and may include hepatosplenomegaly, abnormal liver enzymes, cirrhosis, and acute liver failure. Screening should be considered in all patients with persistently elevated AST/ALT levels, and consists of serum ceruloplasmin testing (56). If low, confirmatory testing should be pursued including 24-h urine copper and/or serum copper levels, slit-lamp eye examination to identify pathognomonic Kayser-Fleischer rings, and possible liver biopsy to confirm the diagnosis, stage liver fibrosis, and quantify hepatic copper overload to guide management. Over 32 different mutations of the Wilsons gene have now been identified and unlike hemochromatosis, there is no predominant mutation. Molecular genetic analyses for the ATP7B mutation can be pursued in cases of diagnostic uncertainty.

Alpha-1 anti-trypsin deficiency is a rare genetic disease in adults, although it represents the most common genetic cause of liver disease in children, occurring at a prevalence of 1:2,500 in North American Caucasians. Defective production of the alpha-1 anti-trypsin protein may result in both panacinar emphysema and chronic obstructive pulmonary disease, as well as progressive liver disease, liver cirrhosis, and hepatocellular carcinoma. Screening should be considered in all patients with persistently abnormal liver AST/ALT levels, and consists of testing for low quantitative levels of lpha-1 anti-trypsin and genotype testing for the PiZZ mutation which results in severe enzyme deficiency (57,58). Those with heterozygote phenotype (most commonly PiMZ) may also be at risk for liver disease, particularly in the presence of concomitant steatosis or viral hepatitis (59).

Drug and supplement-induced liver injury

Prescribed and over-the-counter medications, as well as non-prescribed complimentary alternative medicines or dietary supplements, represent a common source for acute and chronic liver injury. Identification of an offending agent is challenging and requires a comprehensive query of the patient, his or her family, and careful review of available medical and pharmacy records and laboratory data (22). Nearly all medications are associated with at least a small risk of elevation of ALT/AST/alkaline phosphatase or bilirubin with or without hepatotoxicity. Common drug classes that may cause elevated liver chemistries include antibiotics, antiepileptics, nonsteroidal anti-inflammatory agents, HMG-Co-A-reductase inhibitors (statins), anti-tuberculosis drugs, anti-retroviral treatment for HIV, biologic agents such as anti-tumor necrosis factor drugs, and some cancer chemotherapeutic agents. Of note, HMG-Co-A-reductase inhibitors (statins) have been associated with elevated ALT and AST levels but there is an extensive literature on the safety in those with chronic liver disease with only rare cases of hepatotoxicity reported (60,61). In those with high ALT levels (>1,000 IU/l) an accurate history of acetaminophen use either as a single medicine or in combination with analgesic-narcotic combinations is essential. Attributing liver injury to a specific agent frequently requires empiric trials of drug discontinuation to observe full recovery of liver chemistries, although in cases in which the suspected agent is medically required, efforts should be made to identify potential drug alternatives, and/or establish a close surveillance plan to monitor for progressive liver injury or hepatic failure. In cases of acute or severe fulminant hepatitis, liver biopsy may be required to confirm severity of liver injury and establish a diagnosis of offending agent. Specific query for non-prescribed supplements is essential to discovery of associated liver injury. Common herbal supplements associated with hepatotoxicity include chaparral, ephedra, ji bu huan, germander, green tea extract, and shark cartilage (8,62). A helpful resource that is available to clinicians trying to ascertain whether a drug or supplement may be hepatotoxic is the website livertox.nih.gov.

PATIENTS WITH CONFIRMED ALKALINE PHOSPHATASE ELEVATIONS

Cholestatic liver disorders

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is an uncommon chronic liver disease primarily affecting intralobular bile ducts at the microscopic level (63). Although it is a rare cause of elevated liver tests, it is among the most common chronic cholestatic liver disorders and is seen more commonly in women than men. Patients may present with primary complaints of fatigue and pruritus. Lab testing reveals biochemical evidence of cholestasis (elevated alkaline phosphatase with or without elevation of bilirubin), as well as the serologic hallmark for screening and diagnosis: positive anti-mitochondrial antibodies which are observed in over 95% of patients (64). Liver biopsy is not routinely required although may be beneficial in patients with suspected anti-mitochondrial antibodies-negative disease and to stage liver fibrosis.

Primary sclerosing cholangitis (PSC) also represents a rare chronic liver disease which is characterized by chronic immune-mediated inflammation and fibrosis of both intrahepatic and extrahepatic bile ducts, fixed multifocal bile duct strictures, progressive liver fibrosis and cirrhosis, and an increased risk for both hepatocellular carcinoma and cholangiocarcinoma (65). Although no serologic hallmarks have been identified for PSC, IgG and anti-neutrophil cytoplasmic antibody are frequently elevated, and IgG4 may signal a specific IgG4-associated form of PSC. Diagnosis of PSC is established by characteristic imaging findings of thickened, inflamed bile ducts, dilatation of intrahepatic ducts, and focal strictures on MRI cholangiography or endoscopic retrograde cholangio-pancreatography. Although periductal concentric fibrosis or "onion-skin" like patterns of fibrosis are characteristic histologic findings, these signs are uncommonly seen and therefore liver biopsy is rarely required to establish a diagnosis or to significantly alter medical management. There is a common association with inflammatory bowel disease of the colon. Chronic cholestatic liver injury in the absence of PBC or PSC should prompt further investigation for less common etiologies such as bile duct obstructions, medications, sepsis, total parenteral nutrition, vanishing bile duct syndrome, and sarcoidosis (66).

Rare causes

A spectrum of non-hepatic disease may be associated with abnormal liver chemistries and referral to a hepatologist may be