, or more rarely a liver abscess.

Patients with advanced chronic liver disease, especially alcoholic cirrhosis, often develop deterioration of general health, weight loss and a characteristic “cirrhotic habitus” in which wasted extremities and shoulder girdle contrast with a bloated belly from ascites.

Generalized pruritus is a hallmark of cholestatic disorders, especially if chronic. When cholestasis is prolonged – for example, in primary biliary cirrhosis – this may be accompanied by cutaneous lipid deposits (xanthelasma, xanthomas) and by features of malabsorption.

2.1.2 JAUNDICE
This cardinal feature of liver disease indicates hyperbilirubinemia. Bilirubin arises primarily from the physiologic breakdown of senescent red blood cells, with a minor contribution from other heme sources. It is not water-soluble and is therefore transported in plasma attached to albumin. This form of the pigment is called unconjugated bilirubin. The molecule is then taken up by hepatocytes and conjugated in microsomes with glucuronic acid to form bilirubin diglucuronide; the reaction is catalyzed by the enzyme glucuronyl transferase. Other minor conjugates are also formed; their clinical significance is unknown.
TABLE 1. Major clinical manifestations of liver disease

Systemic
Anorexia, malaise, fatigue
Fever
*General deterioration, weight loss, “cirrhotic habitus”
Cholestasis: pruritus, *xanthelasma/xanthomas, *malabsorption problems

Jaundice
Hepatomegaly ± pain
Portal hypertension

Fluid derangements
*Ascites ± edema
Electrolyte disturbances
Functional renal failure (“hepatorenal syndrome”)

Hepatic encephalopathy (portosystemic encephalopathy)
*Cutaneous and endocrine changes
Spider nevi, palmar erythema, Dupuytren’s contractures
Gynecomastia, testicular atrophy, impotence
Amenorrhea
Parotid enlargement

Coagulopathy
Hypoprothrombinemia
Thrombocytopenia
Dysfibrinogenemia

Circulatory changes
Hyperdynamic circulation
*Arterial desaturation, clubbing

* implies chronicity

Transformed bilirubin is then secreted into the bile canaliculus along with the other constituents of bile. A small amount normally enters the blood as conjugated bilirubin. In contrast to unconjugated bilirubin, this form of the pigment is water-soluble and is therefore excreted into urine. Standard assays for bilirubin provide only the total, unconjugated plus conjugated. The “direct” component is conjugated bilirubin. The difference represents the unconjugated component.

After reaching the gut through the biliary tree, bilirubin is transformed by intestinal bacteria into pigmented breakdown products collectively called
urobilinogen; these impart the normal brown color to stool. With impairment of biliary secretion (cholestasis), the stools are therefore often pale, but this is a relatively crude and unreliable diagnostic feature. Some urobilinogen is absorbed from the intestine and recycled through the liver (the enterohepatic circulation), with a portion escaping into the urine.

Various derangements in the above metabolic steps can result in jaundice. An increased bilirubin load from hemolysis may overwhelm the liver’s conjugating capacity, resulting in unconjugated hyperbilirubinemia. This is invariably mild, unless there is also concomitant hepatic dysfunction. Isolated unconjugated hyperbilirubinemia also occurs in some specific defects of bilirubin metabolism, though these are rare except for Gilbert’s syndrome (see Section 5).

In the vast majority of cases, jaundice is due to either hepatocellular disease or biliary obstruction. Both produce multiple defects in the pathway of bilirubin metabolism, including impaired hepatocellular uptake and transport, defective conjugation, decreased canaliculic secretion, and “leakage” of conjugated bilirubin into the circulation. The resultant hyperbilirubinemia is a mixture of unconjugated and conjugated pigment; usually the latter predominates, but the exact proportion varies widely and has no specific diagnostic value.

Clinically, mild jaundice can usually be detected when serum bilirubin is about twice the upper limit of normal, and is best diagnosed by inspecting the patient’s sclerae in natural daylight. More advanced cases are often apparent at a glance. Patients with severe long-standing jaundice sometimes have a generalized muddy-yellow appearance.

2.1.3 HEPATOMEGALY WITH OR WITHOUT PAIN

A readily palpable liver is not necessarily enlarged, for it may merely be low-lying – as, for example, in emphysema. Thus the upper border should be percussed when the edge is palpable.

The “quality” or feel of the liver is at least as important diagnostically as its size. For example, the liver usually retains its rubbery, relatively sharp edge when enlargement is due to fatty infiltration, acute hepatitis or passive congestion, whereas chronic fibrosis typically produces a blunt, indurated edge. Individual cirrhotic nodules are rarely detectable clinically. Palpable lumpiness instead favors malignant infiltration. It is important to remember that major liver disease – including a high proportion of cirrhosis – may not be associated with hepatomegaly.

Abdominal pain is common in biliary or pancreatic disease that might secondarily affect the liver – for example, common duct stone or pancreatic carcinoma – but pain is relatively uncommon in primary hepatic disorders. True hepatic pain is usually due to distention of the liver capsule, typically felt as a deep-seated right upper quadrant ache. This is often accompanied by
hepatic tenderness on physical examination, best elicited by compression of the rib cage or fist percussion over the liver. The commonest causes are acute hepatitis, passive congestion from cardiac failure, and malignancy. Pain from malignancy is sometimes pleuritic in character and may be accompanied by a hepatic friction rub or bruit on auscultation. Some individuals claim discomfort when the liver edge is palpated; this has no special significance and should not be interpreted as hepatic tenderness.

2.1.4 CUTANEOUS AND ENDOCRINE CHANGES
These findings as listed in Table 1 are important clues to chronic liver disease. Their pathogenesis is still poorly understood, but altered metabolism of sex hormones by the diseased liver appears important. The abnormalities may be seen in any chronic hepatic disorder, but are especially prevalent in alcoholic liver disease; this probably relates in part to a direct toxic effect of ethanol on gonadal function.

2.1.5 COAGULATION DISTURBANCES
The liver synthesizes most clotting factors, including vitamin K-dependent factors II, VII, IX and X. Severe hepatocellular dysfunction is therefore often accompanied by an enhanced bruising and bleeding tendency and by abnormal coagulation studies, particularly an increased INR/prothrombin time. Malabsorption of the fat-soluble vitamin K in prolonged cholestasis can also produce an abnormal INR/prothrombin time. Factor V is not vitamin K-dependent but is dependent on liver synthesis; thus a low serum value is indicative of liver dysfunction.

Thrombocytopenia is common in patients with cirrhosis, primarily as a result of hypersplenism from portal hypertension, but usually the platelet counts are not low enough to induce clinical bleeding. In patients with alcoholic liver disease, thrombocytopenia may also be due to direct marrow suppression by alcohol and/or nutritional folate deficiency.

Dysfibrinogenemia can also contribute to the coagulopathy from severe hepatic dysfunction.

2.1.6 CIRCULATORY CHANGES
A hyperdynamic circulation and relatively low blood pressure are sometimes seen in patients with severe liver disease, especially fulminant hepatitis and advanced cirrhosis. The mechanism may relate to increased synthesis of nitric oxide and accumulation of other vasoactive agents that reduce tone and are normally cleared by the liver. Occasional patients with cirrhosis develop intrapulmonary vasodilatation and arterio-venous shunting, with resultant hypoxemia, arterial desaturation and (rarely) clubbing (hepatopulmonary syndrome).
A number of topics will be discussed in later sections, including portal hypertension (Section 14), fluid derangements (Sections 15) and hepatic encephalopathy (Section 16).

2.2 Laboratory, Radiologic and Histologic Evaluations

No single test can assess overall hepatic function, as the liver is a complex organ with interdependent metabolic, excretory and defense functions. Thus a number of laboratory tests are usually combined to detect hepatobiliary abnormalities and to assess their severity, follow the course of the disease, and help establish an etiology. Diagnosis is often based on patterns of abnormality that help distinguish hepatocellular dysfunction from excretory impairment (cholestasis), though overlap is great. In only a minority of cases does a specific laboratory test establish the diagnosis.

Radiologic imaging techniques and liver biopsy often provide essential diagnostic information, but their use should be tailored to the specific clinical circumstances.

2.2.1 SERUM BIOCHEMICAL TESTS

2.2.1.1 Bilirubin

Although this is a relatively insensitive test of liver function, an elevated level of bilirubin is responsible for jaundice and is therefore a classic indicator of hepatic or biliary disease. The degree of bilirubin elevation often correlates poorly with clinical severity, but serial values are useful for following the course of the illness. Fractionation into direct versus indirect bilirubin is not of diagnostic value in most cases of jaundice, and cannot distinguish hepatocellular disease from biliary obstruction. Measuring the fraction of unconjugated hyperbilirubinemia is useful only in cases of mild, isolated bilirubin elevation to corroborate hemolysis or Gilbert’s syndrome (Section 5).

Urine bilirubin has little diagnostic value except in early hepatitis, when bilirubinuria precedes clinical jaundice, and in isolated unconjugated hyperbilirubinemia, when bilirubinuria is absent despite jaundice (unconjugated bilirubin is not cleared into urine). Otherwise bilirubinuria is commonly present in hepatobiliary jaundice of any cause.

2.2.1.2 Aminotransferases (transaminases)

These liver enzymes include alanine aminotransferase (ALT), found primarily in liver cytosol, and aspartate aminotransferase (AST), also found in several other tissues, most notably skeletal and cardiac muscle (Section 3). Both are exquisitely sensitive indicators of hepatocellular injury and provide the best guide to hepatocellular necrosis/inflammation.
The magnitude of elevation covers a very wide range. Levels < 100 IU/mL are common and non-specific, most often observed in chronic liver disease from various causes, but sometimes having little clinical significance. Levels of 100-300 IU/mL are seen in numerous mild/moderate inflammatory processes. In acute viral or drug hepatitis, aminotransferase levels are typically in the 500-1,500 IU/mL range, but in alcoholic hepatitis they are usually < 300 IU/mL, even if the disease is severe. Values > 3,000 IU/mL usually are seen only in acute toxic necrosis or severe hypoxia (“shock liver,” “ischemic hepatitis”); in both disorders levels typically plummet within two to three days, whereas values fall more slowly in viral hepatitis. Aminotransferase levels are variable in biliary obstruction but usually remain < 200 IU, except with acute passage of common duct stone, characterized by a sudden rise to hepatitic levels and a rapid fall over the next one to two days.

The AST to ALT ratio is usually < 1 in most circumstances, but is typically > 2 in alcoholic liver disease; though not absolute, this is diagnostically helpful for alcoholic injury. Alcohol consumption lessens the ALT rise as a result of deficiency of a coenzyme needed for ALT synthesis.

2.2.1.3 Alkaline phosphatase (ALP)
The level of this bile canalicular enzyme is disproportionately increased in impaired bile excretion. Therefore, an elevated ALP is a hallmark of cholestasis. High levels are due to enhanced synthesis rather than hepatocytic leakage; thus, the level usually rises slowly over days or weeks rather than abruptly. A disproportionately elevated ALP is also common in infiltrative disorders, especially malignancy.

ALP isoenzymes also are present in bone and placenta. If the source of an isolated increase in ALP is not clinically clear, a concomitant elevation of g-glutamyl transpeptidase (GGT) indicates a hepatobiliary origin. A form of ALP specific to the liver is 5'-nucleotidase, though this is not routinely available.

2.2.1.4 Gamma-glutamyl transpeptidase (GGT)
Levels of GGT usually parallel ALP, but this microsomal enzyme is also easily inducible – for example, by ethanol and numerous drugs. Thus, GGT is often disproportionately elevated in alcoholic liver disease, although this is too non-specific for diagnostic reliability (Section 3).

2.2.1.5 Proteins
Albumin: Synthesized by the liver, albumin is the major contributor to oncotic pressure in the serum. Decreased levels usually develop only in severe hepatic dysfunction – most often in advanced cirrhosis – and therefore imply a relatively poor prognosis. Albumin usually remains normal in acute hepatitis; falling values in this setting imply an unusually severe course.
Globulins: A non-specific diffuse elevation is common in chronic liver disease, and of no consequence. Sometimes there is disproportionate elevation of IgG in autoimmune hepatitis, of IgM in primary biliary cirrhosis, and of IgA in alcoholic liver disease.

2.2.1.6 International Normalized Ratio (INR) and prothrombin time (PT)
The INR/prothrombin time is a valuable index of the liver’s ability to synthesize vitamin K-dependent clotting factors – a true “function” test. Increasing INR/PT implies relatively severe dysfunction, analogous to low serum albumin, and is especially worrisome in acute hepatitis. An abnormal value may be found in chronic cholestasis due to vitamin K malabsorption rather than impaired hepatic synthesis of clotting factors. Improvement after parenteral administration of vitamin K therefore favors a diagnosis of cholestasis over hepatocellular failure, but there are too many exceptions for diagnostic reliability.

2.2.1.7 Lipids
Complex lipoprotein derangements are common in liver disease, though usually not routinely studied. Cholesterol is often low in acute or chronic liver failure, whereas hypercholesterolemia is associated with prolonged cholestasis. Striking triglyceride elevations occasionally occur in alcoholic liver disease (“alcoholic lipemia”).

2.2.2 SERUM IMMUNOLOGIC TESTS

2.2.2.1 Hepatitis serology
Serology is crucial for the specific diagnosis of hepatitis A, B, C, D and E. See Section 6 for details.

2.2.2.2 Antimitochondrial antibody
This is actually a complex series of antibodies directed against dehydrogenase enzymes in mitochondrial membranes, especially pyruvate dehydrogenase. It serves as a valuable marker for primary biliary cirrhosis, as it is present in > 90% of cases. Its role in the pathogenesis of the disease is unclear. Antimitochondrial antibody is rare in other disorders, though there is occasional overlap with autoimmune hepatitis.

2.2.2.3 Antinuclear factor and antismooth muscle antibody
Such non-specific immune markers are seen relatively commonly in autoimmune hepatitis; they are infrequent in other hepatic diseases.
2.2.2.4 Alpha-fetoprotein
This normal hepatic fetal protein disappears soon after birth. Detection therefore reflects hepatic dedifferentiation. Levels > 250 ng/mL serve as a relatively specific marker for hepatocellular carcinoma, though they are also seen occasionally in other tumors, especially testicular. Values < 100 ng/mL are non-specifically seen in hepatic regeneration – e.g., recovering from hepatitis.

2.2.3 IMAGING PROCEDURES
In general, radiologic imaging is essential for the accurate diagnosis of biliary disease, important for focal liver diseases (e.g., tumor), but overused and of limited value for diffuse hepatocellular disease (e.g., hepatitis, cirrhosis).

2.2.3.1 Ultrasonography (US)
Ultrasound is now the most widely used imaging procedure and is highly reliable for the diagnosis of gallstones (>95% sensitivity) (Figure 4). US is less accurate in detecting common bile duct stones (<40% sensitivity), but reliably establishes the presence of a dilated biliary tree, which usually implies mechanical obstruction. It is therefore the primary initial tool to distinguish intrahepatic from extrahepatic cholestasis. It also detects focal hepatic lesions.

Figure 4. Ultrasound showing stones in the gallbladder.
(e.g., tumor, cysts), sometimes with characteristic diagnostic features. It is less useful in diffuse hepatocellular disease, as features are usually non-specific. Abdominal ultrasound can be useful in the detection of fatty liver (steatosis), which produces a diffuse increase in echogenicity.

Ultrasoundography can also provide important ancillary information relevant to hepatobiliary disease – e.g., ascites, splenomegaly or pancreatic mass. Doppler US is valuable in establishing the patency of hepatic vessels, especially the portal vein. Endoscopic US can detect calculi of the biliary tract and pancreatic masses that are not visualized on standard US, but is not yet widely available.

2.2.3.2 Computerized tomography (CT)
A more expensive alternative to US, CT sometimes provides additional hepatic information, especially in focal lesions (Figure 5). Generally less valuable than US for biliary disease, CT is often more helpful in assessing the pancreas.

2.2.3.3 Direct biliary visualization

*Endoscopic retrograde cholangiopancreatography (ERCP)* Upper endoscopy allows direct cannulation of the common bile duct and/or pancreatic duct; the injection of contrast agent yields excellent definition of ductal anatomy.
ERCP permits definitive visualization of the biliary tree for common duct stone, sclerosing cholangitis and other conditions. It also allows therapeutic intervention – e.g., removal of common duct stones via endoscopic papillotomy or stenting a stricture.

Percutaneous transhepatic cholangiography (PTC) In PTC, direct contrast visualization of the biliary tree is obtained via percutaneous needle puncture of the liver. This is done less often than ERCP, but is especially useful if there is high biliary obstruction – e.g., a tumor at the bifurcation of the hepatic ducts. It also permits therapeutic intervention such as stent insertion to bypass a ductal malignancy.

ERCP and PTC require considerable technical expertise and have significant risks. They should not be undertaken lightly, but are highly valuable in selected cholestatic situations and often obviate laparotomy.

Radionuclide scanning A liver-spleen scan using 99mTc-sulfur colloid can reveal space-occupying lesions and diffuse parenchymal disease, and uptake of colloid by the bone marrow implies chronic liver disease with vascular shunting. However such scans are much less sensitive than US or CT and their use has rapidly waned. A 99mTc-labeled red blood cell (RBC) scan can visualize suspected vascular lesions, especially hemangiomas. Cholescintigraphy using 99mTc-iminodiacetic acid derivatives (termed HIDA scan) can reveal cystic duct obstruction, especially in acute cholecystitis. The HIDA scan also assesses biliary excretion/patency, but results often are less than ideal or misleading. Occasionally 67Ga-citrate scans are used to help detect liver abscess or tumor.

2.2.3.4 MRI and MRCP
Nuclear magnetic resonance imaging (MRI) is an expensive but valuable imaging technique that is becoming widely available. It can detect some lesions poorly seen by US or CT and sometimes can better clarify the nature of focal defects (e.g., hemangiomas). Magnetic resonance cholangiopancreatography (MRCP) can visualize the biliary tree, but in less detail than ERCP. MRCP can be a non-invasive alternative to ERCP to evaluate possible biliary obstruction, but it does not permit therapeutic intervention.

2.2.4 LIVER BIOPSY
Percutaneous liver biopsy provides important diagnostic information at relatively low risk, but is needed in only a minority of cases of hepatic
dysfunction. A small core of liver tissue is obtained at the bedside by needle aspiration under local anesthesia. This usually provides a surprisingly reliable reflection of the underlying disorder, though sampling error can occur in focal disease and some cases of cirrhosis.

The major indications for liver biopsy are shown in Table 2. Transient right upper quadrant pain is not uncommon after biopsy, but significant hemorrhage, bile peritonitis or other major complications are rare if cases are properly selected.

Relative contraindications include a clinical bleeding tendency, INR > 1.4 or prothrombin time more than three seconds greater than control, severe thrombocytopenia (< 70,000/mL), marked ascites, and high-grade biliary tract obstruction. A transjugular approach can be used with relative safety in cases of coagulopathy or severe ascites.

Biopsy of specific hepatic lesions can be obtained under US or CT guidance. Ultrasound guidance can also be used to obtain a routine core biopsy from the liver, and is increasingly used for this purpose, as it minimizes the risks of biopsy.

2.3 Clinical Approach
When faced with a patient with known or suspected liver disease, the physician should attempt to answer several central questions: (1) Is the disorder acute or chronic? (2) Is it primarily a hepatocellular problem (e.g., hepatitis), a disorder of hepatobiliary secretion (cholestasis) or a vascular problem (e.g., portal hypertension)? (3) If hepatocellular, is alcohol, a virus or a drug responsible? If cholestatic, is it an intrahepatic problem or due to mechanical biliary obstruction? If vascular, is it due to cirrhosis or to a less common cause? (4) Is this actually a systemic disorder involving the liver rather than a primary hepatic problem? (5) Are there complications that require specific treatment?

TABLE 2. Indications for liver biopsy

<table>
<thead>
<tr>
<th>Indications for liver biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained liver enzyme abnormalities</td>
</tr>
<tr>
<td>Hepatosplenomegaly of unknown cause</td>
</tr>
<tr>
<td>Diagnosis and staging of alcoholic liver disease</td>
</tr>
<tr>
<td>Cirrhosis – diagnosis and etiology</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
</tr>
<tr>
<td>Unexplained intrahepatic cholestasis</td>
</tr>
<tr>
<td>Acute necrosis, if cause unclear</td>
</tr>
<tr>
<td>Suspected infiltrative disorder, especially malignancy</td>
</tr>
<tr>
<td>Unexplained systemic illness – fever of unknown origin, suspected granulomatous disease, etc.</td>
</tr>
</tbody>
</table>
These and other pertinent questions are approached by bedside clinical judgment coupled with ancillary tests.

Broadly speaking, the most important diagnostic tool is a complete history and physical examination. Laboratory tests, imaging techniques and liver biopsy are valuable and sometimes essential for diagnosis, but in most cases clinical acumen provides the most important diagnostic information. Moreover, clinical judgment determines what additional studies should be undertaken and how to interpret the results. Diagnostic errors most often arise from an inadequate history and physical examination with undue reliance on ancillary tests.

The clinical assessment should emphasize aspects discussed above. Inquire about ethanol, drugs (prescribed, over-the-counter, herbal and illicit) and epidemiologic factors relevant to viral hepatitis, especially in cases of suspected hepatocellular injury. In addition, pursuit of systemic illness is often necessary. A positive family history may also be obtained from patients with certain metabolic diseases such as Wilson’s disease, α₁-antitrypsin deficiency and hemochromatosis. If a cholestatic disorder is suspected, clues to a possible extrahepatic cause should also be sought – e.g., biliary or pancreatic pain, rigors and chills or weight loss. The physical examination may provide valuable information on the size and consistency of the liver, presence or absence of signs of chronic liver injury, and complications such as portal hypertension, fluid retention or encephalopathy.

The extent and nature of laboratory investigations are guided by the initial clinical evaluation. Broadly speaking, a minimal initial study will include CBC plus bilirubin, AST and/or ALT, and ALP. These few simple tests usually clarify whether the problem is primarily a hepatocellular injury (disproportionate aminotransferase elevations) or an excretory problem (predominant ALP elevation). If the former is clinically apparent but the etiology is not, viral hepatitis markers may help. A high AST:ALT ratio > 2 plus a disproportionate elevation of GGT often signals alcoholic injury. A low serum albumin level and high INR usually indicate relatively severe (acute or chronic) hepatocellular dysfunction. If a cholestatic problem seems most likely, early US (or CT) should help distinguish intrahepatic from extrahepatic causation. If US indicates extrahepatic obstruction, direct biliary visualization by ERCP (or PTC) should be considered, whereas liver biopsy may be warranted if the process appears intrahepatic (Figure 6).

As yet there is no reliable biochemical marker of liver fibrosis. Thus laboratory indicators of hepatic dysfunction are often normal or only mildly deranged in cases of inactive cirrhosis; this is a common circumstance. It is well to remember that alcoholic liver disease is the commonest cause of chronic hepatocellular injury, even in patients who initially deny heavy ingestion.
With appropriate evaluation, a diagnosis can readily be established in the large majority of patients with hepatobiliary dysfunction. In some circumstances, especially if the hepatic abnormalities are minor, the wisest approach is simply to follow the patient’s progress with periodic clinical and laboratory assessments.

3. EVALUATION OF ABNORMAL LIVER ENZYME RESULTS IN ASYMPTOMATIC PATIENTS / J.P. Villeneuve

Abnormal results on measurement of serum aminotransferases or alkaline phosphatase in an asymptomatic patient is a common medical problem. In most instances, the elevation of liver enzymes is mild (less than two times the upper normal limit) or moderate (two to 10 times the upper normal limit). A more important elevation of serum aminotransferases (more than 10 times the upper normal limit) suggests a diagnosis of acute hepatitis, and the patient is usually symptomatic.

Aminotransferases are present in the majority of body tissues (Figure 7). Because of their very high concentration in the liver (5,000 to 10,000 times higher than blood concentration), aminotransferases are sensitive indicators of liver-cell injury. Aspartate aminotransferase (AST) is found, in decreasing order, in cardiac muscle, liver, skeletal muscle, kidney, brain, pancreas, spleen, lungs, leucocytes and erythrocytes. The highest level of alanine
aminotransferase (ALT) is in the liver, and levels of this enzyme are accordingly more specific indicators of liver injury.

The first step in the evaluation of a patient with elevated liver-enzyme levels but no symptoms is to repeat the test to confirm the result. If the results are persistently abnormal, the patient should be further evaluated. The cause of the aminotransferase elevation can usually be identified by the pattern of liver enzyme elevation, a careful history and additional testing. It is useful to distinguish between an isolated elevation of aminotransferases with a normal or near-normal alkaline phosphatase (i.e., without cholestasis) and an elevation of aminotransferases with an increase in alkaline phosphatase of at least two or three times the upper normal limit (i.e., with cholestasis), as the evaluation of such patients will differ. The causes of elevations of aminotransferases levels without and with cholestasis are shown in Table 3 and 4.
3.1 Causes of Elevated Aminotransferase Levels Without Cholestasis

### 3.1.1 CHRONIC HEPATITIS C

Chronic hepatitis C is a common cause of elevated aminotransferase levels. The major risk factors for hepatitis C infection are a history of intravenous drug use, blood transfusion or work-related exposure to blood. However, in patients from countries such as Egypt, Italy or Vietnam for example, it is often impossible to determine how the infection was contracted. The initial test for hepatitis C infection is serologic testing for hepatitis C antibodies (anti-HCV). A positive result indicates either an active infection by the virus, or a past infection (resolved hepatitis C). The diagnosis of an active HCV infection responsible for the elevated aminotransferase levels will be confirmed by a positive test for HCV-RNA in serum measured by the reverse-transcriptase polymerase chain reaction (Table 5).
TABLE 5. Laboratory investigation to identify the cause of elevated aminotransferase levels in an asymptomatic patient

<table>
<thead>
<tr>
<th>Marker</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HCV</td>
<td>The presence of anti-HCV suggests chronic hepatitis C. Confirm the diagnosis by measuring serum HCV-RNA.</td>
</tr>
<tr>
<td>HBsAg, anti-HBs and anti-HBc</td>
<td>The presence of HBsAg and anti-HBc indicates chronic hepatitis B. Confirm that the hepatitis B is active by measuring serum HBeAg and HBV-DNA.</td>
</tr>
<tr>
<td>Glycemia, triglycerides</td>
<td>Diabetes and hyperlipidemia are often associated with non alcoholic steato-hepatitis.</td>
</tr>
<tr>
<td>Protein electrophoresis</td>
<td>A polyclonal increase in gamma-globulins suggests autoimmune hepatitis. Confirm by measuring antinuclear, anti-smooth muscle and anti-LKM antibodies.</td>
</tr>
<tr>
<td></td>
<td>A marked decrease in $\alpha_1$-globulin suggests $\alpha_1$-antitrypsin deficiency. Confirm by measuring $\alpha_1$-antitrypsin level and genetic testing.</td>
</tr>
<tr>
<td>Ferritin and transferrin saturation</td>
<td>Iron overload suggests hemochromatosis. Confirm by genetic testing.</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>Decreased ceruloplasmin levels suggest Wilson’s disease, especially in patients less than 40 years old.</td>
</tr>
<tr>
<td>Anti-gliadin and anti-transglutaminase antibodies</td>
<td>Suggest celiac disease.</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>Elevated levels suggest that aminotransferase abnormalities originate from striated muscle.</td>
</tr>
<tr>
<td>Antimitochondrial antibodies</td>
<td>Their presence is diagnostic of primary biliary cirrhosis.</td>
</tr>
<tr>
<td>Abdominal ultrasonography</td>
<td>Mandatory in the investigation of elevated aminotransferase levels with cholestasis.</td>
</tr>
</tbody>
</table>

Abbreviations:
anti-HCV: antibodies against hepatitis C virus; HCV-RNA: ribonucleic acid of the hepatitis C virus; HBsAg: surface antigen of the hepatitis B virus; anti-HBs: antibodies against the surface antigen of the hepatitis B virus; anti-HBc: antibodies against the core antigen of the hepatitis B virus; HBeAg: e antigen of the hepatitis B virus; HBV-DNA: deoxyribonucleic acid of the hepatitis B virus; anti-LKM: anti-liver kidney microsomal antibodies.
3.1.2 CHRONIC HEPATITIS B
The major risk factors for hepatitis B are unprotected sex, intravenous drug use, and mother-to-child transmission in areas where hepatitis B is endemic. Initial tests for hepatitis B infection include serological tests for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc) (Table 5). A negative HBsAg with the presence of anti-HBs and anti-HBc indicates a resolved hepatitis B and does not cause elevated aminotransferases levels. The presence of HBsAg with anti-HBc confirms an infection by the hepatitis B virus. Tests to determine whether there is viral replication include measurement of serum hepatitis Be antigen (HBeAg) and serum hepatitis B virus DNA (HBV-DNA). The presence of HBeAg and/or of serum HBV-DNA indicates active viral replication.

3.1.3 HEPATITIS A
Hepatitis A never evolves towards chronicity, and testing for hepatitis A is unnecessary in the investigation of a chronic elevation of aminotransferase levels.

3.1.4 ALCOHOLIC LIVER DISEASE
The diagnosis of alcoholic liver disease can sometimes be difficult to establish in patients who conceal their alcohol abuse. The presence of an hepatomegaly together with an AST/ALT ratio greater than 2.0 is suggestive of alcoholic liver disease. The lower ALT value in these patients is due to a deficiency in pyridoxal-5-phosphate caused by alcohol. Levels of gamma-glutamyl-transpeptidase (GGT) are also often very elevated in patients with alcoholic liver disease, and this test can be useful to confirm the diagnosis. However, all causes of cholestasis are also associated with elevated GGT levels, and GGT measurement is therefore not specific to diagnose alcoholic liver disease.

3.1.5 NON-ALCOHOLIC STEATO-HEPATITIS
Non-alcoholic steatohepatitis (NASH) is a common cause of elevated aminotransferase levels. The major risk factors for NASH are obesity, diabetes and hypertriglyceridemia. The pathophysiology of NASH is related to insulin resistance. The diagnosis is usually established by excluding other causes of elevated aminotransferase levels and by the demonstration of a hyperechoic liver on ultrasound. Some authors recommend a liver biopsy to confirm the diagnosis and stage the degree of fibrosis.

3.1.6 DRUGS, NATURAL PRODUCTS AND SUBSTANCES OF ABUSE
Almost any medication can cause drug-induced hepatitis, and a meticulous review of drug ingestion is critical for identifying a medication as the cause of elevated aminotransferase levels. Medications most commonly involved include
nonsteroidal anti-inflammatory drugs, antibiotics and antituberculosis drugs, antiepileptic drugs, statins and methotrexate. To establish a cause-effect relationship between a medication and elevated aminotransferase levels, three criteria are useful: the temporal relationship (introduction of the medication a few weeks or months before the elevation of the aminotransferase levels, and resolution of the anomalies after stopping the medication), knowledge of previous cases of drug-induced hepatitis with the suspected medication, and recurrence of elevated aminotransferase levels following accidental or voluntary re-exposure to the medication.

In addition to medications, herbal preparations and illicit drugs or substances of abuse may also cause elevations in liver-enzyme levels (Tables 6 and 7), and their use must be sought for specifically by history-taking.

3.1.7 AUTOIMMUNE HEPATITIS
Autoimmune hepatitis occurs primarily in young or middle-aged women, and is often accompanied by other autoimmune diseases, particularly autoimmune thyroiditis. Autoimmune hepatitis is characterized by a polyclonal hypergamma-globulinemia and the presence of anti-smooth muscle and/or anti-nuclear antibodies, or more rarely of anti-liver kidney microsomal antibodies (anti-LKM). A liver biopsy is essential to confirm the diagnosis and stage the disease.

3.1.8 GENETIC HEMOCHROMATOSIS
Hemochromatosis, a common genetic disorder, must be suspected in patients with elevated aminotransferase levels together with elevated ferritin and transferrin saturation values. However, all causes of liver cell injury (particularly alcoholic liver disease, non-alcoholic steatohepatitis and chronic hepatitis C) can result in increased ferritin and transferrin saturation values because of liver cell necrosis with release of iron in the circulation. In the past, liver biopsy was required to establish a diagnosis of genetic hemochromatosis, but genetic testing is now available to identify the mutation in the hemochromatosis gene (HFE) that causes the disease in the majority of patients of Northern European descent.

3.1.9 WILSON’S DISEASE
Wilson’s disease is a genetic disorder of biliary copper excretion. Although the disease is rare, it must be considered in young individuals with unexplained elevation of aminotransferase levels. A low ceruloplasmin level and/or the presence of Kayser-Fleischer ring at ophtalmologic examination are characteristic of the disease.
TABLE 6. Herbal and natural products that can cause elevated aminotransferase levels

<table>
<thead>
<tr>
<th>Latin name</th>
<th>Common name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alchemilla</td>
<td>Lady’s mantle</td>
</tr>
<tr>
<td>Atractylis gummifera-L</td>
<td>White chameleon</td>
</tr>
<tr>
<td>Callilepsis laureola</td>
<td></td>
</tr>
<tr>
<td>Cassia angustifolia</td>
<td>Senna</td>
</tr>
<tr>
<td>Chelidonum majus</td>
<td>Greater celandine</td>
</tr>
<tr>
<td>Crotalaria</td>
<td>Rattlebox, rattleweed</td>
</tr>
<tr>
<td>Ferula assafoetida</td>
<td>Asafetida</td>
</tr>
<tr>
<td>Gentiana lutea</td>
<td>Gentian</td>
</tr>
<tr>
<td>Hedeoma pulegioides</td>
<td>American pennyroyal</td>
</tr>
<tr>
<td>Heliotropium</td>
<td>White heliotrope</td>
</tr>
<tr>
<td>Humulus lupulus</td>
<td>Hops</td>
</tr>
<tr>
<td>Larrea tridentata</td>
<td>Chapparal, creosote bush</td>
</tr>
<tr>
<td>Sassafras albidum</td>
<td>Sassafras</td>
</tr>
<tr>
<td>Scutellaria sp</td>
<td>Skullcap</td>
</tr>
<tr>
<td>Senecio sp</td>
<td>Groundsel</td>
</tr>
<tr>
<td>Senecio vulgaris</td>
<td>Groundsel</td>
</tr>
<tr>
<td>Symphytum officinale</td>
<td>Comfrey</td>
</tr>
<tr>
<td>Teucrium chamaedrys</td>
<td>Germander</td>
</tr>
<tr>
<td>Valeriana officinalis</td>
<td>Valerian</td>
</tr>
<tr>
<td>Viscum aldum</td>
<td>Mistletoe</td>
</tr>
<tr>
<td>Lipodium serratum</td>
<td>Ji-Bu-Huan</td>
</tr>
<tr>
<td>Ephedra</td>
<td>Ma-Huang</td>
</tr>
<tr>
<td></td>
<td>Chinese herbs: Dai-Saiko-To, Syo-Sailo-To</td>
</tr>
<tr>
<td></td>
<td>Vitamin A</td>
</tr>
<tr>
<td></td>
<td>Shark’s cartilage</td>
</tr>
</tbody>
</table>

TABLE 7. Illicit drugs and substances of abuse that can cause elevated aminotransferase levels

- Cocaine
- Ecstasy (MDMA, 5-methoxy-3,4-methylenedioxyamphetatmine)
- Phencyclidine (PCP)
- Anabolizing steroids
- Glue and solvents (toluene, trichloroethylene, chloroform)
3.1.10 **ALPHA_1-ANTITRYPSIN DEFICIENCY**

Alpha_1-antitrypsin deficiency can be detected by the lack of a peak in \( \alpha_1 \)-globulin on serum protein electrophoresis, as \( \alpha_1 \)-antitrypsin accounts for 90% of serum \( \alpha_1 \)-globulins. Decreased serum levels of \( \alpha_1 \)-antitrypsin by a specific assay and genetic testing will establish the diagnosis. Patients with liver injury due to \( \alpha_1 \)-antitrypsin deficiency usually do not have the pulmonary disease (emphysema) seen in other patients with \( \alpha_1 \)-antitrypsin deficiency.

3.1.11 ** CELIAC DISEASE **

Asymptomatic celiac disease may be the cause of chronic unexplained elevation of aminotransferase levels. The presence of antigliadin and antitransglutaminase antibodies suggests this diagnosis, which can be confirmed by a duodenal biopsy. Elevated aminotransferase levels normalize after a gluten-free diet.

3.1.12 ** MUSCULAR DISEASES **

Muscular diseases (subclinical congenital myopathies or polymyositis) or strenuous exercise can cause elevation of aminotransferases (mostly AST) because of their high concentration in striated muscle (Figure 7). An important elevation of creatine kinase and aldolase will lead to the diagnosis.

3.1.13 ** OTHER CAUSES **

Other rare causes of elevated aminotransferase levels include Cushing’s disease, Addison’s disease, thyroid disorders and the presence of macro-enzymes. Liver biopsy is recommended in patients with persistently elevated values of more than twice the upper normal limit if no cause of elevated aminotransferase levels can be found despite extensive work-up. If the elevation of aminotransferase levels is less than twice the normal value, observation alone is a reasonable strategy. In a few patients (2 to 10% of cases according to various studies), the cause of elevated aminotransferase levels remains unknown.

3.2 ** Causes of Elevated Aminotransferase Levels With Cholestasis **

Some hepatic diseases can cause elevated aminotransferase levels with or without cholestasis (drug-induced liver injury, alcoholic liver disease, autoimmune hepatitis). However, an elevation of alkaline phosphatase levels associated with elevated aminotransferase levels usually suggests a category of diagnoses different from those without cholestasis (Table 4).

Elevations in serum alkaline phosphatase levels originate from liver, bone, or placenta in pregnant women. An elevated GGT level is useful to confirm the hepatic origin of the increased alkaline phosphatase. If the excess alkaline phosphatase is determined to be of liver origin and persists over time, the
patient should be evaluated for chronic cholestatic or infiltrative liver diseases. A partial obstruction of bile ducts or the presence of primary or metastatic liver tumors should first be considered. Abdominal ultrasonography is thus part of the initial evaluation of a patient with cholestasis. Ultrasonography can assess the presence of bile duct dilatation or hepatic tumors. The presence of antimitochondrial antibodies (AMA) is almost pathognomonic of primary biliary cirrhosis. Autoimmune cholangitis is a variant of primary biliary cirrhosis characterized by the presence of antinuclear antibodies instead of AMA.

If the serologic test for AMA is negative and ultrasonography reveals no abnormality, a liver biopsy and/or biliary tract imaging should be performed in patients with significant cholestasis (i.e., alkaline phosphatase level of more than twice the upper limit of normal). Biliary imaging using endoscopic retrograde cholangiography or magnetic resonance cholangiopancreatography will identify cases with sclerosing cholangitis, whereas liver biopsy can diagnose sarcoidosis, granulomatous hepatitis or idiopathic ductopenia. Idiopathic ductopenia is a chronic cholestatic liver disease of unknown origin characterized by the progressive disappearance of interlobular bile ducts. In the presence of mild cholestasis (alkaline phosphatase level less than twice the upper normal value) in an asymptomatic patient with a normal ultrasonography, observation alone is recommended.

3.3 Summary
Elevated levels of serum aminotransferases on routine screening are common. The first step in the evaluation of an asymptomatic patient is to repeat the test to confirm the result. If serum aminotransferases are persistently elevated, further investigation is warranted. It is useful to distinguish elevated aminotransferase levels with or without associated cholestasis (i.e., alkaline phosphatase levels above or below two times the upper normal limit), as the differential diagnosis is different. The main cause of elevated aminotransferases of non-hepatic origin is muscle diseases. Hepatic causes (without cholestasis) include hepatitis B and C, alcohol abuse, non-alcoholic steatohepatitis, drugs, toxins and herbal products, autoimmune hepatitis, hemochromatosis, α1-antitrypsin deficiency, Wilson’s disease, celiac sprue, thyroid disorders, Addison’s disease and Cushing’s disease. Hepatic causes of elevated aminotransferases with cholestasis include bile duct obstruction, hepatic tumors, primary biliary cirrhosis, sclerosing cholangitis, autoimmune hepatitis and overlap syndromes, alcohol abuse, non-alcoholic steatohepatitis, drugs, toxins and herbal products, sarcoidosis, granulomatous hepatitis and idiopathic adult ductopenia. In a small number of subjects (2 to 10% according to various series), the cause of elevated aminotransferases remains unknown despite extensive investigation.
4. THE LIVER AND DRUG DISPOSITION / P. Paré and J.P. Villeneuve

The liver plays a major role in the disposition of lipid-soluble drugs. Lipid solubility allows drugs to be absorbed by passive diffusion through the cellular membranes of the gut epithelium. Drugs are modified by metabolic pathways and converted to water-soluble compounds to be excreted in urine or bile (Figure 8).

Hepatic clearance of drugs is dependent on the liver blood flow, the efficiency of metabolizing enzymes and the extent of plasma protein binding. The clearance of drugs that have a high hepatic extraction ratio (high first-pass extraction) is rate-limited by hepatic uptake and therefore liver blood flow in contact with the hepatocytes (or Kupffer cells for inert substances used in radioisotopic liver-spleen scan). In chronic liver disease, the highly porous sinusoids become progressively capillarized due to deposition of collagen in the space of Disse, limiting the transport of drugs to hepatocytes. Therefore in chronic liver disease, because of capillarization and intra- and extra-hepatic shunting, drugs that usually have high first-pass extraction will have increased systemic bioavailability and potentially greater clinical effects. On the other hand, some drugs have low hepatic extraction ratios and their clearance is not blood flow dependent, but enzyme-dependent. Aging and advanced liver disease with hepatic insufficiency will significantly decrease the amount and activity of these enzymes. Usually, patients with mild liver disease can eliminate drugs almost normally.
The hepatic drug-metabolizing reactions are of two types. In phase 1 (through cytochromes P-450 enzymes), drugs are usually hydroxylated to form intermediate or inactive metabolites. In phase 2, the resulting metabolites are made polar and water-soluble through conjugation with glucuronic acid, sulfate or glutathione. Often, drugs undergo phase I and then phase 2 metabolism. In chronic liver disease and with aging, the amount and activity of phase 1 enzymes decreases along with progressive liver dysfunction, altering the clinical effects of enzyme-dependent drugs. Some drugs do not require phase 1 metabolism and are directly dependent on phase 2 metabolism. The activity of phase 2 enzymes is less affected by chronic liver disease. For instance, when a benzodiazepine is to be used in a patient with advanced liver disease, short-acting drugs that undergo preferentially phase 2 metabolism are

<table>
<thead>
<tr>
<th>Hepatic extraction ratio</th>
<th>Drugs</th>
<th>Clinical effect in chronic liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>High extraction</td>
<td>Labetolol, Propranolol, Lidocaine, Morphine, Pentazocine, Veraprami</td>
<td>Increased</td>
</tr>
<tr>
<td>Low extraction Phase 1</td>
<td>Chlordiazepoxide, Diazepam, Diphenylhydantoin, Indomethacin, Rifampicine, Tolbutamid, Warfarin</td>
<td>Increased</td>
</tr>
<tr>
<td>Low extraction Phase 2</td>
<td>Lorazepam, Oxazepam</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Intermediate extraction</td>
<td>Acetaminophen, Chlorpromazine, Isoniazid, Metoprolol, Nortriptyline, Quinidine</td>
<td>Increased</td>
</tr>
</tbody>
</table>
more suitable than long-acting drugs that undergo first phase 1 metabolism (Table 8). Alcohol and some drugs can induce cytochrome P-450 enzymes and therefore this may result in increased clearance and decreased clinical effects.

4.1 Enzymatic Metabolism
Cytochrome P-450 enzymes (CYPs) are the main system responsible for phase 1 metabolism. More than 20 CYPs have been identified in the human liver. CYPs are distributed selectively in the hepatic lobule, most showing a higher amount in the periportal area, some more confined around the hepatic venule. The localization of CYPs explains in part the distribution of hepatic lesions produced by drugs and toxins converted to intermediate reactive metabolites such as acetaminophen and carbon tetrachloride. CYPs are microsomal oxidases. Esterases and hydroxylases are other enzyme systems involved in phase 1 metabolism.

The CYPs are hemoproteins located in the endoplasmic reticulum. In humans, CYPs that metabolize drugs are members of three gene families (CYP1, CYP2, CYP3). Within each family, subfamilies are identified by capital letters (e.g., 3A, 2C, 1A) and members within subfamilies by Arabic numbers (3A4, 2C9, 1A2).

Each individual CYP can metabolize many drugs. CYP3A4 and CYP3A5 are involved in the metabolism of about 50% of drugs (Figure 9). They are the most abundant of this enzymatic system in the human liver. Some are less abundant and their activity is influenced by genetic polymorphism (2C9, 2C19, 2D6). As a result, there are phenotypes with poor, intermediate, rapid
and even ultra rapid metabolizing activity. These variants often vary according to racial background. CYP2C9 metabolizes commonly used drugs including warfarin and phenytoin, which both have a narrow therapeutic window. Individuals with heterozygous and homozygous mutation of CYP2C9 have marked reduced activity of the enzyme (12% and 5%). As a consequence, establishing warfarin or phenytoin therapy in these individuals is more difficult, exposing them to supratherapeutic or toxic blood concentrations. Genetic polymorphism also occurs with CYP2C19 (3% of Caucasians and up to 23% of Asians are poor metabolizers). CYP3A shows marked inter-individual variability but no significant functional polymorphisms have been found. Table 9 shows examples of substrates of some P-450 cytochromes.

<table>
<thead>
<tr>
<th>CYP</th>
<th>Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>Caffeine, Theophylline</td>
</tr>
<tr>
<td>2A6</td>
<td>Nicotine</td>
</tr>
<tr>
<td>2C9</td>
<td>Warfarin, Phenytoin, ASA and most NSAIDs</td>
</tr>
<tr>
<td>2C19</td>
<td>Diazepam, Tricyclic antidepressants, (TCAs), Omeprazole, Tolbutamide</td>
</tr>
<tr>
<td>2D6</td>
<td>TCAs, Selective serotonin reuptake inhibitors, Beta blockers, Codeine</td>
</tr>
<tr>
<td>2E1</td>
<td>Acetaminophen, Ethanol</td>
</tr>
<tr>
<td>3A4</td>
<td>Erythromycin, clarithromycin, Cyclosporin, tacrolimus, Calcium channel blockers (not diltiazem), Several statins (lo娃-, simv-, atorva-), HIV protease inhibitors, Estrogens, Corticosteroids</td>
</tr>
</tbody>
</table>
In the conjugating phase 2 enzymes, genetic polymorphism of thiopurine methyltransferase is critically important in the metabolism of 6 mercaptopurine and azathioprine: 0.3% of the population are homozygous for a mutation conferring no or minimal enzyme activity and 10% are heterozygous with markedly decreased enzyme activity.

Drug metabolism mediated by CYPs is more affected than conjugation reaction in cirrhosis. The content and activity of CYP1A, 2C19 and 3A are particularly influenced by the severity of liver disease. Furthermore, several drugs and/or environmental substances may act as inducers, competitors or strong inhibitors of some CYPs. Some drugs or food substances are known to be strong inhibitors of some CYPs, potentially exposing patients with or without liver disease to clinical complications (Table 10). Grapefruit juice probably exerts its effect on orally administered drugs by inhibiting the CYP3A4, widely distributed in the intestinal tract (as well as in the liver).

Drug disposition is an important clinical consideration when taking care of patients with chronic liver disease. The route of metabolism and the pharmacokinetic characteristic of the drug used must be evaluated in relationship to the severity of liver dysfunction in order to obtain the desired clinical responses. Adverse events occur more frequently than in healthy individuals unless caution is exercised.

### TABLE 10. Potent inhibitors of some CYPs

<table>
<thead>
<tr>
<th>CYP</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>3A4</td>
<td>Grapefruit juice</td>
</tr>
<tr>
<td></td>
<td>Green tea</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole and other azoles</td>
</tr>
<tr>
<td></td>
<td>Erythro and clarithromycin</td>
</tr>
<tr>
<td>2C9</td>
<td>Fluconazole</td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>2C19</td>
<td>Fluconazole</td>
</tr>
<tr>
<td>1A2</td>
<td>Fluconazole</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones</td>
</tr>
</tbody>
</table>

In the conjugating phase 2 enzymes, genetic polymorphism of thiopurine methyltransferase is critically important in the metabolism of 6 mercaptopurine and azathioprine: 0.3% of the population are homozygous for a mutation conferring no or minimal enzyme activity and 10% are heterozygous with markedly decreased enzyme activity.

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Drug disposition is an important clinical consideration when taking care of patients with chronic liver disease. The route of metabolism and the pharmacokinetic characteristic of the drug used must be evaluated in relationship to the severity of liver dysfunction in order to obtain the desired clinical responses. Adverse events occur more frequently than in healthy individuals unless caution is exercised.
5. CONGENITAL HYPERBILIRUBINEMIAS / P. Paré

The importance of recognizing congenital hyperbilirubinemia lies mainly in distinguishing it from other, more serious hepatobiliary diseases. Except for Crigler-Najjar syndrome, congenital hyperbilirubinemias do not impair either the quality of life or the life expectancy of affected subjects. By definition, patients with familial hyperbilirubinemia have normal standard liver tests. The liver histology is also normal (except for the pigment accumulation in Dubin-Johnson syndrome). With the exception of Gilbert’s syndrome, these syndromes are distinctly uncommon and are divided into two groups on the basis of the type of the serum hyperbilirubinemia (Table 11).

5.1 Unconjugated Hyperbilirubinemia

5.1.1 GILBERT’S SYNDROME
Gilbert’s syndrome is the most common congenital hyperbilirubinemia syndrome, occurring in about 5% of Caucasians. It is probably transmitted through an autosomal dominant mode. Its pathogenesis is related to a partial deficiency in hepatic UDP-glucuronyl transferase, the enzyme responsible for the glucuronidation of bilirubin. In addition, some patients have reduced bilirubin uptake by the hepatocytes, as observed with diagnostic substances (BSP, indocyanine green) and drugs (tolbutamide). The syndrome is usually detected in adolescents and young adults, most commonly in males. Such a sex difference may be explained by testosterone inhibiting, whereas estrogen and progesterone augment the action, of UDP-glucuronyl transferase. Complaints leading to the diagnosis are various (fatigue, nausea, vague abdominal discomfort) and unrelated to the condition. Scleral icterus may be present and fluctuating, but the physical examination is otherwise normal. Liver tests and hemogram (to exclude hemolysis) are normal except for unconjugated serum bilirubin, which is elevated between 20 and 100 mmol/L, whereas conjugated bilirubin is often un-recordably low. Diagnostic tests are available but usually not necessary: fasting for two days or intravenous administration of nicotinic acid significantly increases serum unconjugated bilirubin, while phenobarbital significantly decreases it. No treatment is warranted. Prognosis is excellent.

5.1.2 CRIGLER-NAJJAR SYNDROME
This syndrome may present in two types. Type 1 is a very rare and serious disease characterized by unconjugated hyperbilirubinemia often greater than 400-500 mmol/L. It is due to an absolute deficiency of UDP-glucuronyl transferase. Jaundice occurs almost immediately after birth and may lead to kernicterus with consequent neurologic damage and mental retardation.
<table>
<thead>
<tr>
<th></th>
<th>Gilbert's</th>
<th>Crigler-Najjar type 1</th>
<th>Crigler-Najjar type 2</th>
<th>Dubin-Johnson</th>
<th>Rotor's</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>7% of population</td>
<td>Very rare</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Inheritance</strong></td>
<td>Dominant</td>
<td>Recessive</td>
<td>Dominant</td>
<td>Recessive</td>
<td>Recessive</td>
</tr>
<tr>
<td><strong>Serum bilirubin concentration (µmol/L)</strong></td>
<td>&lt; 100 (all unconjugated)</td>
<td>&gt; 400 (all unconjugated)</td>
<td>&lt; 400 (all unconjugated)</td>
<td>&lt; 100 (about half conjugated)</td>
<td>&lt; 100 (about half conjugated)</td>
</tr>
<tr>
<td><strong>Diagnostic features</strong></td>
<td>Bilirubin concentration ↑ with fasting, ↓ with phenobarbital</td>
<td>No response to phenobarbital</td>
<td>Bilirubin concentration ↓ with phenobarbital</td>
<td>Characteristic urinary coproporphyrin excretion (&gt; 80% isomer 1)</td>
<td>Pigment in centrolobular hepatocytes, Normal gallbladder visualization at oral cholecystography</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Normal</td>
<td>Early death from kernicterus</td>
<td>Usually normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>None needed</td>
<td>Liver graft</td>
<td>Phenobarbital</td>
<td>Avoid estrogens</td>
<td>None available</td>
</tr>
</tbody>
</table>
Kernicterus involves damage to the basal ganglia and cerebral cortex because unconjugated bilirubin is able to penetrate the immature blood-brain barrier of infants. The syndrome is inherited in an autosomal recessive fashion, often with a family history of consanguinity. Phenobarbital treatment is ineffective in inducing UDP-glucuronyl transferase activity; death occurs early. The treatment of choice appears to be hepatic transplantation.

Crigler-Najjar syndrome type 2 is a much more benign condition in which the unconjugated hyperbilirubinemia usually does not exceed 400 mmol/L. Kernicterus rarely develops in these patients (except with prolonged fasting, in which bilirubin can rise). Hepatic UDP-glucuronyl transferase activity is very low or undetectable, but phenobarbital therapy reduces serum bilirubin levels. (Phenobarbital presumably induces even the low levels of this enzyme). Prognosis is quite good despite a lifelong persistent unconjugated hyperbilirubinemia.

5.2 Conjugated Hyperbilirubinemia

Two conditions characterized by congenital conjugated hyperbilirubinemia without cholestasis have been described. Both syndromes are inherited as autosomal recessive traits. Both are uncommon disorders believed to result from specific defects in the hepatobiliary excretion of bilirubin. These conditions are benign, and their accurate diagnosis provides reassurance to the patient. Plasma bilirubin levels are usually in the range of 35-85 mmol/L. Plasma bilirubin may further increase in both conditions during intercurrent infection, pregnancy or use of oral contraceptives. Pruritus is absent and serum bile acid levels are normal, as are routine biochemical liver tests, except for the serum bilirubin concentration. Bilirubinuria is usually present. No treatment is necessary.

Some distinctive features allow differential diagnosis between the two syndromes.

5.2.1 Dubin-Johnson Syndrome

Patients with the Dubin-Johnson syndrome have a black liver, which results from the accumulation of a melanin-like pigment in lysosomes. Visualization of the gallbladder during oral cholecystography is usually delayed or absent. Urinary excretion of total coproporphyrin is normal, whereas the proportion of isomer 1 is higher than in normal controls (> 80%). Finally, the BSP plasma retention test is normal in its initial phase, but there is a secondary rise in plasma BSP concentration at 90 minutes due to reflux of BSP from the hepatocyte to the plasma.
5.2.2 **ROTORS SYNDROME**

In patients with Rotor’s syndrome, the appearance and histology of the liver are normal. Oral cholecystography usually visualizes the gallbladder. Total coproporphyrin excretion is greater than normal, as in other hepatobiliary disorders, and isomer 1 makes a smaller proportion (< 80%) than in Dubin-Johnson patients. The plasma disappearance of injected BSP is delayed, with no secondary rise.

### 6. ACUTE VIRAL HEPATITIS / P.T. Grover and M. Ma

The term hepatitis refers to any inflammatory process causing hepatocellular injury. Hepatitis is clinically classified into acute hepatitis, which is usually a self-limited disease, and chronic hepatitis, in which the inflammation persists beyond six months. The most common etiology of acute hepatitis is viral infection (Table 12) and hepatitis A, B and C are the most common causes of viral hepatitis in North America. Other viruses such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), adenovirus, herpes simplex and Coxsackie virus can cause hepatitis, but in these cases the clinical picture is dominated not by the hepatitis but by the features of the viral illness.
Most viral hepatitis infections cause very mild and non-specific symptoms. When the hepatitis is severe, initial symptoms include malaise, nausea, vomiting, fatigue and a low-grade fever. Right upper quadrant discomfort is common in acute hepatitis, but severe abdominal pain is not a feature. In rare severe cases, there is a risk of fulminant liver failure requiring liver transplantation. These patients with severe hepatitis have significantly elevated serum aminotransferases (ALT and AST) and hepatic synthetic function abnormalities including elevated INR and bilirubin.

In the last decade, the treatment of acute viral hepatitis has not progressed as rapidly as our understanding of these hepatitis viruses’ epidemiology and molecular biology. The mainstay of treatment is still supportive care. The convalescent stage is usually seven to 10 days, with the total illness lasting two to six weeks. Prevention of infection and post-exposure prophylaxis are important in the management of these hepatitis viruses.

6.1 Hepatitis A Virus (HAV)

6.1.1 EPIDEMIOLOGY AND RISK FACTORS
Previously termed “infectious hepatitis,” hepatitis A virus (HAV) is an RNA virus belonging to the enterovirus family. This enteric viral infection is a common disease worldwide and tends to cause mild self-limited illness. However, severe hepatitis and liver failure have been reported. The poor public hygiene in many developing countries and in some communities in developed countries causes fecal-oral spread of hepatitis A virus. The anti-HAV antibody can be detected in 90% of the population in developing countries and in 30-40% of the population in developed countries.

Given the globalization of food distribution and tourism, HAV is no longer just a disease of developing countries. Food and water contamination may lead to epidemic outbreaks. Recent North American outbreaks have been associated with the ingestion of contaminated strawberries imported from developed countries and of raw clams and oysters from polluted water. Person-to-person spread results in sporadic cases. Parenteral transmission is also possible, especially in intravenous drug users, but is much less common. Travelers to endemic areas, children in daycare, health care professionals and homosexual males are at increased risk of contracting Hepatitis A.

6.1.2 CLINICAL COURSE
HAV is transmitted by the fecal-oral route. Increased symptom severity correlates with older age at the time of HAV infection. In developing countries, the infection occurs in childhood and most children have been exposed to the virus. The childhood infection has very mild symptoms and the children
FIRST PRINCIPLES OF GASTROENTEROLOGY

In developed countries with good sanitation, "population immunity" to hepatitis A infection is low in young adults. Few of them have been exposed to the virus during childhood. The hepatitis A infection occurs in adults and the disease tends to be symptomatic.

The infection usually causes mild to moderate acute hepatitis in adults. The incubation period is approximately four weeks and the acute illness lasts two to three weeks. The virus is present in the stool of patients from the prodromal or pre-icteric phase to about two weeks after the onset of jaundice. Person to person oral-fecal spread can occur during this time. There is a brief period of viremia during the acute phase of infection and parenteral transmission can occur in intravenous drug users sharing needles. During acute infection, patients have flu-like symptoms such as malaise, fatigue, anorexia and fever. Mild to moderate jaundice can usually be detected. The liver enzymes AST and ALT are moderately elevated.

Fulminant liver failure causing death or requiring liver transplantation has occurred in elderly patients and patients with underlying chronic liver disease. These patients with fulminant liver failure need hospital admission for supportive care and preparation for liver transplantation. The mortality rate from fulminant hepatitis is very low (0.1%) and rarely, liver transplantation is required. Recovery follows acute hepatitis and patients develop lifelong immunity to HAV. There is no evidence for a chronic carrier state or the development of chronic liver disease.

FIGURE 10. Typical clinical and serologic features of acute hepatitis A.

<table>
<thead>
<tr>
<th>Titer</th>
<th>weeks post exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal HAV</td>
<td>IgG anti-HAV</td>
</tr>
<tr>
<td>IgM anti-HAV</td>
<td></td>
</tr>
</tbody>
</table>
6.1.3 DIAGNOSIS
Both IgM and IgG antibodies to the virus (anti-HAV) can be detected in hepatitis A infection. The presence of an elevated IgM antibody indicates recent infection and is the test being used to diagnose acute infection. The IgM response usually becomes undetectable at six months, but the IgG response persists for life (Figure 10).

6.1.4 TREATMENT
Most patients will do well and can maintain their routine activities although some patients will develop nausea and vomiting severe enough to require intravenous fluid support. The illness is usually self-limited and there is no specific anti-viral therapy for acute hepatitis A. Treatment of active disease is supportive. Most cases can be managed on an outpatient basis. Strict bed rest is not necessary. The patient may undertake any activity that does not exacerbate symptoms. Strenuous exercise has not been associated with adverse outcome during mild to moderate acute HAV infection. Diet can be liberal, encouraging a high calorie intake but excluding alcohol. Fatty foods are poorly tolerated and are best avoided. All unnecessary drugs, especially tranquilizers and sedatives, should be avoided. Return to work and activity should be guided by the patient’s symptoms. Patient education will help alleviate anxiety. Specialist referral is not usually required (Table 13).

6.1.5 PREVENTION
In the community, prevention of hepatitis A is dependent on good sanitation and hygiene. At the time of outbreak, information regarding hygienic measures and immunoprophylaxis should be provided to family members or persons in close contact with the infected individual. This public health intervention is important to prevent the spread of hepatitis A infection. The serum immune globulin and hepatitis A vaccine are two biologic agents used for disease prevention.

Regular immune globulin preparation has been demonstrated to be effective in prevention of hepatitis A and it is used for passive immunoprophylaxis. The preparation consists of concentrated antibodies from pooled human plasma. The immune globulin has an efficacy of 80 – 90% when it is given before or immediately after exposure. It can be used for pre-exposure prophylaxis in travelers to endemic countries requiring short-term, immediate protection. It is also used in post-exposure prophylaxis of household and sexual contacts of an affected individual. The preparation is safe to use for short-term prophylaxis in children under the age of two and in pregnant women traveling to endemic areas. The current recommended dose of immune globulin is 0.02 mL/kg IM within two weeks of exposure.
<table>
<thead>
<tr>
<th></th>
<th><strong>Hepatitis A</strong></th>
<th><strong>Hepatitis B</strong></th>
<th><strong>Hepatitis C</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Need for good sanitation and hygiene.</td>
<td>• Vaccine synthesized from recombinant method</td>
<td>• No vaccine</td>
<td></td>
</tr>
<tr>
<td>• HAV infection confers life-long immunity.</td>
<td>• Minimal side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Minimal side effects</td>
<td>• Confers protection from HDV</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Indication for vaccination</strong></td>
<td><strong>Hepatitis A</strong></td>
<td><strong>Hepatitis B</strong></td>
<td><strong>Hepatitis C</strong></td>
</tr>
<tr>
<td>• Occupational exposure (day care workers, military personnel, health professionals, sewage workers)</td>
<td>• Universal vaccination in Canada</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Homosexual males</td>
<td>• Vaccine synthesized from recombinant method</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Residents and staff at chronic care facilities, jails</td>
<td>• Minimal side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Travellers to endemic areas</td>
<td>• Confers protection from HDV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• IVDU</td>
<td>• No vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Children ≥ 2 years of age in communities with high rates of Hep A</td>
<td>• Chronic liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Chronic liver disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Prophylaxis on exposure</td>
<td><strong>Hepatitis A</strong></td>
<td><strong>Hepatitis B</strong></td>
<td><strong>Hepatitis C</strong></td>
</tr>
<tr>
<td>• All household and sexual contacts</td>
<td>• Needlestick, sexual &amp; household contacts</td>
<td>• Needlestick injury</td>
<td></td>
</tr>
<tr>
<td>• Immune serum globulin 0.02 mL/kg IM if within 2 weeks of exposure</td>
<td>• If seronegative, administer HBIG + start HBV vaccine series</td>
<td>Test for HCV-RNA, AST, bilirubin at baseline 4 and 12 weeks – if positive, treat with PEG-IFN and Ribavirin</td>
<td></td>
</tr>
<tr>
<td>• Vaccine</td>
<td>• Prenatal Routine pre-natal screening with HBsAg</td>
<td>• Perinatal</td>
<td></td>
</tr>
<tr>
<td>• No treatment for casual school or work contacts unless epidemic identified</td>
<td>• Within 24-48 hours of delivery, administer HBIG + start HBV vaccine series</td>
<td>Rare transmission- more likely if mother is immunosuppressed</td>
<td></td>
</tr>
<tr>
<td>• Test infant with HCV RNA</td>
<td>• Sexual transmission rare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Condoms advised for multiple sex partners, anal intercourse and during menses</td>
<td>• If patient hasn’t spontaneously cleared virus at 12 weeks, start antiviral therapy. Studies with IFN monotherapy only.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td><strong>Hepatitis A</strong></td>
<td><strong>Hepatitis B</strong></td>
<td><strong>Hepatitis C</strong></td>
</tr>
<tr>
<td>• Supportive care. Most cases resolve spontaneously. Hospitalization rarely needed. Prophylaxis and prevention of secondary spread is perhaps the most important aspect of treatment.</td>
<td>• In addition to supportive care, if patient hasn’t spontaneously cleared virus at 12 weeks, start antiviral therapy. Studies with IFN monotherapy only.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Activity - Symptom guided return to work; no activity limitations.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Diet – fatty foods poorly tolerated, exclude ETOH, no other restrictions.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Drugs – no role for corticosteroids – may increase the risk of a chronic carrier state; avoid sedatives, tranquillizers</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The hepatitis A vaccine contains live attenuated virus and is safe to be used to induce immunity to the virus. The current vaccines are administered in two doses. It is recommended in persons above the age of two who are inhabitants of communities with high rates of hepatitis A, are at risk of occupational exposure, or are traveling to endemic countries. Intravenous drug users (IVDU), those living in institutions, or those with chronic liver disease or hemophilia should also be vaccinated (Table 13). Because of the high efficacy of the vaccine, post-treatment testing for the development of antibodies is not routinely required. Although the vaccine is very safe, there are no data regarding the safety of the vaccines in children less than two years of age, or in pregnant women. The most common side effect is pain at the site of injection (18-39%).

The immune globulin and vaccine can be given together. In this situation, there is some inhibition of antibody production. But the titer of anti-HAV developed is more than adequate to prevent hepatitis A infection.

### TABLE 14. Risk factors associated with reported cases of acute HBV in the U.S
Source: Data from Centers for Disease Control and Prevention, 1992

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterosexual activity</td>
<td>48</td>
</tr>
<tr>
<td>IV Drug use</td>
<td>11</td>
</tr>
<tr>
<td>Homosexual activity</td>
<td>7</td>
</tr>
<tr>
<td>Health-care employment</td>
<td>2</td>
</tr>
<tr>
<td>Household contact</td>
<td>1</td>
</tr>
<tr>
<td>Transfusion, dialysis</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>30</td>
</tr>
</tbody>
</table>

### TABLE 15. Risk of transfusion-transmitted infection
Source: Data from CMAJ – Canadian Blood Services Database 1990-2000

<table>
<thead>
<tr>
<th>Infection</th>
<th>Risk Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>1/72,000</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1/3 million</td>
</tr>
<tr>
<td>HIV</td>
<td>1/10 million</td>
</tr>
<tr>
<td>HTLV</td>
<td>1/1.1 million</td>
</tr>
</tbody>
</table>
6.2 Hepatitis B Virus (HBV)

6.2.1 EPIDEMIOLOGY AND RISK FACTORS
HBV is a unique DNA virus that replicates through reverse transcription of its mRNA. It behaves more like a retrovirus than a DNA virus. It accounts for 40% of acute viral hepatitis in the U.S. In North America, HBV infection occurs primarily in adolescents and adults because of sexual activity and intravenous drug use (Table 14). In endemic countries, HBV infection occurs frequently in infants and children through maternal-newborn or child to child transmission by contaminated vaccination needles. The vertical transmission of HBV from mother to newborn results in the vast majority of chronic carriers worldwide. HBV infection from transfusion has decreased dramatically since the implementation of routine screening and the use of volunteer blood donors. However, HBV infection through blood transfusion still has the highest risk at one per 72,000 units transfused (Table 15).

6.2.2 CLINICAL COURSE
HBV is a highly infectious virus. The presence of HBeAg or HBV DNA in blood indicates active viral infection and high infectivity. Percutaneous or mucous membrane exposure to infectious blood or body fluid leads to acute infection.
The clinical presentation of acute hepatitis B ranges from subclinical to the rare case of fulminant hepatitis (0.1-0.5%). The incubation period ranges from 60-110 days. Acute hepatitis starts and jaundice occurs in approximately 30% of patients at presentation. During acute illness, patients may have fever, malaise, fatigue, anorexia and elevated liver enzymes. The outcome and development of chronic hepatitis B are frequently age dependent. If the infection is acquired as an adult, the infection is usually self-limited and less than 5% of patients will go on to develop chronic hepatitis (persistent presence of virus after six months of infection). Perinatal transmission is associated with a 90% rate of chronic infection. Lower rates of viral clearance are also found in immunosuppressed patients.

### 6.2.3 DIAGNOSIS

The typical course of HBV infection, appearance of the viral antigens and host immune response are shown in Figure 11. It is important to learn the clinical course of HBV infection and components of HBV in order to understand the multiple serologic HBV tests. HBV consists of a 28 nm central core containing the DNA genome (a single molecule of partially double-stranded DNA) and the viral DNA polymerase. The core is commonly found in the nuclei of infected hepatocytes and the core antigen is antigenically distinct from the HBsAg, which packages the HBV core. Both core antibody (anti-HBc) and surface antibody (anti-HBs) are found in patients who have recovered from the infection. A further viral antigen, termed HBeAg, can be detected in the serum and this HBeAg is a subunit of HBcAg. HBeAg positivity implies viral replication and is an indicator of high infectivity. Mutants that do not produce HBeAg exist; these “pre-core mutants” can

<table>
<thead>
<tr>
<th>Marker</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>HBV infection; may be acute or chronic</td>
</tr>
<tr>
<td>HBsAb</td>
<td>Immune to HBV; may be natural immunity or following vaccination</td>
</tr>
<tr>
<td>HBcAb-IgM</td>
<td>Acute HBV infection (newer and more sensitive assays may also be positive during reactivation of chronic infections)</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Active viral replication and high infectivity</td>
</tr>
<tr>
<td>HBeAb</td>
<td>Low or no infectivity; need only be measured in chronic HBV</td>
</tr>
<tr>
<td>HBV-DNA</td>
<td>Measure of infectivity or replicative state. Available by PCR technique.</td>
</tr>
</tbody>
</table>

### TABLE 16. Interpretation of hepatitis B markers
cause severe hepatitis. During acute infection, the HBsAg, HBeAg and HBV DNA can be detected in blood. The IgM specific anti-hepatitis B core antibody develops early and is a marker indicating acute infection. When the acute hepatitis resolves, the HBsAg is cleared and anti-HBs antibody becomes detectable. The significance of HBV markers and their interpretation are summarized in Table 16 and in Section 7, Table 21.

6.2.4 TREATMENT
Supportive care is the treatment during acute illness. There is no need for antiviral treatment because most acute infections clear completely. In the rare occurrence of fulminant liver failure, the patient should be treated with liver transplantation. For the patients who develop severe chronic HBV infection, anti-viral treatment with interferon or lamivudine will be important to prevent the progression of disease to cirrhosis and liver failure.

6.2.5 PREVENTION
Passive and active immunizations against the HBV are available. A specific immune globulin preparation from pooled plasma has a high titer of hepatitis B surface (anti-HBs) antibody. This hepatitis B immune globulin (HBIG) can offer protection against hepatitis B infection after exposure to the virus. It should be given within 12 hours when there has been a clear-cut exposure, such as an inadvertent “needle-stick” injury or sexual contact. Frequently the hepatitis B immune globulin is given in combination with the vaccine. The immune globulin is also given, along with hepatitis B vaccine, within 24 to 48 hours to the neonates of mothers with acute or chronic hepatitis B to prevent the vertical viral infection from mother to newborn. Routine pre-natal screening with HBsAg is recommended to identify mothers who can transmit the infection to newborns.

The hepatitis B vaccine containing HBsAg, originally manufactured from pooled donor sera, is now synthesized by recombinant DNA technology. Currently there are several commercially available vaccines. These vaccines are safe and effective. After a complete course of vaccination, 95–99% of immunocompetent individuals develop protective antibody that can prevent infection. They develop a high titer of anti-HBs. The side effects are minimal. Many countries have a universal vaccination program for infants or children. Vaccination is recommended for high-risk groups such as health-care workers, homosexuals, intravenous drug users, family contacts of chronic carriers, chronic transfusion recipients and dialysis patients. The eventual goal is eradication of hepatitis B through a successful global vaccination program.
6.3 Hepatitis C Virus (HCV)

6.3.1 EPIDEMIOLOGY AND RISK FACTORS
Hepatitis C was discovered in 1989. It is a single-stranded RNA virus of less than 80 nm in diameter that has been classified as a member of the flavivirus family. It exists as different genotypes. It has a worldwide distribution and is a significant cause of chronic hepatitis. In North America, the genotypes 1, 2 and 3 account for most of the infection. The prevalence of HCV infection ranges from 1% in the general population to as high as 90% in hemophilia patients who have received factor concentrate. The principal mode of HCV transmission is parenteral, but a significant percentage of patients do not have identifiable risk factors. Intravenous drug use is the main cause of hepatitis C infection in developed countries. Contaminated medical instruments are a major source for the spread of hepatitis C in many developing countries. HCV infection from contaminated needles in health-care workers occurs in less than 5%. Transfusion-related cases account for 10%. The current rate of transfusion-related transmission of hepatitis C is only one out of every 3 million units (Table 15). Infection through sexual contact or mother to newborn has been documented, but the infection rate is low.

6.3.2 CLINICAL COURSE
The incubation period is five to 10 weeks (mean seven weeks). The acute phase is clinically mild and the majority of patients anicteric. Because the acute illness can be very mild, detection of acute infection is difficult. Many patients do not know that they have acute hepatitis C infection. Patients with symptomatic acute inflammation are more likely to clear the virus. Chronic infection develops in 70–80% of patients and these patients have a significant risk of developing cirrhosis and chronic liver failure many years in the future.

6.3.3 DIAGNOSIS
Testing for HCV can be divided into serologic tests for detection of antibody (ELISA) and molecular tests for detection of virus (HCV RNA PCR). The presence of anti-HCV antibody suggests viral exposure and is not a marker of immunity. The majority of patients who have been exposed to hepatitis C virus become carriers of the virus. For this reason, there is a tendency to regard the presence of anti-HCV antibody as an indicator of chronic infection. This is not necessarily the case. It is important to confirm the diagnosis of chronic hepatitis C infection by detecting the virus with the PCR test.

The new-generation ELISA (enzyme-linked immunosorbent assay) is the primary screening test. It identifies antibodies to the nonstructural as well as
the structural epitopes of the virus. Because the new test is quite sensitive and specific, it is very useful in identifying patients who have been exposed to hepatitis C virus. An uncertain ELISA result must be confirmed with HCV RNA determination. Hypergammaglobulinemia is a common reason for a false-positive ELISA test. A false negative result can occur in patients who have immunosuppression and renal failure.

The molecular PCR test is the important test that confirms the presence of viremia. The PCR test is sensitive and can help determine the hepatitis C genotype and viral load. The information is useful in the management of chronic hepatitis C, as the genotype can help to predict response to therapy.

6.3.4 TREATMENT
There is a role for treatment of acute hepatitis C if spontaneous viral clearance has not occurred by 12 weeks. Treatment with interferon can clear the virus and eliminate the risk of chronic infection in the majority of the patients. Once chronic infection has been established, treatment is more difficult and less effective. The agent of choice for antiviral treatment has not yet been established. Although most studies have looked at interferon monotherapy, the 2004 American Association for the Study of Liver Diseases (AASLD) guidelines suggest pegylated interferon and ribavirin could be considered.

6.3.5 PREVENTION
There is no vaccine or specific immune globulin available for hepatitis C prevention. Following a high-risk exposure such as a needlestick injury from a known case of hepatitis C, liver enzymes and HCV-RNA should be closely followed to determine whether acute infection has occurred. If acute infection is present, interferon treatment should be provided to eliminate the risk of chronic infection. The risk of sexual transmission is extremely low. In stable, monogamous relationships, the use of condoms is not recommended.

6.4 Hepatitis D Virus (HDV)

6.4.1 EPIDEMIOLOGY AND RISK FACTORS
Hepatitis D (HDV) is a defective RNA virus that requires the presence of hepatitis B surface antigen (HBsAg) for its production. HDV utilizes the HBsAg protein as its external coat and the HBsAg protein helps the virus to enter hepatocytes. The epidemiology of HDV is therefore quite similar to that of hepatitis B virus. HDV is found worldwide, but Italy, Eastern Europe, the Middle East, the South Pacific, South America and Africa have the highest prevalence. In North America, less than 1% of HBsAg-positive patients have
evidence of HDV infection, whereas in parts of Italy 14-50% of HBsAg-positive patients are co-infected with HDV. In the United States and Canada, HDV infection is found almost exclusively among intravenous drug abusers and their sexual partners.

6.4.2 CLINICAL COURSE
Hepatitis D (HDV or delta) infection occurs either as a co-infection with hepatitis B or as a super-infection in a patient who is already a chronic HBV carrier. The acute presentation is that of acute hepatitis or a flare of hepatitis. Co-infection produces a more severe acute hepatitis than that caused by hepatitis B alone, but is usually self-limited and 2% of patients develop chronic HDV infection. Super-infection often results in severe chronic hepatitis that leads to hepatic cirrhosis and liver failure.

6.4.3 DIAGNOSIS
HDV infection should be considered if a patient has severe hepatitis B infection or a chronic hepatitis B carrier has a flare of hepatitis. The diagnosis of HDV infection requires the detection of HDV antigen, anti-HDV or HDV RNA. The HDV virus circulates in association with the delta antigen, but until more sensitive assays are developed, this antigen can be detected only during the early phases of infection. The serologic marker for acute and chronic hepatitis D infection is the antibody to delta antigen (anti-HDV). It often appears late in the course of acute HDV hepatitis.

6.4.4 TREATMENT
There is no proven treatment for acute co-infection of HDV and hepatitis B virus, or for super infection of HDV in the chronic hepatitis B carrier. Treatment is supportive. If fulminant liver failure develops, the patient should be considered for liver transplantation.

6.4.5 PREVENTION
Persons who are at risk for HBV infection are also at risk for HDV infection. Hepatitis B vaccination is protective against both hepatitis B and HDV infection because both viruses share the HBsAg. Hepatitis B carriers should be counseled about avoiding high risk behaviors in order to reduce the risk of HDV superinfection.

6.5 Hepatitis E Virus (HEV)

6.5.1 EPIDEMIOLOGY AND RISK FACTORS
Hepatitis E (HEV) is caused by a single-stranded RNA virus of 27-34 nm in size.
It shares many similarities with hepatitis A. Hepatitis E virus occurs primarily in developing countries where sanitation is inadequate. The fecal contamination of water supply has led to many community outbreaks in Asia, Africa, and Central America. HEV is the leading cause of acute viral hepatitis in young to middle-aged adults in many developing countries. The hepatitis tends to be mild and the overall case fatality ratio is similar to hepatitis A. However, it is associated with a high mortality rate (approaching 20%) in infected pregnant women in the third trimester. Rare cases seen in North America are almost exclusively travelers returning from endemic regions.

6.5.2 CLINICAL COURSE
The clinical presentation is similar to HAV infection. The incubation period is 10-50 days. HEV infection causes self-limited hepatitis and the clinical course tends to be subclinical or mild. Following the incubation, some patients develop jaundice lasting seven to 12 days. These patients also experience malaise, fever, nausea, vomiting, anorexia, abdomen discomfort, headaches and fatigue. Liver enzymes may be elevated for one to two months.

6.5.3 DIAGNOSIS
The diagnosis is based on a history of travel or possible exposure to contaminated water or food and the exclusion of HAV, HBV, or HCV infection. Serological assay anti-HEV and polymerase chain detection assay are available from reference laboratories only.

6.5.4 TREATMENT
Treatment of active disease is supportive. It is not clear whether acquisition of an acute infection will provide lifelong immunity. Chronic infection does not occur with HEV infection.

6.5.5 PREVENTION
There is no immunoprophylaxis for HEV. Travelers going to endemic countries are at risk of contracting hepatitis E. The immune globulin produced in developed countries is ineffective to prevent HEV infection because the preparation contains little or no anti-HEV antibody. It is not clear whether the immune globulin from developing countries would be more effective. Travelers to endemic countries should be advised not to consume any uncooked food or untreated water. Safe practices, such as hand-washing prior to eating and no swimming in polluted water, would decrease the risk of contracting HEV. These recommendations are particularly important to pregnant travelers because of the possibility of fulminant liver failure with HEV infection.
6.6 Epstein-Barr Virus (EBV) and Cytomegalovirus (CMV)

EBV and CMV are herpes viruses that can cause acute viral illness and hepatitis. EBV is a widely dispersed virus and 90-95% of the population is seropositive, most after subclinical infection. Symptomatic infections with infectious mononucleosis are characterized by fatigue, headache, pharyngitis, fever, posterior cervical chain adenopathy, splenomegaly and lymphocytosis. Mild hepatitis is a common presentation, but jaundice, hepatomegaly and severe hepatitis are rare presentations. CMV infection in an immunocompetent host may present with asymptomatic elevation of liver enzymes ALT and AST. More severe CMV hepatic involvement is limited to the immunocompromised hosts, such as AIDS patients and allograft organ recipients receiving anti-rejection therapy.

6.7 Other Viruses

New viruses are continually being discovered. Hepatitis GB was described in 1995, named after the initials of the surgeon who contracted this infection. It is similar to the flaviviruses and shares 25% homology with hepatitis C. The carrier rate in the general population is estimated at 2-5%. Thus far, there is little evidence that Hepatitis GB causes significant liver disease. The most
recent discoveries in the hepatitis field are the TT (transfusion transmitted) virus and the SEN virus. As of yet, no definitive evidence has been found linking them to acute or chronic hepatitis in immunocompetent hosts and therefore diagnostic testing is not warranted outside of a research setting.

6.8 Pathology of Acute Viral Hepatitis
Acute viral hepatitis causes inflammation of the liver parenchyma. There is evidence of hepatocellular degeneration (ballooning, acidophilic bodies, spotty necrosis), inflammation (lobular and portal mononuclear infiltrate) and hepatocyte regeneration (Figure 12). More severe cases demonstrate bridging necrosis between central veins and portal tracts (Figures 13 and 14). Because there is usually preservation of the reticular framework, the liver completely restores itself with hepatocyte regeneration. Liver biopsy is not generally helpful in distinguishing between the different types of acute hepatitis as the histology is quite similar.

6.9 Complications of Acute Viral Hepatitis
Most patients with viral hepatitis recover completely. The most important complication is the development of chronicity, which may follow hepatitis B, C and D. Chronic hepatitis represents continued disease activity beyond six months. This complicates acute hepatitis B infrequently in adults but occurs in acute hepatitis C in over 70% of cases. Chronic hepatitis can be suspected if there are persistent symptoms or persistent elevation of serum aminotransferase levels after six months of infection. Chronic hepatitis does not occur in hepatitis A or E.

Fulminant hepatitis is defined as the development of acute liver cell injury proceeding to liver failure and hepatic encephalopathy within eight weeks in a patient without any known previous liver disease. Clinically, the patient deteriorates with development of deep jaundice, confusion and drowsiness. The encephalopathy can progress into deep coma. Because of massive liver necrosis, there is a decrease of clotting factor synthesis, and hence the INR/PT becomes progressively abnormal. At this stage, mortality is greater than 50% unless a liver transplant can be performed. Death may occur from infection, increased intracranial pressure with cerebral edema, hypoglycemia, or renal failure. Massive hepatic necrosis leads to shrinkage of the liver and architectural collapse is seen histologically (Figures 15 and 16). Despite this, if regeneration occurs, histologic recovery is the rule. Usually a liver biopsy is not required; the procedure is associated with considerable bleeding risk unless done by the transjugular route.

Occasionally acute viral hepatitis exhibits a cholestatic phase, in which the patient becomes intensely pruritic and jaundiced. This occurs most commonly in hepatitis A. The enzyme pattern changes with a fall in the aminotransferase
FIGURE 13. Severe hepatitis. Marked inflammation has resulted in confluent hepatocellular necrosis, termed bridging necrosis (curved arrows), along the portal tracts (P) that surround a residual hepatic lobule (L). (HPS, original magnification x 92.5).

FIGURE 14. Severe hepatitis. High power shows numerous inflammatory cells within the sinusoids as well as foci of hepatocellular necrosis (arrows). Reactive changes, including binucleation and prominent nucleoli, are seen in the viable hepatocytes. (Gomori, original magnification x 370).
FIGURE 15. Submassive necrosis. Extensive hepatocellular necrosis is seen, leaving large areas of connective tissue around the central vein (V) and widening of the portal tracts (P), which have become confluent. Residual bile ducts (arrowheads) are seen in the portal tracts. (HPS, original magnification x 370).

FIGURE 16. Submassive necrosis. High power shows viable hepatocytes on the left, an island of degenerating cells centrally (arrowheads) and residual bile ducts (arrows) in the widened portal tract (HPS, original magnification x 185).
but with an increased alkaline phosphatase value. Biliary tract disease and drug toxicity should be ruled out. Resolution within a few weeks is the usual course.

Relapsing (biphasic) hepatitis can be seen from time to time. Clinically, these patients begin improving, only to have a recurrence of the signs and symptoms of their hepatitis. Resolution is almost always complete. This pattern is most characteristic of hepatitis A. In some cases of hepatitis B, the second phase is due to acute hepatitis D. Hepatitis C is characterized by repeated and wide fluctuations in liver aminotransferase values, but a biphasic clinical course is uncommon.

Immune complex disease can be seen with acute viral hepatitis. This is due to circulating immune complexes of viral proteins and antibody with complement activation. Extrahepatic manifestations in acute hepatitis A are uncommon but include arthritis, vasculitis, thrombocytopenia and aplastic anemia. In hepatitis B, about 5-10% of cases initially develop a serum-sickness-like syndrome characterized by skin rash, angioedema and arthritis. Other immunologic manifestations include pericarditis, aplastic anemia or neurologic abnormalities such as Guillain-Barre syndrome. In acute hepatitis C, 5-10% of cases are associated with a serum sickness reaction as well. The extraintestinal manifestations associated with chronic hepatitis will be discussed in the next chapter.

### TABLE 17. Overview of viral hepatitis

<table>
<thead>
<tr>
<th>Virus type</th>
<th>Transmission</th>
<th>Incubation (days)</th>
<th>Serologic diagnosis</th>
<th>Fulminant Hepatitis</th>
<th>Chronicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fecal/oral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAV RNA</td>
<td>Fecal/oral</td>
<td>20-35</td>
<td>HAV-IgM</td>
<td>0.1-2.0%</td>
<td>No</td>
</tr>
<tr>
<td>HEV RNA</td>
<td>Fecal/oral</td>
<td>10-50</td>
<td>Anti-HEV</td>
<td>1-2% 15-20% (pregnant)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Percutaneous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV DNA</td>
<td>Percutaneous Sexual Perinatal (Asia)</td>
<td>60-110</td>
<td>HBsAg</td>
<td>0.1-0.5%</td>
<td>Adults &lt; 5% Preschoolers 25% Neonates &gt; 90%</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>Percutaneous</td>
<td>35-70</td>
<td>Anti-HCV</td>
<td>&lt; 1%</td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>HDV RNA</td>
<td>Percutaneous Sexual</td>
<td>60-110</td>
<td>Anti-HDV</td>
<td></td>
<td>Usual in superinfection; rare in co-infection</td>
</tr>
</tbody>
</table>
6.10 Summary
Acute viral hepatitis is usually a self-limited disease and in most cases requires supportive care only. For the few patients who develop liver failure, liver transplantation will be required. Chronic infection can develop in patients with HBV, HCV and HDV infection. The important features of the different types of viral hepatitis are summarized in Tables 13 and 17.

7. CHRONIC VIRAL HEPATITIS / P.T. Grover and V. Bain
The term chronic hepatitis means active, ongoing inflammation of the liver persisting for more than six months, detectable by biochemical and histologic means. It does not imply an etiology. The biochemical hallmark of chronic hepatitis is an increase in the serum aminotransferases (AST and ALT) with minimal elevation of alkaline phosphatase. When the inflammation is severe and/or prolonged, hepatic dysfunction may become apparent with an increase in serum bilirubin, and prothrombin time INR, and a decrease in serum albumin. Typically, biochemical tests are used to identify and follow patients with chronic hepatitis, while liver biopsies serve to more precisely define the nature of the chronic hepatitis and provide useful information regarding the extent of damage and prognosis.

Histologically, chronic hepatitis is characterized by infiltration of the portal tracts by inflammatory cells. These cells are predominantly mononuclear, and include lymphocytes, monocytes and plasma cells. Liver biopsy is the gold standard for evaluation of the grade (degree of inflammation) and stage (degree of fibrosis/cirrhosis) of chronic viral hepatitis. The most commonly used system for grading and staging of hepatitis is the META VIR system established in France (Table 18). Histologic or inflammatory activity (A score) is determined by an algorithm incorporating the amount of portal and lobular inflammation.
FIGURE 17A. Mild chronic hepatitis. This portal tract contains a chronic inflammatory infiltrate that is confined to the portal triad and does not extend past the limiting plate (arrowheads).

FIGURE 17B. Moderately severe chronic hepatitis. Inflammatory cells are shown infiltrating and destroying the periportal hepatocytes (arrow) and disrupting the limiting plate (piecemeal necrosis) (arrowheads).

FIGURE 17C. METAVIR staging system. F1= Minimal fibrosis without bridging; F2/3= Bridging fibrosis in which fibrous tissue connects the joining triads; F4= Cirrhosis. The slide on the bottom right represents chronic hepatitis and a hepatoma.
and necrosis and ranges from A0-A3. The degree of fibrosis (F score) is evaluated separately to obtain the stage of disease and ranges from F0-F4 (Figure 17A-D). There are several other histologic scoring systems in use as well.

By far, the commonest cause of chronic hepatitis is a viral infection of the liver. Other causes include autoimmune hepatitis, drug-induced hepatitis, Wilson’s disease, $\alpha_1$-antitrypsin deficiency, and steatohepatitis. Primary biliary cirrhosis and primary sclerosing cholangitis may occasionally mimic chronic hepatitis, but are not usually classified as such. An approach to help determine the etiology of chronic hepatitis is summarized in Table 19.

7.1 Chronic Viral Hepatitis

7.1.1 GENERAL CONSIDERATIONS
Of the known viral infections of the liver, only hepatitis B (HBV), hepatitis C (HCV), and hepatitis D (HDV) can cause chronic liver disease. HBV and HCV
make up the vast majority of these cases. A careful assessment of risk factors is helpful in determining the cause of chronic hepatitis (Table 19). In most cases, selected laboratory tests will provide confirmation of the diagnosis.

The clinical presentation of chronic hepatitis can include no symptoms, unexplained fatigue, or complications of cirrhosis including ascites, variceal bleeding and encephalopathy.

General treatment considerations include counselling about reducing the risk of transmission, vaccination for hepatitis A and B if a patient is seronegative and vaccination for pneumococcus and influenza in the presence of cirrhosis. Patients are screened for complications of chronic liver disease and co-existing causes of liver dysfunction. Complete abstinence or minimal alcohol intake is advised because of the risk of accelerated progression of viral hepatitis.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key points in the history</th>
<th>Useful lab tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>Sexual history (homosexuality, use of prostitute services, promiscuity), family history, country of origin, IV drug use</td>
<td>HBsAg – if positive, measure HBeAg, HBeAb and HBV-DNA</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Blood transfusions (pre-1990), IV drug use (even once), tattoos, ear or body piercing, sexual promiscuity, HCV-positive partner, incarceration</td>
<td>anti-HCV, HCV RNA</td>
</tr>
<tr>
<td>Drug-induced hepatitis</td>
<td>Careful history of all drugs and herbs: common offenders include isoniazid, nitrofurantoin, NSAIDs, antibiotics</td>
<td>None</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Family history, neurologic or psychiatric symptoms in children or young adults</td>
<td>Serum ceruloplasmin 24-hr urinary copper Liver biopsy, hepatic copper quantitation</td>
</tr>
<tr>
<td>$\alpha_1$-antitrypsin deficiency</td>
<td>Family history of liver or lung disease (emphysema)</td>
<td>$\alpha_1$-antitrypsin levels and P-i-typing</td>
</tr>
<tr>
<td>Nonalcoholic Steatohepatitis</td>
<td>Obesity, recent weight gain, diabetes mellitus, corticosteroids intestinal by-pass surgery</td>
<td>Oral Glucose Tolerance Test, HBA1c, triglycerides, abdominal ultrasound</td>
</tr>
</tbody>
</table>
7.1.2 HEPATITIS B VIRUS

7.1.2.1 Evolution to chronic liver disease
A number of factors determine whether an individual will clear an acute HBV infection or progress to a chronic carrier state. Of these, the age at infection is most important. Carrier rates in vertically infected newborns are greater than 90% as compared to less than 5% in adult-acquired infection. The immunologic status of the host is also important, as immunocompromised individuals (e.g., HIV, renal failure, post-transplant) are more likely to become chronic carriers. The severity of the acute disease has also been correlated with

| TABLE 20. Comparison of HBeAg positive and HBeAg negative chronic hepatitis |
|-------------------------------|-----------------------------------|---------------------------------|
| **Etiology**                  | **HBeAg positive**                | **HBeAg negative**              |
| Epidemiology                  | Most common type in North America | Higher incidence in Asia, Europe and other Mediterranean countries |
| Natural history               | Lower rate of progression to cirrhosis | Higher rate of progression to cirrhosis |
| Treatment response            | Higher sustained response rate to IFN-α therapy | Lower sustained response rate to IFN-α therapy |
| Monitoring of treatment response | HBeAg seroconversion to anti-HBe positive | Normalization of liver enzymes and marked reduction in HBV DNA |

<table>
<thead>
<tr>
<th>TABLE 21. Seromarkers of HBV infection and vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Infection</strong> (eAg +ve)</td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>HBsAg</td>
</tr>
<tr>
<td>Anti-HBs</td>
</tr>
<tr>
<td>IgM anti-HBc</td>
</tr>
<tr>
<td>IgG anti-HBc</td>
</tr>
<tr>
<td>HBeAg</td>
</tr>
<tr>
<td>Anti-HBe</td>
</tr>
<tr>
<td>HBV DNA</td>
</tr>
</tbody>
</table>

7.1.2 HEPATITIS B VIRUS

7.1.2.1 Evolution to chronic liver disease
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outcome. In general, the milder the acute illness, the more likely that progression to chronic liver disease will occur. Presumably, individuals with mild acute disease are those with a suboptimal immunologic response to the virus, whereas patients with more severe acute disease are manifesting a prompt and effective immunologic attack on hepatocytes harbouring HBV.

7.1.2.2  Hepatitis B genotypes
Hepatitis B can be classified into at least seven genotypes with varied geographical distribution. Genotype A is the most common in North American-born caucasians and blacks. Genotypes B and C are more commonly associated with perinatally acquired infection and are found predominantly in people born outside of North America. Although different genotypes may play a role in altered natural history, disease activity and treatment efficacy, genotype testing is not generally available.

7.1.2.3  Hepatitis B mutations
HBV is prone to the development of mutations because of the lack of proof-reading function of reverse transcriptase. Pre-core variants are encountered most frequently. The pre-core region of HBV codes for HBeAg. A mutation in the pre-core region creates a premature stop codon so that HBeAg cannot be produced. Clinically this presents as chronic HBeAg negative hepatitis.
The patient has ongoing inflammation as suggested by elevated transaminases as well as viremia with detectable HBV DNA in the absence of HBeAg. The mutation is associated with genotypes B and D and is most commonly found in Mediterranean countries and in Asia.

A comparison between HBeAg positive and negative cases is presented in Table 20. Clinically, confusion may arise in distinguishing HBeAg negative chronic hepatitis from an inactive hepatitis B carrier. HBeAg negative chronic hepatitis is suggested by features of active inflammation (elevated ALT, biopsy demonstrating active inflammation) and the presence of viral replication (HBV-DNA > 10^5 copies/mL). Other causes of coincidental hepatitis must also be excluded at the time (e.g., drugs, HDV).

### 7.1.2.4 Presentation
The majority of patients with chronic hepatitis B are asymptomatic or have mild fatigue only. The patients might give a history of parenteral exposure to blood, unprotected sex, or a family history of hepatitis B infection. Incidentally discovered liver enzyme abnormalities frequently alert the physician to the possibility of underlying viral infection. Screening of family and sexual contacts of known cases will often discover additional cases.

Uncommonly, hepatitis B may present with extrahepatic manifestations due to polyarteritis nodosa or membranous glomerulonephritis. Both of these are secondary to circulating antigen-antibody immune complexes.
7.1.2.5 Diagnosis

Interpretation of hepatitis B serology was discussed in the acute hepatitis section (Section 6). A summary of the interpretation of seromarkers of hepatitis B is provided in Table 21. The definition of chronic hepatitis B requires positive HBsAg for greater than six months. As discussed above, it can be divided into HBeAg positive and HBeAg negative disease. Viral markers are helpful to determine the phase of disease (Figure 18). HBeAg and HBV-DNA in serum confirm active HBV replication. When HBV-DNA is > 10^5 copies/mL, there is a high viral load, which indicates a high degree of infectivity (all physiologic fluids are potentially infectious). Although a negative HBV-DNA indicates very low or absent infectivity, sensitive polymerase chain reaction (PCR) technique will still detect virus. If HBeAg is negative, there is usually lower infectivity although, as we have discussed, this may represent a pre-core mutant. Core antibody serology is not usually required in the routine assessment of chronic hepatitis B (Table 22).

7.1.2.6 Phases and Natural History

The phases of chronic HBV infection have been well defined (Figure 18). The first six months of the illness represent the acute hepatitis phase of the infection. This acute phase is not often seen in chronically infected patients who have contracted the virus at birth or in early childhood. Chronic hepatitis has three phases, termed the replicative, inflammatory and inactive phases. As the replicative phase is most often observed after perinatal viral transmission, it is uncommon in Western countries. During the replicative phase, HBeAg is positive as is HBV-DNA indicating high levels of viral replication. Despite this, the aminotransferases are normal or near normal and the liver biopsy is relatively inactive. For unknown reasons, patients may then enter the inflammatory phase in which their immune system now recognizes those hepatocytes harboring virus and begins to attack them. Accordingly, the aminotransferases become elevated and the biopsy shows chronic hepatitis, often of a severe degree. The level of viral replication as measured by the HBV-DNA will decline. If the patient has successfully cleared (a relative term representing at least a 2-3 log drop in the HBV DNA) viral replication, they will enter an inactive phase characterized by normalization of the aminotransferases and relative inactivity on the liver biopsy. HBeAg will be cleared and anti-HBe will form (seroconversion). Seroconversion is associated with histologic and biochemical remission in most patients. Spontaneous seroconversion occurs in 10-15% of patients/year. This number is reduced in perinatally acquired infection. HBeAg negative patients (i.e., pre-core mutants) do not meet criteria for eAg seroconversion as they are eAg negative at baseline.

The natural history of hepatitis B is outlined in Figure 19. Patients are at variable risk of developing cirrhosis and hepatocellular carcinoma (HCC):
TABLE 22. Laboratory assessment prior to therapy

<table>
<thead>
<tr>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg - if positive, measure</td>
<td>anti-HCV</td>
</tr>
<tr>
<td>HBeAg and anti-HBe</td>
<td>HCV RNA (qualitative +/- quantitative)*</td>
</tr>
<tr>
<td>Measure HBV DNA if ALT elevated</td>
<td>HCV genotyping</td>
</tr>
<tr>
<td>ALT, ALP, bilirubin, albumin, PT INR</td>
<td>ALT, ALP, bilirubin, albumin, PT INR</td>
</tr>
<tr>
<td>CBC, HIV, anti-HCV</td>
<td>HBsAg, HIV</td>
</tr>
<tr>
<td>Liver biopsy highly recommended but not mandatory</td>
<td>CBC, glucose, TSH, ANA, smooth muscle antibody (SMA), quantitative immunoglobulins, creatinine, B-HCG Abdominal Ultrasound ECG (if age &gt; 50, cardiac disease history) Liver biopsy recommended but not mandatory</td>
</tr>
</tbody>
</table>

*To reduce testing costs, serum may be saved for HCV-RNA quantitation and only used as required (see text).

Adapted from the 2004 Canadian Consensus Conference Guidelines on the Management of Chronic Hepatitis

TABLE 23. Risk factors for the development of HCC with chronic HBV

<table>
<thead>
<tr>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Family history of HCC</td>
</tr>
<tr>
<td>Age &gt; 45 years</td>
</tr>
<tr>
<td>Hepatitis C co-infection</td>
</tr>
</tbody>
</table>

*Risk in cirrhotic and non-cirrhotic patients

TABLE 24. Choosing Lamivudine versus IFN for treatment of Hepatitis B

<table>
<thead>
<tr>
<th>Favoring Lamivudine</th>
<th>Favoring IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Needle phobia</td>
<td>• Ideal characteristics for IFN:</td>
</tr>
<tr>
<td>• HIV co-infection</td>
<td>• AST &gt; 100</td>
</tr>
<tr>
<td>• Other immunosuppression (e.g., transplantation)</td>
<td>• Active liver biopsy</td>
</tr>
<tr>
<td>• Patients with depression, low wbc, low platelets, autoimmune disease</td>
<td>• Low serum HBV-DNA</td>
</tr>
<tr>
<td>• Decompensated cirrhosis</td>
<td>• Recent infection</td>
</tr>
<tr>
<td>• Vertical transmission</td>
<td></td>
</tr>
<tr>
<td>• Cost concerns</td>
<td></td>
</tr>
</tbody>
</table>
a) Cirrhosis - The severity and duration of the inflammatory phase is one of the main factors that determine whether a patient will develop cirrhosis. The progression of chronic hepatitis to cirrhosis occurs in 20 – 30% of all chronic hepatitis B patients. Progression is more likely in patients with replicative HBeAg negative pre-core mutant than for HBeAg positive chronic hepatitis.

b) Hepatocellular cancer - Although patients with cirrhosis are at the highest risk of developing hepatocellular cancer, non-cirrhotic HBsAg carriers patients are also at risk (see Table 23 for other high risk predictors). The risk of hepatocellular carcinoma in chronically infected patients is estimated to be 100 times higher than that for non-carriers. The five year rate of progression of compensated cirrhosis to HCC is estimated at 6-15%. Surveillance for hepatocellular carcinoma has been recommended in chronic carriers by performing a serum α-fetoprotein and an abdominal ultrasound every six to 12 months. As suggested by the 2004 Canadian Consensus Guidelines, some low risk groups (inactive disease, non-cirrhotic) may not require surveillance. Although surveillance is widely practiced, it has not been shown to reduce mortality. Data regarding cost-benefit of biannual surveillance has been variable depending on patient risk and stage of disease. Further studies are needed to confirm or refute current practices.

7.1.2.7 Treatment Indications

Treatment of chronic hepatitis B is indicated when both of two conditions are met:

a) Hepatic inflammation as evidenced by elevated transaminases and/or active inflammation on liver biopsy

b) Active viral replication as evidenced by HBeAg positive or HBV DNA > 10^5 copies/mL (or perhaps a lower value but this is not yet well defined). HBV DNA may be increased alone in the case of a pre-core mutant.

As stated in the 2004 Canadian Consensus Guidelines, liver biopsy is highly recommended in patients with evidence of active disease (elevated transaminases). If a patient does not meet criteria for treatment at the time of assessment (normal ALT or HBV DNA negative), their liver enzymes should be checked every six to 12 months. If elevated liver enzymes are detected, HBV DNA should be checked to confirm reactivation.

A complete virologic response is defined as the sustained loss of HBsAg. This occurs in a minority of patients therefore, other endpoints are used to define treatment success (partial virologic response). These are:

a) HBeAg seroconversion (HBeAg positive to anti-HBe positive)

b) Marked reduction of HBV DNA (< 10^5 copies/mL)
Seroconversion correlates with improved long-term outcome including a reduced risk of liver decompensation and development of HCC. The durability of seroconversion may be lower in perinatally acquired infection. In the case of HBeAg negative patients, successful response to treatment is measured by a combination of biochemical and virologic factors:

a) Normalization of AST and ALT

b) HBV DNA < $10^5$ copies/mL

7.1.2.8 Treatment Medications

Both interferon-α and lamivudine are available to treat this chronic infection. The advantages of interferon-α are that it has a finite treatment duration (16 weeks in HBeAg positive patients, 12 months in HBeAg negative patients), as well as a durable treatment response in HBeAg positive patients. However, it costs more, has more side effects than lamivudine and can only be administered parenterally. Lamivudine is a nucleoside analogue with very potent antiviral effects against HBV. It is administered orally, and has less adverse effects than interferon-α. It can even be used in patients with decompensated cirrhosis. The optimal treatment duration is not known however, and many patients will have recurrence of HBV infection when lamivudine is stopped. Long term therapy is limited by the development of drug resistant mutants (20% at one year and up to 50% at three years). There is also the potential for a flare of hepatitis after lamivudine withdrawal. At this time there is no proven benefit to combination therapy with lamivudine and interferon-α but additional studies are ongoing.

Adefovir is the most recent development. It is a phosphonate nucleotide analog of AMP that has anti-viral activity against HBV. In short term trials (48 weeks), the drug has been well tolerated without the development of drug-resistant mutants. Concerns about nephrotoxicity have been raised with higher dose therapy. The likelihood of HBeAg seroconversion is similar with the three medications ($α$-IFN – 15-30%; lamivudine – 15-20%; adefovir – 12%). The clinical factors useful in choosing between lamivudine and interferon-α are outlined in Table 24.

Factors predicting response to therapy are listed in Table 25. Asians often have a poor response, likely because most have perinatally acquired infections with normal or minimally elevated transaminases.

7.1.2.9 Prevention

Active immunization is important to prevent transmission of HBV infection from a chronic carrier to family and monogamous sexual contacts. Condoms should be used to prevent infection in those with multiple sexual partners. The safety of the vaccine is well established. Universal vaccination is recommended...
in Canada either neonatally or as a pre-adolescent. The eventual goal is eradication of hepatitis B with successful vaccination. On a global scale, there have been many barriers to this goal but its realisation would have profoundly positive effects in many countries. Information regarding hepatitis B prophylaxis recommendations are found in the acute hepatitis chapter.

### 7.1.3 HEPATITIS C VIRUS

Chronic hepatitis C has become the most common cause of chronic hepatitis in most areas. The identified cases may represent only the tip of the iceberg, with most cases still undiagnosed. Many cases are identified after investigation of raised liver enzymes in asymptomatic individuals or after screening of blood donors. Other patients present to physicians with fatigue, malaise, or less commonly, manifestations of advanced liver disease.

Extrahepatic manifestations of chronic hepatitis C include cryoglobulinemia, lymphoma, porphyria cutanea tarda, lichen planus, keratoconjunctivitis sicca, thyroiditis and membranoproliferative glomerulonephritis.

Risk of diabetes is also significantly increased in individuals with chronic hepatitis C. Treatment of HCV may result in improvement of selected extrahepatic manifestations.

#### 7.1.3.1 HCV genotype

As a result of RNA mutations, HCV has evolved different genotypes over time. Thus far, six HCV genotypes and 50 subtypes have been identified.
Genotype 1 is the most common in North America accounting for approximately 75% of cases. Genotype 2 and 3 each account for 10%. Although genotype does not affect the severity of HCV infection or its progression, it has significant therapeutic implications.

7.1.3.2 Epidemiology
Although HCV infection can be transmitted by the same routes as HBV infection, the majority of cases are related to intravenous drug abuse (60-70%). Ten percent of patients with chronic HCV infection will have had a previous blood transfusion. Patients receiving blood products prior to 1990 are highest risk. With current screening of blood donors, the risk of transmission of HCV with a blood transfusion is only one in 3 million units transfused. In the remaining patients a source of infection is often difficult to find. Non-parenteral transmission through sexual or intimate contact and maternal-infant exposure occur much less often than is the case for HBV infection. Other factors associated with a low rate of viral transmission are needlestick injuries, and intranasal cocaine use.

7.1.3.3 Natural History
The natural history of HCV infection has been better defined with the availability of anti-HCV serologic testing (Figure 20). Widespread application of this test has revealed that 60-85% of patients with acute HCV infection will
remain chronically infected. Of the patients with chronic hepatitis, 20% will be cirrhotic by 25 years. Thereafter, an additional 1% per year develops cirrhosis. Accelerated progression is seen in patients with heavy alcohol use, obesity and co-infection with HIV or HBV. More recent studies looking at younger (< 40 years) patients, have suggested significantly lower (2-8%) rates of cirrhosis at 20 years.

Chronic hepatitis C is a risk factor for the development of hepatocellular carcinoma. The increased risk is mostly limited to patients with cirrhosis and is estimated at 1-4% per year after the development of cirrhosis. Risk factors

**Figure 21.** Monitoring treatment response in genotype 1 HCV patients on PEG-.
for the development of HCC in the presence of HCV are listed in Table 26. The current screening practice is abdominal ultrasound and serum \( \text{AFP} \) every six to 12 months.

### 7.1.3.4 Treatment

Before discussing the treatment of hepatitis C, it is necessary to define two variables:

a) Sustained virologic response (SVR) – This is defined as a negative HCV RNA at 24 weeks after discontinuation of anti-viral treatment. In most cases, this is believed to represent cure with a subsequent relapse rates of less than 2%.

b) Early virologic response (EVR) – This refers to a 2 log decrease or undetectable HCV RNA at 12 weeks of treatment. Failure to achieve EVR is a surrogate marker for lack of SVR and justifies treatment termination because less than 2% of patients will attain a sustained response if therapy is continued. If the HCV RNA has dropped by 2 logs at 12 weeks, but
remains detectable (20% of patients), it should be rechecked at 24 weeks. If it remains detectable, treatment should be terminated at that point (Figure 21). It is not necessary to test for EVR in Genotype 2 and 3 patients because of the high rate of treatment success. The monitoring of these patients on treatment is therefore much simplified.

The most important predictor of response to antiviral treatment is HCV genotype. The second most important predictor is viral load. Better results are seen in patients with viral load < 800,000 IU/mL. Predictors of a sustained virological response are listed in Table 27.

Treatment of chronic hepatitis C should be considered in all patients without contraindications. The decision to initiate treatment is complex and needs to be individualized on the basis of virologic features as well as patient factors that influence the risk for disease progression and likelihood of treatment response. Patient motivation is essential for treatment adherence. In general, hepatic inflammation (elevated transaminases and active inflammation on liver biopsy), as well as virologic evidence of infection (positive HCV RNA), are both required for treatment initiation. Patients with normal liver enzymes, cytopenias, cirrhosis and HIV-HCV co-infection may also be considered for treatment by experienced practitioners.

Prior to treatment, HCV genotype is determined. Serum is saved for HCV RNA quantitation in genotype 1 patients in case it is required at week 12 to see if there is an EVR. The 2004 Canadian Consensus Conference Guidelines

<table>
<thead>
<tr>
<th>PEG IFN α (2a,2b)</th>
<th>Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu-like symptoms (headache, nausea, fatigue, fever)</td>
<td>CBC weak</td>
</tr>
<tr>
<td>Thrombocytopenia, Leukopenia</td>
<td>1,2,3,4,6,8,10,then q monthly</td>
</tr>
<tr>
<td>Weight loss</td>
<td>TSH q 3 monthly</td>
</tr>
<tr>
<td>Depression, anxiety, insomnia</td>
<td>Weight 3 monthly</td>
</tr>
<tr>
<td>Worsening of autoimmune diseases (thyroid, psoriasis, autoimmune hepatitis)</td>
<td>ALT, bil, glucose, U/A q monthly</td>
</tr>
<tr>
<td>Reversible alopecia</td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td></td>
</tr>
</tbody>
</table>

| | ・Flu-like symptoms (headache, nausea, fatigue, fever) | ・CBC weak |
| | ・Thrombocytopenia, Leukopenia | ・1,2,3,4,6,8,10,then q monthly |
| | ・Weight loss | ・TSH q 3 monthly |
| | ・Depression, anxiety, insomnia | ・Weight 3 monthly |
| | ・Worsening of autoimmune diseases (thyroid, psoriasis, autoimmune hepatitis) | ・ALT, bil, glucose, U/A q monthly |
| | ・Reversible alopecia | |
| | ・Retinopathy | |
state that as the most sensitive measure of disease severity, liver biopsy is recommended but not mandatory prior to treatment. Patients with genotype 2 and 3 infection may not need liver biopsy because of the high likelihood of cure.

The therapeutic agents available to treat chronic hepatitis C have evolved in the last 15 years. The improvement in SVR’s with developments in therapy is outlined in Figure 22. Current therapy is a combination of pegylated interferon and ribavirin, an oral nucleoside analog. There are two pegylated α-IFN preparations available in Canada (PEGASYS (α-2a) and PEGINTRON (α-2b)). A head-to-head trial comparing the efficacy of these two agents is underway. Pegylation of IFN offers the advantages of reduced immunogenicity and most importantly, enhanced pharmacokinetics with a much longer serum half-life. As compared to Peg α-2a, Peg α-2b is smaller, has a shorter half-life, wider volume of distribution (weight based dosing) and is partially renally excreted. Peg α-2a is completely excreted through the biliary system. The combination of PEG-IFN and ribavirin has achieved an SVR of 42-52% in genotype 1 patients and 78-82% in genotype 2 and 3 patients. Genotype 1 patients are treated for 48 weeks and genotype 2 and 3 patients for 24 weeks. Contraindications to treatment are included in Table 28 and adverse effects and monitoring of therapy in Table 29. Medication doses are included in Table 30.

A vaccine for HCV has not been developed, but is an active area of research. There are currently insufficient data to advocate the use of immune serum globulin for the prevention of HCV infection. Condoms should be used during

![Figure 22: Progress in Treatment of HCV.](image-url)

*Note: These are overall SVRs and it is important to consider genotype specific results (see text)*
the acute phase of the illness and indefinitely for patients who are immuno-
compromised. Couples in whom one is chronically infected with hepatitis C
must make their own decision with regards to condom use after being advised
of the risks. The risk of spread to regular sexual partners is 2-5%. In clinical
practice, most couples choose not to use condoms. Vertical transmission from a
normal mother to her newborn is rare, however, the risk of HCV vertical trans-
mission is much higher if the mother is co-infected with HIV (15%).

7.1.4 HEPATITIS D VIRUS
Chronic hepatitis D usually results from HDV super-infection of an HBV
carrier. Less commonly, acute HBV/HDV co-infection leads to chronic infec-
tion. Either way, chronic hepatitis D is usually aggressive and severe with
rapid progression to cirrhosis. Fortunately, HDV is rare in North America.

The diagnosis is made by testing for anti-HDV in the serum of HBV
 carriers with risk factors for HDV infection. HDV antigen and HDV-RNA
in serum or liver can also be measured, but only in a limited number of
laboratories. In North America this virus is most often transmitted by intravenous
drug abuse and possibly also through the sexual route. In Mediterranean coun-
tries intra-familial transmission has been reported. Treatment with interferon for
HDV infection has been disappointing. Similarly, the use of lamivudine either
alone or in combination with interferon has also been ineffective although expe-
rience is limited. Because of the dependency of HDV on HBV, the prevention of
HBV infection with vaccination can prevent HDV infection.

| TABLE 30. Treatment for Hepatitis C |
|-------------------------------------|------------------|------------------|------------------|
| Treatment Duration | PEG-INTERFERON α-2b | PEG-INTERFERON α-2a | RIBAVIRIN |
| Genotype 1 SVR – 42%-52% | 48 weeks | 1.5 mg/kg/week | 180 mg sc/week | (α-2a) |
| | | | | 1,000 mg/d (< 75 kg) |
| | | | | 1,200 mg/d (> 75 kg) |
| | | | (α-2b) |
| | | | ≤ 64 kg – 800 mg/d |
| | | | 64-84 kg – 1,000 mg/d |
| | | | ≥ 85 kg – 1,200 mg/d |
| Genotype 2 & 3 SVR – 78%-82% | 24 weeks | 1.5 mg/kg/week | 180 mg sc/week | 800 mg/d |
7.2 Drug-Induced Chronic Hepatitis
Many drugs can cause chronic hepatitis. Whether to discontinue an implicated drug depends to some extent on whether the drug is merely causing mild persistent enzyme abnormalities or hepatic dysfunction with severe histologic abnormalities. In severe cases fibrosis, cirrhosis and death from liver failure or complications of portal hypertension can result. Examples of drugs capable of causing chronic hepatitis that may progress to liver failure and portal hypertension are oxyphenisatin, isoniazid, nitrofurantoin, alpha methyldopa, and dantrolene. If a drug is essential to the health of the patient however, and there are no unrelated agents that can be substituted, it is reasonable to continue therapy under close clinical supervision providing the enzyme abnormalities are mild and not associated with symptoms or functional derangements (i.e., serum bilirubin, albumin and PT INR remain normal). Liver biopsy may be helpful in defining the severity of liver injury.

7.3 Autoimmune Hepatitis
Autoimmune hepatitis is an immunologically mediated disorder of the liver that predominantly affects females with a personal or family history of autoimmune disease. The etiology is unknown. The onset may be insidious or acute. The hepatic presentation can be that of sudden hepatic failure, chronic hepatitis or inactive cirrhosis. The most common complaints include fatigue, amenorrhea, complaints associated with an accompanying rheumatological disorder such as arthritis, or those associated with thyroid disease. Physical findings include jaundice (in severe cases), spider nevi, palmar erythema and
hepatosplenomegaly. Laboratory investigations reveal reduced serum albumin, hypergammaglobulinemia with pronounced elevation of IgG levels, positive antinuclear factor (ANA) and smooth-muscle antibody. This is the classic or Type 1 autoimmune hepatitis. Type 2 autoimmune hepatitis lacks smooth muscle antibody and is associated with antibodies to liver/kidney microsome (anti-LKM hepatitis). Liver biopsy is essential to establish the diagnosis and severity of both types of autoimmune hepatitis as well as to exclude other liver disease. Cirrhosis is present in over 50% of autoimmune hepatitis on initial biopsy.

Treatment is initiated with high-dose corticosteroids (prednisone 40-60 mg/day) for four to six weeks. The dose is then tapered to a maintenance level (e.g., 5-10 mg/day) just sufficient to keep the liver enzymes within normal range. Often azathioprine is used for its steroid-sparing effect, either by starting it with the steroids or by adding it later. Following discontinuation of treatment, most patients will relapse, requiring re-initiation of therapy. The goal of therapy is to maintain disease control with the smallest amount of drug. Untreated autoimmune hepatitis progresses rapidly to cirrhosis (three to five years). Although corticosteroids may not prevent cirrhosis, they are clearly lifesaving in this otherwise fatal condition. With careful titration of their medication, most patients remain in stable condition for years. In the remaining minority, liver transplantation is highly successful.

7.4 Alcoholic Hepatitis
This condition is usually readily diagnosed on clinical grounds (see Section 8). These features are contrasted with those of viral hepatitis in Table 31. Alcoholic hepatitis can be severe and fatal.

8. ALCOHOLIC LIVER DISEASE / F. Wong

Liver disease is the fourth commonest cause of death in adults ages 20 to 70 years in Canada. Alcohol is still one of the commoner causes of chronic liver disease in this country. Not all those who abuse alcohol develop liver damage. The incidence of cirrhosis amongst alcoholics is approximately 10 – 20%. The mechanism for the predisposition of certain people to develop cirrhosis is still unknown. The amount of alcohol ingested has been shown in epidemiological studies to be the most important factor in determining the development of cirrhosis. Males drinking in excess of 60 g and females in excess of 40 g of alcohol per day for 10 years are at a high risk of developing cirrhosis. The alcohol content rather than the type of beverage is important and binge drinking is less injurious to the liver than continued daily drinking. Women are more susceptible to liver damage than men. They are likely to develop cirrhosis at an earlier age,
present at a later stage and have more severe liver disease with more complications. Genetics may play a role in the development of alcoholic liver disease. Patterns of alcohol drinking behaviour are inherited. Alcohol is metabolized to acetaldehyde by alcohol dehydrogenase, and then to acetate by acetaldehyde dehydrogenase. Genetic pleomorphism of these enzyme systems can lead to different rates of alcohol elimination, and contributes to the individual’s susceptibility to alcohol damage. Some studies have reported an increased frequency of the gene that encodes for alcohol dehydrogenase in patients with alcoholic liver disease, leading to increased production of acetaldehyde. Alcoholics with decreased acetaldehyde dehydrogenase activity also develop alcoholic liver disease at a lower cumulative intake of alcohol than others. Alcohol has a direct hepatotoxic effect and does not require pre-existing malnutrition, but malnutrition may play a permissive role in producing alcohol hepatotoxicity. There is a threshold of alcohol toxicity beyond which no dietary supplements can offer protection. Obesity may also be an independent risk factor for the development of alcoholic liver disease. Finally, hepatitis C infection appears to play a role in the development of advanced alcoholic liver disease. Patients with alcoholic liver disease and hepatitis C infection tend to develop their disease at a younger age, have more severe histological features and decreased survival. In addition, the presence of hepatitis C is a major risk factor for the development of hepatocellular carcinoma in patients with alcoholic cirrhosis.
The spectrum of liver disease covers the relatively benign steatosis to the potentially fatal alcoholic hepatitis and cirrhosis (Figure 23).

**8.1 Alcoholic Fatty Liver**

Fatty liver is the most frequent hepatic abnormality found in alcoholics. It is a toxic manifestation of ethanol ingestion, appearing within three to seven days of excess alcohol intake. Metabolic changes associated with ethanol ingestion result in increased triglyceride synthesis, decreased lipid oxidation and impaired secretion by the liver. This results in the accumulation of triglyceride in the hepatocytes, mainly in the terminal hepatic venular zone. In more severe cases, the fatty change may be diffuse. The fat may be macrovesicular (large droplets) or microvesicular (small droplets), which represents more active lipid synthesis by the hepatocytes. Fatty liver may occur alone or be part of the picture of alcoholic hepatitis or cirrhosis.

Clinically, the patient is usually asymptomatic and examination reveals firm smooth hepatomegaly. Occasionally the fatty liver may be so severe that the patient is anorexic, nauseated and has right upper quadrant pain or discomfort. This usually follows a prolonged heavy alcoholic binge. Liver function tests are frequently normal, although the GGT is invariably elevated whilst the aminotransferases and alkaline phosphatase may be slightly increased. The patient is never jaundiced and hepatic synthetic function (albumin and prothrombin time) is preserved. A fatty liver is usually detected by ultrasound. Liver biopsy is required to make a definitive diagnosis. When fatty liver is not associated with alcoholic hepatitis, the prognosis is excellent. Complete abstinence from alcohol and a nutritious diet will lead to disappearance of the fat over four to six weeks.

**8.2 Alcoholic Hepatitis**

Alcoholic hepatitis may occur separately or in combination with cirrhosis. There are all grades of severity. It is a condition characterized by liver cell necrosis and inflammatory reaction. Histologically, hepatocytes are swollen due to an increase in intracellular water secondary to increase in cytosolic proteins. Steatosis, often of the macrovesicular type, is present. Alcoholic hyaline or Mallory bodies are purplish red intra-cytoplasmic inclusions consisting of clumped intermediate microfilaments (Figure 24). Polymorphs are seen surrounding Mallory body-containing cells and also within damaged hepatocytes. Collagen deposition is usually present. It is maximal in the zone 3 and extends in a perisinusoidal pattern to enclose hepatocytes, giving it a “chicken wiring” effect. Changes in the portal triad are inconspicuous. Marked portal inflammation suggests an associated viral hepatitis such as hepatitis C, whereas fibrosis suggests complicating
chronic hepatitis. When the acute inflammation settles, a varying degree of fibrosis is seen which may eventually lead to cirrhosis.

Clinically, mild cases of alcoholic hepatitis are only recognized on liver biopsy in patients who present with a history of alcohol abuse and abnormal liver function tests. In the moderately severe case, the patient is usually malnourished and presents with a two to three week prodrome of fatigue, anorexia, nausea and weight loss. Clinical signs include a fever of < 40°C, jaundice and tender hepatomegaly. In the most severe case, which usually follows a period of heavy drinking without eating, the patient is gravely ill with fever, marked jaundice, ascites, evidence of a hyperdynamic circulation, such as systemic hypotension, and tachycardia. Florid palmer erythema and spider nevi are present with or without gynecomastia. Hepatic decompensation can be precipitated by vomiting, diarrhea or intercurrent infection leading to encephalopathy. Hypoglycemia occurs often and can precipitate coma. Gastrointestinal bleeding is common, due to the combination of a bleeding tendency and portal hypertension. Signs of malnutrition and vitamin deficiencies are common. Acetaminophen is a hepatotoxin when taken in large quantity. Alcohol increases the patient’s susceptibility to liver damage by acetaminophen due to induction of metabolizing enzymes and smaller doses of acetaminophen in an alcoholic may precipitate liver failure.
Laboratory abnormalities include elevations of the aminotransferases, bilirubin, alkaline phosphatase and GGT. The aminotransferase levels rarely exceed 300 IU/L, except in association with acetaminophen ingestion, with the AST/ALT ratio > 2. Hyperbilirubinemia can be quite marked, with levels reaching 300 to 500 µmol/L, and is a reflection of the severity of the illness. The increase in GGT is proportionally greater than that of alkaline phosphatase. There is also leukocytosis of up to 20 to 25 X 10^9/L, and prolongation of the prothrombin time, which does not respond to vitamin K. The serum albumin falls. Serum IgA is markedly increased with IgG and IgM raised to a lesser extent.

Patients with acute alcoholic hepatitis often deteriorate during the first few weeks in hospital, with a mortality rate of 20-50%. Bad prognostic indicators include spontaneous encephalopathy, markedly prolonged prothrombin time unresponsive to vitamin K and severe hyperbilirubinemia of greater than 350 µmol/L. The condition may take one to six months to resolve even with complete abstinence. Alcoholic hepatitis progresses to cirrhosis in 40% of clinical episodes.

8.3 Alcoholic Cirrhosis
Established cirrhosis is usually a disease of middle age after the patient has had many years of drinking. Although there may be a history of alcoholic hepatitis, cirrhosis can develop in apparently well nourished, asymptomatic patients. Occasionally, the patient may present with end-stage liver disease with malnutrition, ascites, encephalopathy and a bleeding tendency. A history of alcohol abuse usually points to the etiology. Clinically, the patient is wasted. There may be bilateral parotid enlargement, palmer erythema, Dupuytren’s contractures and multiple spider nevi. Males develop gynecomastia and small testes. Hepatomegaly is often present, affecting predominantly the left lobe due to marked hypertrophy and there are signs of portal hypertension including splenomegaly, ascites and distended abdominal wall veins. At the late stage, the liver may become shrunken and impalpable. There may be signs of alcohol damage in other organ systems such as peripheral neuropathy and memory loss from cerebral atrophy. Alcoholic cirrhosis is also associated with several renal problems. These include IgA nephropathy, renal tubular acidosis and the development of hepatorenal syndrome. There is an association between viral hepatitis B and C and alcoholic cirrhosis.

Histologically, the cirrhosis is micronodular. The degree of steatosis is variable and alcoholic hepatitis may or may not be present. Pericellular fibrosis around hepatocytes is widespread. Portal fibrosis contributes to the development of portal hypertension. There may be increased parenchymal iron deposition. When marked, genetic hemochromatosis has to be excluded. With continued cell necrosis and regeneration, the cirrhosis may progress to a macronodular pattern.
Biochemical abnormalities include a low serum albumin, elevated bilirubin and aminotransferases. AST and ALT levels rarely exceed 300 IU/L and the AST/ALT ratio usually exceeds 2. With recent alcohol ingestion, GGT is disproportionately raised, and is a widely used screening test for alcohol abuse. With severe disease, the prothrombin time may be prolonged. Portal hypertension results in hypersplenism leading to thrombocytopenia, anemia and leukopenia. Other non-specific serum changes in acute and chronic alcoholics include elevations in uric acid, lactate and triglyceride, as well as reductions in glucose, potassium, phosphate and magnesium.

The prognosis of alcoholic cirrhosis depends on whether the patient can abstain from alcohol; this in turn is related to family support, financial resources and socio-economic state. The presence of hepatitis also influences prognosis. Patients who abstain have a five-year survival rate of 60 to 70%, which falls to 40% in those who continue to drink. Women have a shorter survival than men. Bad prognostic indicators include low serum albumin, increased prothrombin time, low hemoglobin, encephalopathy, persistent jaundice and azotemia. Zone 3 fibrosis and perivenular sclerosis are also unfavourable features. Complete abstinence may not improve prognosis when portal hypertension is severe, although at the earlier stage of cirrhosis, the portal pressure may actually fall with abstinence. Hepatocellular carcinoma occurs in 10% of stable cirrhotics and the incidence is higher in patients who also have hepatitis C infection. This usually develops after a period of abstinence and macronodular cirrhosis is present. Treatment strategies can be instituted if detected early (see below), therefore long-term follow-up and periodic screening is advisable.

8.4 Management
Early recognition of alcoholism is important. Physicians should have a high index of suspicion when a patient presents with anorexia, nausea, diarrhea, right upper quadrant tenderness and an elevated GGT. The most important therapeutic measure is total abstinence from alcohol. Support groups and regular follow-up can reinforce the need for abstinence. Withdrawal symptoms should be treated with a short-acting benzodiazepine. A nutritious, well-balanced diet with vitamin supplements should be instituted. Alcoholic fatty liver responds to alcohol withdrawal and a nutritious diet. Patients with severe alcoholic hepatitis should be admitted to hospital and complications of liver failure treated appropriately. Specific treatment for alcoholic hepatitis includes the use of corticosteroid (40 mg/day for four weeks and then taper). Recent meta-analyses of 13 randomized controlled trials showed a significant benefit of steroids for patients with severe alcoholic hepatitis complicated by encephalopathy. There is reduction of the short-term mortality of about 50%
in patients with severe alcoholic hepatitis. A discriminant function of > 32 is a predictor of poor prognosis and favourable response to corticosteroid therapy. Discriminant function = 4.6 X (prothrombin time - control prothrombin time) in seconds + serum bilirubin in µmol/L ÷ 17. Propylthiouracil has been used to dampen the hepatic hypermetabolic state in alcoholic hepatitis. In one long-term randomized controlled trial, there was a significantly reduced two-year mortality rate in patients who continued to drink moderately. Those who were abstinent from alcohol did not derive any benefits. However, other investigators have not been able to reproduce these positive results. Therefore, current evidence cannot support the routine of propylthiouracil in acute alcoholic hepatitis. Testosterone and anabolic androgenic steroids have been tried with conflicting results. Intravenous amino acid supplements have been given to the severely protein malnourished with varying degrees of success. Oral supplementation is the preferred route if the patient can tolerate a diet. Infliximab, an anti-tumor necrosis factor alpha (TNF-α) antibody, theoretically could dampen the inflammatory process in alcoholic hepatitis. Two recent trials showed that the patients with alcoholic hepatitis treated with infliximab had more infectious complications. Insulin and glucagons are both hepatotrophic agents. Their use in alcoholic hepatitis could theoretically improve hepatic regeneration. However, patients treated with both agents have had complications and even deaths from hypoglycemia. Therefore, these agents should not be used except in the setting of a clinical trial. Pentoxifylline, an anti-inflammatory agent with anti-TNF-α properties, has been shown in one study to reduce the incidence of new-onset type 1 hepatorenal syndrome and mortality at one month. Pentoxifylline is safe and cheap, and could be used despite the lack of a confirmatory study.

Patients who are also infected with viral hepatitis B or C should be assessed for their suitability to receive anti-viral therapy. Untreated viral hepatitis can certainly hasten the fibrotic process in alcoholic cirrhosis. Colchicine has been tried as an antifibrotic agent to reduce the extent of cirrhosis and hence portal pressure without much success. Patients with alcoholic cirrhosis should also be assessed for complications of liver failure and portal hypertension. This includes a surveillance gastroscopy to assess for the presence of esophageal varices and prophylactic β-blocker therapy instituted for those with large esophageal varices. The recent advent of a transjugular intrahepatic portosystemic stent shunt (TIPS) has replaced a surgical portocaval shunt as the treatment of choice for uncontrolled bleeding esophageal varices, although the mortality rate is very high in those patients with acute alcoholic hepatitis. Hepatic encephalopathy remains a complication, but can usually be controlled with prophylactic lactulose.
Ascites is managed with a low sodium diet and diuretic therapy. Ascites frequently settles down in those patients who abstain from alcohol for more than six months. In patients whose ascites becomes refractory to diuretic therapy, TIPS should be considered as a treatment option, especially in those patients who have been abstinent from alcohol for more than six months. Every effort should be made to exclude spontaneous bacterial peritonitis and prevent hepatorenal syndrome, two life threatening complications of ascites. Periodic screening for the presence of hepatoma should be made, since effective treatments are available if hepatomas are detected early. Surgical resection in the stable compensated cirrhotic patient or local ablative therapy such as intra-lesional radiofrequency ablation in the mildly decompensated patient should be offered. Hepatic transplantation is a treatment option for patients with end-stage alcoholic cirrhosis and this is the treatment of choice in the patient with decompensated alcoholic cirrhosis. Ethical issues surrounding the use of such a scarce resource for a self-inflicted disease still need to be settled, especially when it relates to liver transplantation for patients who have active alcoholic hepatitis. In the centres that transplant alcoholic cirrhosis, the results are comparable to those in patients with other forms of cirrhosis.

9. NON-ALCOHOLIC FATTY LIVER DISEASE / G. Kichian and W. Wong

Non-alcoholic fatty liver disease (NAFLD) has emerged as a common and potentially important cause for elevated liver enzymes. It is frequently linked to obesity and type 2 diabetes, and is now recognized as an important contributor to cryptogenic cirrhosis. With up to 60% of the North American population estimated to be overweight and with the increasing rate of type 2 diabetes, NAFLD is projected to become a significant cause for liver related morbidity and mortality. This chapter will outline the current understanding of NAFLD, and suggest an approach to its management.

9.1 Definition

A term first coined by Ludwig in 1981, non-alcoholic steatohepatitis (NASH) is a condition that has the histologic appearance of alcoholic hepatitis in the absence of significant alcohol abuse. NAFLD, on the other hand, describes conditions of fatty infiltration in the liver in the absence of significant alcohol intake and other known causes of liver disease, with a spectrum of disease activity that can range from benign steatosis to cirrhosis. NASH, therefore, is a clinically advanced subset of NAFLD with features of hepatitis that can advance to cirrhosis.
9.2 Pathogenesis

The mechanisms underlying fatty infiltration and subsequent inflammation and fibrosis have been derived from animal models and observational studies in patients with NAFLD and remain largely speculative. Several studies have described the presence of insulin resistance in patients with NAFLD, but it remains to be proven whether insulin resistance is a cause or consequence of the disease. The association with diabetes was long established in patients with NAFLD, but more recent studies have suggested that insulin resistance can be found in the absence of elevated serum glucose levels. These studies have demonstrated elevated fasting serum insulin level and documented peripheral insulin resistance using the euglycemic clamp technique. Similarly, in the leptin deficient ob/ob mouse, which is an accepted animal model of NAFLD, the severity of fatty infiltration and subsequent liver inflammation and fibrosis is clearly associated with insulin resistance.

The presence of fat in the liver is a relatively common occurrence and, in itself, is not believed to be deleterious. Nevertheless, in a minority of patients, fat infiltration can be associated with chronic inflammation leading to fibrosis, resulting in NASH. This sequential insult to the liver, referred to as the “two-hit” hypothesis, therefore involves two elements: steatosis, and factors that can promote inflammation such as cytokines and oxidative stress. Of the numerous cytokines that are believed to play a role, tumor necrosis factor alpha (TNF-\(\alpha\)) is the most studied and is clearly demonstrated to be present in tissue biopsies and serum of patients or animal models of NAFLD. TNF-\(\alpha\) production is closely linked to high adipose tissue mass and it can be involved in promoting insulin resistance by down-regulating insulin receptor substrate 1 (IRS-1). TNF-\(\alpha\) production has also been demonstrated secondarily to endotoxemia from bacterial translocation. A recent study demonstrated elevated TNF-\(\alpha\) mRNA levels in livers of ob/ob mice and showed that manipulations of intestinal flora of these mice with probiotics can decrease the TNF-\(\alpha\) mRNA. The degree of liver inflammation and TNF-\(\alpha\) production was reduced with both probiotics and antibodies to TNF-\(\alpha\).

With respect to oxidative stress, multiple possible sources have been identified and include cytochrome P450, peroxisomal \(\beta\) oxidation, mitochondrial electron leak, reactive lipid peroxidation products, and recruited inflammatory cells. The mechanism of oxidative stress damage to hepatocytes is believed to be secondary to the overwhelming of the protective mechanisms of excess fat handling including the synthesis of triglycerides and VLDLs, enzymatic removal of fat peroxidation products, and proper function of hepatic mitochondria. Finally, it remains to be proven whether a genetic predisposition is critical for progression of steatosis to NASH.
9.3 Diagnosis

Patients evaluated for NAFLD are generally asymptomatic and are incidentally discovered to have mild elevation in their transaminases. A minority of patients with more advanced disease can present with fatigue, malaise, hepatomegaly, and/or right upper quadrant pain. In the worst-case scenario, patients can have an initial presentation of advanced liver disease with obvious stigmata and/or complications of portal hypertension, with a subsequent evaluation suggestive of longstanding NAFLD.

The initial workup for NAFLD starts, as with any other liver disease, with a comprehensive history to look for risk factors associated with liver dysfunction. These factors include alcohol use, exposure or high-risk activity that could predispose to viral hepatitis, use of prescription, over-the-counter and herbal medications, and family history of liver disease. Given that the biochemical, radiologic and histologic findings of NAFLD are identical to those of alcoholic liver disease, it is critical to obtain a comprehensive history of alcohol use. The quantity of alcohol consumption per day should be elicited with levels > 20 g/day being consistent with alcoholic liver disease. It should also be recognized that patient self-reporting of alcohol use is notoriously inaccurate. Therefore, where possible, corroborative information should be obtained from family members or other physicians. Biochemical parameters such as random alcohol levels, serum \( \gamma \)-glutamyltransferase levels (GGT), mean corpuscular volume, and AST/ALT ratio > 2 could also help in suggesting alcohol use when there is doubt about the diagnosis.

A history of conditions associated with NAFLD should next be established. These include type 2 diabetes, obesity, hypercholesterolemia, hypertriglyceridemia, hypertension, total parenteral nutrition, severe weight loss, and use of medications associated with steatosis such as tamoxifen, amiodarone and corticosteroids. A nutritional history with emphasis on the type and quantity of foods being consumed, the progression of weight gain and/or dieting, and participation in physical activity is also important to elicit. Finally, a family history of type 2 diabetes could suggest a genetic predisposition to insulin resistance.

The physical examination should be comprehensive and not only focus on finding stigmata of chronic liver disease. Important aspects of the exam include the weight and height to determine body mass index, an accurate measure of the blood pressure, an endocrine assessment including thyroid exam, signs of hypercholesterolemia, and a careful evaluation of the liver size and texture.

Laboratory investigations are intended to rule out viral, autoimmune, and genetic causes of liver disease. Serum cholesterol, triglycerides, and fasting glucose should be part of the initial evaluation. In NAFLD, ALT and AST levels are usually mildly elevated (less than two-fold normal) with an AST:ALT
ratio of $< 1$. Nevertheless, in the absence of significant alcohol consumption, an AST:ALT ratio of $> 2$ could be present and indicative of advanced liver disease. A mild rise in alkaline phosphatase can accompany NAFLD. However, a significant rise should prompt an evaluation for an alternate diagnosis. On the other hand, while an elevated ferritin should prompt further evaluation of the iron status, it is commonly seen in patients with NAFLD.

An abdominal ultrasound is the least expensive and most accessible radiologic modality to assess NAFLD. When the fat content involves $> 30\%$ of hepatic lobules, ultrasound can detect NAFLD with a sensitivity of $83\%$ and specificity of $100\%$. Features on ultrasound that suggest fatty infiltration include diffuse hyperechoic texture, vascular blurring, and deep attenuation. CT and MRI have also been used to assess NAFLD and shown to be more sensitive when the fatty infiltration is patchy or focal. CT attenuation values of the liver decrease with fatty infiltration by about 1.6 Hounsfield units for every milligram of triglyceride deposited per gram of liver tissue. MRI T1-weighted gradient-echo images obtained with echo times keeping the water and fat spins out of phase show a loss of hepatic signal with fatty infiltration. However, the utility of all imaging modalities remains limited by their inability to distinguish simple steatosis from steatohepatitis.

Although a relatively invasive procedure, liver biopsy remains the gold standard for the diagnosis of NAFLD and NASH. It is the only diagnostic tool that can confidently establish the diagnosis, ascertain the degree of inflammation and fibrosis, and potentially determine the long-term prognosis of the disease. Nevertheless, the value of a liver biopsy for the diagnosis of NAFLD in routine clinical practice for patients with mild elevation in liver enzymes remains hotly debated. The argument against universal biopsy is that the information provided is unlikely to significantly impact on treatment plan. On the other hand, advocates of liver biopsy argue that patients at increased risk of disease progression could be identified, and be offered experimental therapy. Histologic features of NAFLD include macrovesicular fat, Mallory’s hyaline bodies, ballooning hepatocytes, perisinusoidal (zone 3) fibrosis, and lobular neutrophilic infiltrates. While there remains no universally accepted histologic grading system for NAFLD, the Brunt criteria of grading based on the combination of steatosis and inflammatory changes and staging based on the degree of fibrosis have been shown to be useful in predicting clinical outcome in retrospective studies.

### 9.4 Natural History

It is difficult to estimate the proportion of patients with elevated ALT who have NAFLD, as the majority of these patients do not undergo a liver biopsy. Nevertheless, it is estimated that 10-15\% of normal individuals and 70-80\% of obese individuals have steatosis. More importantly, 3\% of normal individuals
and up to 20% of obese individuals could have steatohepatitis from studies on automobile and air crash victims who underwent liver biopsy. Moreover, a recent study demonstrated that NAFLD can be found in patients with normal ALT levels, thereby suggesting that the prevalence of NAFLD in the population is likely underestimated.

There is a paucity of studies on the natural history of NAFLD because the true disease prevalence is not known, and large, prospective studies requiring repeat liver biopsies are difficult. Based on a few small studies on patients that had a firm diagnosis of NAFLD on biopsy and then followed a number of years later with a second biopsy, patients with simple steatosis rarely progress to NASH, whereas up to 20% of patients with NASH can progress to cirrhosis. At initial presentation, up to 30-40% of patients can have advanced fibrosis and 10-15% may have cirrhosis. Patients with NASH are thought to have increased mortality rate compared to age-matched controls. However, it is not known whether the increased mortality is secondary to comorbidities associated with NAFLD (e.g., coronary artery disease, type 2 diabetes) or progression of liver disease.

A number of retrospective studies have analyzed patients with cryptogenic cirrhosis and identified clinical features typical of NAFLD in a significant proportion. However, confirmation of NASH as the underlying cause of the cirrhosis was not possible in these patients because their biopsies were devoid of steatosis. This was not entirely unexpected as the progression of fibrosis in the liver frequently leads to the disappearance of fat. There are also a number of studies that have demonstrated the presence of hepatocellular carcinoma (HCC) in patients with cryptogenic cirrhosis with associated clinical features of NAFLD. Combined, these studies have speculated that NASH is the underlying etiology of the majority of cryptogenic cirrhosis, and that it could progress to HCC.

9.5 Management
Studies on the therapy of NAFLD suffer from the same limitations, and there are no published randomized controlled studies to guide management. The current approach focuses on correction of known risk factors of NAFLD and includes supervised and gradual weight loss, increased physical activity, and adequate glycemic control in diabetic patients. A dietitian consult may be helpful to counsel and monitor gradual weight loss, as abrupt weight loss could lead to worsened steatosis. It is not known if weight loss actually diminishes steatosis, but there is evidence that liver enzymes can improve with as little as a 10% reduction in weight. It is therefore reasonable to advocate sustained weight loss with increased physical activity and a change in the composition and quantity of food as an initial intervention.
Pharmacologic therapy of NAFLD has so far focused on the two arms of the pathogenesis of the disease: insulin resistance and oxidative stress. A number of small studies have demonstrated improvement in liver enzymes with the use of biguanides (metformin) and thiazolidinediones but need confirmation and lack in long-term follow up. Similarly, a number of hepatoprotective drugs including vitamin E, ursodeoxycholic acid, betaine, lecithin, β-carotene, and selenium have shown marginal benefit in improving liver enzymes and reversing inflammation but still remain experimental. Lastly, liver transplantation may need to be considered when the disease progresses to cirrhosis and end stage liver failure.

10. DRUG-INDUCED LIVER DISEASE / J.B. Simon

Drugs are an important and common cause of hepatic injury. This is not surprising, as the liver is the predominant site of drug clearance, biotransformation and excretion. Abnormalities cover a wide spectrum from minor non-specific derangements to fulminant hepatic necrosis. The two most common, however, are acute inflammation and cholestasis, which can closely mimic viral hepatitis and biliary obstruction respectively. Various other acute and chronic disease patterns also occur (as noted below). Thus drug-induced liver disease is complex, has protean manifestations, and can stimulate a wide variety of other hepatic disorders.

The pathogenesis varies with the offending agent, and in most cases is poorly understood. Sometimes the drug or one of its metabolites exerts a direct toxic effect on liver membranes. This type of injury is predictable and dose-related, but is relatively infrequent. Much more commonly, the injury occurs unpredictably in only a tiny fraction of individuals receiving the drug and is independent of dosage. In some such instances genetic predisposition or idiosyncratic metabolism of the drug may be responsible. Immune hypersensitivity is often invoked, but only a minority of cases have concomitant evidence of an allergic reaction such as a rash, arthralgias or eosinophilia. Many instances of putative hypersensitivity may actually be due to toxic intermediate drug metabolites in rarely susceptible individuals. In most situations the reasons for individual susceptibility are unknown, and the precise pathogenesis of the hepatic injury is equally obscure.

Diagnosis requires, first and foremost, a careful history of drug ingestion, including over-the-counter herbal and illicit agents as well as prescribed medications. A temporal association is also important in cases of acute dysfunction: injury typically develops within days or a few weeks of starting the drug. Other reactions involve chronic insidious injury and therefore require prolonged drug exposure – e.g., methotrexate fibrosis and oral contraceptive-induced adenomas. Liver biopsy sometimes provides an important clue to certain drug injuries, but
more commonly the histologic pattern is non-specific and/or mimics other primary liver disorders. Thus in many cases the diagnosis of drug injury remains uncertain or unproven even after appropriate patient assessment.

The prognosis is variable. Acute damage usually resolves when the offending agent is withdrawn, but cases of severe acute necrosis can be fatal or result in postnecrotic scarring. In cases of chronic injury, further hepatocellular damage and inflammation will generally cease when the drug is stopped, but any concomitant fibrosis will be irreversible.

No physician can know the innumerable drugs capable of producing liver injury. Rather, it is best to maintain a constant awareness of the possibility, to understand the general types of damage, and to learn the most common agents responsible for each. Table 32 gives an arbitrary classification and examples of drug-induced hepatic injury. A few of the more important examples are briefly discussed below.

<table>
<thead>
<tr>
<th>Type and example</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute hepatocellular injury</strong></td>
<td></td>
</tr>
<tr>
<td>Toxic necrosis (e.g., CCl₄, acetaminophen)</td>
<td>Membrane damage, some via toxic metabolite; dose-related, predictable</td>
</tr>
<tr>
<td>Hepatitis-like (e.g., isoniazid, methyldopa)</td>
<td>Idiosyncrasy; ? immune, ? metabolic; unpredictable, not dose-related</td>
</tr>
<tr>
<td><strong>Cholestasis</strong></td>
<td></td>
</tr>
<tr>
<td>Inflammatory (e.g., chlorpromazine)</td>
<td>Unknown; unpredictable; periportal inflammation and cholestasis</td>
</tr>
<tr>
<td>Pure (e.g., oral contraceptives)</td>
<td>Exaggeration of normal hormonal effect on bile transport; ? genetic idiosyncrasy; pure cholestasis, no inflammation</td>
</tr>
<tr>
<td><strong>Miscellaneous acute/subacute</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Chronic liver disease</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis (e.g., isoniazid, methyldopa)</td>
<td>Idiosyncrasy; ? immune, ? metabolic</td>
</tr>
<tr>
<td>Chronic cholestasis (e.g., chlorpromazine)</td>
<td>Unknown; rare</td>
</tr>
<tr>
<td>Fibrosis/cirrhosis (e.g., methotrexate)</td>
<td>Dose-related, insidious toxic metabolic damage</td>
</tr>
<tr>
<td>Tumor: adenomas (oral contraceptives)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
10.1 Acute Hepatocellular Injury

This takes at least two distinct forms, both characterized clinically and biochemically by features of acute liver cell destruction.

10.1.1 TOXIC NECROSIS

This involves direct membrane damage by the parent drug or a toxic metabolite. It is therefore dose-related and a predictable occurrence in anyone ingesting a sufficient quantity of the drug. Sometimes the histologic injury is characteristic – e.g., zonal necrosis and fat in carbon tetrachloride toxicity. In severe cases, aminotransferase levels may reach several thousand IU/mL – much higher than typically seen in acute viral hepatitis, thereby giving a clue to the diagnosis.

Acetaminophen is the most important example (Figure 25). This widely used analgesic is largely excreted as harmless conjugates, but a portion is transformed by hepatic microsomes to a toxic intermediate metabolite.
Normally this is safely eliminated by conjugation with hepatic glutathione, but a large enough dose of acetaminophen will deplete the available glutathione stores. Once this occurs, cell necrosis results from binding of the toxic intermediate to liver macromolecules. The threshold for an injurious dose of acetaminophen is usually about 10-15 g acutely; this is far beyond the normal dosage and is generally ingested only in suicide attempts. Alcoholics are susceptible at much lower dosage, however, as a result of heightened microsomal transformation coupled with nutritional depletion of glutathione. Acetaminophen should be suspected in an alcoholic with extremely high AST/ALT levels, as values rarely exceed 300 IU/mL in uncomplicated alcoholic hepatitis. Another clue to acetaminophen toxicity is a disproportionately elevated INR.

Acetaminophen hepatotoxicity typically becomes apparent only 36 to 48 hours after ingestion; by then it is too late to modify the process. Fortunately, injury is successfully aborted by early therapy with N-acetylcysteine, which repletes hepatic glutathione levels. This should be given within 10 to 16 hours of acetaminophen ingestion to be effective, though some benefit may be achieved even at 24 to 36 hours. To guide therapy, nomograms are available relating the probability of liver injury to blood acetaminophen levels and to the amount of time since ingestion.

10.1.2 ACUTE HEPATITIS
This pattern of injury closely mimics acute viral hepatitis clinically, biochemically and histologically. Unlike toxic necrosis, it occurs unpredictably, is not dose-related and affects only rare individuals exposed to the drug. Reasons for the idiosyncratic susceptibility are obscure. Numerous agents can produce this injury pattern; methyl dopa, isoniazid and halothane are classic examples, the latter usually producing damage only after repeated exposure to the anesthetic. Other relatively common examples include propy thiouracil, phenytoin, sulfonamides and various nonsteroidal anti-inflammatory drugs. Acute hepatitis from isoniazid or diclofenac occasionally develops only after several months of drug therapy. This is an exception to the general rule of a temporal relationship, and the association may therefore be overlooked.

10.2 Cholestasis
This type of reaction also takes at least two distinct forms.

10.2.1 INFLAMMATORY TYPE
Chlorpromazine and other phenothiazines, carbamazepine, chlorpropamide, erythromycin estolate, amoxicillin-clavulanic acid and many other drugs can produce an acute periportal necro-inflammatory reaction. This is characterized
clinically and biochemically by a predominant cholestatic disorder with variable features of concomitant hepatocellular inflammation. Differentiation from extrahepatic biliary obstruction may be required.

**10.2.2 PURE TYPE**

Certain steroid hormonal drugs, most notably oral contraceptives and methyltestosterone, can produce relatively pure impairment of bile flow with little or no associated hepatocellular injury (bland cholestasis). This appears to be due to an idiosyncratic exaggeration of the physiologic effect of sex hormones on bile canalicular transport, and may have a genetic component. The patient typically develops insidiously progressive pruritus, dark urine, and jaundice without associated systemic symptoms. Laboratory tests show high ALP with normal or minimally elevated AST/ALT levels. The liver biopsy is usually unremarkable aside from histologic cholestasis. Women who develop this reaction to oral contraceptives are predisposed to cholestasis of pregnancy, which appears to be similar or identical in pathogenesis (Section 20).

Oral contraceptives are also associated with other, less common hepatobiliary effects. These are listed in Table 33.

**10.3 Miscellaneous Acute and Subacute Reactions**

Many hepatic drug reactions involve a variable mixture of hepatocellular and excretory impairments that do not neatly fit any of the above categories. Laboratory and histologic features are variable and non-specific. Occasionally granulomatous inflammation occurs (e.g., with sulfonamides or quinidine), often with acute systemic features. Differentiation from an infective granulomatous disorder may be challenging. A few drugs can produce an alcoholic
hepatitis-like picture, including typical histologic features (e.g., amiodarone). Other unusual patterns of drug injury have also been described. Various herbal remedies are increasingly recognized as a cause of liver damage with variable manifestations, including, rarely, a fulminant hepatitis. An acute pattern of hepatic necrosis is occasionally produced by cocaine and is probably of ischemic origin.

10.4 Chronic Liver Disease
Though the large majority of drug-induced hepatic injury is acute or subacute, in a few reactions there is an insidious development of chronic disease. These vary in type.

10.4.1 CHRONIC HEPATITIS
A few agents that induce acute hepatitis are also capable of producing chronic inflammation if drug ingestion continues. Methyldopa and isoniazid are the prime examples. Clinically, biochemically and histologically the reaction may be indistinguishable from idiopathic or immune chronic hepatitis. The disorder typically resolves when the drug intake ceases.

10.4.2 CHRONIC CHOLESTASIS
In rare instances cholestatic injury from phenothiazines or other agents becomes prolonged and self-perpetuating even though the drug is discontinued. This is termed drug-induced “vanishing duct syndrome” and can simulate primary biliary cirrhosis, though immunologic features of the latter are lacking. Hepatic intra-arterial chemotherapy with floxuridine can produce a sclerosing cholangitis-like picture, probably owing to ischemic injury of the bile ducts.

10.4.3 FIBROSIS/CIRRHOSIS
Insidiously progressive hepatic fibrosis and eventual cirrhosis can occur from methotrexate, some chemotherapeutic agents, and chronic ingestion of arsenicals or vitamin A in megadoses. Scarring typically develops subclinically and with little or no biochemical evidence of hepatic dysfunction. Liver biopsy is therefore the only way to establish the diagnosis. Patients receiving long-term methotrexate therapy for psoriasis or rheumatoid arthritis should generally undergo biopsy after cumulative drug dosage reaches about 1.5 g, and at occasional intervals thereafter.

10.4.4 TUMORS
Prolonged intake of oral contraceptives is associated with an increased risk of developing benign hepatic adenomas. These are usually asymptomatic but
occasionally produce an acute abdomen due to intraperitoneal rupture and hemorrhage. In rare instances, oral contraceptive-induced adenomas become malignant.

Other unusual drug-related tumors are known to occur as well – e.g., angiosarcoma from chronic exposure to vinyl chloride.

11. INHERITED LIVER DISEASE / E.A. Roberts and P.C. Adams

11.1 α₁-antitrypsin Deficiency
The glycoprotein produced by the liver, α₁-antitrypsin, constitutes the majority of the α₁ globulin fraction found on serum protein electrophoresis. Its deficiency is inherited, and it can result in panacinar pulmonary emphysema or hepatic disease. Various types of liver disease are possible, including neonatal hepatitis syndrome, cirrhosis and hepatocellular carcinoma.

α₁-antitrypsin is a protease inhibitor which inactivates leukocyte elastase. Its production is controlled by a highly polymorphic gene on chromosome 14. The inheritance is autosomal co-dominant. α₁-antitrypsin is described in terms of protease inhibitor (Pi) phenotype. Normal individuals are PiMM. Patients with liver disease most frequently are PiZZ. They have only 15-20% of the normal concentration of α₁-antitrypsin in serum.

Diagnosis of α₁-antitrypsin deficiency is suggested by a very low α₁-globulin concentration on serum protein electrophoresis and decreased serum α₁-antitrypsin levels, and it is confirmed by phenotyping. The characteristic changes found on liver biopsy include the presence of periodic acid Schiff (PAS)-positive, diastase-resistant globules in hepatocytes; these globules are α₁-antitrypsin within the endoplasmic reticulum. With the Z allele, newly synthesized α₁-antitrypsin cannot be exported from the endoplasmic reticulum. It accumulates there and is later degraded. Cirrhosis will develop in approximately 15% of patients with PiZZ. The risk to PiMZ heterozygotes of developing liver disease is somewhat increased. Infusion of recombinant α₁-antitrypsin may be beneficial for preventing lung disease associated with α₁-antitrypsin deficiency but is ineffective for treating α₁-antitrypsin deficiency liver disease. Gene therapy may become a possibility in the future. Patients with advanced forms of liver disease may be candidates for liver transplantation.

11.2 Wilson’s Disease
Wilson’s disease is an inherited disorder characterized by accumulation of copper in the liver, central nervous system and certain other organs. The disease has a prevalence of 1:30,000. Inheritance is autosomal recessive; the gene responsible (ATP7B) is on chromosome 13. The gene product is an intracellular copper-transporting ATPase, mainly expressed in the liver. Wilson’s disease
may present as liver disease, neurological disease or psychiatric disorders. Hepatic disease tends to be more frequent in children and young adults. The hepatic presentation of the disease is variable and may include fulminant hepatic failure (with intravascular hemolysis and renal failure), fatty liver, liver disease resembling autoimmune hepatitis, and cirrhosis. Copper deposition in the central nervous system results in extrapyramidal symptoms of rigidity, choreoathetoid movements and ataxia. Biochemical abnormalities include a low serum ceruloplasmin and elevated 24-hour urinary copper excretion. Liver biopsy may not be diagnostic, and copper stains are unreliable. Therefore, measuring hepatic copper concentration in the biopsy is often necessary. The Kayser-Fleischer ring (copper deposition in Descemet’s membrane of the cornea) is characteristic of Wilson’s disease, although rarely it is present with chronic cholestatic diseases. Many younger patients, however, do not have Kayser-Fleischer rings. A careful slit lamp examination by an ophthalmologist is required when Wilson’s disease is suspected since Kayser-Fleischer rings are almost never evident by visual inspection. Treatment is life-long with either the chelating agent D-penicillamine or alternative drug therapies for those intolerant of D-penicillamine. Patients with advanced liver disease unresponsive to medical treatment are candidates for liver transplantation.

11.3 Hemochromatosis

Hemochromatosis is an iron-storage disorder in which there is an inappropriate increase in the absorption of iron from the gut. This leads to iron deposition in various organs with eventual impairment, especially of the liver, pancreas, heart and pituitary. The term hemochromatosis is preferred for genetic hemochromatosis with other diseases associated with iron overload, referred to as secondary iron overload.

The gene for hemochromatosis (HFE) on chromosome 6 was discovered in 1996. The HFE protein is similar to a MHC class-I protein. A genetic test for hemochromatosis has demonstrated that more than 90% of typical hemochromatosis patients have a C282Y mutation of the HFE gene. The presence of a single mutation in most patients is in marked contrast to other genetic diseases in which multiple mutations were discovered (cystic fibrosis, Wilson’s disease, α1-antitrypsin deficiency). The C282Y mutation creates a conformational change in the HFE protein which normally interacts with the transferrin receptor and hepcidin to regulate iron uptake. A second minor mutation, H63D, was also described in the original report. Hemochromatosis is one of the most common genetic diseases, inherited as an autosomal recessive trait affecting one in 200 of the Caucasian population. Since genetic testing has been introduced, an increasing number of homozygotes have been described without iron overload. This incomplete penetrance
of the gene may explain the discrepancy between the high prevalence in genetic studies and the clinical impression that hemochromatosis is an uncommon condition.

The homozygote has continued iron accumulation leading to target organ damage. Normally the body iron content of 3 to 4 g is maintained such that mucosal iron absorption is equal to that of loss and the absorption of iron is equal to that of loss. In hemochromatosis, the absorption of iron is inappropriate to the needs of the body, resulting in absorption of 4 mg/day or more. In advanced disease, the total body iron accumulation may be 40-60 g.

### TABLE 34. Interpretation of genetic testing for hemochromatosis

<table>
<thead>
<tr>
<th>Mutation Pattern</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C282Y homozygote</strong></td>
<td>This is the classical genetic pattern that is seen in &gt; 90% of typical cases. Expression of disease ranges from no evidence of iron overload to massive iron overload with organ dysfunction. Siblings have a one-in-four chance of being affected and should have genetic testing. For children to be affected, the other parent must be at least a heterozygote. If iron studies are normal, false positive genetic testing or a non-expressing homozygote should be considered.</td>
</tr>
<tr>
<td><strong>C282Y / H63D – Compound heterozygote</strong></td>
<td>This patient carries one copy of the major mutation and one copy of the minor mutation. Most patients with this genetic pattern have normal iron studies. A small percentage of compound heterozygotes have been found to have mild to moderate iron overload. Severe iron overload is usually seen in the setting of another concomitant risk factor (alcoholism, viral hepatitis).</td>
</tr>
<tr>
<td><strong>C282Y heterozygote</strong></td>
<td>This patient carries one copy of the major mutation. This pattern is seen in about 10% of the Caucasian population and is usually associated with normal iron studies. In rare cases the iron studies are high in the range expected in a homozygote rather than a heterozygote. These cases may carry an unknown hemochromatosis mutation and liver biopsy is helpful to determine the need for venesection therapy.</td>
</tr>
<tr>
<td><strong>H63D homozygote</strong></td>
<td>This patient carries two copies of the minor mutation. Most patients with this genetic pattern have normal iron studies. A small percentage of these cases have been found to have mild to moderate iron overload. Severe iron overload is usually seen in the setting of another concomitant risk factor (alcoholism, viral hepatitis).</td>
</tr>
<tr>
<td><strong>H63D heterozygote</strong></td>
<td>This patient carries one copy of the minor mutation. This pattern is seen in about 20% of the Caucasian population and is usually associated with normal iron studies. This pattern is so common in the general population that the presence of iron overload may be related to another risk factor. Liver biopsy may be required to determine the cause of the iron overload and the need for treatment in these cases.</td>
</tr>
<tr>
<td><strong>No HFE mutations</strong></td>
<td>There will likely be other hemochromatosis mutations discovered in the future. If iron overload is present without any HFE mutations, a careful history for other risk factors must be reviewed and liver biopsy may be useful to determine the cause of the iron overload and the need for treatment. Most of these cases are isolated, non-familial cases. Genetic testing for new iron mutations in ferroportin, hepcidin, or hemojuvelin is not widely available.</td>
</tr>
</tbody>
</table>
Most patients are asymptomatic until the 5th or 6th decade, at which time they can present with non-specific symptoms of arthritis, diabetes, fatigue or hepatomegaly. Other symptoms include pigmentation of the skin (melanin deposition), impotence and dyspnea secondary to congestive heart failure. The classic triad of skin pigmentation, diabetes and liver disease (bronze diabetes) occurs in a minority of patients and is a late stage of the disease. The attribution of symptoms to hemochromatosis has become increasingly difficult since studies using control subjects without HFE mutations have shown a similar prevalence of non-specific symptoms such as fatigue, arthralgias, and diabetes.

A patient with suspected hemochromatosis or unexplained liver disease can be screened for the disease with a serum ferritin and transferrin saturation (serum iron/TIBC). These tests increase with age and are more abnormal in males than females because of the regular menstrual blood loss in women. Serum ferritin increases with body iron stores but is commonly elevated with fatty liver, daily alcohol consumption and chronic inflammation. The diagnosis was previously confirmed by liver biopsy, which demonstrates marked parenchymal iron deposition with iron staining of the tissue. The hepatic iron concentration and the hepatic iron index (hepatic iron concentration/age) can be helpful in distinguishing genetic hemochromatosis from the increased iron overload that is seen in other chronic liver diseases such as alcoholic liver disease and chronic hepatitis C. MRI scanning can detect moderate to marked iron overload in the liver. Genetic testing has led to a re-evaluation of the role of liver biopsy in hemochromatosis and biopsy has moved from a diagnostic test done in most cases to a prognostic test done in selected cases with liver dysfunction. C282Y homozygotes, detected as young adults with a serum ferritin < 1000 µg/L, a normal AST and without hepatomegaly, will not require a liver biopsy. Genetic testing is particularly useful in the evaluation of a patient with other risk factors for iron overload such as alcoholic liver disease or viral hepatitis (Table 34).

The heterozygote individual may have normal or minor derangements in iron metabolism that have no clinical significance. A patient that carries both the major mutation (C282Y) and the minor mutation (H63D) is called a compound heterozygote. These patients may have mild to moderate iron overload but are often normal. The treatment of hemochromatosis involves the removal of excess body iron. Iron is best removed from the body by weekly or twice weekly phlebotomy of 500 mL of blood until the body iron stores are within normal limits. The duration of treatment varies with the age and sex of the patient but older males may require weekly venesections for over three years. A serum ferritin is measured every three months to assess progress and when the serum ferritin is in the low normal range (50 µg/L), the frequency of venesections is decreased to three or four per year. The goal of therapy is to prevent any further tissue damage. Unfortunately, many of the symptoms do not improve following iron depletion. The most common cause of death is liver
failure and/or hepatocellular carcinoma once cirrhosis has become established. Siblings of the patient with hemochromatosis must be screened with serum ferritin, transferrin saturation and genetic testing as the siblings have a one-in-four chance of being affected. Genetic testing can now identify heterozygotes so the screening of a spouse with genetic testing can be helpful to predict the risk in children. Screening of the general population for hemochromatosis has found many genetic mutations but not much clinical disease. Genetic screening has the potential to identify cases at birth but raises ethical issues such as genetic discrimination. Chelating agents such as desferoxamine (parenteral) are reserved for the patient with iron overload secondary to an iron loading anemia such as thalassemia. Future research is in progress to look for new genes that may cause iron overload, or may modify the clinical expression of hemochromatosis.

12. CHOLESTASIS / J. Heathcote

Cholestasis simply means failure of flow of bile. The cause of this failure can arise anywhere in the biliary system, from the liver cell down to the ampulla of Vater. For clinical purposes it is easiest to think of cholestasis as being either intra- or extrahepatic (Table 35).

12.1 Intrahepatic Cholestasis

Drug toxicity is the commonest cause of cholestasis occurring at the cellular level. The injury may be predictable, as with estrogens (for example), or unpredictable, as with most idiopathic drug reactions. (However, as more intracellular mechanisms become understood – e.g., the polymorphic nature of drug-metabolizing enzymes – fewer reactions will be found to be “unpredictable.”) Histologically and clinically, cholestatic drug reactions can be considered as “bland” or “inflammatory.” Systemic sepsis is often associated with cholestasis. Endotoxins have been shown to affect both intracellular and canalicular function. If sepsis occurs on a background of cirrhosis, the cholestasis is much more profound.

Most acute and chronic liver diseases exert a cholestatic effect via interruption of intracellular transport mechanisms or damage to the small interlobular bile ducts. Damage to small bile ducts is not at all unusual in acute and chronic hepatitis, particularly with hepatitis C. Cholestasis is also a common feature of relapsing hepatitis A, but does not carry any particular significance.

Several chronic liver diseases specifically target the intrahepatic and sometimes the extrahepatic bile ducts. The diseases of the liver that are associated with paucity of bile ducts are numerous. Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are the best-known examples; other diseases that destroy bile ducts are chronic drug reactions, chronic liver allograft rejection and graft-versus-host disease sarcoidosis to name but a few.
In children, intrahepatic bile duct paucity may be syndromatic (Alagille's) or nonsyndromatic. PSC is commonly misdiagnosed as autoimmune hepatitis, as overt cholestasis may be absent. Cystic fibrosis may give rise to focal biliary cirrhosis as a result of inspissated bile in the ducts.

There are a number of congenital cholestatic syndromes termed the progressive familial intrahepatic cholestatic syndromes. They are due to defects of canalicular transporters, some for bile acids and another for phosphatidylcholine. Different mutations in these transporters may be responsible for benign recurrent cholestasis and cholestasis of pregnancy.

Many infiltrations may cause a biochemical pattern similar to anicteric cholestasis – e.g., lymphomas, amyloid and granulomas of any etiology, and sometimes simple fat.

### 12.2 Extrahepatic Cholestasis

Diseases of the large bile ducts are generally due to stones, strictures or tumors. The AIDS epidemic brought its own forms of cholestatic problems: fungal, protozoal and viral cholangitis, now rarely seen since HIV is controllable.
Parasites causing biliary obstruction in immunocompetent individuals are not unusual in the developing world, e.g., ascariasis. Malignant tumors causing biliary obstruction include pancreatic and bile duct carcinomas as well as lymphomas.

12.3 Primary Biliary Cirrhosis (PBC)

12.3.1 Diagnosis

The more accurate term for this disease is chronic nonsuppurative granulomatous cholangitis. It predominantly affects women in middle age and is frequently associated with autoimmune phenomena outside the liver (renal tubular acidosis, vitiligo, thyroiditis, sicca syndrome, CREST syndrome, celiac disease, rheumatoid arthritis and, less often, glomerulonephritis and vasculitis). It is presumed that PBC is also an autoimmune disease, although the inciting antigen has not been identified.

PBC is rarely diagnosed at the first visit, because one-third or more of patients are asymptomatic. The biochemical pattern seen in PBC is typically cholestatic: elevated alkaline phosphatase, GGT and 5′nucleotidase (5′NT), with modest elevations of the aminotransferases. An elevated bilirubin is associated with progressive, symptomatic disease, indicating a poor prognosis. The most common symptom of this illness is fatigue, very hard to define yet
very distressing to the patient. Other symptoms include pruritus, xanthelasma and, later in the course of the disease, ascites, jaundice and encephalopathy. Portal hypertension occurs early in this disease, as it is presinusoidal in nature; thus, variceal hemorrhage may be a presenting symptom. Many patients with PBC present with nonhepatic associations, Raynaud's, osteoporosis, sicca syndrome and rheumatoid arthritis being the most common. Some patients with PBC have been misdiagnosed as having the chronic fatigue syndrome.

The diagnostic hallmarks for PBC include a cholestatic serum biochemistry as described above, elevated serum cholesterol, elevated serum IgM and a positive mitochondrial antibody test. If all these features are present, a diagnostic liver biopsy is not essential but does help to indicate prognosis. The biopsy is subject to great sampling error and all four “stages” may be seen in one specimen (Figure 26, Table 36).

12.3.2 MANAGEMENT

The management of PBC includes symptomatic, preventive and specific measures.

There is little one can do for the fatigue, although a sympathetic and understanding ear helps. Pruritus can generally be controlled by using the anion exchange resin, cholestyramine. There are, however, many who suffer gastrointestinal side effects from this drug, so rifampin 150 mg b.i.d. or t.i.d. can be tried instead. Ultraviolet light also helps, so that pruritus is less in the summer. A trip down south always helps in the winter! The third line of therapy is opioid antagonists, which are very effective but may cause “withdrawal” symptoms if not started in very low doses.

For the most part, the complications of long-term cholestasis can be prevented, except for the osteoporosis. Once the serum bilirubin is elevated, steatorrhea may occur with subsequent malabsorption of fat-soluble vitamins. Calcium and vitamin D supplements should be given to all patients with PBC. Fat intake should not be reduced, as this will not affect the serum cholesterol. Despite the hypercholesterolemia, there is no increase in incidence of

<table>
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<th>TABLE 36. Diagnostic features of primary biliary cirrhosis</th>
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<tr>
<td>Antimitochondrial antibody positive</td>
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<tr>
<td>Elevated serum alkaline phosphatase</td>
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<tr>
<td>Elevated serum cholesterol</td>
</tr>
<tr>
<td>Typical liver histology</td>
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<tr>
<td>Normal ERCP or MRCP</td>
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</table>
ischemic heart disease in PBC. The newer bisphosphonates may help the osteoporosis, which may cause wedging of the vertebrae.

Many specific therapies for PBC have been tried, none with resounding success. Some are definitely contraindicated – notably prednisone, because it promotes osteoporosis. Treatment with ursodeoxycholic acid (UDCA) is the current standard of care. It has very few side effects and causes a dramatic fall in all the biochemical markers for this disease, and may improve survival free of transplant in PBC patients. Untreated, the mean survival of symptomatic PBC is 12 years. Treatment with UDCA in a dose of 13-15 mg/kg/day reduces the rate of liver failure, e.g., ascites, jaundice.

The survival of those with asymptomatic disease is much longer, and some may never progress, as < 50% of patients with asymptomatic PBC die of their liver disease.

12.4 Secondary Biliary Cirrhosis
Any disease that permanently and progressively damages bile ducts and is not caused by PBC may lead to secondary biliary cirrhosis, sometimes (although not usually) in the absence of overt jaundice. The most obvious cause is biliary atresia; other pediatric conditions include the various hypoplastic duct
syndromes, other biliary tree abnormalities – Caroli’s disease, choledochal cysts, sclerosing cholangitis – and cystic fibrosis, which causes focal biliary cirrhosis. In adults the commonest cause of secondary biliary cirrhosis is probably primary sclerosing cholangitis (PSC), although iatrogenic bile duct strictures also feature.

Primary sclerosing cholangitis is the most common cause of secondary biliary cirrhosis in adults. It affects about 10% of patients with ulcerative colitis or Crohn’s colitis and only 30% of patients with PSC have no background of inflammatory bowel disease at the time of presentation. Patients are commonly asymptomatic. Just as with PBC, PSC causes presinusoidal portal hypertension, so variceal bleeding may present early – i.e., prior to the onset of jaundice (Table 37). A cholestatic enzyme pattern in any patient with liver problems should prompt the suspicion of PSC. The diagnosis is made only by ERCP (Figure 27), not by liver biopsy. Because liver biopsy is not helpful diagnostically it is performed only to see if the patient is cirrhotic. If PSC is suspected prior to ERCP, then antibiotic coverage should be given at the time of the procedure. Sepsis is the major complication of this disease and needs to be avoided if possible, as infection outside the liver precludes liver transplantation – the treatment of choice for decompensated disease. Prior to transplantation the only treatment available is symptomatic and/or preventive, as described for PBC. As yet there have been no therapeutic trials of any reasonable size performed in PSC and hence there is no standard therapeutic intervention, although UDCA therapy certainly leads to a fall in the serum markers of cholestasis and theoretically it should improve the bile flow.

12.5 Approach to the Patient with Cholestasis

12.5.1 Diagnosis
The history in any patient is always of utmost importance. A complete drug
history should be taken, including prescribed and over-the-counter drugs. A past history of cholecystectomy should never be forgotten; common bile duct stones are not unusual, even in the absence of symptoms and/or dilated bile ducts on ultrasound. Manifestations of other autoimmune disease should be sought. A history of chills and fever would make one suspect extrahepatic (nonmalignant) biliary disease.

Examination should make special note of the patient's temperature. Signs of chronic cholestasis include scratch marks, shiny nails, increased skin pigmentation, xanthelasma, xanthomatous neuropathy, and jaundice, which in its later stages takes on a greenish hue. Hepatosplenomegaly is common in PBC, PSC and biliary atresia, and with infiltrations like lymphoma.

12.5.2 LABORATORY CONFIRMATION
The standard biochemical tests are most helpful. Liver function tends to remain normal for long periods in patients with anicteric cholestasis, but the enzyme markers (alkaline phosphatase, GGT, 5’NT) are always elevated. In those with prolonged jaundice, coagulation abnormalities (correctable with vitamin K) are common. If the results of these tests confirm the clinical suspicion, then the next step is an ultrasound to look at the bile ducts. If there is jaundice associated with fever or chills, there should be no delay with the ultrasound examination of the abdomen.

12.5.3 FURTHER MANAGEMENT
Further management will depend entirely on whether the patient has dilated ducts (Figure 28). If the ducts are dilated, the management will be interventional. If the ducts are not dilated but there is still a suspicion that the problem lies in the extrahepatic biliary system (common bile duct stones following cholecystectomy, PSC), then an ERCP may still be indicated. In most circumstances, an ERCP is more helpful than Magnetic Resonance Cholangiography (MRC) when investigating possible extrahepatic biliary obstruction, as it also allows for therapeutic intervention. The true value of MRC for diagnostic purposes is uncertain and may be superseded by endoscopic ultrasound (EUS) in the future.

If the history, physical exam and ultrasound all support a diagnosis of intrahepatic cholestasis, then a liver biopsy may be indicated to make a diagnosis, if this is not already obvious at the bedside (e.g., sepsis, drug reactions). Cholestatic drug reactions may take many months to clear after the drug has been withdrawn. A clinical diagnosis of PBC needs to be confirmed by a positive anti-mitochondrial antibody test +/- a liver biopsy.

There will always be patients in whom no diagnosis can be made immediately. In the absence of jaundice, the physician has time to observe. Granulomas
of the liver are the most likely cause of a “missed” diagnosis on biopsy. Electromicroscopy may be helpful when a drug reaction is suspected.

13. CIRRHOSIS OF THE LIVER / J. Heathcote

Cirrhosis is a chronic diffuse liver disease that is characterized by fibrosis and nodule formation (Figure 29). Fibrosis is not synonymous with cirrhosis. Nodules without fibrosis are not cirrhosis, as disturbed architecture is essential for the diagnosis of cirrhosis. The condition most commonly results from liver cell necrosis and the subsequent collapse of hepatic lobules due to many factors which may cause inflammation and/or ischemia or toxic damage (e.g., excess iron, copper). Recovery occurs with formation of diffuse fibrous septa and nodular regrowth of hepatocytes. Thus, the ultimate histologic pattern is similar regardless of etiology. Liver cell necrosis is often absent when the liver is ultimately examined either by biopsy or at post mortem.

In the past, it was thought that cirrhosis was irreversible but it is now well recognized that if the injurious agent is removed, e.g., hepatitis C, copper, even hepatitis B, fibrosis regresses with time as part of the ongoing remodeling process characteristic of liver tissue.
13.1 Etiology
Known causes of cirrhosis account for about 90-95% of the cases. Most common etiologies include excess alcohol, chronic viral hepatitis and non-alcoholic steatohepatitis (NASH) (Table 38). Less common causes include hemochromatosis and the autoimmune liver diseases: autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, and chronic biliary obstruction. Other metabolic causes include $\alpha_1$-antitrypsin deficiency, Wilson's disease and galactosemia and tyrosinemia. The remaining 5-10% of patients with cirrhosis of the liver have no known cause, a condition termed cryptogenic cirrhosis. Over the last 10 years, the rate of cryptogenic cirrhosis has fallen from 30% to current levels. The most likely cause for this fall has been the availability of testing for hepatitis C and the recognition that the pathologic hallmarks of NASH often disappear once cirrhosis is present.

The etiology of the cirrhosis usually cannot be determined by the pathologic appearance of the liver (with some notable exceptions, including hemochromatosis and $\alpha_1$-antitrypsin deficiency).

13.2 Pathology
*Micronodular cirrhosis* is characterized by thick, regular septa, by small,
regenerating nodules of uniform size, and by involvement of every lobule. Often associated with the persistence of the injurious agent, this may represent the liver's relative impairment for regeneration, as may be seen in alcoholism, old age, ischemia and malnutrition.

Macronodular cirrhosis is characterized by nodules of variable size, some containing large areas of intact or regenerating parenchyma within each large nodule.

Mixed macronodular and micronodular cirrhosis may result from vigorous regrowth in a previous micronodular cirrhosis (Figure 30).

13.3 Clinical Features
The clinical features of cirrhosis relate to those features that are peculiar to the cause of the cirrhosis but more importantly to the magnitude of the hepatocellular failure and the presence of portal hypertension, along with the ability of the surviving hepatocytes to compensate for the loss. Thus, patients are categorized as having compensated or decompensated cirrhosis, each having its own clinical pathologic correlations. In the fully compensated state, there may be no symptoms whatever, the disease being suspected by a finding of an enlarged liver or spleen or found incidentally at the time of some abdominal surgery.

<table>
<thead>
<tr>
<th>Table 38. Causes of cirrhosis</th>
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<tbody>
<tr>
<td><strong>Viral hepatitis</strong></td>
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<tr>
<td>Hepatitis B</td>
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<tr>
<td>Hepatitis C</td>
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<tr>
<td>Hepatitis D</td>
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<tr>
<td>Alcohol</td>
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<tr>
<td><strong>Metabolic</strong></td>
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<tr>
<td>NASH</td>
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<tr>
<td>Hemochromatosis</td>
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<tr>
<td>Wilson's disease</td>
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<tr>
<td>α,2-antitrypsin deficiency</td>
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<tr>
<td>Galactosemia</td>
</tr>
<tr>
<td>Tyrosinemia</td>
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<tr>
<td>Autoimmune</td>
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<tr>
<td>Sclerosing cholangitis</td>
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<tr>
<td>Primary biliary cirrhosis</td>
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<tr>
<td>Autoimmune Hepatitis</td>
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<tr>
<td><strong>Drug-induced</strong></td>
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<tr>
<td><strong>Conjestic</strong></td>
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<tr>
<td><strong>Cardiac</strong></td>
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<tr>
<td><strong>Budd-Chiari</strong></td>
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<tr>
<td><strong>Cystic fibrosis</strong></td>
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or during radiological investigation of the abdomen. With progression of the
disease, features of hepatocellular failure and portal hypertension emerge.

With hepatocellular failure, patients may complain of weakness, fatigue,
weight loss and a general deterioration of health. Physical examination may
reveal the stigmata of chronic liver disease, although these are often missing
in those with chronic viral hepatitis (Section 7).

The ease of diagnosis of cirrhosis is dependent on the degree of liver
decompensation. A high index of suspicion is necessary; the condition may be
revealed only by a positive history of excess alcohol ingestion along with the
finding of hepatomegaly. Thorough inquiry into all the risk factors for acquisi-
tion of viral hepatitis needs to be made, including blood transfusion, injection
drug use (ever), tattoos, body piercing and multiple sexual partners as well as
family history. When signs of decompensation are present, the diagnosis is much
easier; the clinical features of ascites, asterixis, variceal hemorrhage, jaundice
and other signs of hepatocellular failure may be present.

Biochemical tests attempt to identify the specific etiology of the liver
disease and to assess the degree of hepatocellular dysfunction. With deterio-
rating hepatic function, albumin falls, serum bilirubin rises, and the INR/
prothrombin time becomes increased and incorrectable by parenteral vitamin K.
Liver enzymes, while helpful in assessing ongoing activity, are not of much help in assessment of the functional severity, as serum aminotransferase levels may even be within the normal range despite severe liver disease. Alkaline phosphatase is usually raised, but the level does not reflect the degree of hepatic dysfunction. Commonly a normochromic, normocytic anemia is found, with target cells noted in the blood smear. Occasionally a macrocytic anemia is present, but if gastrointestinal bleeding has taken place, the anemia may be microcytic as a result of iron loss. Depressed leukocyte and platelet counts may be present secondary to hypersplenism. The urine often contains urobilinogen and bilirubin if the patient is jaundiced. Patients with ascites exhibit a marked reduction in urinary sodium excretion. Ultrasound of the abdomen is the most helpful imaging test and will reveal an inhomogeneous nodular liver with splenomegaly if cirrhosis is advanced, but ultrasound does not reliably detect cirrhosis and neither does a CT scan. Cirrhosis can only be reliably diagnosed by a liver biopsy with histologic examination. Liver biopsy may also be helpful in establishing an etiology and degree of activity of the underlying process. When a persistent coagulopathy or ascites is present, biopsy via the transjugular route is necessary.

Prognosis depends on the degree of hepatocellular function and the etiology. The latter will determine the likelihood of whether the causative agent can be removed. Clearly the prognosis is improved if the alcoholic patient can abstain, if the patient with hemochromatosis has iron removed by venesection or if excessive copper is removed in those with Wilson's disease. In addition, if attention is paid to preventative strategies, delay or even prevention of complications is possible. Thus all cirrhotic patients should be advised to avoid aspirin or NSAIDs (which promote GI bleeding and ascites), aminoglycoside antibiotics (which promote renal failure), and narcotics (which promote encephalopathy). All episodes of infection should be treated promptly, as septicemia leads to rapid deterioration in a cirrhotic. Beta blockers should be considered for prophylaxis against variceal hemorrhage in all cirrhotics with grade II or larger varices. Early detection of hepatocellular carcinoma by screening using ultrasound on a regular, at least annual basis likely improves outcome. Liver transplant is the first treatment for small HCC. Once decompensated liver disease is present (jaundice, ascites, neurologic impairment, bleeding, coagulopathy, hyponatremia) the prognosis is poor and liver transplant should be considered, if appropriate.

### 13.4 Treatment
Clearly, where there is a specific treatment for the underlying etiology of the liver disease this should be offered. Viral hepatitis B and C with or without alcohol excess are the most common causes of cirrhosis world-wide and there
have been marked improvements in antiviral therapies leading to improved outcomes. All patients should consume a healthy, adequate diet and avoid alcohol. Otherwise the management is that of regular surveillance and early detection of hepatocellular failure. Hepatocellular failure or decompensated cirrhosis may be manifested by any of the following: coagulopathy, jaundice (in noncholestatic liver disease), hepatic encephalopathy, variceal bleeding or ascites. The Child-Pugh classification of cirrhosis, which is a very useful guide to calculate the risk of an invasive procedure, takes into account these variables plus nutritional status (Table 39). Once decompensation occurs, management includes the control of ascites, avoidance of drugs that are poorly metabolized by the liver and the prompt treatment of infection and variceal hemorrhage. Liver transplantation is now becoming the treatment of choice for many with end-stage decompensated liver disease (see Section 15). The Model for Endstage Liver Disease (MELD) score has now been developed to rank patients on the waiting list for a liver transplant.

**14. PORTAL HYPERTENSION / S.S. Lee and S.K. Baik**

Portal hypertension is defined as increased pressure in the portal vein. With the right atrial pressure as a zero reference, normal portal venous pressure is approximately 4-8 mmHg. The portal vein is formed by the confluence of the splenic and superior mesenteric veins. In a noncirrhotic normal person, blood
flows in the portal vein at an average rate of approximately 1-1.2 L/min. The simple phenomenon of increased pressure in this venous circulation unleashes a wide array of hemodynamic and metabolic consequences, including some of the most lethal and distressing complications of chronic liver disease.

14.1 Etiology
The causes of portal hypertension are diverse (Table 40). Since portal pressure is the product of portal blood flow and intrahepatic resistance, any condition causing an increase in flow or resistance will increase portal pressure. An example of a “pure” flow increase is postsurgical or traumatic splenic arteriovenous fistula. The marked increase in splenic and thus portal venous blood

### TABLE 40. Causes of portal hypertension

<table>
<thead>
<tr>
<th>Prehepatic</th>
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<tr>
<td>Splenic AV fistula</td>
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<tr>
<td>Splenic or portal vein thrombosis</td>
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<tr>
<td>Massive splenomegaly</td>
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<tr>
<td>Intrahepatic</td>
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<td>Sarcoidosis</td>
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<td>Schistosomiasis</td>
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<td>Nodular regenerative hyperplasia</td>
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<td>Congenital hepatic fibrosis</td>
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<tr>
<td>Idiopathic portal fibrosis</td>
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<tr>
<td>Early primary biliary cirrhosis</td>
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<td>Chronic active hepatitis</td>
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<td>Myeloproliferative disorders</td>
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<td>Graft-vs-host disease</td>
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<td>Established cirrhosis</td>
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<td>Alcoholic hepatitis</td>
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<tr>
<td>Alcoholic terminal hyaline sclerosis</td>
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<tr>
<td>Veno-occlusive disease</td>
<td></td>
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<tr>
<td>Posthepatic</td>
<td>Postsinusoidal</td>
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<tr>
<td>Budd-Chiari syndrome</td>
<td></td>
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<tr>
<td>Membranous IVC web</td>
<td></td>
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<tr>
<td>Right heart failure</td>
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</tr>
<tr>
<td>Constrictive pericarditis</td>
<td></td>
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</tbody>
</table>
flow leads to the development of portal hypertension. Almost all other causes of portal hypertension are mediated predominantly by increased intrahepatic resistance, although evidence indicates that most high-resistance syndromes are also accompanied by increased portal venous flow. In many conditions, the cause of the increased resistance is evident: static factors such as inflammation and fibrosis lead to vascular distortion, architectural disturbance and impingement of the intravascular spaces. Dynamic factors may be just as important. Such dynamic factors include activation of hepatic stellate cells (also called myofibroblasts, fat-storing cells or Ito cells), which are normally relatively quiescent sinusoidal cells. When activated, these cells constrict the sinusoidal endothelial space, leading to increased microvascular portal pressure.

Other less-evident mechanisms are predominant in other conditions. For example, in acute alcoholic hepatitis, swelling of hepatocytes and collagen deposition in the space of Disse lead to narrowing and distortion of sinusoidal spaces. The reasons for the increased mesenteric (and thus portal venous) blood flow in high-resistance states remain unclear. One theory postulates that a circulating vasodilatory humoral factor that would normally be inactivated by the liver escapes into the systemic circulation through shunts or hepatocellular insufficiency.

There are two separate and somewhat overlapping classification systems for the causes of portal hypertension, using either the liver or the hepatic sinusoid as the reference point. The former classifies conditions into prehepatic, intrahepatic and posthepatic causes, while the latter divides conditions into presinusoidal, sinusoidal and postsinusoidal causes (Table 40). However, the exact site of increased resistance in many intrahepatic causes of portal hypertension has recently been questioned, and it is likely that the predominant resistance sites could change according to the stage of many disease processes. For example, early primary biliary cirrhosis is thought to produce mainly presinusoidal hypertension, but as dense cirrhosis supervenes, sinusoidal hypertension becomes more important. Similarly, an early lesion of alcoholic liver disease, the central or terminal hyaline sclerosis, characterized by zone 3 fibrosis, would cause postsinusoidal hypertension, with sinusoidal hypertension predominating as cirrhosis becomes established. In practical terms, there are reasons for trying to correctly classify resistance sites. One is for predicting responses to surgical shunting procedures: presinusoidal conditions generally have well-preserved hepatocellular function and thus respond well to diversion of portal blood, whereas sinusoidal and postsinusoidal conditions tend to be associated with varying degrees of hepatic insufficiency. Another is that ascites generally occurs only with sinusoidal and postsinusoidal hypertension.
14.2 Pathophysiology

Portal pressure can be measured by several methods. A catheter inserted into a hepatic vein and then wedged provides a good estimate of the upstream portal venous pressure, unless the site of resistance is proximal to the intrahepatic portal vein (as in portal vein thrombosis wherein the wedged hepatic vein pressure will be normal in the presence of significant portal hypertension). The spleen, liver or portal vein can be directly percutaneously punctured by small-gauge (20-22 gauge) needles to obtain reliable estimates of portal pressure. Measurement of portal pressure is mostly used for research purposes, as its invasiveness precludes wide clinical use.

Portal hypertension leads to many clinical complications. Ascites is directly related to the development of sinusoidal or postsinusoidal hypertension. Portosystemic collateral vessels form in an attempt to decompress the portal hypertension (Table 41). The most troublesome site of collateral formation is around the proximal stomach and distal esophagus (gastroesophageal varices). Some of these dilated veins grow to more than 2 cm in diameter (Figure 31). Therefore, acute variceal bleeding can be one of the most dramatic presentations in clinical medicine (Figure 32). Variceal bleeding and hepatocellular failure are the two commonest causes of death in cirrhosis. Indeed the mortality rates for variceal bleeding range from 15-50% depending on the degree of hepatic

<table>
<thead>
<tr>
<th>Location</th>
<th>Portal circulation</th>
<th>Systemic circulation</th>
<th>Clinical consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal stomach and distal esophagus</td>
<td>Coronary vein of stomach</td>
<td>Azygos vein</td>
<td>Submucosal gastroesophageal varices</td>
</tr>
<tr>
<td>Anterior abdominal wall</td>
<td>Umbilical vein in falciform ligament</td>
<td>Epigastric abdominal wall veins</td>
<td>Caput medusae</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>Splenic vein branch</td>
<td>Left renal vein</td>
<td>Usually none</td>
</tr>
<tr>
<td></td>
<td>Sappey’s veins (around liver and diaphragm)</td>
<td>Retzius’s vein</td>
<td>Usually none</td>
</tr>
<tr>
<td>Anorectal</td>
<td>Middle and superior hemorrhoidal veins</td>
<td>Inferior hemorrhoidal vein</td>
<td>May be mistaken for hemorrhoids</td>
</tr>
</tbody>
</table>

Table 41. Common sites of portosystemic collateral formation
function: Child-Pugh class A, B, and C patients have, respectively, 15%, 20-30% and 40-50% mortality rates when their varices bleed.

The risk of bleeding from gastroesophageal varices is related to several factors. First, a threshold minimum level of portal pressure of approximately 10-12 mmHg is necessary for varices to form. However, above this level it is unclear whether absolute height of portal pressure affects the bleeding risk. Factors such as intrathoracic pressure gradients induced by coughing, straining or sneezing, and damage to the variceal wall by acid reflux into the esophagus do not play a role. The two factors most important in determining bleeding risk are variceal size and local variceal wall characteristics. Several studies have shown that small varices almost never bleed, while the bleeding risk of medium-sized varices is approximately 10-15% over two years, and that of large varices, approximately 20-30% over the same period. It is now clear that certain endoscopic characteristics of the varices are also predictive of high bleeding risk. These endoscopic features are the red and blue color signs. Small localized wall defects such as thin-walled blebs or sacs in the wall look like red spots or streaks and have variously been termed “red wale markings,” “cherry-red spots,” or “red streaks,” while a diffuse pronounced blue color indicates a large varix (vein) with stretched mucosa covering it.

**Figure 31.** Endoscopic view of large esophageal varices that almost completely obscure the lumen.

**Figure 32.** Endoscopic view of an acute variceal bleed, within the first few seconds. Arrow points to a jet of blood spurring from a varix at approximately the 10:00 position in the field of view. (Photo courtesy of Dr. Atsushi Toyonaga, Kurume University Hospital, Japan).
Approximately 30-50% of upper GI bleeding episodes in patients with portal hypertension originate from nonvariceal sources. Patients with alcoholic cirrhosis have an increased incidence of acid-peptic disease, mostly erosive gastritis. This is probably due to a toxic effect of alcohol on the gastric mucosa. It is now clear that the majority of nonvariceal upper GI bleeding in patients with all types of cirrhosis is due to a peculiar form of gastropathy seen in the stomach in portal hypertension. Several features distinguish this portal hypertensive gastropathy from the erosive or inflammatory gastritis seen in noncirrhotic patients (Table 42). The major symptom of portal hypertensive gastropathy is bleeding. Pain or dyspepsia are uncommon as presenting features of this type of gastropathy. The appropriate treatment for this condition is still unclear, but it probably responds to measures to decrease portal pressure, although a possible role for cytoprotective agents has also been suggested.

### 14.3 Diagnosis

Diagnosing portal hypertension is usually easy. The patient often has concomitant ascites and splenomegaly, along with the stigmata of chronic liver disease. In contrast, all the prehepatic and many of the presinusoidal conditions have well-preserved liver function and rarely have ascites. Abdominal wall collaterals radiate outward from the umbilicus. When they are very prominent, it is easy to see why this condition is termed “caput medusae,” after the fearsome

<table>
<thead>
<tr>
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<th>Portal hypertensive gastropathy</th>
<th>Inflammatory gastritis</th>
</tr>
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<tbody>
<tr>
<td><strong>Endoscopic appearance</strong></td>
<td>Mosaic pattern, speckled red spots</td>
<td>Discrete red erosive lesions</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td>Predominantly fundus</td>
<td>Predominantly antrum</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Scant inflammatory cell infiltrate, prominent vascular dilatation, mucosal and submucosal lesions</td>
<td>Heavy inflammatory cell infiltrate, mucosal lesions</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Surgery, ? beta blockers, ? cytoprotective agents</td>
<td>Acid suppression, cytoprotective agents</td>
</tr>
</tbody>
</table>
creature in Greek mythology with the serpentine hairdo. Dilated abdominal wall veins, especially in the upper abdomen, are common, but caput medusae is rare. When caput medusae veins become so large that a venous hum is audible by auscultation, this is the Cruveilhier-Baumgarten sign. A much commoner diagnostic clue may be the presence of anorectal varices masquerading as hemorrhoids. Gastroesophageal variceal bleeding produces large-volume, brisk bleeding with hematemesis and, later, melena or hematochezia. Portal hypertensive gastropathy may also produce brisk bleeding, but usually causes low-volume slow oozing manifested mainly by melena or iron-deficiency anemia.

14.4 Management
Managing the acute bleeding episode consists of general resuscitative measures such as volume and blood replacement, and specific measures to stop the bleeding. Various pharmacological, mechanical and surgical modes of arresting hemorrhage are used, usually in that order. Vasoconstrictive drugs to stop bleeding include vasopressin and somatostatin or their longer-acting analogues, terlipressin and octreotide, respectively. Vasopressin infusions induce generalized arteriolar and venous constriction, with resultant decreased portal venous flow and thus pressure, and at least temporary cessation of bleeding in 60-90% of cases. However, the generalized vasoconstriction also may rarely result in peripheral vascular ischemia, myocardial ischemia or infarction and renal tubular damage. Terlipressin appears to have significantly less of these side effects and has therefore largely supplanted vasopressin for treatment of acute variceal bleeding.

Octreotide, because of its longer duration of action than somatostatin, is logistically easier to administer than the latter drug, and thus has become more popular. Unlike the case for vasopressin and terlipressin, the exact mechanism of action of somatostatin and octreotide remains unsettled. These drugs probably suppress the release of vasodilatory hormones such as glucagons, leading to a net vasoconstrictive effect. Side effects are relatively infrequent, and the overall frequency of side effects similar to terlipressin. In objective terms, terlipressin and octreotide/somatostatin are probably equal in efficacy and side effects, so one cannot be definitively recommended over the others. Whatever drug is used, it is generally advisable to continue drug therapy for 72 hours and at least six to 12 hours after the initial bleeding stops, to prevent rapid rebleeding.

Mechanical modes of therapy include inflatable balloons from direct tamponade. The Sengstaken-Blakemore tube has both an esophageal and a small gastric balloon; the Linton-Nachlas tube, with only a large gastric balloon, is attached to a small weight to staunch the cephalad flow of blood in the varices.
Both tubes carry significant complication rates (15%), especially in inexperienced hands. The most common complications of esophageal balloon therapy for varices include aspiration, esophageal perforation and ischemic (pressure) necrosis of the mucosa.

The most common nonsurgical therapies are endoscopic variceal sclerotherapy and band ligation. For sclerotherapy, highly irritant solutions such as ethanolamine or polidocanol are injected through endoscopic direct vision into and around the bleeding varix. The subsequent inflammation leads to eventual thrombosis and fibrosis of the varix lumen. Possible complications include chest pain, dysphagia, and esophageal ulcerating and strictureing. Because of these adverse effects, sclerotherapy has almost disappeared from routine clinical use in this country. It has been replaced by endoscopic band ligation (Figure 33), which is equally effective but carries much less side effects. The method of variceal band ligation is similar to the rubber band ligations used to fibrose anorectal hemorrhoids. The combination of endoscopic therapy and either balloon tamponade or drug therapy to control actively bleeding varices is successful in 90-95% of cases.

When all the above measures fail, emergency surgery may be tried. Emergency portacaval shunt surgery has been abandoned because of a 30-50% operative mortality rate. The simplest and probably the best surgical choice in the emergency situation is esophageal transaction, in which a mechanical device transects and removes a ring of esophageal tissue, and then staples the ends together. Another type of portosystemic “surgery,” the transjugular intrahepatic portosystemic stent-shunt (TIPS), has virtually
eliminated the need for emergency surgery. In this procedure, an intrahepatic shunt between branches of the hepatic and portal veins is made by balloon dilation of liver tissue, and then an expandable metal stent of approximately 1 cm diameter is lodged into the fistula. The procedure can be done by a radiologist using fluoroscopy-guided catheterization, and requires only light sedation and local anesthesia.

Once the acute bleeding episode has been treated, how do we reduce the risk of future rebleeding? Before considering any other therapy, some obvious common-sense measures should be taken. For example, patients with cirrhosis caused by alcohol (the cause of approximately 50% of cirrhosis in Canada) absolutely must stop drinking; the rebleeding and mortality rates in patients who continue alcohol use are much higher than in those who remain abstinent.

Prophylactic therapy to prevent bleeding may be divided into primary (to prevent the first bleed in a patient with varices who has never bled) and secondary prophylaxis (to prevent rebleeds). There is still much conflicting literature on these two topics, but for now, the following preliminary recommendations can be made. First, patients with large varices that have never bled should be started on beta-blocker therapy at doses sufficient to reduce the resting heart rate by 20-25%. Beta-adrenergic antagonists are thought to produce arteriolar and venous constriction and significantly reduce blood flow through portosystemic collaterals while modestly reducing portal pressure. Endoscopic sclerotherapy/banding, TIPS and surgery carry risks and are more expensive. Indeed, recent cost/benefit analysis suggests that beta-blockers are clearly the most cost-effective strategy for primary prophylaxis.

The appropriate secondary prophylaxis regimes remain controversial. There is probably a minority subgroup that responds favorably to beta-blocker therapy, but they cannot be easily identified. One approach is to perform enough endoscopic ligation sessions (usually 3-4) to obliterate varices or reduce them to small size. Treatment failures on this regime (e.g., those with recurrent bleeding) could be considered either for TIPS or surgery (portacaval shunt). Decompression of the portal venous system should not be done in patients with a history of, or active, encephalopathy; it would only change the mode of death (encephalopathy/liver failure vs variceal bleed), not the outcome.

Prehepatic causes of portal hypertension such as portal vein thrombosis generally respond well to some type of portal-mesenteric diversion procedure such as mesocaval or portacaval shunting. In these cases, normal liver function protects against the development of encephalopathy or hepatic insufficiency when portal blood is diverted from the liver.

The definitive treatment for most of the complications of end-stage liver disease, including recurrent GI bleeding due to severe portal hypertension, is
orthotopic liver transplantation. The presence of a surgical portacaval or mesocaval shunt complicates the transplantation procedure; thus major shunting operations should only be used as a last resort in the patient who does not respond to all other modes of therapy, including TIPS. In practice, such resistant patients are extremely rare.

14.5 Cirrhotic Cardiomyopathy

Portal hypertension is associated with cardiovascular disturbances. The circulation becomes hyperdynamic, manifesting as increased cardiac output, and decreased arterial pressure and systemic vascular resistance. Paradoxically, despite the increased cardiac output at rest, when the heart is stressed by stimuli such as exercise, drugs or major surgery, the ventricular contractile response is blunted. When this phenomenon was first recognized about three decades ago, it was simply presumed to be mild or latent alcoholic cardiomyopathy. However, studies both in humans and animal models of non-alcoholic cirrhosis have amply demonstrated impairment of cardiac function regardless of the etiology of cirrhosis. Thus this peculiar syndrome of increased basal cardiac output, but attenuated cardiac response to physiologic, pharmacologic or surgical stimuli is now known as “cirrhotic cardiomyopathy.”

Both systolic and diastolic left ventricular contractile dysfunction has been observed. For example, a normal person can easily triple the resting cardiac output in response to submaximal exercise; the cirrhotic patient can only double the cardiac output. Diastolic indices indicate a stiff noncompliant ventricle. Electrophysiological abnormalities include a prolonged electrocardiographic QT interval, which has been observed in 30-50% of cirrhotic patients. At present the definitive diagnostic criteria for cirrhotic cardiomyopathy have yet to be agreed upon, although an expert consensus group is working on this with results to be released in late 2005. Therefore, for now, cirrhotic cardiomyopathy can be tentatively defined by these criteria: 1) baseline increased cardiac output but blunted ventricular response to stimuli, 2) systolic and/or diastolic dysfunction, 3) absence of overt left ventricular failure at rest, 4) electrophysiological abnormalities including prolonged Q-T interval in the ECG.

Histological changes of cirrhotic cardiomyopathy include ventricular hypertrophy and dilatation, myocardial fibrosis, subendocardial edema, and nuclear and cytoplasmic vacuolation of cardiomyocytes.

The pathogenesis remains unclear, but several factors are thought to contribute. These include downregulation of the cardiac β-adrenergic receptor system, cardiomyocyte plasma membrane physicochemical changes, and overactivity of cardiodepressant substances such as nitric oxide and carbon monoxide.
The optimum management of cirrhotic cardiomyopathy remains uncertain. Since cirrhotic cardiomyopathy is usually subclinical, its clinical significance is generally unappreciated. But overt ventricular failure may develop during the challenge of significant stimuli such as liver transplantation or portosystemic shunting procedures. Because the cardiac reserve function is borderline in patients with cirrhosis, cardiovascular status should be carefully monitored, especially when patients undergo stresses such as hepatic surgery. Standard treatment for heart failure including oxygen supplementation, diuretics and afterload reduction is required when overt cirrhotic ventricular failure occurs.

14.6 Hepatopulmonary Syndrome and Portopulmonary Hypertension
Pulmonary abnormalities are also observed in cirrhotic patients. In the pulmonary circulation, systemic arterial hypoxemia due to pulmonary vasodilatation commonly occurs even though its clinical manifestations are usually not apparent. Hepatopulmonary syndrome is defined as the triad of liver disease, arterial hypoxemia, and intrapulmonary vascular dilatation, in the absence of any intrinsic heart or lung disease. Hepatopulmonary syndrome is thought to be an important cause of hypoxemia in patients with cirrhosis, although the much rarer pulmonary hypertension can also cause hypoxemia in these patients.

Hypoxemia in the hepatopulmonary syndrome is likely associated with pulmonary vascular dilatation, which results in ventilation-perfusion mismatching. The pathogenesis of pulmonary vasodilation in hepatopulmonary syndrome is not yet clear. Histological findings in the lungs including precapillary and capillary dilatation, and anatomic arteriovenous communications have been reported in some patients with hepatopulmonary syndrome. An imbalance between vasodilator and vasoconstrictor systems may lead to a decreased vascular resistance in the lung. In support of this theory, several studies suggest that nitric oxide overactivity plays a major role in vasodilatation of hepatopulmonary syndrome. After liver transplantation, reversal of the increased levels of exhaled nitrites and nitrates, the end-products of nitric oxide metabolism, occurs and arterial $O_2$ saturation returns to normal values. Moreover, in the cirrhotic-rat model, increased levels of endothelial nitric oxide synthetase are correlated with alterations in gas exchange. The clinical manifestations of decreased Pa$O_2$ are usually mild because the high resting cardiac output generally tends to minimize the development of severe arterial hypoxemia. However, some patients with a significant intrapulmonary shunt secondary to portal hypertension suffer from a more severe arterial hypoxemia with $O_2$ diffusion limitation, which is clinically more evident.

Hepatopulmonary syndrome is diagnosed by the following criteria: 1) the presence of chronic liver disease, 2) arterial hypoxemia (Pa$O_2 < 70$ mmHg)
without a definite parenchymal lesion in the chest X-ray, 3) pulmonary vascular dilatation demonstrated by echocardiography including contrast and transesophageal imaging, or by lung perfusion scan.

Supplemental oxygen therapy can be tried for symptomatic hepatopulmonary syndrome. However, because of ventilation/perfusion mismatching, such treatment may be ineffective in raising arterial oxygen tension. Several drugs including aspirin, indomethacin, and oral almitrine bismesylate have been tried to improve ventilation-perfusion relationships, but with limited success in improving hypoxemia. Interventional radiology is a therapeutic option in highly selected patients. This treatment should be reserved for patients suspected to have an arteriovenous shunt, with severe hypoxemia and a poor response to 100% oxygen therapy. In such patients, coil embolotherapy can obliterate the distinct arteriovenous communications that cause hypoxemia due to right-to-left intrapulmonary shunting.

Complete resolution of the syndrome after orthotopic liver transplantation has been documented, especially in children. However, patients with significant intrapulmonary shunting and severe hypoxemia have an increased perioperative mortality with liver transplantation.

Another pulmonary vascular consequence of cirrhosis is portopulmonary hypertension, defined as pulmonary arterial hypertension associated with vascular or microvascular occlusive or constrictive processes in advanced liver disease. The pathogenesis is unclear but may be secondary to the hyperkinetic, high-flow circulatory state, increased central blood volumes in the lung, and non-embolic pulmonary vasoconstriction or obliteration.

In some patients with portopulmonary hypertension, continuous infusion with intravenous prostaglandin I2 can ameliorate pulmonary hemodynamics. Increased cardiopulmonary mortality following liver transplantation occurs in patients with moderate to severe pulmonary hypertension. Therefore, the clinical importance of both hepatopulmonary syndrome and portopulmonary hypertension has become recognized with the increasing popularity of liver transplantation.

15. ASCITES AND SPONTANEOUS BACTERIAL PERITONITIS / F. Wong

15.1 Ascites
Ascites is a detectable collection of free fluid in the peritoneal cavity. The risk of developing ascites after the diagnosis of cirrhosis is approximately 50% over 10 years. The two-year survival after the onset of ascites is 50%. This is reduced to six months with the development of refractory, or diuretic-resistant, ascites. This contrasts with a survival rate of 80% in two years
following liver transplantation. Ascites also predisposes patients to life-threatening complications such as spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome. Therefore, the development of ascites is an indication for referral for assessment for liver transplantation.

The pathogenesis of ascites in cirrhosis has remained controversial. Sodium retention is central to the development of ascites. What leads to the development of sodium retention in cirrhosis is the controversy. There is now ample evidence to support that sodium retention in cirrhosis, although subtle, begins before the development of ascites. At the pre-ascitic stage of cirrhosis, erect posture induces sodium and hence water retention, via the activation of the intra-renal renin-angiotensin system in that posture. When the patient assumes a supine posture, there is redistribution of the excess volume to the upper part of the body. The circulation vasodilates and becomes hyperdynamic. The renal circulation improves and the excess sodium is then excreted.

As the cirrhotic process progresses, changes in the circulation occur. The hyperdynamic circulation, which is only present in the supine posture in the pre-ascitic stage, becomes more obvious and eventually appears also in the erect posture. This is the result of increasing vasodilatation occurring both in the splanchnic and systemic circulations, due to the presence of excess vasodilators. The Peripheral Arterial Vasodilatation Hypothesis proposes that, in cirrhosis, arterial vasodilatation leads to a decrease in splanchnic and systemic vascular resistance with pooling of blood in the splanchnic circulation, resulting in a reduction of the effective arterial blood volume. This in turn further activates various neurohumoral pressor systems to increase renal sodium and water retention in an attempt to restore the effective arterial blood volume and maintain blood pressure. The renal circulation, however, is exquisitely sensitive to the vasoconstrictive effects of these neurohumoral pressor systems and the glomerular filtration rate decreases. This further enhances renal sodium retention. When the increased renal sodium and water retention cannot keep pace with the arterial vasodilatation, the cascade of further activation of neurohumoral pressor systems follows, leading to further sodium and water retention. Hepatic dysfunction also stimulates renal sodium retention, through some yet undefined mechanism, as sodium excretion is related to a threshold of hepatic function. In the presence of sinusoidal portal hypertension, some of the excess fluid is preferentially localised to the peritoneal cavity as ascites (Figure 34).

Clinically, the first evidence of ascites is weight gain. Peritoneal fluid of less than 2 L is difficult to detect clinically and ultrasound is useful in defining small amounts of ascites. The abdomen is distended, often with fullness in the flanks. Bulging flanks and the presence of flank dullness are the most
sensitive physical signs for ascites, whereas eliciting a fluid wave or confirming shifting dullness are the most specific. Complications related to ascites and increased intra-abdominal pressure, such as umbilical hernia may be present. Scrotal and leg edema are found with severe fluid retention. A pleural effusion can accompany ascites and it is usually on the right side. This is due to the presence of a diaphragmatic defect which allows ascitic fluid to pass into the pleural cavity. Occasionally, only a pleural effusion is present without any ascites. Patients will also demonstrate signs and symptoms of a hyperdynamic circulation, such as systemic hypotension, resting tachycardia and warm periphery, as well as evidence of portal hypertension such as distended abdominal wall veins radiating from the umbilicus. Other complications of cirrhosis such as jaundice and muscle wasting, which can be quite profound, may also be present.

Examination of ascitic fluid by diagnostic paracentesis should be performed at first presentation, or when there is alteration of the patient's clinical state, such as a sudden increase in the amount of ascitic fluid, worsening of encephalopathy, abdominal pain or presence of fever, in order to rule out other complications such as SBP, hepatocellular carcinoma or other non-cirrhotic
causes of ascites (Table 43). Ascitic fluid analysis should include a total polymorphonuclear (PMN) count, protein and albumin concentrations and cultures. Exactly 10 mL of ascitic fluid should be directly inoculated into blood culture bottles at the bedside. This increases the diagnostic yield from 50% to > 80% when the PMN count is > 250 cells/µL which is diagnostic of SBP. Variants of SBP are shown in Table 44. A serum-ascitic fluid albumin gradient (SAG) of > 11g/L has a > 97% accuracy in predicting cirrhotic ascites. Likewise, a serum-ascitic albumin gradient of < 11g/L confers a > 97% accuracy in excluding portal hypertension as a cause of the ascites. A high protein content may be associated with congestive heart failure or Budd-Chiari syndrome and may be seen in pancreatic ascites. A low ascitic protein count (< 10 g/L) puts the cirrhotic patient at increased risk for developing SBP. Either abdominal ultrasound or CAT scan of the abdomen may be used for detection of ascites. In particular, abdominal ultrasound can detect only a few millilitres of ascitic fluid and is highly sensitive (> 95%) and specific (> 90%). It can also direct the site of paracentesis.

TABLE 43. Indications for diagnostic paracentesis

<table>
<thead>
<tr>
<th>Indication</th>
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<tr>
<td>New-onset ascites</td>
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<tr>
<td>Hospital admission of the cirrhotic patient</td>
</tr>
<tr>
<td>Development of:</td>
</tr>
<tr>
<td>– peritoneal signs/symptoms – e.g., fever, abdominal pain</td>
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<tr>
<td>– alterations in GI motility</td>
</tr>
<tr>
<td>– encephalopathy</td>
</tr>
<tr>
<td>– renal insufficiency</td>
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<tr>
<td>Ascitic patient with GI hemorrhage</td>
</tr>
</tbody>
</table>

TABLE 44. Variants of spontaneous bacterial peritonitis

<table>
<thead>
<tr>
<th>Ascitic fluid analysis</th>
<th>PMN count</th>
<th>Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spontaneous infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis</td>
<td>&gt; 250 cell/µL</td>
<td>single</td>
</tr>
<tr>
<td>Monomicrobial non-neutrocytic bacterascites (MNNB)</td>
<td>&lt; 250 cell/µL</td>
<td>single</td>
</tr>
<tr>
<td>Culture-negative neutrocytic ascites (CNNA)</td>
<td>&gt; 250 cell/µL</td>
<td>negative culture</td>
</tr>
<tr>
<td><strong>Secondary infections</strong></td>
<td>&gt; 250 cell/µL</td>
<td>multiple</td>
</tr>
</tbody>
</table>
The management of cirrhotic ascites begins with treatment of the etiologic factors, if possible, such as abstinence from alcohol. Patients with decompensated cirrhosis from hepatitis B should also be treated with antiviral therapy such as lamivudine, which reverses the decompensation. Although bed rest will result in redistribution of body fluid, salt and fluid restriction is required to mobilise the ascites. The patient is usually prescribed a low salt diet containing 44-66 mmol sodium per day, which is lower than that contained in a no-added salt diet. Professional dietary advice is necessary and patients require specific instructions regarding where to purchase low salt food. Salt substitutes are contraindicated as they often contain potassium chloride and can therefore predispose the patients who are taking potassium-sparing diuretics to the development of hyperkalemia. Patients should be carefully monitored with daily weights and frequent 24-hour urinary sodium excretion measurements. Urinary creatinine is measured simultaneously to assess completeness of the collection. Random urine sodium assessments are unreliable as urine sodium excretion varies over the course of the day. However, a urine Na/K ratio of > 1 predicts a urinary sodium excretion of > 78 mmol/day with > 95% accuracy. Measurement of abdominal girth is unreliable as gaseous distension is common. The rate at
which ascitic patients gain or lose weight can be used to assess compliance with
the low salt diet and efficacy of treatment (Figure 35).

Diuretic therapy, in addition to salt and fluid restriction, will be required in
90% of patients to manage ascites. Spironolactone, a distal diuretic with anti-
aldosterone activity, is the preferred first line diuretic. This is because ascitic
patients usually have hyperaldosteronism. Furthermore, any sodium reabsorp-
tion that is blocked by loop diuretics at the Loop of Henle will be reabsorbed
when the sodium is delivered to the distal tubule. Combination diuretic therapy,
with both a distal potassium-sparing and a loop diuretic, acting on two
different sites of the nephron, is now the standard of care. Spironolactone is
usually started at a dose of 100 mg/day. Spironolactone has a slow onset and
offset of action because its half-life in cirrhotic patients can be as long as
35 hours. Therefore, frequent dose adjustments are unnecessary and patients
should still be monitored even after spironolactone is discontinued. One of its
unacceptable side effects is painful gynecomastia. Amiloride, another potassium-
sparing diuretic, is a less potent but certainly acceptable alternative. The starting
dose is 5 mg/day. Either potassium-sparing diuretic is usually combined with
furosemide, starting at 40 mg/day. The combination can be increased in a
stepwise fashion (Table 45). Electrolyte abnormalities and renal dysfunction
are common and patients should be monitored regularly. Initial out-patient
management may be attempted if the volume of ascites is small and in
the absence of concomitant gastrointestinal hemorrhage, encephalopathy,
infection or renal failure. Hypokalemia and hypochloremic alkalosis can

TABLE 45.  Step-wise approach to the use of diuretic therapy for the management of ascites.*

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>100 mg</td>
<td>200 mg</td>
<td>300 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>Amiloride</td>
<td>5 mg</td>
<td>10 mg</td>
<td>15 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40 mg</td>
<td>80 mg</td>
<td>120 mg</td>
<td>160 mg</td>
</tr>
</tbody>
</table>

Increase diuretics if 1. weight loss < 1.5 kg in 1 week, and
2. patient is compliant with low-Na diet, and
3. renal function is normal, and
4. no electrolyte abnormalities or encephalopathy

*Monitor 1. daily weights
2. weekly postural symptoms/signs
3. twice-weekly electrolytes, renal function
4. symptoms/signs of encephalopathy
precipitate encephalopathy. Too-rapid mobilisation of fluid will result in worsening of renal function and one should aim at a weight loss of 0.5 kg/day. Patients with peripheral edema can have their fluid mobilized more rapidly, as the edema fluid can easily be absorbed to replenish the intravascular volume. Symptoms of encephalopathy, a serum sodium ≤ 125 mmol/L or a serum creatinine of ≥ 130 mmol/L should be dose-limiting. Daily weights and at least twice-weekly electrolytes and renal function should be monitored initially. Urine sodium excretion must be greater than the oral sodium intake for the patient to lose weight. Weight loss of greater than 0.5 kg/day should be discouraged. This is because the amount of ascitic fluid that can be mobilized each day is ≤ 700 mL. Therefore, weight loss of > 0.5 kg per day usually means loss of fluid from the circulatory volume, thus predisposing the patient to the development of renal failure.

Refractory ascites is defined as ascites unresponsive to 400 mg of spironolactone or 30 mg of amiloride plus up to 160 mg of furosemide daily for two weeks in a patient who has been compliant with sodium restriction. Non-compliance with sodium restriction is a major and often overlooked cause of so-called “refractory” ascites. Other causes of refractory ascites include the development of SBP, hepatocellular carcinoma and intrinsic renal pathology. Refractory ascites without any underlying cause usually indicates a grave prognosis, with only 50% survival at six months. Large volume paracentesis is now recognized as a safe and effective therapy for the treatment of refractory ascites. Removal of ascitic fluid volume of up to 5 L without the simultaneous infusion of plasma expanders is safe in non-edematous patients. Larger volumes can be removed in edematous patients. In one large randomized controlled trial, large volume paracentesis was safer and more effective than diuretic therapy for management of ascites with reduced length of hospitalization. There was, however, no survival advantage of paracentesis over diuretic therapy. Albumin infusion of 6-8 g/L of ascitic fluid removed has been recommended for repeated large volume paracenteses. This is because patients may develop a post-paracentesis syndrome known as circulatory dysfunction. This is characterized by a further rise in renin-angiotensin activity and the development of renal impairment. The risk factors for the development of post-paracentesis circulatory dysfunction are unknown. There is still some controversy regarding the use of albumin post-paracentesis, as patients who do not receive albumin have not been shown definitively to have greater mortality. Other plasma expanders, such as hemaccel, dextran 70 and pentaspan, have also been used and are equally effective. However, one group in Barcelona has suggested that albumin is superior to all the other volume expanders.

A peritoneovenous shunt may be considered in selected patients with good liver reserve. It can be dramatically effective in resolving the ascites, decreasing
frequency of hospitalizations and decreasing diuretic requirement. However, because of its many complications, which include thrombosis of the superior vena cava, infection and blockage or dislodgement of the shunt, peritoneovenous shunts are not inserted often these days. Furthermore, there are better treatment options for ascites and fewer surgeons are now technically skilled with the procedure.
A transjugular intrahepatic portosystemic stent shunt or TIPS has recently been shown to be an effective means of managing refractory ascites. A communication is created between a branch of the portal vein and a branch of the hepatic vein and held open by a metal stent. This reduces the sinusoidal portal pressure and allows a slow but effective elimination of the ascites. There are now four published randomized controlled trials showing that TIPS is better than large volume paracentesis in the control of ascites. There is still a debate as to whether TIPS provides a survival advantage over large volume paracentesis. Without diuretics, sodium excretion begins after the first month, and slowly increases thereafter. Complete resolution of ascites eventually occurs in approximately two-thirds of patients, and a partial response in the other third. It is now recognised that patients with very advanced liver disease have higher morbidity and mortality after TIPS. It is therefore not recommended for patients with a Child-Pugh score of > 12. Elderly patients also fared less well. Predictors of early mortality include active bleeding at the time of TIPS insertion for ascites, a prior history of encephalopathy, significant jaundice (bilirubin > 51 mmol/L) and elevated transaminases (ALT > 1,000 IU/L). Absolute contra-indications to TIPS insertion include ongoing high-grade encephalopathy, cardiac or intrinsic renal disease, non-compliance with sodium and water restriction and the very elderly (> 70 years). The major complications are shunt stenosis and hepatic encephalopathy. Therefore, regular assessments of shunt patency with doppler ultrasound and/or angiography are required. Prophylactic use of lactulose can reduce the incidence of encephalopathy. Shunt hemolysis should be considered, in addition to worsening liver function, if the serum bilirubin increases post-TIPS insertion. In the suitably selected patient, the result can be very gratifying with improved nutritional status once the ascites is eliminated. Liver transplantation should always remain a treatment option in these patients. An algorithm for the management of ascites appears in Figure 36.

15.2 Spontaneous Bacterial Peritonitis
Spontaneous bacterial peritonitis is a common and often fatal complication of cirrhosis. It is a clinical syndrome in which ascites becomes infected in the absence of a recognisable cause of peritonitis. Its recent increased incidence may be due to greater recognition. The yearly risk of developing SBP after the onset of ascites is approximately 20-30%. Risk factors include prior episode of SBP, recent variceal hemorrhage, an ascitic fluid protein of less than 10 g/L and jaundice (bilirubin > 43 mmol/L). In most cases, the infection occurs after admission into hospital. About one third of cases of SBP are asymptomatic and the clinician should not hesitate in performing a diagnostic paracentesis.
The indications for diagnostic paracentesis to rule out a diagnosis of SBP are shown in Table 43.

SBP may present with fever and/or abdominal pain. More often, its presentation is atypical with worsening of encephalopathy or renal function. The “gold standard” for diagnosing SBP is an ascitic fluid PMN count of > 250 cells/µL. A variant of SBP known as culture-negative neutrocytic ascites are culture negative cases of suspected SBP with an ascitic fluid PMN count of > 250 cells/µL. The patients with culture-negative neutrocytic ascites have the same clinical presentation and carry the same unfavourable prognosis as those with SBP (Table 44). Positive culture results may take 48 hours and Gram stains of ascitic fluid are only positive in 10-50% of infected patients. Therefore, treatment for suspected SBP should start immediately after the diagnostic PMN count rather than waiting for positive culture results. Another variant of SBP is monomicrobial non-neutrocytic bacterascites. In this scenario, the ascitic PMN count is < 250 cells/µL, but the subsequent ascitic culture is positive. It is not known whether this represents an early stage of SBP. It is recommended that the patient undergo repeat paracentesis. If either the ascitic culture is again positive or the PMN count is > 250 cells/µL, then the patient should be treated as presumed SBP. Gram negative bacilli account for 70% of cases of SBP. E. coli is the commonest pathogen isolated (Table 46). Anaerobic organisms are uncommon causes of SBP as the oxygen tension in the ascitic fluid is too high for their survival. Among these, Bacteroides species appear to be more common than other anaerobes. A management algorithm for SBP is shown in Figure 37. Cefotaxime, a broad-spectrum, third-generation cephalosporin is now recognized as the treatment of choice for SBP. Its spectrum includes most organisms responsible for SBP and it is not nephrotoxic in the therapeutic range. A five-day course of Cefotaxime 2 g intravenously every eight to 12 hours is as effective as a ten-day course. Other treatment options include intravenous followed by oral amoxicillin/clavulanic acid, or intravenous ciprofloxacin followed by oral treatment, or oral ofloxacin in

<table>
<thead>
<tr>
<th>Gram-negative bacilli</th>
<th>Gram-positive organisms</th>
<th>Anaerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>Streptococcus</td>
<td>Bacteroides</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>Group D streptococcus</td>
<td>Clostridia</td>
</tr>
<tr>
<td>C. freundii</td>
<td>S. pneumoniae</td>
<td>Lactobacillus</td>
</tr>
<tr>
<td>Proteus</td>
<td>S. aureus</td>
<td></td>
</tr>
<tr>
<td>Enterobacter</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
patients without septic shock, encephalopathy, azotemia, gastrointestinal bleed or ileus. These options explore the possibility of giving part of the treatment course as outpatients, thereby shortening the hospital stay. However, monitoring patient compliance becomes mandatory if this course of action is to be followed. Aminoglycosides should not be used since cirrhotic patients are particularly sensitive to their nephrotoxic effects and monitoring serum aminoglycosides levels is no guarantee against aminoglycoside-induced nephrotoxicity. One study has shown that the concomitant use of albumin can reduce the risk of renal impairment in these patients. However, the study has not been repeated and therefore the routine use of albumin in this setting cannot be recommended.

The response to treatment should be assessed by both evaluating the symptoms and signs of infection and performing at least one follow-up paracentesis after 48 hours of antibiotic therapy. Clinical improvement should parallel a fall in the ascitic PMN count. Although no specific PMN decrease cut-off has been established, a reduction of less than 25% in relation to the pre-treatment value is often considered to represent failure of antibiotic treatment.

FIGURE 37. Management of spontaneous bacterial peritonitis.
Secondary bacterial peritonitis should be considered if the following features are present: (i) poor clinical response to antibiotic therapy; (ii) multiple organisms are grown from the ascitic fluid; (iii) ascitic fluid protein concentration > 10 g/L or ascitic glucose < 3 mmol/L; (iv) PMN count remains high despite antibiotic therapy. Antibiotic coverage should then be broadened with the addition of metronidazole and ampicillin. Radiographic examinations are required to exclude perforation of the gastrointestinal tract with emergency surgery only where gut perforation is confirmed.

Despite successful treatment of SBP, the prognosis of these patients remains poor. The one-year probability of SBP recurrence is 40-70% in patients who have had previous episodes of SBP. Routine selective intestinal decontamination with oral non-absorbable antibiotics has proved to be effective in reducing recurrence. Norfloxacin 400 mg daily is the drug of choice as it also has the advantages of rarely causing bacterial resistance and having a low incidence of side effects when administered chronically. Ciprofloxacin 750 mg weekly is equally effective. Trimethoprim/sulfamethoxazole 160/800 mg daily is an alternative and may confer greater gram-positive coverage. Cirrhotic patients with upper gastrointestinal bleeding are at a high risk for developing severe bacterial infections, including SBP, within the first days of the hemorrhagic episode. One randomized controlled trial using norfloxacin 400 mg twice daily for seven days showed a significant reduction in both bacteremia and SBP. A meta-analysis also reported that antibiotic prophylaxis was effective in improving survival in cirrhotic patients with gastrointestinal hemorrhage. Short-term in-patient prophylaxis therefore is recommended. However, the optimal dose and the duration of treatment in this setting have not been worked out. There is no evidence to support routine primary prophylaxis of all ascitic patients against SBP, and indiscriminate use of antibiotics in cirrhosis may lead to the development of antibiotic resistance. However, in certain settings such as patients with significant jaundice or low protein ascites, it may be prudent to consider primary SBP prophylaxis. Despite decreased SBP recurrence rates with prophylactic antibiotics, no change in mortality has yet been demonstrated. All patients who have experienced one episode of SBP should be considered for liver transplantation.

16. HEPATIC ENCEPHALOPATHY / L.J. Worobetz

Hepatic encephalopathy (HE), also known as portosystemic encephalopathy, is a complex, potentially reversible neuropsychiatric condition that occurs as a consequence of acute or chronic liver failure.

The clinical presentation of a patient with HE is variable. Patients with HE usually have features of advanced chronic liver disease with the accompanying physical and laboratory stigmata of severe liver dysfunction. Physical findings
may include muscle wasting, jaundice, ascites, edema and spider telangiectasia. Fetor hepaticus, a sickly, sweet smell from the mercaptanes in the breath of patients with HE may be present. Patients with fulminant hepatic failure and HE may lack those physical signs of chronic liver disease. The clinical manifestations of this syndrome range from subtle abnormalities detectable only by psychomimetic testing to overt coma. Hepatic encephalopathy is characterized by changes in personality, consciousness, behavior and neuromuscular function and has been the subject of a number of grading systems (Table 47). HE may be present in as many as 80% of patients with cirrhosis. Early features include reversal of the diurnal sleep pattern and progress to include apathy, hypersomnia, irritability and personal neglect. In later stages, delerium and coma may occur. Neurologic signs may include hyperreflexia, rigidity and myoclonus. Asterixis (asymmetric flapping motions of the outstretched, dorsiflexed hands) may be present but is not diagnostic of HE as it may occur in other causes of metabolic encephalopathy. Clinically, a number of encephalopathy patterns can be observed. Hepatic encephalopathy associated with acute liver failure is rapid in onset and progression and is almost always complicated by cerebral edema, which can lead to seizures and lateralizing neurologic signs. Encephalopathy associated with chronic liver disease may present acutely or less commonly in a chronic refractory pattern with progression to debilitating syndromes such as dementia, spastic paraparesis, cerebellar degeneration and extrapyramidal movement disorders.

In approaching the patient with severe liver disease who has an altered level of consciousness or other neurologic features, it is important to rule out other causes of mental status change and neurologic disease. This includes exclusion of central nervous system disease such as subdural hematoma, tumor or CVA as well as CNS infection and drug overdose. One may need to distinguish the neurologic changes commonly seen in patients with alcoholic liver disease and Wilson’s disease.

This syndrome of HE is not a single clinical entity. It may reflect either a reversible metabolic encephalopathy, brain atrophy, brain edema or any combination of these conditions. The mechanisms of brain dysfunction in liver failure are not clearly known. In advanced HE, the effects of brain swelling, impaired cerebral perfusion and abnormalities in neurotransmitter systems cannot be distinguished. Factors of importance in the pathogenesis of HE are the shunting of portal venous blood around the liver into the systemic circulation and the presence of hepatocellular dysfunction. Encephalopathy probably results from a number of mechanisms that include, in part, one or more toxic products of gut origin that are usually metabolized by the liver entering the systemic circulation and reaching the brain. Abnormalities of ammonia metabolism are most frequently implicated in the pathophysiology
The normal gut flora produce a urease enzyme that enzymatically cleaves NH3 from protein in the lumen. Ammonia derived from colonic bacteria and from deamination of glutamine in the small bowel is absorbed into the portal circulation. The intact liver clears almost all of portal vein ammonia, converting it to glutamine and preventing its entry into the systemic circulation. In severe liver disease, ammonia reaches the systemic circulation because of spontaneously created vascular shunts within and around the hepatocytes and the inability of the liver to metabolize the ammonia. Increased blood-brain barrier permeability likely facilitates the entrance of ammonia and other toxic metabolites into the brain. This contributes to astrocyte swelling and edema. Alternative proposals of gut-derived toxins include endogenously produced benzodiazepine-like substances which activate GABA-ergic transmission and neurotoxic short-chain fatty acids, phenols and mercaptanes which may potentiate ammonia toxicity. Another hypothesis proposes that increased levels of short-chain fatty acids and aromatic amino acids associated with decreased levels of branched-chain amino acids cause production of false neurotransmitters. As well, the principal neuro-inhibitory neurotransmitter γ-aminobutyric acid (GABA) is increased in encephalopathy. False neurotransmitters, including an endogenous modulator of GABA receptors, suggests involvement of the GABA-diazepam receptor complex in the pathogenesis of HE. Thus, the synergistic action of ammonia with other toxins likely accounts for many of the abnormalities occurring in liver failure.

**TABLE 47. Grading of hepatic encephalopathy**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Level of consciousness</th>
<th>Intellectual function</th>
<th>Personality behavior</th>
<th>Neuromuscular abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>lack of awareness</td>
<td>short attention span</td>
<td>euphoria</td>
<td>tremor</td>
</tr>
<tr>
<td></td>
<td>hypersonnia</td>
<td></td>
<td>depression</td>
<td>incoordination</td>
</tr>
<tr>
<td></td>
<td>insomnia</td>
<td></td>
<td>irritability</td>
<td>mild asterix</td>
</tr>
<tr>
<td></td>
<td>day/night reversal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>lethargic</td>
<td>loss of time</td>
<td>decreased inhibitions</td>
<td>slurred speech</td>
</tr>
<tr>
<td></td>
<td></td>
<td>grossly impaired</td>
<td>personality change</td>
<td>hypoactive reflex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>amnesia</td>
<td>anxiety/aphaty</td>
<td>ataxia</td>
</tr>
<tr>
<td>3</td>
<td>somnolence</td>
<td>loss of place</td>
<td>bizarre behavior</td>
<td>hyperactive reflex</td>
</tr>
<tr>
<td></td>
<td>confusion</td>
<td>amnesia</td>
<td>paranoia/anger</td>
<td>clonus</td>
</tr>
<tr>
<td></td>
<td>semi-stupor</td>
<td>meaningful</td>
<td>rage</td>
<td>rigidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>inability to compute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>unrousable</td>
<td>no intellect</td>
<td>none</td>
<td>dilated pupils</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>coma</td>
</tr>
</tbody>
</table>
TABLE 48. Common precipitants of hepatic encephalopathy

<table>
<thead>
<tr>
<th>Increased ammonia production, absorption or entry into the brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive dietary protein</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
</tr>
<tr>
<td>Electrolyte disturbance (hypokalemia)</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Azotemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Spontaneous bacterial peritonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary</td>
</tr>
<tr>
<td>Pulmonary</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Large volume paracentesis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcotics, tranquilizers, sedatives</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Portosystemic shunting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic or surgically placed stents</td>
</tr>
<tr>
<td>Spontaneous shunts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal vein thrombosis</td>
</tr>
<tr>
<td>Hepatic vein thrombosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Hepatocellular carcinoma</th>
</tr>
</thead>
</table>

such as the changes in blood-to-brain transport of neurotransmitter precursors, the metabolism of amino acid neurotransmitters and cerebral glucose oxidation. These changes may lead to activation of inhibitory (GABA, serotonin) and impairment of excitatory (glutamate, catecholamines) neurotransmitter systems, resulting in enhanced neural inhibition and HE.

There is no specific diagnostic test for hepatic encephalopathy. The history and the clinical examination, including a complete mental status and neurologic examination, are the most important tools for diagnosing HE and distinguishing it from other causes of neurologic disease and encephalopathy. The presence of asterixis is helpful but is not pathognomonic for HE. Blood tests
help verify the presence and severity of liver disease and rule out other causes of encephalopathy such as renal failure, hypoxia, CO₂ retention and drug overdose. Blood tests are also helpful in identifying precipitating factors of HE such as hypoglycemia, azotemia, electrolyte imbalance and infection. An elevated serum ammonia is often observed but correlates poorly with the degree of encephalopathy and may be normal in up to 10% of cases with HE. Lumbar puncture and brain imaging studies such as CT scan or MRI may be necessary to rule out other CNS pathology. The cerebrospinal fluid is usually normal and may show increased protein with increased GABA levels. The EEG shows slow, triphasic wave activity mainly over frontal areas, and although this is highly sensitive and characteristic of HE, it is not specific for this condition. In patients with clinical symptoms of HE, neuropsychiatric testing is not necessary but may be helpful in establishing the diagnosis of mild HE. A Psychometric Hepatic Encephalopathy Score (PHES) can be used which includes a battery of five paper-pencil tests including the line tracing test, digit symbol test, serial dot test and two number connection tests.

Hepatic encephalopathy occurring in acute liver failure is usually accompanied by cerebral edema and carries with it a poor prognosis. Unless the liver shows signs of spontaneous recovery, these patients should be considered for orthotopic liver transplantation. Patients with grade 3 or 4 encephalopathy are usually managed in intensive care, as there is often associated multi-organ failure. Management may include elective ventilation, mannitol infusion and intracranial pressure monitoring.

Provision of meticulous medical and nursing care to these confused and often comatose patients is very important for their recovery and to avoid complications.

Most HE occurs in patients with chronic liver disease and is due to a clinically apparent precipitating event or the development of a spontaneous or surgically created portosystemic shunt (Table 48). The most important aspect of management is the prompt recognition and treatment of these precipitating factors. Exogenous factors include increased dietary protein, constipation, administration of certain drugs (sedatives, narcotics), gastrointestinal bleeding, azotemia, hypoxia and infection (urinary, respiratory, spontaneous bacterial peritonitis). Development of underlying hepatocellular carcinoma may present as worsening HE. Dehydration, hyponatremia and alkalosis, often the result of diuretic therapy should be corrected. Correction of hypokalemia is essential as hypokalemia increases renal ammonia production.

The next goal of therapy is to lower the level of neurotoxic substances by reducing or excluding protein from the diet and by emptying nitrogenous wastes from the gut. Dietary protein may be restricted to 20 g/day and gradually increased until the patient’s protein tolerance has been established. Vegetable protein is much better tolerated and increasing the calorie:nitrogen ratio
may improve protein tolerance. Constipation is avoided by the use of laxatives and, in more urgent cases, cleaning of the gut with enemas or colonic lavage. A commonly used laxative is lactulose, a synthetic disaccharide that is degraded by intestinal bacteria into lactate and acetate to produce stool acidification and an osmotic diarrhea. The acidification of colonic contents reduces ammonia absorption in part by trapping nitrogenous compounds in the lumen. The daily dose of lactulose should be titrated to produce two to four soft, acidic (pH < 6.0) stools per day. For most patients, this will be between 15-30 cc PO OD to QID. Patients in coma or with a small bowel ileus can receive lactulose by enema. An excessively sweet taste, flatulence, diarrhea and cramping are the most common side effects. Lactitol can be used instead of lactulose. Too much diarrhea can result in fluid and electrolyte depletion with renal failure and can worsen HE. Lactulose can be used chronically to reduce the frequency of episodes of encephalopathy. Alternatively, antibiotics such as neomycin and metronidazole may be used. These inhibit urea-splitting and deaminating bacteria, reducing the production of ammonia and other potential toxins. Neomycin-use is now limited due to its potential nephrotoxic and ototoxic side-effects. Because of potential toxicity, long-term antibiotics are not recommended. Limited data support the combined use of lactulose and antibiotics in selected resistant cases for short term.

Other potential therapeutic approaches exist, particularly when HE becomes refractory. On the basis of increased aromatic amino acids and decreased branched-chain amino acids (BCAA) found in HE and the effect on neurotransmitter synthesis, nutritional support with formulas rich in BCAA but low in aromatic amino acids has been suggested. Most studies with oral BCAA have shown clinical improvement of low-grade HE and increased protein tolerance, whereas studies with IV BCAA have produced inconclusive and conflicting results. Intravenous ornithine aspartate has been proven helpful, and the efficacy of the oral form is being tested in controlled trials. Two of the five enzymes involved in the metabolism of ammonia to urea are zinc-dependent. On this basis, the significant incidence of zinc deficiency in cirrhosis, and some studies showing improvement of HE with zinc replacement, this deficiency should be sought and corrected if present. Decreased dopaminergic neurotransmission activity has also been suggested to play a role in HE. However, controlled trials failed to demonstrate any beneficial effect of levodopa or bromocryptine treatment. In controlled trials, benzodiazepine receptor antagonists such as flumazenil showed only modest success, which argues against a major role of endogenous benzodiazepines in the pathogenesis of HE. Other therapies being explored include the use of probiotics to modify enteric bacteria population and the use of sodium benzoate to help eliminate ammonia from the body. HE as a complication of spontaneous or surgically
created portosystemic anastomoses or transjugular intrahepatic portosystemic shunts (TIPS) is usually managed successfully with conventional therapy. Refractory HE complicating TIPS can be helped by implanting a reducing stent to reduce blood flow through the TIPS. Orthotopic liver transplantation has the potential to entirely reverse HE. Thus, this procedure should be considered in all patients with HE whose liver disease makes them suitable for liver transplantation.

17. HEPATORENAL SYNDROME / K.M. Peltekian

Patients with end-stage liver disease and ascites may develop a form of renal dysfunction due to renal vasoconstriction known as hepatorenal syndrome (HRS). The histological appearance of the kidneys in HRS is normal, and the kidneys regain a normal or near-normal function after liver transplantation. This chapter will provide a review of this unique pathophysiological disorder focussing on diagnosis, clinical features, and therapy of HRS.

17.1 Definition

According to the International Ascites Club consensus conference on HRS, “hepatorenal syndrome is a clinical condition that occurs in patients with chronic liver disease, advanced hepatic failure, and portal hypertension characterized by impaired renal function and marked abnormalities in the arterial circulation and activity of the endogenous vasoactive systems. In the kidney there is marked renal vasoconstriction that results in low glomerular filtration rate (GFR), whereas in the extra-renal circulation there is predominance of arterial vasodilation, which results in reduction of total systemic vascular resistance and arterial hypotension.”

HRS occurs in up to 10% of patients with advanced liver disease and ascites. Although the urinary sodium concentration is < 10 mEq/L in most patients with HRS, it is not considered a major diagnostic criterion (Table 49). Two different clinical types of HRS have been described according to the intensity and onset of renal dysfunction (Table 49). The dominant features of type 1 HRS are marked renal failure with oliguria and anuria plus increased serum urea and creatinine. Despite an extreme reduction of GFR, serum creatinine levels in patients with HRS are usually lower than values observed in acute renal failure in patients without liver disease. This is due to lower hepatic creatine production and lower endogenous production of creatinine secondary to muscle mass wasting in patients with advanced liver disease due to cirrhosis. Type 1 HRS is associated with very poor survival, with a median survival time of two weeks. In contrast, type 2 HRS is characterized by less severe and stable reduction of GFR (Table 49). Patients are in better clinical condition
than those with type 1 HRS, and their survival is markedly longer. The dominant clinical feature of these patients is diuretic resistant ascites due to combination of severe sodium retention, reduced GFR, and marked stimulation of anti-natriuretic systems.

### 17.2 Pathogenesis

Arterial vasodilation theory better explains the relationship between changes in renal circulation, activation of vasoconstrictor mechanisms, and presence of marked disturbances in systemic hemodynamics (Figure 38). Renal hypoperfusion represents extreme manifestation of underfilling of arterial circulation secondary to the marked vasodilation of the splanchnic vascular bed. This arterial underfilling would result in progressive baroreceptor-mediated activation of vasoconstrictor systems including the renin-angiotensin and sympathetic nervous systems eventually causing vasoconstriction not only in the renal circulation but also in other vascular beds. The most important factor responsible for splanchnic vasodilation is nitric oxide, though other factors such as prostaglandins and vasodilator peptides may also play a role.
17.3 Differential Diagnoses

Hepatorenal syndrome needs to be distinguished from other causes of renal failure. Iatrogenic renal insufficiency must be ruled out, including drug-induced disease from aminoglycosides, nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors. Hepatorenal syndrome must also be distinguished from prerenal azotemia and acute tubular necrosis. Prerenal azotemia is ruled out by lack of sustained benefit by expansion of intravascular volume with colloids. Acute tubular necrosis has a high urinary sodium.

In addition, cirrhosis, especially alcohol-related cirrhosis, may be associated with IgA nephropathy. Hepatitis B and C may result in glomerulopathies often associated with proteinuria. Acetaminophen toxicity can also cause concomitant liver and renal failure with high urinary sodium excretion.
17.4 Treatment

Treatment of established hepatorenal syndrome is difficult and survival without liver transplantation dismal. Hemodialysis is frequently used as a temporizing measure to control azotemia and maintain electrolyte balance for those who are on a liver transplantation waiting list. Continuous venovenous hemofiltration causes less hypotension—a frequent occurrence sometimes associated with ischemia. Although isolated reports have shown reversal of HRS with peritoneovenous shunt, no controlled studies have shown survival benefits with this procedure. Transjugular intrahepatic portosystemic shunt (TIPS) is used as an alternative therapy in management of patients with bleeding esophageal varices that do not respond to standard therapy and in patients with refractory ascites. Isolated reports have documented the use of TIPS in patients with HRS. However, liver transplantation is the ideal treatment for HRS because it cures the liver disease and allows recovery of renal function.

In recent years, drugs with vasoconstrictor effects in the splanchnic circulation have shown some promise. The drug combination octreotide and midodrine (an α-adrenergic agonist), along with albumin infusion, has been reported from Europe in the treatment of type I HRS. All eight patients treated with midodrine, octreotide, and volume expansion had improvement in renal function. No adverse effects were reported in these patients.

18. LIVER TRANSPLANTATION / L.B. Lilly, N. Girgrah and G.A. Levy

Starzl performed the first human liver transplant in 1963 in a 3-year-old boy with biliary atresia. The first successful liver transplant was not performed until 1967 when a one and a half year old girl with hepatocellular carcinoma was transplanted, but died of recurrent tumor at 17 months. One-year-survival in the early years was 25 to 35% using methylprednisilone and azathioprine as immunosuppression; however, with the introduction of cyclosporine in the early 1980s, liver transplantation became a clinical reality and now offers one and five year survivals in excess of 85 and 70%, respectively.

With the dramatic improvement in results, liver transplantation soon became recognized as the definitive management for end stage liver disease. The number of liver transplant centres in North America has proliferated to more than 170 and presently more than 5,000 liver transplants are performed yearly in the United States alone. In Canada, there are active centres in Halifax, NS; Montreal, PQ; Toronto and London, ON; Edmonton, AB and Vancouver, BC and close to 400 liver transplants are performed yearly. One-year survival rates of 80-90% are now expected. The rate-limiting step in the application of transplantation to liver disease has become donor availability.
18.1 Assessment for Transplantation

A patient should be considered for liver transplantation when three conditions are met: 1) the diagnosis of irreversible acute or chronic liver failure is made, from which the anticipated survival is clearly inferior to that of transplantation; 2) no alternative medical or surgical therapy exists (TIPS for refractory ascites, for example); and 3) no absolute contraindications or significant comorbidities that might significantly raise the risk of transplantation are present. In most patients with chronic liver disease, it is the development of complications of portal hypertension (ascites, variceal hemorrhage or encephalopathy) that prompts referral for transplantation.

The most common indications for liver transplantation in adults and children are shown in Table 50. End-stage liver disease due to hepatitis C is currently the most common indication in adults, comprising close to 50% of patients on the waiting list. In most programs, patients with alcoholic liver disease make up a further 15-20%, with hepatitis B contributing approximately 5-10%. Cholestatic liver disease (10-15%) and cirrhosis attributable to hemochromatosis, α1 antitrypsin deficiency or autoimmune hepatitis, in addition to occasional patients with polycystic liver disease and other unusual indications make up the difference. Most programs perform fewer than 5% of their transplants for fulminant liver failure.

Transplantation for hepatitis B has become less controversial. While initial efforts were plagued by high recurrence rates and suboptimal patient survival due to the lack of effective antiviral therapy, current strategies using HBIG in combination with lamivudine have significantly reduced disease recurrence, resulting in patient and graft survival rates similar to those for other indications. Most programs require that patients have low levels of viral replication prior to transplantation to ensure optimal outcomes.

Hepatocellular carcinoma, particularly in patients with viral hepatitis, is an increasingly common indication for organ replacement today; in Toronto, for example, close to a third of patients transplanted in 2003 had hepatomas. The best results have been described in patients with unifocal tumour less than 5 cm in diameter and with no evidence of vascular or lymphatic invasion, or with multiple lesions numbering no more than three and no larger than 3 cm, again in the absence of evidence of invasion or spread.

Physicians should be aware of their transplant centre’s policy when considering patients for referral. The exclusion of patients with contraindications to liver transplantation (outlined in Table 51) allows the best use of scarce donor resources while maximising patient benefit.

Given the scarcity of donor organs, selection of the patient and the timing of the transplantation require individual assessment. The patient with decompensated cirrhosis should not be moribund, thereby increasing the risk of the
procedure to an unacceptable degree, nor should the patient be in such a stable condition that she/he might be able to live an independent life in the absence of liver transplantation.

**18.2 Preoperative Workup**

The principles behind the liver transplant workup are to definitively establish the etiology of the liver disease, and to identify contraindications to surgery. Assessment by a multidisciplinary team, which includes medical, surgical, anaesthetic, radiology, social and psychiatric specialists, is performed in patients in order to ensure the success of the transplantation process.

**18.3 Timing of Transplantation**

With improving results of liver transplantation, quality of life criteria may merit consideration in referral for transplantation; however, at present the scarcity of organs permits only the sickest to benefit from transplantation. It is clear that transplantation is best considered prior to the development of

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**TABLE 50. Liver transplantation: indications**

<table>
<thead>
<tr>
<th>Cirrhosis related to viral hepatitis</th>
</tr>
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<tbody>
<tr>
<td>• B ± D (HBV-DNA negative)</td>
</tr>
<tr>
<td>• C</td>
</tr>
<tr>
<td>• Non A–E</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cholestatic liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primary biliary cirrhosis</td>
</tr>
<tr>
<td>• Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>• Biliary atresia</td>
</tr>
<tr>
<td>• Cholestatic sarcoidosis</td>
</tr>
<tr>
<td>• Graft-vs-host disease</td>
</tr>
<tr>
<td>• Chronic ductopenic rejection</td>
</tr>
<tr>
<td>• Secondary sclerosing cholangitis</td>
</tr>
<tr>
<td>• Drug-induced cholestasis and biliary cirrhosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alcoholic cirrhosis</th>
</tr>
</thead>
</table>

| Fulminant hepatic failure (viral hepatitis A–E, herpes, adenovirus, Wilson’s disease, drugs, Reye’s syndrome) |

| Neoplasms (hepatoma, hepatoblastoma, fibrolamellar CA, cholangiocarcinoma, hemangiosarcoma) |

| Metabolic liver disease (α1-antitrypsin deficiency, Wilson’s disease, hemochromatosis, glycogenosis type 4, tyrosinemia, Gaucher’s disease, cystic fibrosis) |

| Vascular disease (Budd-Chiari syndrome, veno-occlusive disease) |

| Congenital (Caroli’s disease, choledochal cyst, polycystic disease, hemangioma) |
catastrophic complications and the need for life support, although waiting times can be expected to increase as patients are referred and listed earlier.

18.4 Model for End-Stage Liver Disease (MELD)

The overall principle underlying organ allocation in liver transplantation is that potential recipients who are sickest and who are at significant risk of dying should be offered donor livers. In Canada, livers are allocated to potential liver recipients based on overall waiting time, ABO blood type compatibility as well as medical status. Liver allocation on the basis of medical status includes the following: status 1, patient home waiting for liver transplantation; status 2, patient hospitalized; status 3, patient in a step-down unit with renal failure and/or encephalopathy; status 4, patient in the intensive care unit, intubated and ventilated. Organs are prioritized and allocated nationally and regionally in Canada based first on medical status and then length of time on the waiting list. In a country such as Canada, where there are relatively few liver transplant programs, this organ allocation algorithm has in the past served the population well, although there are some shortcomings and subjectivity, particularly in stratifying those patients who fall in the medical status 1 or 2 category.

The Model for End-stage Liver Disease (MELD) is a score that incorporates the patient’s INR, bilirubin and serum creatinine and was originally developed as a predictor of survival in patients with end-stage liver disease for the insertion of a transjugular intrahepatic portosystemic stent (TIPS). MELD
scores are rounded to the nearest integer and yield values from 6 to 40. MELD was subsequently validated as predictor of survival in patients on the waiting list, and therefore, in the United States, the United Network for Organ Sharing (UNOS) adopted the MELD scoring system for organ allocation in February of 2002.

The main features that distinguish MELD from the Child-Turcotte-Pugh (CTP) score, another system originally devised to predict survival in cirrhotic patients undergoing surgical shunts and subsequently used to predict survival in patients with advanced liver disease, is the absence of the two subjective clinical parameters, ascites and encephalopathy, and the incorporation and acknowledgement of renal dysfunction as a powerful predictor of survival in these patients. MELD is based on three biochemical variables that are readily available, reproducible and objective. Moreover, MELD appears to predict mortality independent of etiology of the underlying chronic liver disease as well as the occurrence of complications of portal hypertension, such as variceal hemorrhage and spontaneous bacterial peritonitis. Table 52 demonstrates the MELD formula and shows three-month mortality figures to potential transplant recipients based on MELD and Child-Turcotte-Pugh scores.

**18.5 Living Donor Liver Transplantation**

Adult living donor liver transplantation (LDLT) evolved in the late 1990s to address the issue of relatively fixed supply, that is, static organ donation rates, and ever increasing demand with growing liver transplant waiting lists and waiting list mortality. At the Toronto General Hospital, the liver transplant waiting is currently greater than 250 patients, with waiting times for medical status 1 patients approaching 4 to 5 years and waiting list mortality in the range of 25-30%. There are risks to the living donor including a risk of death of up to 0.5% and substantial morbidity. A highly publicized death of a donor in

### TABLE 52. Three month mortality for potential liver transplant recipients based on Model for End-Stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) score

<table>
<thead>
<tr>
<th>MELD</th>
<th>CTP</th>
</tr>
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<tbody>
<tr>
<td>&lt;9</td>
<td>124</td>
</tr>
<tr>
<td>10-19</td>
<td>1800</td>
</tr>
<tr>
<td>20-29</td>
<td>1098</td>
</tr>
<tr>
<td>30-39</td>
<td>295</td>
</tr>
<tr>
<td>&gt;40</td>
<td>120</td>
</tr>
<tr>
<td>&lt;7-9</td>
<td>318</td>
</tr>
<tr>
<td>10-12</td>
<td>2357</td>
</tr>
<tr>
<td>13-15</td>
<td>588</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>%Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9</td>
</tr>
<tr>
<td>6.0</td>
</tr>
<tr>
<td>19.6</td>
</tr>
<tr>
<td>52.6</td>
</tr>
<tr>
<td>71.3</td>
</tr>
<tr>
<td>4.3</td>
</tr>
<tr>
<td>11.2</td>
</tr>
<tr>
<td>40.1</td>
</tr>
</tbody>
</table>

MELD Score = 9.57 x loge creatinine mg/dL + 3.78 x loge bilirubin mg/dL + 11.20 x loge INR + 6.53

Table adapted from Weisner et al. Gastroenterology 2003; 124:91-96

scores are rounded to the nearest integer and yield values from 6 to 40. MELD was subsequently validated as predictor of survival in patients on the waiting list, and therefore, in the United States, the United Network for Organ Sharing (UNOS) adopted the MELD scoring system for organ allocation in February of 2002.

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January 2002 subsequently tempered enthusiasm for living donation and led to a decrease LDLT activity in the US. Presently, LDLT comprises less than 5% of total adult liver transplant activity in the US. The ethics, as well as the appropriate application of LDLT continue to evolve in the US and Canada.

At the Toronto General Hospital, close to 100 adult living donor liver transplants have been done since April 2000 with no donor deaths and with recipient and graft survivals similar to deceased donor liver transplantation. Given the lengthy waiting times and rising waiting list mortality, most recipients are being offered LDLT in situations where a suitable living donor comes forth. Presently, only recipients who are candidates for deceased donor liver transplantation are being considered for LDLT; however, this may change as the ethics in this field evolve. Controversies in LDLT include recurrence of hepatitis C in the living donor allograft as well as the role of LDLT in potential recipients with HIV or hepatocellular carcinoma that fall outside current practice guidelines for liver transplantation.

18.6 Operative Procedure
Technical details of the procedure are beyond the scope of this discussion; however, there are several salient points to be reviewed. During the procedure the liver is mobilized and both inflow to the liver and inferior vena caval return to the heart interrupted. This may cause hemodynamic instability, which, if not correctable, may require the use of veno-veno bypass (in which IVC and portal blood are diverted through a bypass circuit to the axillary vein) or the use of an alternate surgical approach. The liver is subsequently removed and the new graft sewn in place. Although the liver is flushed of the high potassium preservation solution prior to reperfusion, there can be significant cardiac abnormalities upon removing the clamps and reperfusing the liver. These intraoperative events demand a thorough preoperative assessment of cardiac status.

18.7 Postoperative Management
Issues that must be addressed in the postoperative period include management of fluid and electrolytes, respiratory function, monitoring of neurologic status, immunosuppression and graft function.

In most cases patients are quickly extubated within 24 hours of surgery. However, ventilatory support may be needed for an extended period, particularly when there is delayed graft function, presence of large pleural effusions, pulmonary infiltrates and/or diaphragmatic dysfunction or paralysis. Patients who were deeply encephalopathic prior to transplantation typically require an extended period of ventilatory support and ICU care.

Most patients are in a state of fluid overload after transplantation. These patients usually have a low serum albumin and respond well to colloid supplementation and
diuretics. Renal insufficiency, occasionally requiring dialysis, is not uncommon postoperatively, particularly as patients undergoing surgery deteriorate as waiting lists lengthen. Renal failure may be due to a combination of factors including pre-existing renal disease, hepatorenal syndrome, intraoperative blood loss and hypotension leading to tubular necrosis, drug induced nephrotoxicity (especially cyclosporine or tacrolimus), poor liver function and sepsis.

Graft function resumes almost immediately following transplantation; abnormalities of coagulation are sensitive markers of hepatic dysfunction and coagulation parameters should return to normal levels within 48 hours in most patients. Delayed graft function and primary non-function are rare events and may present with coagulopathy, encephalopathy, hypoglycaemia, hyperkalemia or renal failure. The failure of coagulation parameters to normalise is therefore an ominous sign of graft failure and suggests the need for retransplantation.

The causes of significant hepatic dysfunction within the first 48 hours include accelerated cellular rejection, primary nonfunction or hepatic artery thrombosis. These can be difficult to differentiate on clinical grounds and radiological investigations such as ultrasound with Doppler or angiography may be required for diagnosis.

Most patients wake up within several hours of liver transplantation, whereas patients with fulminant hepatic failure may require 1-3 days to return to normal neurologic status after liver transplantation. In such patients, the monitoring of intracranial pressure may help both with patient selection and in perioperative management. Immediately following transplantation, narcotics and sedatives are kept to a minimum. Confusion and seizures can occur, and are usually related to metabolic disturbances (e.g., low serum magnesium levels), but are a recognized complication of both cyclosporine and tacrolimus. At the University of Toronto all patients are placed on a continuous infusion of magnesium sulphate for the first 72-96 hours postoperatively, followed by oral supplementation for three months.

18.8 Immunosuppression

Cyclosporine. The introduction of cyclosporine (currently available in the microemulsified form as Neoral®) is considered one of the most important factors in improving results of liver transplantation. With its introduction, the one year graft survival increased abruptly from 30% to > 70%. Cyclosporine binds to a specific cell protein, cyclophilin, and through a series of intracellular events prevents activation of T-cells and production of interleukin-2 (IL-2). The drug is given preferentially by the oral route; intravenous infusion is rarely required. The dosage of cyclosporine is adjusted to maintain a trough cyclosporine level of 300-400 ng/mL or a two-hour level (C2) of 1,000-1,400 ng/mL in the early postoperative period. Daily monitoring of
cyclosporine levels in the immediate postoperative period is mandatory as the compound has a narrow therapeutic index (efficacy vs. toxicity). Cyclosporine interacts with many drugs, such as antibiotics and calcium channel blockers, and caution must therefore be exercised in giving any drug to patients who are taking cyclosporine. Common side effects of cyclosporine include renal dysfunction, tremor and headaches.

**Tacrolimus (FK506; Prograf®).** Tacrolimus is another calcineurin inhibitor, and binds to FK binding protein before subsequently inhibiting T-cell activation by blocking IL-2 production in a similar fashion to cyclosporine. Monitoring is through trough levels, with a target of approximately 10-15 ng/mL early following transplantation. Recent trials suggest similar rates of rejection of 20-25% with both compounds. Nephrotoxicity of tacrolimus is similar to cyclosporine, with hypertension also equally common. The incidence of post transplant diabetes mellitus and diarrhoea may be higher in patients receiving tacrolimus than those on cyclosporine. Tacrolimus may play a role in the management of chronic rejection.

**Corticosteroids.** All patients receive methylprednisilone perioperatively, often at a dose of 500 mg in the operating room. Subsequently, this is tapered rapidly to a dose of 20 mg/day. Steroids are discontinued within the first six months to a year in the majority of patients. Major side effects include an increased incidence of infections (bacterial and fungal), hyperglycemia, impaired wound healing, osteoporosis and hypercholesterolemia. Steroid-free protocols for the transplantation of patients with hepatitis C are currently under evaluation.

**Mycophenolate Mofetil (MMF / Cellcept®).** MMF is a potent reversible non-competitive inhibitor of inosine monophosphate dehydrogenase. It acts as a selective inhibitor of T- and B-cell proliferation by blocking the production of guanosine nucleotides and interfering with the glycosylation of adhesion molecules. The main side effect of MMF is bone marrow suppression. However, it has no nephrotoxicity and is an important agent in triple drug regimens, allowing a decrease in the dosage, and therefore the toxicity, of calcineurin inhibitors. Many patients also experience significant gastrointestinal side effects and dose modification is common. Drug levels are not currently monitored in most transplant centres.

**Anti-Lymphocyte Products.** Anti-lymphocyte products can be monoclonal (OKT3) or polyclonal (ALG, ATG, thymoglobulin). In either case the aim of therapy is to prevent or treat rejection through lymphocyte depletion. The use of these products has been associated with higher rates of viral infections, in particular cytomegalovirus (CMV), as well as an increased risk of lymphoproliferative disorders. OKT3 has been associated with side effects secondary to the release of tumour necrosis factor and IL-1 then can range from mild flu-like symptoms to life threatening pulmonary edema and circulatory collapse.
In liver transplantation the use of these drugs is generally limited to induction immunosuppression in the presence of renal failure or significant neurologic dysfunction (to spare the use of calcineurin inhibitors), and in the treatment of steroid-resistant rejection.

**Rapamycin (Rapamune®).** This secondary macrolide metabolite has a distinctly different mechanism of action than the calcineurin inhibitors. It binds to the FK binding protein, and inhibits the growth factor dependent proliferation of hematopoetic and non-hematopoetic cells at G1 to S phase through calcium independent signals. It has been shown to effectively prevent allograft rejection as well as reverse ongoing rejection in animal models, and is widely used in human renal transplantation. No major side effects on other organ systems have been observed. Early clinical trials in liver transplantation have suggested an increased risk of thrombosis in the early post-transplant period, and this agent remains under investigation in Canada.

**RAD (Everolimus®).** Similar to rapamycin, this compound is undergoing clinical trials in human liver transplantation; recent trials have established its benefit in heart transplantation where its use has now resulted in a reduction of chronic allograft vasculopathy.

**IL-2 Receptor antagonists.** Basiliximab (Simulect®) and Daclizumab (Zenapax®) are IL-2 receptor specific monoclonal antibodies, which inhibit proliferation of T-cells by binding to the alpha chain of the IL-2 receptor complex on activated T-cells. They have been shown to reduce the incidence of acute allograft rejection in kidney transplantation and improve the one-year graft and patient survival. The role of these agents in liver transplantation, particularly in calcineurin- or steroid-sparing protocols, remains unclear.

**Campath-1H.** Campath-1H is a humanized monoclonal antibody directed at CD52, which is on lymphocytes and other cells of the immune system. It has been tested extensively in lymphoid malignancies, autoimmune diseases including rheumatoid arthritis, multiple sclerosis, and organ transplantation. Currently, studies are being implemented to further assess its safety and efficacy in solid organ organ transplantation. Immune cell depletion using Campath-1H appears to be particularly useful in organ transplantation in that lower doses of maintenance immunosuppressive drugs are needed. This feature has been suggested to be important in tolerance induction.

### 18.9 Postoperative Complications

Complications common to any surgical procedure can occur with liver transplantation. However, there are several adverse events peculiar to liver transplantation. The most concerning of post-operative complications is primary non-function (PNF) of the new graft. The incidence of PNF ranges from 2 to 10% and becomes evident by coagulation parameters that worsen and cannot be
corrected, increasing acidosis, renal failure, and deterioration in the patient’s mental status. The etiology of PNF is unclear, and the treatment is urgent retransplantation. Primary graft dysfunction of a less significant degree has been managed with some success with prostaglandin E-1 and/or N-acetyl cysteine.

**Vascular thromboses** that occur in the early postoperative period are generally technical in nature. Although thrombectomy of both portal vein and hepatic artery has been reported with some success, retransplantation is usually required should these vessels thrombose.

The **bile duct** has been termed the Achilles heel of liver transplantation. Problems occur in 10-20% of cases. Early leaks are secondary to ischemia, sepsis, or severe rejection. The bile duct can be irreversibly damaged in hepatic artery thrombosis immediately post transplant.

**Acute allograft rejection** occurs in 20-30% of transplant patients, usually in the first three months after transplantation. Rejection is suspected in patients with rising liver enzymes. Patterns of enzyme elevation can be either hepatocellular (high AST) or cholestatic (high bilirubin and alkaline phosphatase). Fever, malaise and right upper quadrant discomfort are late signs and should not be required for diagnosis of rejection. Diagnosis is confirmed by liver biopsy. Histologic findings include periportal inflammation with mononuclear cells and eosinophils, bile duct injury and endophlebitis. Episodes of cellular rejection usually respond to high dose steroid therapy. Those patients whose rejection fails to respond to steroids are usually treated with a seven to 14 day course of antithymocyte globulin (monoclonal or polyclonal). Tacrolimus may have a role in treating rejection refractory to either steroids or OKT3. Failure to respond to immunosuppressive therapy may result in ductopenic rejection (chronic rejection) leading to biliary cirrhosis, which results in the need for re-transplantation in 2-5% of all transplanted patients.

The major cause of death following liver transplantation is related to infections. The three main determinants of risk of infection in transplant recipients are: those related to surgical problems, the net state of immunosuppression and environmental exposure. There are similar patterns of infection in all forms of organ transplantation. Immunosuppressed patients are at risk for bacterial, viral and fungal infections. Bacterial infections with non-opportunistic organisms are usually seen in the early postoperative period, while opportunistic bacterial infections are seen one to two months or more after transplantation. Viral infections are seen frequently in immunosuppressed patients and usually occur at six weeks or later. The most important pathogen affecting transplant recipients is Cytomegalovirus (CMV), which causes both direct effects including tissue injury and clinical disease and a variety of indirect effects. Seronegative recipients of organs from seropositive donors have a greater than 50% risk of symptomatic disease in the absence of prophylaxis.
The diagnosis of disease due to CMV is accomplished by demonstrating viremia or tissue invasion. Patients who are mismatched or those who receive anti-lymphocyte products are therefore generally treated pre-emptively with ganciclovir or valganciclovir, often for three months following engraftment. Other viral infections seen in the transplanted recipient include herpes simplex, Epstein-Barr virus, varicella zoster and Adenovirus. Fungal infections are diagnosed in up to 20% of liver transplant patients and carry with them a significant mortality rate. Infections in general are usually proportional to the degree of immunosuppression.

18.10 Results of Liver Transplantation
A one-year survival of > 85% after liver transplantation is now typical. Most mortality occurs within the first 90 days, and is often related to the pre-operative debility of the recipient. After one year, few patients or grafts are lost. Furthermore, 60% of patients return to gainful employment, demonstrating that this procedure is not only of benefit to the patient, but to society as a whole. Though there are few reports of cost effectiveness, investigators in Pittsburgh have demonstrated that liver transplantation is less expensive than costs of caring for similar patients treated for complications of cirrhosis.

Patients with diseases such as cholestatic liver disease that tend not to recur after liver transplantation have an excellent long-term prognosis (greater than 80% five-year survival; see Table 53). In contrast, patients transplanted for

<table>
<thead>
<tr>
<th>Result</th>
<th>Cause of liver failure</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>Cholestatic liver disease&lt;br&gt;Autoimmune hepatitis&lt;br&gt;Alcoholic cirrhosis&lt;br&gt;Metabolic disease&lt;br&gt;Congenital disease</td>
<td>Low recurrence rates</td>
</tr>
<tr>
<td>Good</td>
<td>HCV&lt;br&gt;HBV&lt;br&gt;HCC (small tumors)</td>
<td>Moderate recurrence rates</td>
</tr>
<tr>
<td>Fair</td>
<td>Fulminant hepatic failure&lt;br&gt;Retransplantation&lt;br&gt;Biliary atresia</td>
<td>Results affected by the pretransplant status of the patient</td>
</tr>
<tr>
<td>Poor</td>
<td>Large tumors&lt;br&gt;Cholangiocarcinoma</td>
<td>High recurrence rates</td>
</tr>
</tbody>
</table>
hepatitis C have a poorer long-term outlook due to the problem of recurrent
disease, with at least 95% of patients developing virological recurrence, and
at least 20% progressing to cirrhosis within five years. High pre-transplant
HCV RNA titres and the occurrence of steroid-requiring rejection are probably
the most important determinants of post transplant recurrence and survival.
The role of currently available interferon-based regimens in managing post
transplant recurrent hepatitis C is under intense investigation. Retransplantation
in patients losing their grafts to hepatitis C is associated with poor patient
and graft survival.

18.11 Recent Advances and Future Directions
The availability of new immunosuppressive agents targeting different sites in
the immunologic cascade offers the potential to individualize therapy for
transplant patients. For example, in patients with metabolic bone disease,
there is now the opportunity to perform transplantation avoiding steroids
using combinations of rapamycin, CellCept® and low dose calcineurin
inhibitors (CNI). Similarly, use of sirolimus and avoidance of CNIs in patients
transplanted for hepatocellular carcinoma may improve long-term outcomes.

Isolated hepatocyte transplantation may offer treatment of metabolic liver
diseases and has been successful in the laboratory setting. Artificial liver
support systems have shown initial promise in fulminant hepatic failure and
may reduce the need for transplantation.

The elusive goal of tolerance has been produced in animal models and if
induced in humans would obviate the need for immunosuppression and its
associated complications. Xenotransplantation sits on the horizon and the use
of transgenic animals may eventually offer a solution to the shortage of donor
organs and permit a wider application of liver transplantation to liver disease.

19. NEOPLASMS OF THE LIVER / L.J. Worobetz

Neoplasms of the liver can be divided into benign and malignant, with malig-
nant tumors being either primary or secondary from a cancer that has metas-
tasized from elsewhere. The sites from which metastases occur frequently
include lung, colon, pancreas, breast, stomach and ovary. In North America,
primary hepatic neoplasms are uncommon, with metastatic tumor being the
most common malignant tumor of the liver. Worldwide, especially in areas
such as the Far East, hepatocellular carcinoma (HCC) is much more prevalent
than metastatic disease.

19.1 Benign Tumors of the Liver
Benign tumors of the liver are detected more frequently than in the past, in
part as a result of the increased use of diagnostic imaging tests, including ultrasound and CT scanning, for reasons unrelated to the tumors. Benign tumors are divided into three categories: hepatocellular, cholangiocellular and non-epithelial.

19.1.1 HEPATOCELLULAR ADENOMA
Hepatocellular adenoma is a mass lesion of the liver characterized by the benign proliferation of hepatocytes. They are seen primarily in females in their third and fourth decades. The increasing prevalence has paralleled the introduction of the oral contraceptive, suggesting a hormonal influence in their pathogenesis. The estimated risk for women on oral contraceptives for seven years is five times the normal rate and increases to 25 times with use longer than nine years. The tumors usually involve the right lobe, may be >10 cm in diameter and less commonly are multiple. Clinical features include an asymptomatic presentation, pain in the right hypochondrium or palpable mass. The most alarming presentation is an acute hemoperitoneum following rupture of the adenoma, which carries an appreciable mortality. Liver enzymes and function tests are usually normal. Diagnosis is usually established with imaging techniques including ultrasound and CT scanning. Radionuclear scanning may show the characteristic lack of colloid uptake due to absence of Kupffer cells in the adenoma. Hepatic arteriography is useful for diagnosis as about 50% of adenomas are avascular with hepatic arteries surrounding the lesion; the remainder are hypervascular. Because adenomas mimic normal hepatic tissue, liver biopsy is of limited diagnostic use. The risk of malignancy is up to 10% with an increased risk in the larger, multiple tumors. Management includes stopping oral contraceptives and resection of larger, symptomatic tumors.

19.1.2 FOCAL NODULAR HYPERPLASIA
Focal nodular hyperplasia (FNH) is a benign disorder characterized by a focal nodular hyperplastic hepatic lesion. This is a common lesion occurring in 3% of the population, more commonly found in females between the ages of 30 and 50 years. Although potentially multiple, most patients (80%) have a solitary lesion varying from 1 mm to 19 cm, but usually 3-5 cm. The characteristic histologic features include the central scar with fibrous connective tissue radiating into the nodules, nodules lacking normal lobular architecture with absence of central veins and portal tracts and presence of Kupffer cells and hypervascularity.

The lesion is usually asymptomatic and incidentally discovered on an imaging study for an unrelated reason. Liver enzymes are usually normal with occasionally an elevation of γ-glutamyl transeptidase. Ultrasound will often not detect the lesion as it is usually isodense to the surrounding tissue.
Doppler flow studies may demonstrate the increased vascularity often present. CT scanning is the most useful for diagnosis with the arterial phase being hyperdense relating to the hypervascularity and the portal phase showing isodensity and preservation of the central scar hypodensity. Technetium sulfur colloid scan will show normal or increased uptake in the lesion relating to the presence of the Kupffer cells in the lesion. No treatment is needed if the patient is asymptomatic, which is usually the case. These lesions rarely rupture. Controversy still exists as to the role of oral contraceptives in the initiation and promotion of these lesions.

### 19.1.3 NODULAR REGENERATIVE HYPERPLASIA

Nodular regenerative hyperplasia (NRH) is a benign proliferative process in which the normal hepatic architecture is entirely replaced by diffuse regenerative nodules of hepatocytes. NRH is relatively common occurring in 3% or autopsies. It occurs in predominantly older patients and is associated with other conditions that may contribute to its formation. These conditions are classified as lymphoproliferative, rheumatologic (rheumatoid arthritis, amyloidosis, vasculitis, collagen vascular diseases) and other (drugs, toxins, anabolic steroids). Gross examination of the liver reveals the entire hepatic parenchyma replaced by nodules varying in size from 0.1 to 4 cm. The histologic findings include the nodular regeneration with curvilinear compression of the central lobe and lack of fibrous scar that distinguishes it from cirrhosis. The clinical presentation of patients with NRH can vary. Usually, the associated condition predominates and the NRH is an incidental finding. Liver enzymes are normal or mildly elevated with normal liver function. The physical findings are variable and may include hepatomegaly and splenomegaly with evidence for portal hypertension. The diagnosis of NRH can be difficult but suspected in a patient with a nodular liver with evidence of portal hypertension but with preserved LFTs. Imaging studies of the liver will show isoechoic nodules and may be confused with cirrhosis. In the majority of patients, management is of the primary predisposing disease with reassurance of the underlying liver disease. Uncommonly symptoms of portal hypertension will dominate and dictate management.

### 19.1.4 Cavernous Hemangioma

Hemangiomas are the most common benign tumor of the liver and are seen in about 0.5-7% of the general population. These are usually detected by imaging techniques done for other reasons. These vascular lesions are usually asymptomatic and are more common in women. Hemangiomas present at all ages but are most common in the third to fifth decades. Lesions larger than 4 cm are called *giant cavernous hemangiomas*. If hemangiomas are
symptomatic, pain is the most common complaint. The only physical sign may be an enlarged liver with an arterial bruit heard over the lesion. Ultrasound findings include an echogenic lesion with diagnosis being confirmed by RBC-labeled nuclear scan, bolus-enhanced CT scan, MRI or, if necessary, angiography. The lesion does not require any treatment as there is no malignant potential and hemorrhage is rare.

19.1.5 SOLITARY HEPATIC CYST
Solitary hepatic cysts are relatively common and usually asymptomatic. They are usually discovered incidentally during the evaluation of the abdomen with an ultrasound for an unrelated reason. Solitary cysts are found in 3.5% of the population, more common in females and in right lobe of liver. They may be symptomatic with localized RUQ pain if large. Rarely there may be intracystic hemorrhage, infection or more rarely malignancy. Treatment is rarely required. For the rare symptomatic lesion, percutaneous cystic drainage with alcohol or doxycycline sclerosis therapy or surgical cyst fenestration may be needed.

19.2 Malignant Tumors of the Liver

19.2.1 PRIMARY HEPATOCELLULAR CARCINOMA
Hepatocellular carcinoma (HCC) is a neoplasm of increasing incidence worldwide representing 5% of all cancers. In Africa, HCC makes up 50% of all malignant tumors in men and is usually found in young adults. In North America, it represents only 1-2% of malignant tumors.

Although many factors potentially contribute to HCC, the disease is usually limited to individuals with pre-existing liver disease. Approximately 60-80% of patients in North America with HCC have a cirrhotic liver, and more than 10% of individuals with cirrhosis will develop HCC. Although the most powerful risk factor is the existence of liver cirrhosis regardless of etiology, cirrhosis related to viral hepatitis, alcohol and hemochromatosis carries a higher risk. Hepatitis B virus has a clear association with the development of HCC, with the tumor occurring 22 times more frequently among carriers of hepatitis B surface antigen than among the general population. Integrated DNA sequences of hepatitis B virus have been identified in the genome of both tumor cells and normal hepatocytes of patients with HCC, suggesting that viral integration occurs before the development of the tumor. Hepatitis C also appears to be a causative agent for the development of HCC. Antibodies to hepatitis C have been found in more than 50% of cases of HCC who had no evidence for hepatitis B infection. The hepatitis C virus does not appear to integrate into the host genome, and thus the mechanism for the hepatocarcinogenesis is unclear. Noncirrhotic causes of HCC include the ingestion
of aflatoxins (metabolites of the mould Aspergillus flavus) and ingestion of hormone supplements, including oral contraceptives and exogenous androgens.

The clinical recognition of HCC may be difficult, as the tumor often occurs in patients with underlying cirrhosis and the signs and symptoms may simply suggest progression of the underlying liver disease. Detection may also be the result of surveillance ultrasound for HCC in patients with known cirrhosis. The most frequent feature is the development of a painful mass in the right upper quadrant accompanied by constitutional symptoms of anorexia and weight loss. In the patient with cirrhosis, the presentation may include the development of ascites, encephalopathy or abrupt clinical deterioration. A hepatic friction rub or bruit may be heard over the lesion. Patients may present with one of the many paraneoplastic syndromes, including erythrocytosis, hypercalcemia, dysproteinemia or hypoglycemia. Routine blood tests including liver function usually reflect the underlying chronic liver disease. Normal liver enzymes do not rule out the diagnosis. The oncofetal antigen $\alpha_1$-fetoprotein (AFP), is usually elevated in the serum, with levels > 500 µg/L in 70-80% of cases. Diagnostic criteria for HCC include two imaging techniques (contrast ultrasound, CT, MRI or angiography) that demonstrate the characteristic arterial hypervascularity of a focal lesion > 2 cm or one imaging technique showing hypervascularity along with AFP > 200 µg/mL. Lesions < 2 cm often require percutaneous aspiration for histologic diagnosis as imaging studies are less diagnostic. Tumor staging should be on the basis of US and spiral CT.

In general, the prognosis for patients with HCC is very poor, with the median survival of North American patients only six to 20 months. The prognosis of the patient with HCC is dependent on: (a) the stage, aggressiveness and growth rate of the tumor; (b) the general health of the patient; (c) the liver function of the patient. Up to 70% have metastatic disease at the time of diagnosis. In patients with non-invasive localized disease, options to consider include surgical resection, liver transplantation and percutaneous techniques. These should be considered in patients with a single HCC < 5 cm or three nodules smaller than 3 cm without evidence of metastasis. Patients with preserved liver function (Child A) may be considered for resection although the recurrence rate may exceed 50% at three years. Patients with poor liver function (Child B and C) should be considered for transplantation. The results of surgery are often complicated by the presence of underlying cirrhosis, the occasional mult centric nature of the tumor and the presence of micrometastases. Non-surgical techniques for localized disease include the use of percutaneous ethanol injection resulting in a 80% remission rate in localized lesions < 3 cm. Other ablative techniques under investigation include radiofrequency, microwave, cryotherapy, laser therapy and arterial embolization.
Patients with intermediate-advanced HCC who are not candidates for curative surgery have a three-year survival of 10-50% with survival best correlated with severity of underlying liver disease. Such patients can be considered for trans-arterial embolization. The effect of systemic chemotherapy is questionable. We look forward to newer therapies that may include monoclonal antibodies with chemotherapy and gene therapy with cytotoxic agents.

Screening strategies for HCC in patients with known cirrhosis, especially secondary to chronic viral hepatitis, have included ultrasound and AFP determinations every six to 12 months. The AFP as a screening test has a sensitivity of 39-64%, a specificity of 76-91% and a positive predictive value of 9-32%. Ultrasound is a better tool with sensitivity of 71% and specificity of 93% but a positive predictive value of only 14%. This approach identifies tumors at an earlier stage but has not yet been shown to improve morbidity or mortality rates.

19.2.2 HEPATOBlastoma
Hepatoblastoma is a malignant tumor that develops in children under the age of five years, with over 50% of the cases occurring before the age of two years. About one-third of patients with hepatoblastoma have birth defects in other organs. Patients may present with failure to thrive, weight loss or a rapidly enlarging liver mass. The tumors are composed of immature hepatocytes occasionally accompanied by a mesenchymal component such as bone, and have the potential for growth to a large size. Treatment consists of surgical resection followed by radiotherapy and chemotherapy. The five-year survival rate is 15–35%.

19.2.3 METASTATIC TUMORS
In North America, the most common malignant tumor to affect the liver is metastasis from primary carcinoma elsewhere. Common sources include colorectal, breast, lung or urogenital cancer as well as neuroendocrine tumors. It is sometimes difficult to distinguish primary from metastatic carcinoma in the liver. Metastases are often multiple with smaller lesions, whereas HCC have a dominant larger mass. In most cases, metastases are readily imaged by ultrasound, CT or MRI. The diagnosis is usually confirmed by needle biopsy. Occasionally, metastases have histologic or immunohistochemical features that suggest a primary site.

For most cases, metastatic disease implies advanced disease with poor prognosis and few therapeutic options. Exceptions include metastatic colorectal carcinoma and neuroendocrine tumors. Surgical resection for focal metastatic colorectal carcinoma confined to the liver may increase five-year survival rates up to 40%. Cryotherapy and chemotherapy for unresectable
colorectal disease may prolong survival. Resection for localized neuroendocrine tumors and drug therapy (interferon, octreotide) for more advanced disease may help prolong survival and reduce symptoms from hormone release (carcinoid syndrome, Zollinger-Ellison syndrome).

19.3 Investigation of the Solitary Hepatic Lesion
The discovery of a liver mass is usually under one of two circumstances. It may be an incidental finding as a result of an imaging study done for unrelated reasons in a patient with or without symptoms or as a part of routine surveillance for detection of hepatocellular carcinoma. The subsequent evaluation is different in each circumstance.

A solid lesion may be found in a patient without chronic liver disease who may or may not have symptoms. The most common lesion is a hemangioma. If this appears typical on ultrasound in a patient with no risk factors for liver disease, no
Further therapy or follow-up is necessary. If not typical, a RBC-labeled nuclear scan or a CT scan, preferably a tri-phasic study or a contrast-enhanced ultrasound, are indicated. If risk factors for HCC exist, then AFP should be requested, as an elevation in someone without pre-existing liver disease is highly suspicious for HCC. Lesions not typical for either HCC or hemangioma may be considered for other imaging studies (nuclear colloid scan, MRI) and if not diagnostic, the patient needs imaging follow-up for up to two years. Liver biopsy has a less dominant role as the nature of larger lesions can usually be established on basis of imaging studies. In lesions not diagnostic on imaging studies, biopsy/aspirate can be considered but are often inaccurate because of difficulty with needle placement and histologic differentiation of well-differentiated HCC, normal liver and high grade dysplasia (Figure 39).

In the patient with known cirrhosis who is undergoing regular HCC screening, the action taken upon detection of a lesion at ultrasound depends on size of

FIGURE 40. Mass found on screening for hepatocellular carcinoma (HCC).
lesion. If it is < 1 cm and the AFP is normal, repeat the ultrasound in three months. If the lesion is > 2 cm, a serum AFP > 200 ng/mL or another imaging study (CT/MRI/angiography) verifying the characteristic hypervascularity will establish the diagnosis of HCC. Lesions between 1 and 2 cm may be further defined by CT scan which may describe the hypervascularity of HCC and may require fine needle aspiration for histologic diagnosis of HCC (Figure 40).

20. LIVER DISEASE IN PREGNANCY / R.P. Myers and E.A. Shaffer

20.1 Normal Pregnancy

Pregnancy is a state of altered, but normal, physiology. Although hepatic complications are uncommon during pregnancy, prompt diagnosis and treatment is essential so as to minimize adverse maternal and fetal outcomes. The anatomic and physiologic changes that accompany pregnancy may alter physical findings and liver biochemistries, yet normal pregnancy does not significantly affect liver metabolism or function. Due to an increase in endogenous estrogens, the pregnant state is normally mildly cholestatic. Serum alkaline phosphatase levels are significantly higher in the third trimester than in the non-pregnant state and may remain elevated for up to six weeks following delivery. In contrast, pregnancy does not markedly alter the levels of total bilirubin, aminotransferases, γ-glutamyl transpeptidase (GGT), 5'-nucleotidase, or the prothrombin time/INR (reflecting the coagulation factors synthesized in the liver). In pregnancy, the expanded plasma volume causes dilution and hence a decline in serum albumin and total protein, whereas serum globulin, total cholesterol and triglyceride levels increase.

Pregnancy does not change liver size. In the third trimester, the enlarging uterus displaces the liver superiorly and posteriorly. Therefore, a palpable liver suggests significant hepatomegaly and underlying liver disease. A small amount of peripheral edema is also common during pregnancy (from the hypoalbuminemia and the enlarged uterus causing pelvic venous compression), as are some findings that usually connote chronic liver disease, such as spider angiomata and palmar erythema. These latter features reflect the high circulating estrogen levels.

Liver diseases occurring during pregnancy can be divided into three categories: (1) acute liver disease coincident with pregnancy; (2) pregnancy occurring in a patient with chronic liver disease; and (3) liver diseases unique to pregnancy (Table 54).

20.2 Acute Liver Disease Coincident with Pregnancy

Any liver disease that can afflict young women may arise during pregnancy. Of these, acute infection with a hepatotropic virus is the most common cause of jaundice in pregnancy. In general, pregnancy does not affect the course of
viral hepatitis, except for that due to the hepatitis E virus (HEV), which occurs mainly in developing countries. Although usually mild and self-limited, HEV infection during pregnancy can have a high rate of acute liver failure (up to 58%) and a high maternal mortality: 1.5%, 8.5%, and 21% during the first, second, and third trimesters, respectively. HEV infection during the third trimester is associated with increased fetal complications including death.

Although uncommon, infection with the herpes simplex virus (HSV) poses a considerable risk of fulminant hepatitis in pregnant women. Infected women typically have marked elevations in aminotransferases (often > 1,000 IU/L), coagulopathy, and encephalopathy, but not jaundice. The diagnosis is supported by a vesicular rash on the vulva or cervix and appropriate serologic

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Intrahepatic cholestasis of pregnancy</th>
<th>Acute fatty liver of pregnancy of HELLP Syndrome of Pregnancy</th>
<th>Pre-eclampsia/eclampsia</th>
<th>Viral hepatitis</th>
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</thead>
<tbody>
<tr>
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<td>3</td>
<td>2-3</td>
<td>1, 2, 3</td>
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<tr>
<td>Family history</td>
<td>+</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>Pruritus</td>
<td>+</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Abdominal pain</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Presence of eclampsia</td>
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<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Tender hepatomegaly</td>
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<td>±</td>
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Biochemical features

<table>
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<tr>
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<th>Aminotransferases</th>
<th>Hepatitis serology</th>
<th>DIC / thrombocytopenia</th>
<th>Hypoglycemia</th>
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<tr>
<td></td>
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<td>&gt; 1,000</td>
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<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Fetal MR low (1-2%) – prematurity</th>
<th>Fetal MR to 35%</th>
<th>Fetal MR high ~ 35%</th>
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<tbody>
<tr>
<td>Maternal MR rare</td>
<td>&lt; 3% with early delivery and care</td>
<td>Maternal MR less</td>
<td>Recurrence ~ 25%</td>
</tr>
<tr>
<td>Recurrence 60-70%</td>
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Other

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<tr>
<th>GGT ↑ Bilirubin</th>
<th>ALP ↑ (4x) &gt;&gt; WBC ↑; PLT ↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal early to ↑</td>
<td>INR/PT ↑; uric acid ↑</td>
</tr>
<tr>
<td>LDH &gt; 600</td>
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TABLE 54. Differential diagnosis in major liver diseases during pregnancy
testing. Liver biopsy demonstrates extensive hepatocyte necrosis and intranuclear herpetic inclusions. Affected women respond rapidly to intravenous acyclovir and do not require delivery for improvement.

Alterations in gallbladder motility and biliary lipid composition produce a lithogenic state during pregnancy. Although gallstones (and biliary sludge) are frequently identified among pregnant women, symptoms are uncommon. In fact, biliary sludge frequently disappears postpartum. In symptomatic women, conservative medical therapy is generally advised until the postpartum period. Endoscopic retrograde cholangiopancreatography (ERCP) and/or cholecystectomy however may be performed if necessary (e.g., in women with symptomatic choledocholithiasis leading to acute cholecystitis or pancreatitis).

Since pregnancy is a hypercoagulable state, women with thrombophilias (such as protein C or S deficiency or antiphospholipid antibody positively), are at increased risk of thrombotic complications. This may take the form of the Budd-Chiari syndrome with painful hepatomegaly, liver failure, and ascites. Finally, since hepatic adenomas are estrogen responsive, enlargement of these tumours, and rarely hepatic rupture, may occur during pregnancy.

20.3 Pregnancy Occurring in a Patient with Chronic Liver Disease

Pregnancy is unusual in patients with severe chronic liver disease, which causes anovulation and infertility. With better treatment modalities and care, many women with chronic viral hepatitis and those successfully treated for other chronic liver diseases (e.g., following immunosuppression for autoimmune hepatitis) can conceive. The degree of hepatic impairment and portal hypertension determine the risk for the mother during pregnancy. Hemorrhage from esophageal varices, most often during the second trimester or labour, is the most important complication in women with cirrhosis. Variceal bleeding occurs due to expansion of the plasma volume associated with pregnancy and increased flow through the azygous system. Additional complications include hepatic failure, postpartum hemorrhage due to coagulopathy, and more frequent fetal growth restriction and loss.

Although the impact of pregnancy on women with early-stage hepatitis B and C appears to be minimal, these infections may be transmitted to the fetus. Hepatitis B virus (HBV) infection poses a high risk of neonatal transmission, particularly in hepatitis B-e-antigen (HBeAg) positive mothers in whom this risk is approximately 90%. As a result, all pregnant women are now screened for hepatitis B surface antigen (HBsAg). If positive, the neonate should receive immunoprophylaxis with hyperimmune globulin and hepatitis B vaccine to prevent infection. The risk of transmission of the hepatitis C virus (HCV) is much lower (approximately 5%), and dependent on the maternal level of viremia. Co-infection with HIV, which enhances HCV replication,
increases the risk of transmission 4-5-fold. Unfortunately, immunoprophylaxis is not available. Breastfeeding is safe for the offspring of women with chronic hepatitis B (once appropriately immunized) and C.

Patients who are stable following liver transplantation may conceive and deliver normal infants while on immunosuppressant therapy. The pregnancy should be delayed at least six months following transplantation due to the risk of acute rejection and cytomegalovirus infection during the early post-transplantation period. Although outcomes are generally good, pregnancy in the transplant recipient carries a high risk of pre-eclampsia and worsening hypertension. This risk may be lessened with tacrolimus-based immunosuppression. Such patients with chronic liver disease warrant a multidisciplinary team of obstetricians, perinatologists, and hepatologists.

20.4 Liver Diseases Unique to Pregnancy
The gestational stage of the pregnancy is a useful guide to the differential diagnosis of liver disease in the pregnant woman in whom acute liver diseases coincident with pregnancy and pre-existing hepatic conditions have been excluded. Whereas hyperemesis gravidarum typically begins in the first trimester, cholestasis of pregnancy usually occurs in the second or third trimester, and the disorders associated with pre-eclampsia in the third trimester.

20.4.1 HYPEREMESIS GRAVIDARUM
Nausea and vomiting are common during early pregnancy, occurring in 50-90% of women. In an extreme form, intractable symptoms lead to dehydration and ketosis, necessitating hospitalization. This syndrome is termed hyperemesis gravidarum; the etiology is unknown. Symptoms typically begin during the first trimester and resolve by 20 weeks of gestation. Hepatic involvement occurs in approximately 50% of patients. Aminotransferases are typically less than 1,000 IU/L and jaundice is rare. Liver biopsy, rarely necessary due to the characteristic presentation, reveals non-specific findings including steatosis (fatty liver). Management is supportive and aimed at alleviating the vomiting and correcting any fluid and electrolyte abnormalities. Maternal and fetal outcomes are excellent.

20.4.2 CHOLESTASIS OF PREGNANCY
Cholestasis of pregnancy accounts for 20-25% of cases of jaundice during pregnancy. The etiology is unknown. There is a clear genetic predisposition, likely autosomal dominant, with an increased frequency in women of Scandinavian and Chilean descent. The cholestasis likely represents an exaggerated response of the liver to the normal increase in endogenous estrogens during
pregnancy. The increased susceptibility of affected women and their relatives (including men) to the cholestatic effects of exogenous estrogen supports this theory. Recently, specific defects in hepatic transport have been identified in some women who later develop cholestasis when pregnant.

Pruritus beginning in the late second or third trimester is the hallmark of cholestasis of pregnancy. The pruritus is most severe at night and on the palms and soles. In half of these patients, jaundice follows. Other cholestatic features include dark urine, and occasionally, acholic (clay-colored) stools. Otherwise, women generally feel well without nausea, vomiting, or abdominal pain. Laboratory investigations revealed raised serum alkaline phosphatase, bile acids, and cholesterol, but often normal or mildly elevated GGT. The aminotransferases (AST, ALT) are usually modestly elevated, but may approach 1,000 IU/L, occasionally making distinction from acute hepatitis difficult. The evaluation of the pregnant woman with cholestasis involves excluding other causes of jaundice and pruritus, including viral hepatitis, primary biliary cirrhosis (which can be uncovered by the estrogenic state) and biliary tract disease by the appropriate laboratory and imaging investigations. Ultrasound and cholangiography are normal. Liver biopsy is rarely necessary; only bland cholestasis without inflammation would be evident.

Although a benign condition for the mother (other than the inexorable pruritus), cholestasis of pregnancy is associated with an increased risk of prematurity and fetal wastage. Management is primarily symptomatic. Ursodeoxycholic acid in a dose of 13-15 mg/kg/day appears to improve liver biochemistry, symptoms, and fetal outcome. Bile salt-binding agents, such as cholestyramine, may lessen the pruritus, but aggravate the fat malabsorption associated with this disease, often necessitating parenteral vitamin K supplementation. S-adenosylmethionine, rifampin, steroids, and phenobarbital have been used, but with equivocal results. Delivery should occur as soon as fetal lung maturity is documented to prevent the increased risk of stillbirth.

Symptoms usually abate within two weeks of delivery, sometimes at the onset of labor with the presumed drop in estrogens. There is a high likelihood of recurrence with subsequent pregnancies and with the use of exogenous estrogens, including oral contraceptives. Affected women also have a greater risk for the development of gallstones, perhaps reflecting the defect in hepatic transport.

20.4.3 ACUTE FATTY LIVER OF PREGNANCY
Acute fatty liver of pregnancy (AFLP) is rare (approximately 1 in 13,000 deliveries), but has serious consequences for mother and fetus. AFLP almost invariably presents in the third trimester, with a peak frequency around 36-37 weeks gestation. Occasionally, it becomes apparent only after delivery. There is an association with nulliparity, twin gestations, and pregnancies with a male
fetus. Pre-eclampsia is present in 50% of cases. Presentation can vary from non-specific symptoms to acute liver failure with profound coagulopathy, jaundice, encephalopathy, and hypoglycemia. Nausea and vomiting with or without abdominal discomfort are common. Pruritus is uncommon and should suggest the possibility of an alternative diagnosis such as cholestasis of pregnancy. Severe cases have an inexorable downhill course unless the fetus is delivered; even then, deterioration may continue for a further 48 to 72 hours. Management involves aggressive supportive care. The only definitive treatment is prompt delivery (Table 55).

Laboratory features include moderately elevated aminotransferases, usually around 300 IU/L, but may range from normal to 1,000 IU/L. Jaundice is common but variable. The prothrombin time/INR is prolonged and fibrinogen levels reduced. Liver biopsy, which may be performed via the transjugular route due to the coagulopathy, reveals microvesicular steatosis (the nucleus is located in the centre of the cell with tiny fat droplets scattered throughout the cytoplasm). The changes are most prominent in the central zone while sparing periportal hepatocytes.

Diagnosis requires a high index of suspicion, as the presentation is often non-specific. AFLP should be considered whenever marked nausea and vomiting develop in the third trimester of pregnancy. Ultrasound, CT, or MRI scans may suggest hepatic steatosis and help exclude complications such as subcapsular hematoma or another entity such as choledocholithiasis. Acute viral hepatitis must be excluded via appropriate serologic testing. Liver biopsy is diagnostic, and should be performed if the results will alter management. For example, differentiation of AFLP from acute viral hepatitis is important to determine whether rapid delivery is indicated, since delivery can be life saving in AFLP.

The etiology of AFLP likely represents a defect in intermediary fat metabolism due to mitochondrial dysfunction. Infants born of affected pregnancies may be deficient in one of the enzymes of mitochondrial fatty acid beta oxidation, long chain 3-hydroxyl-acyl Co-A dehydrogenase (LCHAD). Some affected women are heterozygous deficient for LCHAD; thus an inherited partial deficiency in fatty acid beta oxidation may be uncovered in susceptible women by a fetus that is fully deficient. Because of the association between AFLP and LCHAD deficiency, mother and child should be tested for defects in LCHAD where testing is available. The risk of AFLP does not appear to be increased in subsequent pregnancies.

20.4.4 LIVER DISEASE OF PRE-ECLAMPSIA

Pre-eclampsia is a disease of unclear etiology characterized by sustained
hypertension and proteinuria after the 20th week of gestation. Hepatic involvement, typically in the form of the HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, occurs in approximately 20% of women with severe pre-eclampsia, usually in the third trimester. Many patients are asymptomatic and diagnosed via routine laboratory testing in the setting of pre-eclampsia. As many as 30% are diagnosed postpartum; some have no hypertension or proteinuria at the time of presentation. Patients may experience nausea, vomiting, abdominal discomfort, and symptoms typical of pre-eclampsia (e.g., headache and blurred vision). Jaundice is uncommon.

The diagnosis rests on clinical grounds. The aminotransferases are elevated, but variable. In one study, the mean AST was 250 IU/L with a range from 70 to over 6,000 IU/L. Hemolysis is modest, being detected via a peripheral blood smear and elevated lactate dehydrogenase levels. The thrombocytopenia may be modest to very severe; idiopathic thrombocytopenic purpura must be considered in the differential diagnosis. Liver biopsy reveals periportal hemorrhage and fibrin deposition with periportal hepatocyte necrosis. Biopsy is rarely warranted and should be undertaken cautiously due to the risk of subcapsular hematoma and hepatic rupture associated with this condition. Hepatic infarction is an additional complication of pre-eclampsia. Affected women have fever, marked elevations in the aminotransferases, anemia, and leukocytosis. The disorder may resolve spontaneously or lead to death from multi-organ failure.

Management of pre-eclampsia and the HELLP syndrome is obstetrical, consisting of careful fetal monitoring and prompt delivery. Although HELLP syndrome may recur in subsequent pregnancies, adverse long-term hepatic sequelae for the mother and child are not seen.

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**TABLE 55. Termination of pregnancy**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Acute fatty liver of pregnancy (AFLP)</td>
</tr>
<tr>
<td>Severe pre-eclampsia</td>
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<tr>
<td>Spontaneous rupture of the liver</td>
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<table>
<thead>
<tr>
<th>Not Necessary</th>
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<tbody>
<tr>
<td>Viral hepatitis</td>
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<td>Intrahepatic cholestasis of pregnancy</td>
</tr>
<tr>
<td>Congenital hyperbilirubinemas</td>
</tr>
<tr>
<td>Most chronic liver diseases</td>
</tr>
</tbody>
</table>
21. VASCULAR DISORDERS OF THE LIVER / L.J. Worobetz

The most frequent abnormality of the circulation to affect the liver is congestive heart failure, which leads to reduced outflow of blood from the liver. Other causes of hepatic congestion include constrictive pericarditis, obstruction of the inferior vena cava and hepatic veins (Budd-Chiari syndrome) and occlusion of the small hepatic veins (veno-occlusive disease). Increased resistance to hepatic venous outflow results in congestive hepatomegaly, dilation of hepatic venules and sinusoids, and hypoxia. The hypoxia in turn leads to hepatocyte damage with possible fibrosis and cirrhosis, the latter termed cardiac cirrhosis. In patients with sudden hypotension as may be seen in acute myocardial infarction, the sudden reduction in blood flow to the liver may result in ischemic hepatitis (Figure 41).

21.1 Ischemic Hepatitis

Ischemic hepatitis refers to the situation of acute circulatory failure and resulting hypoperfusion of the liver causing acute hepatocyte injury. Although ischemic hepatitis can result from any cause of acute hypotension, it is most commonly seen in patients with acute cardiac disease such as acute myocardial infarction. Patients with pre-existing liver disease, especially alcoholic liver disease, may be particularly prone to such injury. Clinical evidence of liver failure is usually absent. The biochemical pattern resembles that of acute viral hepatitis with serum transaminases rising rapidly to levels eight to 10 times normal. Characteristically these return rapidly to normal within seven days if the underlying cause of hypotension is corrected. The serum bilirubin and alkaline phosphatase may rise slightly but also may be delayed simulating a cholestatic pattern. In difficult diagnostic cases, the liver biopsy would show characteristic zone 3 injury. Often there is additional evidence of end-organ hypoperfusion, especially acute renal injury. The aim of therapy is to restore cardiac output and reverse the underlying cause of hemodynamic instability. No specific drug therapy currently exists for the hepatic injury with the outcome depending entirely on the cardiovascular status of the patient.

21.2 Congestive Heart Failure

Patients with either acute or chronic congestive heart failure will commonly have biochemical and clinical features of liver disease that reflect passive hepatic congestion. Features often reflect, however, the combination of passive congestion and reduced cardiac output on the liver. Clinical features of hepatic congestion commonly include tender hepatomegaly and general abdominal discomfort. Classical features of chronic liver disease are not usually seen. Features
of right heart failure may include raised jugular venous pressure and positive hepatojugular reflux. In tricuspid insufficiency, the liver may be pulsatile. Ascites, which may be present, often has a high protein content. Characteristic biochemical abnormalities include a moderate elevation of aminotransferases (< 300) and a mild elevation of alkaline phosphatase, especially in acute congestion where there may be also an ischemic insult. The level of bilirubin elevation correlates well with degree of heart failure and may be disproportionately elevated to the liver enzymes. Laboratory tests and imaging studies are otherwise aimed at assessing and monitoring the severity of liver disease (albumin, INR) and eliminating other causes of liver disease. In difficult diagnostic cases, a liver biopsy will reveal classical zone 3 changes with central vein and sinusoidal dilatation and hemorrhage. Chronic cases may develop characteristic fibrotic changes with possible cirrhosis. The prognosis is directly related to the severity of the heart failure and its response to therapy.

21.3 Budd-Chiari Syndrome

Budd-Chiari syndrome is defined as any pathophysiologic process that results in interruption or diminution of the normal blood flow out of the liver and implies thrombosis of the hepatic veins and/or suprahepatic inferior vena cava. It is distinguished from the two other causes that cause decreased outflow from the liver: hepatic veno-occlusive disease and right heart failure. Budd-Chiari syndrome is a rare disorder of diverse etiologies with an underlying cause identified in over 80% of cases. As many as 50% will have an underlying chronic myeloproliferative disorder (polycythemia vera, essential thrombocytosis, myeloid metaplasia) with its associated hypercoagulability. Other hypercoagulable states that predispose include paroxysmal nocturnal hemoglobinuria, protein C and S deficiency as well as oral contraceptives and pregnancy. Other causes include infections and mechanical obstructive lesions such as tumors and membranous vascular webs.

Budd-Chiari syndrome is more common in women and usually presents in the third or fourth decade. The syndrome can be classified as fulminant, acute, subacute or chronic. The clinical presentation is dependant on the extent and the rapidity of the vascular occlusion. In the acute disease, patients present with rapidly developing tender hepatomegaly and marked ascites leading to liver failure with jaundice, possible variceal bleed and coma. The biochemical tests are abnormal with the elevation of AST and ALT reflecting the degree of vascular congestion and resulting ischemic hepatocellular damage. Liver function can rapidly deteriorate with progressive hyperbilirubinemia and increasing INR. The serum-ascites fluid albumin gradient is high, with the total protein level in the ascitic fluid > 2.5 g/dL. The subacute and chronic
presentations have been present for several weeks to more than six months and may have features of ascites or variceal bleeding. The liver biopsy shows large hemorrhagic areas with congestion, atrophy and necrosis around the center of the lobule. The degree of necrosis and presence of fibrosis will help determine the urgency for decompression or indeed liver transplantation. Doppler ultrasound is now the diagnostic procedure of choice with a sensitivity and specificity of 85%. The typical ultrasound features include inability to visualize normal hepatic venous connections to the vena cava and absence of any wave form in the hepatic vein. In difficult diagnostic cases, contrast CT scan, MRI or IVC hepatic venography may help establish diagnosis and rule out any anatomic cause for the thrombosis. The decision regarding treatment depends on etiology, anatomy and acuteness of the illness. Principles of therapy include medical support and relief of the hepatic venous outflow obstruction in order to prevent hepatic necrosis. Conventional therapy including diuretics does not reverse hepatic congestion but will be helpful in managing consequences of portal hypertension and ascites. Heparin is often used in the initial stages of therapy. Thrombolytic therapy with urokinase or tissue plasminogen activator has been used successfully in some cases. Placement of TIPS can decompress the portal system and potentially stabilize patients especially where thrombolytics have failed and allow consideration of liver transplantation. An alternative is the placement of a surgical shunt. Those with a fulminant form with liver failure should be considered for liver transplantation.

21.4 Veno-Occlusive Disease

Veno-occlusive disease (VOD) refers to the obstruction of small and medium-sized intrahepatic veins and is increasingly referred to as sinusoidal obstruction syndrome (SOS). This reflects the fact that obstruction usually begins in the sinusoid. Casual factors include pyrrolizidine alkaloids, hepatic irradiation, azathioprine and graft-versus-host disease related to bone marrow transplantation. The presentation mimics the Budd-Chiari syndrome. In the acute form, presentation may include hepatomegaly, ascites and hyperbilirubinemia. The chronic form leads to cirrhosis and portal hypertension with esophageal varices. The liver biopsy characteristically shows intense congestion around the hepatic venule with thickened obstructed hepatic veins. There is no effective therapy available. Treatment is largely supportive as 70-85% recover spontaneously. Control of the ascites may be required by sodium restriction and use of diuretics. TIPS can control refractory ascites but has not shown to prolong survival. Liver transplantation may be the only hope for many.
21.5 Portal Vein Thrombosis
Thrombosis of the portal venous system (PVT) in children is most commonly due to infection with neonatal umbilical sepsis in 25%. In adults, cirrhosis is a major cause accounting for 15-30%. Other causes include trauma, local inflammatory condition (pancreatitis), neoplasia (hepatoma), hypercoagulable conditions, or may be idiopathic. Patients usually present with massive hematemesis from bleeding esophageal varices that is recurrent. Splenomegaly is present. Chronic PVT may present with ascites. Biochemical tests of the liver are normal or only mildly elevated. Because liver function is usually preserved, encephalopathy is uncommon and bleeding episodes are better tolerated. Diagnosis may be confirmed by Doppler ultrasound studies of the portal vein or a venous phase of hepatic angiography. Treatment is usually directed at defining a cause for the thrombosis and controlling the bleeding esophageal varices. For the prevention of further bleeding episodes, one can consider variceal banding or the use of β-blockers. Although more technically difficult, the placement of a transjugular intrahepatic portosystemic shunt (TIPS) may be necessary. Because of normal liver parenchyma, surgical approaches such as mesocaval shunt may be considered and are generally better tolerated than by patients with chronic liver disease.
SUGGESTED READING LIST

Section 1 Liver Structure and Function

Section 2 Approach to the Patient with Liver Disease
Green RM, Flamm S. AGA technical review on the evaluation of liver chemistry tests. Gastroenterology 2002; 123:1367-1384.

Section 3 Evaluation of Abnormal Liver Enzyme Results in Asymptomatic Patients

Section 4 The Liver and Drug Disposition

Section 5 Congenital Hyperbilirubinemias

Section 6 Acute Viral Hepatitis

Section 7 Chronic Viral Hepatitis

Section 8 Alcoholic Liver Disease


Section 9  Non Alcoholic Fatty Liver Disease


Section 10  Drug-Induced Liver Disease


Section 11  Inherited Liver Disease


Section 12  Cholestasis
Section 13 Cirrhosis of the Liver

Section 14 Portal Hypertension

Section 15 Ascites and Spontaneous Bacterial Peritonitis

Section 16 Hepatic Encephalopathy
Section 17 Hepatorenal Syndrome


Section 18 Liver Transplantation


Section 19 Neoplasms of the Liver


Section 20 Liver Disease in Pregnancy


Section 21  Vascular Disorders of the Liver

OBJECTIVES

Section 1. Liver Structure and Function
1. Describe the morphological features of the normal liver.
2. Know its blood supply.
3. Describe the biliary system.
4. Define the metabolic functions of the liver.
5. Recognize the means by which the liver disposes of drugs and xenobiotic agents.
6. Know the basis for bile formation and the enterohepatic circulation of bile salts.
7. Recognize the importance of the canalicular export pumps for bile formation.
8. Realize the functions of the biliary tract.

Section 2. Approach to the Patient with Liver Disease
1. Describe the major clinical manifestations of liver disease.
2. What is jaundice? Briefly summarize the metabolism of bilirubin.
3. List the major biochemical tests for evaluation of liver disease.
4. What common imaging tests are used for hepatobiliary disease?
5. List the indications for liver biopsy.
6. Discuss a clinical approach to jaundice.

Section 3. Evaluation of Abnormal Liver Enzyme Results in Asymptomatic Patients
1. Recognize the causes of elevated liver-enzyme levels.
2. Differentiate causes of elevated liver-enzyme levels with and without cholestasis.
3. Establish a plan of investigation.

Section 4. The Liver and Drug Disposition
1. Recognize that liver blood flow and metabolizing enzymes are both crucial determinants of drug disposal.
2. Understand the metabolic pathways leading to drug excretion from the body.
3. Know the differential implication of P450 cytochrome enzymes in drug metabolism.
Section 5. Congenital Hyperbilirubinemas
1. Recognize the different causes of congenital hyperbilirubinemia.

Section 6. Acute Viral Hepatitis
1. Understand the major modes of transmission of hepatitis A-E.
2. Discuss the clinical presentation and natural history of acute hepatitis A-E.
3. Know the serologic tests used to make the diagnosis of acute hepatitis A-E.
4. Discuss prevention and management options available for acute hepatitis A-E.
5. Recognize the complications of acute hepatitis.

Section 7. Chronic Viral Hepatitis
1. Define chronic viral hepatitis and list histologic features of the disease.
2. Understand the natural history, serologic markers and treatment indications for hepatitis B.
3. Understand the natural history, treatment indications and the importance of genotype in hepatitis C.
4. Define early virologic response and sustained virologic response in hepatitis C.
5. List the therapeutic options for hepatitis B and C and their side effects and contraindications.

Section 8. Alcoholic Liver Disease
1. Understand the pathogenesis and presentations of the different clinical syndromes associated with alcoholic liver disease.
2. Learn about the management issues with the different alcoholic syndrome.

Section 9. Non-Alcoholic Fatty Liver Disease
1. Understand the difference between NAFLD and NASH and their associated risk factors.
2. Recognize the paucity of data with respect to the natural history of this disease and develop a strategy for evaluating patients with NAFLD.
3. Recognize that there are no current proven effective treatments for NAFLD.

Section 10. Drug-Induced Liver Disease
2. What forms of acute hepatic necrosis can be produced by drugs?
3. What variants of cholestatic disease can drugs produce?
4. What is the mechanism of acetaminophen-induced liver necrosis?
5. List hepatic reactions to oral contraceptives.
6. What forms of chronic liver disease can drugs cause?

Section 11. Inherited Liver Disease
1. To describe the disease mechanisms and clinical features of liver disease associated with $\alpha_1$-antitrypsin deficiency and Wilson’s disease.
2. To develop an approach to the clinical diagnosis of hemochromatosis.
3. To interpret genetic testing for hemochromatosis.

Section 12. Cholestasis
1. Understand cholestasis may be intrahepatic and/or extrahepatic.
2. Understand the biochemical pattern of disease is similar to infiltrations.
3. Learn that liver biopsy is helpful in intrahepatic cholestasis.
4. Understand that magnetic resonance imaging ± endoscopic ultrasound is/are used to investigate extrahepatic cholestasis.

Section 13. Cirrhosis of the Liver
Understand that:
1. Cirrhosis frequently goes unidentified and can only be reliably diagnosed on liver biopsy.
2. Obesity is now one of the most common causes of cirrhosis in North America.
3. Cirrhosis is reversible if the cause is eradicated.
4. Hepatoma complicates all cirrhosis and should be screened for.
5. Decompensated cirrhosis requires liver transplantation.

Section 14. Portal Hypertension
1. Describe the pathophysiology of portal hypertension.
2. Classify the causes of portal hypertension into categories.
3. Understand the pathophysiology, anatomy, and emergency and prophylactic management of variceal bleeding.
4. Understand the pathogenesis, clinical characteristics and management options of cirrhotic cardiomyopathy and pulmonary complications of cirrhosis.

Section 15. Ascites and Spontaneous Bacterial Peritonitis
1. Diagnose cirrhotic versus non-cirrhotic ascites and to differentiate the various stages of cirrhotic ascites.
2. Understand the basic pathophysiology of ascites formation.
3. Understand the latest in the management of ascites.
4. Recognise spontaneous bacterial peritonitis.
5. Be up to date with the recent development in the treatment of spontaneous bacterial peritonitis.

**Section 16. Hepatic Encephalopathy**
1. Be able to recognize the clinical features of hepatic encephalopathy in its various grades from 1 to 4.
2. Be able to establish a differential diagnosis of the possible precipitating factors of hepatic encephalopathy.
3. Discuss the therapeutic principles as applied to the therapy of HE, including the mechanisms of action of lactulose.

**Section 17. Hepatorenal Syndrome**
1. Differentiate hepatorenal syndrome from other causes of renal insufficiency in patients with advanced liver disease.
2. Explain the pathogenesis of hepatorenal syndrome.
3. Manage patients with hepatorenal syndrome.

**Section 18. Liver Transplantation**
Discuss:
1. Who is a candidate for liver transplantation.
2. What is living related liver transplantation.
3. What is the MELD score and how can it be used to better allocate organs.
4. What are the results of liver transplantation.
5. How can immunosuppressive agents be tailored to individualize therapy.

**Section 19. Neoplasms of the Liver**
1. Be aware of the workup of a patient that is found to have an asymptomatic liver lesion.
2. Be aware of the need for screening for hepatocellular carcinoma in patients with cirrhosis and the workup followed in the event of finding a liver lesion in a patient with cirrhosis.

**Section 20. Liver Disease in Pregnancy**
1. Identify the changes that normally occur in the liver during pregnancy.
2. Recognize a classification of liver disease in pregnancy: liver diseases that develop during pregnancy; pregnancy in women with underlying chronic liver disease, and intercurrent liver disease during pregnancy.
3. Know the use of gestational age of the pregnancy as an excellent guide to the differential diagnosis of liver disease that occurs in the pregnant woman.
4. Be able to manage the common forms of liver disease that occur during pregnancy.
5. List the conditions for which termination of pregnancy is mandatory or not necessary.

Section 21. Vascular Disorders of the Liver
1. Appreciate the ways in which the liver can be affected by abnormalities in the circulatory system.
2. Be able to recognize the clinical and biochemical abnormalities that are seen with ischemic hepatitis and congestive heart failure.

PRACTICE POINTS

Section 1. Liver Structure and Function
1. The liver is a metabolically complex organ with roles in protein, fat, and carbohydrate metabolism; disposition of drugs and toxins; and bile formation. Recent studies examining mechanisms of bile formation have demonstrated the vital roles of a variety of transporters including the BSEP and the multidrug resistance proteins. The liver’s rich blood supply forms the basis of its functional segmentation (Couinaud’s segments) that assists in the planning of surgical resections.

Section 2. Approach to the Patient with Liver Disease
1. Liver disease can manifest as nonspecific systemic symptoms.
2. The most important tool for diagnosing the cause of liver disease is a careful history and physical examination.
3. The clinical “feel” of a palpable liver is as diagnostically important as its size.
4. Bilirubin fractionation is usually of little value in patients with jaundice.
5. Disproportionate aminotransferase elevations favour a hepatocellular inflammatory disorder; disproportionate alkaline phosphatase elevations, a cholestatic or infiltrative disorder.
6. Abdominal ultrasound can often distinguish extrahepatic from intrahepatic cholestasis.
7. Rigors and chills in a jaundiced patient suggest acute cholangitis rather than a hepatic disorder.

Section 3. Evaluation of Abnormal Liver Enzyme Results in Asymptomatic Patients
1. The first step in the investigation of elevated liver-enzymes levels in an asymptomatic patient is to repeat the test. If the anomalies persist, the
cause of liver-enzyme elevation should be sought.
2. It is useful to distinguish isolated aminotransferase levels elevation from elevation with cholestasis, as the causes differ.
3. Non-alcoholic steato-hepatitis is a common cause of elevated liver-enzyme levels.

Section 4. The Liver and Drug Disposition
1. In chronic liver disease, clearance of drugs dependent on liver blood flow and/or phase 1 metabolism (P450 cytochrome enzymes) is impaired.
2. In chronic liver disease, drugs metabolized by phase 2 enzymes (mainly conjugation) are eliminated largely unchanged.
3. In health and in liver disease, substances and drugs can markedly inhibit the metabolism of several drugs.

Section 5. Congenital Hyperbilirubinemas
1. Unconjugated hyperbilirubinemia in absence of hemolysis, is usually secondary to congenital defect in glucuronidation of bilirubin.
2. Except for Crigler-Najjar type I syndrome, congenital hyperbilirubinemia does not impact on life expectancy or quality of life of affected individuals.

Section 6. Acute Viral Hepatitis
1. The causes of acute viral hepatitis have a similar non-specific presentation (low-grade fever, nausea, right-upper quadrant pain, fatigue).
2. The modes of transmission range from predominantly fecal-oral (hepatitis A and E) to parenteral, sexual or perinatal (hepatitis B-D).
3. Acute viral hepatitis is generally mild and self-limited. Synthetic function abnormalities (INR, bilirubin, albumin) suggest more serious hepatic injury.
4. The management of acute viral hepatitis centers around prevention of viral transmission and supportive care. Vaccines are available for hepatitis A and B. Anti-viral therapy is used for acute hepatitis C.
5. Complications of acute viral hepatitis include fulminant hepatic failure, chronic hepatitis and extrahepatic manifestations (immune complex mediated).

Section 7. Chronic Viral Hepatitis
1. Chronic viral hepatitis is defined as hepatic inflammation persisting for greater than 6 months. Histologic features can be graded and staged using the METAVIR classification system.
2. Hepatitis B: Active hepatic inflammation is suggested by elevated transaminases. Active viral replication is confirmed by an elevated HBV DNA.
Serology allows one to differentiate between hepatitis B eAg positive and B eAg negative disease, each of which have distinct clinical features.

3. Hepatitis C: The sustained virologic response and early virologic response are important concepts when monitoring treatment response. The most important predictor of response to antiviral treatment is HCV genotype.

4. Treatment of hepatitis B and C is clearly indicated with evidence of active inflammation and active viral replication.

5. Patients with chronic hepatitis B and C are at risk of developing cirrhosis and hepatocellular carcinoma. In order to screen for hepatocellular carcinoma, patients with chronic hepatitis B or cirrhosis (hepatitis B or C) should be screened with q 6-12 monthly ultrasound and serum α-fetoprotein.

Section 8. Alcoholic Liver Disease
1. Alcoholic liver disease is still relatively common, and in the correct clinical setting, should be considered as a plausible diagnosis.

2. Fatty liver disease associated with excess alcohol intake is a reversible condition if the patient can stay abstinent from alcohol.

3. Acute alcoholic hepatitis can lead to liver failure with high mortality rates. Given the fact that liver transplantation is not an option for patients with alcoholic hepatitis, new treatments are being continuously investigated.

4. Alcoholic cirrhosis often co-exists with viral hepatitis B or C, which can lead to rapid progression of cirrhosis. Treatment of the viral hepatitis and abstinence from alcohol are two factors that can significantly improve the prognosis.

5. Patients with alcoholic cirrhosis should be monitored regularly for complications of cirrhosis including hepatomas.

Section 9. Non-Alcoholic Fatty Liver Disease
1. Although most cases of NAFLD are associated with obesity, it can occur in patients without obvious risk factors.

2. A high BMI associated with type II DM and possibly AST:ALT > 1 puts NAFLD patients at risk for NASH.

3. Although there are currently no effective medical interventions for NAFLD, control of metabolic factors such as hyperglycemia, hyperlipidemia, and weight loss can improve liver enzymes and possibly benefit patients at risk of progression to cirrhosis.

Section 10. Drug-Induced Liver Disease
1. Drugs are a common cause of liver damage.

2. The most important clue to the diagnosis of drug hepatotoxicity is a detailed history.
3. Drug-induced liver disease has many patterns and can mimic a wide variety of other hepatic disorders.
4. Stopping the offending agent will usually reverse the hepatic injury.

Section 11. Inherited Liver Disease
1. \( \alpha_1 \)-antitrypsin deficiency is an important genetic cause of infantile liver disease.
2. Adults who are heterozygotes for \( \alpha_1 \)-antitrypsin deficiency may present with clinically-significant liver disease (with fibrosis or cirrhosis) later in life.
3. Wilson’s disease can present as hepatic, neurological or neuropsychiatric disease, and with other disorders (arthritis, renal disease, repeated spontaneous abortion).
4. Older adults are being diagnosed with Wilson’s disease, and therefore it should be considered for unexplained liver disease regardless of age.
5. Cessation of treatment in a stable patient with hepatic Wilson’s disease can lead to severe, often uncorrectable, hepatic decompensation; occurrence of new neurological findings may occur in any non-compliant patient. Treatment is life-long, and patients require regular monitoring.
6. Since a single mutation (C282Y) of the hemochromatosis gene (HFE) explains more than 90% of typical cases, genetic testing is a very helpful diagnostic blood test.
7. Fatty liver and daily alcohol consumption are the most common causes of an elevated ferritin.
8. It is rare for a patient with hemochromatosis to have any organ damage when the serum ferritin is < 1000 µg/L.

Section 12. Cholestasis
1. Chronic cholestasis generally presents with pruritus, not jaundice.
2. Determine whether cholestasis is intra or extrahepatic.
3. Stones in LBD may be painless.
4. Cholestatic drug reactions may follow a single exposure and be prolonged (> 6 months).
5. Sepsis within biliary tree is rapidly fatal.

Section 13. Cirrhosis of the Liver
1. Suspect cirrhosis if platelets < 150 x 10⁹/L and/or polyclonal gammopathy.
2. Avoid unnecessary invasive procedures/surgery in all cirrhotics.
3. Educate patients with cirrhosis about importance of long term monitoring (ultrasound screening for HCC) and preventative strategies (vaccination against viral hepatitis, drugs to avoid).
Section 14. Portal Hypertension

1. Portal hypertension is defined as increased pressure in the portal vein, and is caused by several conditions, which can be classified according to the site of major resistance to portal flow.
2. Its major complication is bleeding from gastroesophageal varices; approximately 1/3 of patients with large varices bleed in the first two years after discovery.
3. Various drugs and other nonsurgical treatments such as endoscopic band ligation are the mainstays of treating acute bleeding.
4. Between 30-50% of all upper GI bleeding in cirrhotic patients originates from portal hypertensive gastropathy. The management of portal hypertensive gastropathy includes measures to reduce portal pressure.
5. Cirrhotic cardiomyopathy is generally defined as a blunted ventricular contractile response to stressful stimuli, in the face of high resting cardiac output.
6. Hepatopulmonary syndrome is defined as arterial hypoxemia in patients with cirrhosis, in the absence of a primary lung disorder.
7. Portopulmonary hypertension refers to a pulmonary arterial hypertension in patients with portal hypertension.

Section 15. Ascites and Spontaneous Bacterial Peritonitis

1. The first step in the management of ascites is to carefully adjust the sodium intake versus the sodium output to achieve a negative sodium balance.
2. Diuretics should be used as adjunctive therapy to dietary sodium restriction.
3. Large volume paracentesis and TIPS are the mainstay of treatment for refractory ascites.
4. Liver transplant should be considered for all patients with ascites.
5. Spontaneous bacterial peritonitis, if untreated, is associated with a high mortality rate. Therefore empirical treatment should be started as soon as there is suspicion that peritonitis is present.
6. Secondary prophylaxis is mandatory for patients who have recovered from spontaneous bacterial peritonitis. There is no data to support the use of primary prophylaxis against the first episode of bacterial peritonitis.
7. Indiscriminate use of antibiotics in cirrhotic patients is to be discouraged, as this will increase antibiotic resistance.

Section 16. Hepatic Encephalopathy

1. In most patients with chronic liver disease presenting with hepatic encephalopathy, a precipitating factor can be identified.
2. The shunting of blood around the liver into the systemic circulation and the presence of hepatocellular dysfunction are important in the pathogenesis of HE.
Section 17. Hepatorenal Syndrome
1. Nephrotoxic agents should be avoided because of the risk of developing HRS. Non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, aspirin, aminoglycosides, and iodine-containing contrast agents are commonly associated with HRS in patients with cirrhosis.
2. A diagnostic paracentesis should be considered in all patients who have cirrhosis with ascites who develop HRS to exclude the presence of spontaneous bacterial peritonitis. The use of empiric antibiotics in this situation is not justified.
3. One can not assume that all patients who have cirrhosis with renal impairment have HRS. Other causes of renal failure need to be considered in the differential diagnosis.
4. In patients with cirrhosis who have decompensated, evaluation of candidacy for liver transplantation should be performed before the onset of HRS. This helps physicians decide the aggressiveness of treatment when HRS develops. Liver transplant evaluation in a hospitalized patient with type 1 HRS may be too late, given the limited number of solid organ donors.

Section 18. Liver Transplantation
1. Liver transplantation is the most effective form of therapy for end stage liver disease. Results of transplantation have improved over the past 10 years and graft and patient survival at 1 year is approaching or exceeding 90%.
2. Advances in our understanding of the molecular events of lymphocyte activation have led to the introduction of a number of novel new agents which will allow for individualization of therapy to better meet the patient’s needs.
3. Shortages of human organs have led to unacceptably long waiting times with high mortality on the waiting list. This has led centres to consider liver transplants from related living adults.

Section 19. Neoplasms of the Liver
1. The most common benign lesions of the liver are the solitary liver cyst and the hemangioma.
2. Hepatocellular carcinoma is most commonly found in patients with pre-existing liver disease, especially cirrhosis.
3. Screening for HCC in patients with cirrhosis includes the consideration of liver ultrasound and alpha-fetoprotein every 6-12 months.
Section 20. Liver Disease in Pregnancy
1. Hepatic complications are uncommon during pregnancy, but potentially associated with adverse maternal and fetal outcomes necessitating immediate delivery. Therefore a rational approach to their diagnosis is essential.
2. Pre-existing liver conditions and the gestational age of the pregnancy should be considered in establishing a differential diagnosis. At all stages, illnesses unrelated to pregnancy, including viral hepatitis and cholelithiasis, must be considered.
3. Pregnancy-specific hepatic complications include hyperemesis gravidarum (typically in the first trimester), cholestasis of pregnancy (usually in the second or third trimester), and the disorders associated with pre-eclampsia (e.g., AFLP and HELLP; typically in the third trimester).

Section 21. Vascular Disorders of the Liver
1. Congestive heart failure is the most frequent circulation abnormality affecting the liver.

RESEARCH AGENDA

Section 1. Liver Structure and Function
1. Further studies should focus on the roles of known bile salt transporters and identification of as-yet undiscovered transporters. Such research may help to elucidate mechanisms of cholestasis and potential therapeutic targets for cholestatic liver conditions.

Section 2. Approach to the Patient with Liver Disease
1. The search for markers of liver fibrosis.

Section 3. Evaluation of Abnormal Liver Enzyme Results in Asymptomatic Patients
1. Develop non-invasive tests to assess the extent of liver fibrosis without liver biopsy in patients with chronic liver diseases.
2. Elucidate the pathogenesis and develop effective treatment for non-alcoholic steato-hepatitis.

Section 4. The Liver and Drug Disposition
1. Find precise clues to predict impaired clearance of drugs in chronic liver disease.
2. Improve understanding of effect of liver dysfunction or disease on the activity of the metabolizing enzymes.
Section 5. Congenital Hyperbilirubinemias
1. Explore gene therapy for Criggler-Najjar type 1 syndrome.

Section 6. Acute Viral Hepatitis
1. Development of a vaccine for preventing hepatitis C injection is currently a biological challenge.
2. Supportive therapy of patients with fulminant acute hepatitis needs further development.

Section 7. Chronic Viral Hepatitis
2. Testing of combinations of antiviral agents to increase efficacy and decrease viral resistance.
3. Results of the head-to-head trial comparing PEG interferon α-2a with PEG interferon α-2b.
4. Development of a vaccine for hepatitis C.

Section 8. Alcoholic Liver Disease
1. New developments are in the area of treatment of acute alcoholic hepatitis, especially anti-cytokines to counteract the damaging effects of the inflammatory cytokines.

Section 9. Non-Alcoholic Fatty Liver Disease
In NAFLD, more research is needed:
1. To understand the pathophysiology;
2. To understand the natural history and risk of advanced liver disease;
3. To improve treatment.

Section 10. Drug-Induced Liver Disease
1. Current areas of research interest include the molecular pathogenesis of various forms of drug-induced liver damage, and the increasing importance of herbal and naturopathic remedies as a cause of hepatic injury.

Section 11. Inherited Liver Disease
1. Determining the basis for clinical variability in these genetic liver diseases: why only some people with α1-antitrypsin deficiency get liver disease and why some people with Wilson's disease have mainly liver disease and others mainly neurological disease.
2. Developing new treatments as disease mechanisms are better understood.
Section 12. Cholestasis
2. Pathogenesis of autoimmune biliary disorders (PBC & PSC).
3. EVS and MRI in the diagnosis and management of extrahepatic biliary disease.

Section 13. Cirrhosis of the Liver
1. Sensitive and specific non-invasive tests to measure degree of hepatic fibrosis.
2. Identification malignant clones of hepatocytes at their inception.
3. Role of bacterial infection in precipitating hepatic decompensation.

Section 14. Portal Hypertension
1. Further clarification of basic cellular mechanisms of pathogenesis in the liver and gut circulation, particularly the dynamic factors.
2. Clinical studies to better predict which patients with varices bleed and the optimum pharmacological, endoscopic and surgical methods of treating these bleeds and preventing bleeding are also needed.
3. Elucidation of mechanisms involved in pulmonary vasodilatation in cirrhosis.
4. Treatment strategies for hepatopulmonary syndrome and pulmonary hypertension need further studies.

Section 15. Ascites and Spontaneous Bacterial Peritonitis
1. Aquaretic agents are now being developed for treatment of hyponatremia as well as for reduction of ascites.

Section 16. Hepatic Encephalopathy
1. Improve understanding of the pathophysiology of hepatic encephalopathy.
2. Discover new therapeutic approaches to hepatic encephalopathy.

Section 17. Hepatorenal Syndrome
1. Many researchers are working on the characterization of the nitric oxide-arginine pathway and its role in the development of HRS. This understanding and the recently identified therapeutic approaches lend a note of optimism to the future management of a syndrome that is so often incompatible with recovery.

Section 18. Liver Transplantation
1. Results of transplantation for hepatitis C virus infection have worsened over the past several years forcing investigators to examine whether changes in immunosuppression, donor selection have contributed to this state.
2. Furthermore, as HCV recurs universally, there is a need for research into development of antivirals which will improve long-term results similar to that seen in hepatitis B virus infection.

Section 19. Neoplasms of the Liver
1. To better understand the natural history of small hepatocellular carcinoma.
2. To improve methods to accurately diagnose early hepatocellular carcinoma in presence of chronic liver disease.

Section 20. Liver Disease in Pregnancy
1. Recent studies elucidating the mechanisms of bile formation have improved our understanding of the mechanisms of cholestasis of pregnancy. For example, several mutations in the multidrug resistance gene-3 (MDR3) have been identified in isolated patients. Similarly, genetic defects in mitochondrial beta fatty acid oxidation in women and their infants with AFLP have been reported.
2. Further research is necessary to identify other genetic defects in bile formation and mitochondrial function, both known and unknown, in patients with these disorders so that rational therapeutic strategies can be developed.

Section 21. Vascular Disorders of the Liver
1. To better understand the metabolic pathways leading to cell damage/death in the presence of blood flow impairment to the liver.