donation or for insurance or employment. The wide availability of batteries of liver tests makes it relatively simple to demonstrate the presence of liver injury as well as to rule it out in someone in whom liver disease is suspected.

Evaluation of patients with liver disease should be directed at (1) establishing the etiologic diagnosis, (2) estimating disease severity (*grading*), and (3) establishing the disease stage (*staging*). *Diagnosis* should focus on the category of disease (hepatocellular, cholestatic, or mixed injury) as well as on the specific etiologic diagnosis. *Grading* refers to assessment of the severity or activity of disease—active or inactive as well as mild, moderate, or severe. *Staging* refers to estimation of the point in the course of the natural history of the disease, whether early or late; or precirrhotic, cirrhotic, or end-stage. This chapter introduces general, salient concepts in the evaluation of patients with liver disease that help lead to the diagnoses discussed in subsequent chapters.

CLINICAL HISTORY

The clinical history should focus on the symptoms of liver disease—their nature, patterns of onset, and progression—and on potential risk factors for liver disease. The manifestations of liver disease include constitutional symptoms such as fatigue, weakness, nausea, poor appetite, and malaise and the more liver-specific symptoms of jaundice, dark urine, light stools, itching, abdominal pain, and bloating. Symptoms can also suggest the presence of cirrhosis, end-stage liver disease, or complications of cirrhosis such as portal hypertension. Generally, the constellation of symptoms and their patterns of onset rather than a specific symptom points to an etiology.

Fatigue is the most common and most characteristic symptom of liver disease. It is variously described as lethargy, weakness, listlessness, malaise, increased need for sleep, lack of stamina, and poor energy. The fatigue of liver disease typically arises after activity or exercise and is rarely present or severe after adequate rest; i.e., it is "afternoon" rather than "morning" fatigue. Fatigue in liver disease is often intermittent and variable in severity from hour to hour and day to day. In some patients, it may not be clear whether fatigue is due to the liver disease or to other problems such as stress, anxiety, sleep disturbance, or a concurrent illness.

Nausea occurs with more severe liver disease and may accompany fatigue or be provoked by smelling food odors or eating fatty foods. Vomiting can occur but is rarely persistent or prominent. Poor appetite with weight loss occurs frequently in acute liver disease but is rare in chronic disease except when cirrhosis is present and advanced. Diarrhea is uncommon in liver disease except with severe jaundice, in which a lack of bile acids reaching the intestine can lead to steatorrhea.

Right-upper-quadrant discomfort or ache ("liver pain") occurs in many liver diseases and is usually marked by tenderness over the liver area. The pain arises from stretching or irritation of Glisson's capsule, which surrounds the liver and is rich in nerve endings. Severe pain is most typical of gallbladder disease, liver abscess, and severe veno-occlusive disease but is also an occasional accompaniment of acute hepatitis.

Itching occurs with acute liver disease, appearing early in obstructive jaundice (from biliary obstruction or drug-induced cholestasis) and somewhat later in hepatocellular disease (acute hepatitis). Itching also occurs in chronic liver diseases—typically the cholestatic forms such as primary biliary cirrhosis and sclerosing cholangitis, in which it is often the presenting symptom, preceding the onset of jaundice. However, itching can occur in any liver disease, particularly once cirrhosis develops.

Jaundice is the hallmark symptom of liver disease and perhaps the most reliable marker of severity. Patients usually report darkening of the urine before they notice scleral icterus. Jaundice is rarely detectable with a bilirubin level <43 μmol/L (2.5 mg/dL). With severe cholestasis, there will also be lightening of the color of the stools and steatorrhea. Jaundice without dark urine usually indicates indirect (unconjugated) hyperbilirubinemia and is typical of hemolytic anemia and the genetic disorders of bilirubin conjugation, the common and benign form being Gilbert's syndrome and the rare and severe form being Crigler-Najjar syndrome. Gilbert's syndrome affects up to 5% of the general population; the jaundice in this condition is more noticeable after fasting and with stress.

Major risk factors for liver disease that should be sought in the clinical history include details of alcohol use, medication use (including herbal compounds, birth control pills, and over-the-counter medications), personal habits, sexual activity, travel, exposure to jaundiced or other high-risk persons, injection drug use, recent surgery, remote or recent transfusion of blood or blood products, occupation, accidental exposure to blood or needlestick, and familial history of liver disease.

For assessing the risk of viral hepatitis, a careful history of sexual activity is of particular importance and should include the number of lifetime sexual partners and, for men, a history of having sex with men. Sexual exposure is a common mode of spread of hepatitis B but is rare for hepatitis C. A family history of hepatitis, liver disease, and liver cancer is also important. Maternal-infant transmission occurs with both hepatitis B and C. Vertical spread of hepatitis B can now be prevented by passive and active immunization of the infant at birth. Vertical spread of hepatitis C is uncommon, but there are no reliable means of prevention. Transmission is more common among HIV-coinfected mothers and is also linked to prolonged and difficult labor and delivery, early rupture of membranes, and internal fetal monitoring. A history of injection drug use, even in the remote past, is of great importance in assessing the risk for hepatitis B and C. Injection drug use is now the single most common risk factor for hepatitis C. Transfusion with blood or blood products is no longer an important risk factor for acute viral hepatitis. However, blood transfusions received before the introduction of sensitive enzyme immunoassays for antibody to hepatitis C virus in 1992 is an important risk factor for chronic hepatitis C. Blood transfusion before 1986, when screening for antibody to hepatitis B core antigen was introduced, is also a risk factor for hepatitis B. Travel to a developing area of the world, exposure to persons with jaundice, and exposure to young children in day-care centers are risk factors for hepatitis A. Tattooing and body piercing (for hepatitis B and C) and eating shellfish (for hepatitis A) are frequently mentioned but are actually types of exposure that quite rarely lead to the acquisition of hepatitis.

Hepatitis E is one of the more common causes of jaundice in Asia and Africa but is uncommon in developed nations. Recently, non-travel-related (*autochthonous*) cases of hepatitis E have been described in developed countries, including the United States. These cases appear to be due to strains of hepatitis E virus that are endemic in swine and some wild animals (genotypes 3 and 4). While occasional cases are associated with eating raw or undercooked pork or game (deer and wild boars), most cases of hepatitis E occur without known exposure, predominantly in elderly man without typical risk factors for viral hepatitis. Hepatitis E infection can become chronic in immunosuppressed individuals (such as transplant recipients, patients receiving chemotherapy, or patients with HIV infection), in whom it presents with abnormal serum enzymes in the absence of markers of hepatitis B or C.

A history of alcohol intake is important in assessing the cause of liver disease and also in planning management and recommendations. In the United States, for example, at least 70% of adults drink alcohol to some degree, but significant alcohol intake is less common; in population-based surveys, only 5% of individuals have more than two drinks per day, the average drink representing 11–15 g of alcohol. Alcohol consumption associated with an increased rate of alcoholic liver disease is probably more than two drinks (22–30 g) per day in women and three drinks (33–45 g) in men. Most patients with alcoholic cirrhosis have a much higher daily intake and have drunk excessively for ≥10 years before onset of liver disease. In assessing alcohol intake, the history should also focus on whether alcohol abuse or dependence is present. Alcoholism is usually defined by the behavioral patterns and consequences of alcohol intake, not by the amount. *Abuse* is defined by a repetitive pattern of drinking alcohol that has adverse effects on social, family, occupational, or health status. *Dependence* is defined by alcohol-seeking behavior, despite its adverse effects. Many