Noninvasive Tests to Detect Hepatic Fibrosis Although liver biopsy is the standard for the assessment of hepatic fibrosis, noninvasive measures of hepatic fibrosis have been developed and show promise. These measures include multiparameter tests aimed at detecting and staging the degree of hepatic fibrosis and imaging techniques. FibroTest (marketed as FibroSure in the United States) is the best evaluated of the multiparameter blood tests. The test incorporates haptoglobin, bilirubin, GGT, apolipoprotein A-I, and α2-macroglobulin and has been found to have high positive and negative predictive values for diagnosing advanced fibrosis in patients with chronic hepatitis C, chronic hepatitis B, and alcoholic liver disease and patients taking methotrexate for psoriasis. Transient elastography (TE), marketed as FibroScan, and magnetic resonance elastography (MRE) both have gained U.S. Food and Drug Administration approval for use in the management of patients with liver disease. TE uses ultrasound waves to measure hepatic stiffness noninvasively. TE has been shown to be accurate for identifying advanced fibrosis in patients with chronic hepatitis C, primary biliary cirrhosis, hemochromatosis, nonalcoholic fatty liver disease, and recurrent chronic hepatitis after liver transplantation. MRE has been found to be superior to TE for staging liver fibrosis in patients with a variety of chronic liver diseases, but requires access to a magnetic resonance imaging scanner.

Ultrasonography Ultrasonography is the first diagnostic test to use in patients whose liver tests suggest cholestasis, to look for the presence of a dilated intrahepatic or extrahepatic biliary tree or to identify gallstones. In addition, it shows space-occupying lesions within the liver, enables the clinician to distinguish between cystic and solid masses, and helps direct percutaneous biopsies. Ultrasound with Doppler imaging can detect the patency of the portal vein, hepatic artery, and hepatic veins and determine the direction of blood flow. This is the first test ordered in patients suspected of having Budd-Chiari syndrome.

USE OF LIVER TESTS

As previously noted, the best way to increase the sensitivity and specificity of laboratory tests in the detection of liver disease is to employ a battery of tests that includes the aminotransferases, alkaline phosphatase, bilirubin, albumin, and prothrombin time along with the judicious use of the other tests described in this chapter. Table 358-1 shows how patterns of liver tests can lead the clinician to a category of disease that will direct further evaluation. However, it is important to remember that no single set of liver tests will necessarily provide a diagnosis. It is often necessary to repeat these tests on several occasions over days to weeks for a diagnostic pattern to emerge. Figure 358-1 is an algorithm for the evaluation of chronically abnormal liver tests.

GLOBAL CONSIDERATIONS

The tests and principles presented in this chapter are applicable worldwide. The causes of liver test abnormalities vary according to region. In developing nations, infectious diseases are more commonly the etiology of abnormal serum liver tests than in developed nations.

Acknowledgment

This chapter represents a revised version of a chapter in previous editions of Harrison's in which Marshall M. Kaplan was a co-author.

359 The Hyperbilirubinemias

Allan W. Wolkoff

BILIRUBIN METABOLISM

The details of bilirubin metabolism are presented in Chap. 58. However, the hyperbilirubinemias are best understood in terms of perturbations of specific aspects of bilirubin metabolism and transport, and these will be briefly reviewed here as depicted in Fig. 359-1.

Bilirubin is the end product of heme degradation. Some 70–90% of bilirubin is derived from degradation of the hemoglobin of senescent red blood cells. Bilirubin produced in the periphery is transported to the liver within the plasma, where, due to its insolubility in aqueous solutions, it is tightly bound to albumin. Under normal circumstances, bilirubin is removed from the circulation rapidly and efficiently by hepatocytes. Transfer of bilirubin from blood to bile involves four distinct but interrelated steps (Fig. 359-1).

1. *Hepatocellular uptake:* Uptake of bilirubin by the hepatocyte has carrier-mediated kinetics. Although a number of candidate bilirubin transporters have been proposed, the actual transporter remains elusive.
2. *Intracellular binding:* Within the hepatocyte, bilirubin is kept in solution by binding as a nonsubstrate ligand to several of the glutathione-S-transferases, formerly called ligandins.
3. *Conjugation:* Bilirubin is conjugated with one or two glucuronic acid moieties by a specific UDP-glucuronosyltransferase to form bilirubin mono- and diglucuronide, respectively. Conjugation disrupts the internal hydrogen bonding that limits aqueous solubility of bilirubin, and the resulting glucuronide conjugates are highly soluble in water. Conjugation is obligatory for excretion of bilirubin across the bile canalicular membrane into bile. The UDP-glucuronosyltransferases have been classified into gene families based on the degree of homology among the mRNAs for the various isoforms. Those that conjugate bilirubin and certain

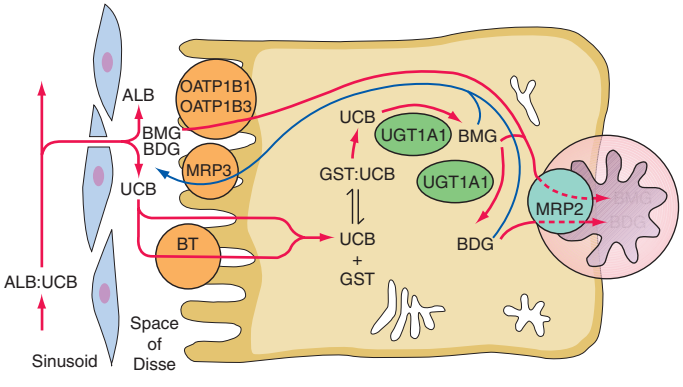

FIGURE 359-1 Hepatocellular bilirubin transport. Albumin-bound bilirubin in sinusoidal blood passes through endothelial cell fenestrae to reach the hepatocyte surface, entering the cell by both facilitated and simple diffusional processes. Within the cell, it is bound to glutathione-S-transferases and conjugated by bilirubin-UDP-glucuronosyltransferase (UGT1A1) to mono- and diglucuronides, which are actively transported across the canalicular membrane into the bile. In addition to this direct excretion of bilirubin glucuronides, a portion are transported into the portal circulation by MRP3 and subjected to reuptake into the hepatocyte by OATP1B1 and OATP1B3. ALB, albumin; BDG, bilirubin diglucuronide; BMG, bilirubin monoglucuronide; BT, proposed bilirubin transporter; GST, glutathione-S-transferase; MRP2 and MRP3, multidrug resistance–associated proteins 2 and 3; OATP1B1 and OATP1B3, organic anion transport proteins 1B1 and 1B3; UCB, unconjugated bilirubin; UGT1A1, bilirubin-UDP-glucuronosyltransferase.