TABLE 357-2 CAGE QUESTIONS[a]

Acronym	Question
C	Have you ever felt you ought to *c*ut down on your drinking?
A	Have people *a*nnoyed you by criticizing your drinking?
G	Have you ever felt *g*uilty or bad about your drinking?
E	Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (*e*ye-opener)?

[a]One "yes" response should raise suspicion of an alcohol use problem, and more than one is a strong indication of abuse or dependence.

alcoholics demonstrate both dependence and abuse, and dependence is considered the more serious and advanced form of alcoholism. A clinically helpful approach to diagnosis of alcohol dependence and abuse is the use of the CAGE questionnaire (Table 357-2), which is recommended for all medical history-taking.

Family history can be helpful in assessing liver disease. Familial causes of liver disease include Wilson's disease; hemochromatosis and α_1 antitrypsin deficiency; and the more uncommon inherited pediatric liver diseases—i.e., familial intrahepatic cholestasis, benign recurrent intrahepatic cholestasis, and Alagille syndrome. Onset of severe liver disease in childhood or adolescence in conjunction with a family history of liver disease or neuropsychiatric disturbance should lead to investigation for Wilson's disease. A family history of cirrhosis, diabetes, or endocrine failure and the appearance of liver disease in adulthood suggests hemochromatosis and should prompt investigation of iron status. Abnormal iron studies in adult patients warrant genotyping of the *HFE* gene for the C282Y and H63D mutations typical of genetic hemochromatosis. In children and adolescents with iron overload, other non-*HFE* causes of hemochromatosis should be sought. A family history of emphysema should provoke investigation of α_1 antitrypsin levels and, if levels are low, for protease inhibitor (Pi) genotype.

PHYSICAL EXAMINATION

The physical examination rarely uncovers evidence of liver dysfunction in a patient without symptoms or laboratory findings, nor are most signs of liver disease specific to one diagnosis. Thus, the physical examination complements rather than replaces the need for other diagnostic approaches. In many patients, the physical examination is normal unless the disease is acute or severe and advanced. Nevertheless, the physical examination is important in that it can yield the first evidence of hepatic failure, portal hypertension, and liver decompensation. In addition, the physical examination can reveal signs—related either to risk factors or to associated diseases or findings—that point to a specific diagnosis.

Typical physical findings in liver disease are icterus, hepatomegaly, hepatic tenderness, splenomegaly, spider angiomata, palmar erythema, and excoriations. Signs of advanced disease include muscle wasting, ascites, edema, dilated abdominal veins, hepatic fetor, asterixis, mental confusion, stupor, and coma. In male patients with cirrhosis, particularly that related to alcohol use, signs of hyperestrogenemia such as gynecomastia, testicular atrophy, and loss of male-pattern hair distribution may be found.

Icterus is best appreciated when the sclera is inspected under natural light. In fair-skinned individuals, a yellow tinge to the skin may be obvious. In dark-skinned individuals, examination of the mucous membranes below the tongue can demonstrate jaundice. Jaundice is rarely detectable if the serum bilirubin level is <43 μmol/L (2.5 mg/dL) but may remain detectable below this level during recovery from jaundice (because of protein and tissue binding of conjugated bilirubin).

Spider angiomata and palmar erythema occur in both acute and chronic liver disease; these manifestations may be especially prominent in persons with cirrhosis but can develop in normal individuals and are frequently found during pregnancy. Spider angiomata are superficial, tortuous arterioles and—unlike simple telangiectases—typically fill from the center outward. Spider angiomata occur only on the arms, face, and upper torso; they can be pulsatile and may be difficult to detect in dark-skinned individuals.

Hepatomegaly is not a highly reliable sign of liver disease because of variability in the liver's size and shape and the physical impediments to assessment of liver size by percussion and palpation. Marked hepatomegaly is typical of cirrhosis, veno-occlusive disease, infiltrative disorders such as amyloidosis, metastatic or primary cancers of the liver, and alcoholic hepatitis. Careful assessment of the liver edge may also reveal unusual firmness, irregularity of the surface, or frank nodules. Perhaps the most reliable physical finding in the liver examination is hepatic tenderness. Discomfort when the liver is touched or pressed upon should be carefully sought with percussive comparison of the right and left upper quadrants.

Splenomegaly, which occurs in many medical conditions, can be a subtle but significant physical finding in liver disease. The availability of ultrasound methods for assessment of the spleen allows confirmation of the physical finding.

Signs of advanced liver disease include muscle wasting and weight loss as well as hepatomegaly, bruising, ascites, and edema. Ascites is best appreciated by attempts to detect shifting dullness by careful percussion. Ultrasound examination will confirm the finding of ascites in equivocal cases. Peripheral edema can occur with or without ascites. In patients with advanced liver disease, other factors frequently contribute to edema formation, including hypoalbuminemia, venous insufficiency, heart failure, and medications.

Hepatic failure is defined as the occurrence of signs or symptoms of hepatic encephalopathy in a person with severe acute or chronic liver disease. The first signs of hepatic encephalopathy can be subtle and nonspecific—change in sleep patterns, change in personality, irritability, and mental dullness. Thereafter, confusion, disorientation, stupor, and eventually coma supervene. In acute liver failure, excitability and mania may be present. Physical findings include asterixis and flapping tremors of the body and tongue. *Fetor hepaticus* refers to the slightly sweet, ammoniacal odor that can develop in patients with liver failure, particularly if there is portal-venous shunting of blood around the liver. Other causes of coma and disorientation should be excluded, mainly electrolyte imbalances, sedative use, and renal or respiratory failure. The appearance of hepatic encephalopathy during acute hepatitis is the major criterion for diagnosis of fulminant hepatitis and indicates a poor prognosis. In chronic liver disease, encephalopathy is usually triggered by a medical complication such as gastrointestinal bleeding, over-diuresis, uremia, dehydration, electrolyte imbalance, infection, constipation, or use of narcotic analgesics.

A helpful measure of hepatic encephalopathy is a careful mental-status examination and use of the trail-making test, which consists of a series of 25 numbered circles that the patient is asked to connect as rapidly as possible using a pencil. The normal range for the connect-the-dot test is 15–30 sec; it is considerably longer in patients with early hepatic encephalopathy. Other tests include drawing of abstract objects or comparison of a signature to previous examples. More sophisticated testing—e.g., with electroencephalography and visual evoked potentials—can detect mild forms of encephalopathy but are rarely clinically useful.

Other signs of advanced liver disease include umbilical hernia from ascites, hydrothorax, prominent veins over the abdomen, and *caput medusa*, a condition that consists of collateral veins radiating from the umbilicus and results from recanulation of the umbilical vein. Widened pulse pressure and signs of a hyperdynamic circulation can occur in patients with cirrhosis as a result of fluid and sodium retention, increased cardiac output, and reduced peripheral resistance. Patients with long-standing cirrhosis and portal hypertension are prone to develop the hepatopulmonary syndrome, which is defined by the triad of liver disease, hypoxemia, and pulmonary arteriovenous shunting. The hepatopulmonary syndrome is characterized by platypnea and orthodeoxia: shortness of breath and oxygen desaturation that occur paradoxically upon the assumption of an upright position. Measurement of oxygen saturation by pulse oximetry is a reliable screening test for hepatopulmonary syndrome.

Several skin disorders and changes are common in liver disease. Hyperpigmentation is typical of advanced chronic cholestatic diseases such as primary biliary cirrhosis and sclerosing cholangitis. In these