The availability and convenience of automated biochemical batteries have resulted in the determination of liver tests on a large number of patients. Multiphasic screening studies reveal that 1 to 4 percent of asymptomatic patients have abnormal liver tests.\(^1,2\) This finding results in the difficult decision of when and how to pursue the cause of mildly elevated liver tests in a patient without obvious symptoms or signs of disease. Although somewhat of a misnomer, the term liver function tests (LFTs) is firmly entrenched in our medical vocabulary and encompasses the following tests found in most automated biochemistry batteries: albumin, bilirubin, aspartate aminotransferase (AST) and alkaline phosphatase (ALP). Some laboratories will also include alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT). This paper will focus on the diagnostic approach to mild elevations of the enzymes which represent hepatocellular necrosis, AST and ALT, and those representing cholestasis, ALP and GGT. The diagnostic role of certain disease-specific markers including viral hepatitis serology, antinuclear antibody (ANA), antismooth muscle antibody (ASMA), ceruloplasmin, iron studies and ferritin levels will also be outlined.

General causes of abnormal LFTs include laboratory error, statistical quirks, artifacts, disease of other organ systems and liver disease of either a minor or significant degree.\(^3\) Abnormal LFTs related to factors other than liver disease can usually be identified by standard history and physical examination and serial LFTs. It is important that all patients with abnormal LFTs be investigated to some extent despite a tendency in daily practice to dismiss minor abnormalities. Not all patients will require extensive evaluation; in fact, minor aminotransferase elevations may resolve in one-third of subjects with repeat testing.\(^4\) Factors that should be considered in determining the extent of evaluation include the patient's general health, the probable and possible diagnosis, the availability of therapy, the response to tincture of time, the costs of additional tests and patient discomfort and risks.

**Aminotransferases**

The aminotransferases (formerly called transaminases) are the most sensitive measures of hepatocyte integrity. AST (formerly SGOT) is found in liver, cardiac muscle, skeletal muscle, kidney, brain, pancreas, lung, erythrocytes and leukocytes.\(^5\) ALT (formerly SGPT) is present in the highest concentration in liver, and thus is more specific than AST for the presence of liver disease. Serum levels of AST and ALT are elevated to some extent in all liver diseases, with the highest values (1000 U/L) occurring in viral hepatitis, drug or toxin-induced necrosis, and shock and/or ischemia to the liver. Slight or moderate elevations are seen in most other liver disorders including chronic liver disease (chronic hepatitis and cirrhosis), cholestatic conditions, hepatic tumors and fatty liver. The absolute level of enzyme elevation does not correlate with the extent of hepatocyte damage or prognosis.\(^6\) In alcoholic liver disease, the ratio of AST to ALT in serum is helpful diagnostically, with a ratio of more than 2 suggestive of hepatic damage due to alcohol.\(^7\) Low ratios of AST/ALT (less than 2) have been advocated as an indicator of viral hepatitis; however, in general an ALT greater than 300 U/L is more discriminatory for viral hepatitis.\(^8\)

There are only a few studies documenting the results of thorough evaluation of patients with mild elevations of AST and/or ALT. In a Scandinavian study by Hultcrantz et al,\(^8\) 139 consecutive patients who had chronic, moderate elevations of AST and ALT, were asymptomatic, and had negative physical examinations underwent evaluation that included liver biopsy. Fatty liver was noted in 63 percent, chronic hepatitis in 20 percent, and miscellaneous liver diseases in 17 percent. The authors found that only hepatitis B serology, ferritin and alpha-1 antitrypsin levels were helpful diagnostically. In an American study by Van Ness and Dieth,\(^9\) 90 patients with abnormal liver tests were evaluated. Many of the patients in this study had symptoms or physical findings of liver disease. Twenty-six percent had chronic hepatitis, 23 percent chronic liver disease, 24 percent miscellaneous disease (including hemochromatosis, drug-induced hepatitis and autoimmune hepatitis), and 19 percent fatty liver. Freidman et al\(^9\) evaluated 100 healthy blood donors with ALT levels greater than 2.25 standard deviations above the mean and attempted to establish a clinical diagnosis for each individual. Twenty-two percent had fatty liver, 5 percent alcoholic liver disease, 3 percent resolving hepatitis, and 1 percent each hemochromatosis and cytomegalovirus hepatitis. In addition, 45 percent of patients had no clinical diagnosis but reported daily alcohol use, suggesting fatty liver as a cause of an elevated ALT. A final study by Hay et al\(^11\) involved 47 individuals with chronic, 3- to 8-fold
elevation of AST levels and no evidence for alcoholic and/or drug-related liver disease or viral hepatitis. Liver biopsy revealed chronic hepatitis in 72 percent, steatohepatitis in 34 percent, and miscellaneous liver diseases in 6 percent.

The above studies suggest that fatty liver is frequently the cause of mild elevations of AST or ALT (as well as ALP and GGT). Infiltration of liver cells with fat may result in fatty liver alone from causes such as alcohol abuse, obesity and/or diabetes mellitus. On the other hand, fatty liver may be associated with significant liver disease such as alcoholic hepatitis and/or cirrhosis in alcoholic patients or nonalcoholic steatohepatitis (NASH) in a small percent of obese, diabetic individuals. NASH encompasses a spectrum of histologic abnormalities on liver biopsy that includes fatty hepatitis, fatty fibrosis and fatty cirrhosis. There is no direct evidence that fat causes damage to liver cells or that fat alone accounts for the development of more progressive liver disease in the alcoholic or nonalcoholic obese patient. The incidence of fatty liver in obese subjects is high, ranging from 60 to 90 percent while the incidence of NASH is not precisely known, it is probably in the order of a few percent.

Fatty liver seldom causes symptoms in the obese subject, although some experience mild right upper quadrant pain. Palpable hepatomegaly may or may not be present. Mild abnormalities of aminotransferases, ALP and GGT have been found to range from 20 to 90 percent in these subjects. In one recent study of obese patients, the LFT most frequently abnormal was ALT, with a mean elevation of 2.3 times the upper limits of normal. Elevations of both ALT and AST occurred in 54%, with a ratio of ALT to AST 1.9:1. This ratio is opposite to that found in alcoholic liver disease, where AST is often two-fold greater than ALT. Ultrasound examination of fatty liver shows a bright echo pattern, and computed tomography reveals decreased attenuation value.

Fatty liver may persist for many years without progression. Weight reduction of 10% will dramatically improve or normalize abnormal liver tests associated with obesity, such that it appears reasonable to try weight reduction in obese patients with abnormal LFTs and no clinical or biochemical evidence of primary liver disease before embarking on more extensive evaluation with liver biopsy.

The entity NASH has only been recently described in the medical literature. It was first recognized in 1973 as a complication of jejunoileal bypass performed for morbid obesity and appears to occur most often in middle-aged females with obesity and other medical conditions such as diabetes, hypertension, hypothyroidism and the postmenopausal state. The majority of these patients are asymptomatic and are only diagnosed after evaluation of mild to moderate elevations of LFTs. AST and ALT are only mildly to moderately elevated, while bilirubin, albumin and prothrombin time are usually normal. Histologically the fatty changes are virtually identical to those seen in alcoholic liver disease with hepatocyte damage distinguished by the presence of Mallory bodies and an inflammatory infiltrate. Although it is an indolent condition, NASH does have the potential to progress to cirrhosis in some patients. In a study of 49 patients with NASH, five patients progressed to fibrosis, two to cirrhosis and one developed hepatic decompensation and portal hypertension. The factors which promote this progression are unclear.

Table 1.
Stepwise evaluation of isolated (or predominant) mild elevation of AST.

1. Repeat and confirm the abnormality
- if resolved, no further evaluation; recheck in 3-12 months
2. Confirm hepatic origin by measuring ALT and CK
- if ALT normal and CK elevated, evaluate for heart or muscle disease
3. Perform history and physical examination
- if drug-induced or alcoholic liver disease suspected, repeat test(s) 2-8 weeks after drug withdrawal or alcohol abstinence
- if specific diagnosis suspected, obtain appropriate disease-specific marker
- if no diagnosis (or fatty liver) suspected, obtain all disease-specific markers
- if fatty liver suspected and all disease-specific markers negative or normal, follow serial liver test(s) during period of dieting
- if test(s) normalize with weight loss, presume fatty liver
4. Consider hepatic imaging test (US or CT) to exclude other diseases and/or confirm fatty liver (low CT attenuation value)
5. Consider liver biopsy when test(s) abnormality persists longer than 6 months and diagnosis uncertain

- Step 2 and 3 often done at same time
** Disease-specific markers include:
  Acute hepatitis A: IgM anti-HAV
  Acute or chronic hepatitis B: HBsAg and anti-HBc
  Chronic hepatitis C: anti-HCV
  Autoimmune chronic active hepatitis: ANA and ASMA
  Hemochromatosis: serum iron, transferrin saturation and serum ferritin
  Wilson’s disease: serum ceruloplasmin
  Alpha-1-antitrypsin deficiency; alpha-1-antitrypsin level

The first step in the approach to the patient with an isolated, mild elevation of AST (or predominantly elevated AST when ALP and/or GGT is also elevated) is to repeat and confirm the abnormality (Table 1). If the AST is again abnormal, its hepatic origin should be confirmed by measuring the serum ALT and creatine kinase levels, and a history and physical examination should be performed. If clues for a specific diagnosis are found, then the appropriate disease-specific marker(s) can be
obtained. If drug-induced hepatotoxicity (recent use of a new drug) or alcoholic liver disease (alcohol abuse) is suspected, the offending agent should be stopped and the abnormal LFTs repeated over two to eight weeks. If the abnormality persists, determination of all specific markers of liver disease is warranted. These should include hepatitis serology for types A, B and C hepatitis; serum iron, transferrin saturation, and serum ferritin; ANA and ASMA; serum ceruloplasmin; and an alpha-1 antitrypsin level. While the biochemical evaluation is under way, consideration should be given to hepatic imaging using either ultrasound or CT scan. If the patient is obese, serial LFTs over a period of dieting can be helpful in suggesting benign fatty liver if LFTs improve with weight loss. Liver biopsy should be considered in those patients who, even though asymptomatic, have persistent abnormalities of unknown etiology for six months or longer. Although liver biopsy is an invasive procedure, it is quite safe with a risk of death ranging from 0.015 - 0.017 percent in two large studies.6

Alkaline Phosphatase

Alkaline phosphatase (ALP) has been isolated from liver, bone, small bowel, kidney and placenta. Mild, insignificant elevations may be seen in persons over 50 years of age, women in the third trimester of pregnancy, and children who are actively growing.5,18 ALP may be increased in parenchymal liver disease, particularly alcoholic liver disease and infiltrative processes such as neoplasms, but is most characteristically increased in cholestatic diseases. In partial biliary obstruction, the ALP may be mildly to moderately elevated while the patient is asymptomatic and the serum bilirubin normal. Such increases are thought to be related to the enhanced synthesis and release of alkaline phosphatase from cell membranes stimulated by exposure to retained bile salts.5 The absolute level of alkaline phosphatase cannot distinguish between intrahepatic and extrahepatic obstruction nor suggest a specific diagnosis.

The significance of mild elevations of ALP (1.5 - 2 times the upper limits of normal) has not been extensively studied.3,18,19 One study demonstrated that mild increases in alkaline phosphatase are often transient (more than one-half of cases) and unexplained (approximately one-quarter of cases).19 Elevation of alkaline phosphatase greater than two-fold is usually associated with significant liver disease.

Evaluation of an isolated or predominant, mild elevation of ALP with other LFTs normal or near normal should begin by repeating the ALP to confirm the elevation (Table 2). If it is confirmed, serum GGT should be determined to document an hepatobiliary origin of the ALP elevation. If the GGT is normal, the patient should be evaluated for the presence of bone disease. If the GGT is elevated, it is appropriate to pursue further evaluation for hepatobiliary disease with history and physical examination. These may lead to the suspicion of a specific diagnosis for which an individual test(s) can be ordered for confirmation. As with the aminotransferases, if drug-induced or alcoholic liver disease is suspected, the agent should be stopped and the test(s) repeated in 2-8 weeks. If the elevation of ALP is only mild and has been stable for a prolonged period in a patient with obesity, hyperlipidemia and/or diabetes, it may represent fatty liver or, less likely, NASH. If the ALP elevation is moderate or marked in degree, evaluation for intrahepatic disease such as primary biliary cirrhosis with an antimitochondrial antibody or for extrahepatic disease with imaging tests (US or CT) should be undertaken. If imaging studies show dilated ducts or a biliary process is suspected on clinical grounds, then endoscopic retrograde cholangiopancreatography (ERCP) is typically performed. If this study is normal, a liver biopsy will often provide a diagnosis.

Table 2.
Stepwise evaluation of isolated (or predominant) mild elevation of ALP

1. Repeat and confirm the abnormality
   - if resolved, no further evaluation; recheck in 12 months

2. Confirm hepatobiliary origin by measuring GGT
   - if GGT normal, evaluate for bone disease

3.* Perform history and physical examination
   - if drug-induced or alcoholic liver disease suspected, repeat test(s) 2-8 weeks after drug withdrawal or alcohol abstinence
   - if specific diagnosis suspected, obtain appropriate disease-specific marker or imaging test
   - if fatty liver suspected and imaging study normal, follow serial liver tests(s) during period of dieting
   - if test(s) normalize with weight loss, presume fatty liver

4.* Obtain hepatic imaging test (US or CT)
   - if ducts are dilated or biliary disease is suspected, perform ERCP
   - if ducts are not dilated or parenchymal liver disease is suspected, perform liver biopsy

5. Perform liver biopsy when test(s) abnormality persists longer than 3-6 months and diagnosis uncertain after steps 1 to 4 completed

* Step 3 and 4 often done at same time, since imaging tests are routine in the evaluation of an elevated ALP

Gamma-glutamyltransferase

Serum gamma-glutamyltransferase (GGT) is often used to confirm that an elevation in ALP has a hepatobiliary origin. GGT is included in some but not all screening biochemistry profiles, which can result in the dilemma of determining the significance of an isolated elevation of GGT and whether any evaluation is appropriate.

GGT is a membranous enzyme which catalyzes the transfer of gamma-glutamyl groups from glutathione to amino acids. It is present in high concentration in hepatocytes, the biliary tree and the pancreas. It is also present in kidney, heart, intestine, spleen and brain and may be elevated in diseases of these organs.
GGT is extremely sensitive for hepatobiliary disease and may rise in both cholestatic and hepatocellular processes. Increase in GGT tends to parallel that of ALP. The sensitivity of GGT diminishes its clinical usefulness in the differential diagnosis of liver disease. It is inducible by number of drugs, including phenytoin and phenobarbital, as well as by alcohol ingestion. In a study of 58 patients monitored during phenytoin therapy, mean baseline GGT increased 3-fold by the sixth month of therapy.

The sensitivity of GGT is highest, however, when hepatic injury is present. Moussavian et al found that GGT was elevated in only 52 percent of alcoholics without known liver disease. In addition the long serum half-life of GGT (26 days) can cause problems in interpretation. One study found high levels of GGT despite three months of abstinence from alcohol.

In summary, the greatest usefulness for GGT is in distinguishing ALP elevation from bone or placenta from that of hepatic origin. GGT may be elevated by regular, heavy alcohol ingestion and also is induced by multiple medications, both of which may occur in the absence of liver injury. In general, an extensive evaluation of an isolated elevation of GGT in an asymptomatic patient with all other profile liver tests normal is not warranted.

REFERENCES