

AGA Technical Review on the Evaluation of Liver Chemistry Tests

This literature review and the recommendations therein were prepared for the American Gastroenterological Association Clinical Practice Committee. The paper was approved by the Committee on March 3, 2002 and the AGA Governing Board on May 19, 2002.

The widespread availability and frequent use of serum chemistry tests have resulted in a dramatic increase in the number of normal and abnormal liver chemistry test values that must be evaluated by physicians. Serum liver chemistry tests increasingly are obtained not only on patients with suspected liver disorders, but also for screening asymptomatic individuals. Liver chemistry tests commonly are used for periodic health screening, blood banking, and insurance physicals and during hospitalization for medical, surgical, or psychiatric illnesses unrelated to hepatic disorders. Abnormal elevations of serum liver chemistries may occur in 1%–4% of the asymptomatic population.^{1,2} Therefore, to provide high-quality, cost-effective health care, a rational approach for the appropriate evaluation of serum liver chemistries is essential for all practicing physicians. As with the evaluation of all medical tests, the interpretation of liver chemistries must be performed within the context of the patient's risk factors for disease, symptoms, and historical and physical examination findings.

Criteria Used to Include and/or Exclude Data for Consideration

In the data analysis used for this technical review, it should be stated that there are no type 1 data (well-designed randomized controlled trials) and few type 2 data (well-designed cohort [prospective or retrospective] studies with concurrent or historical controls) directly addressing the evaluation of liver chemistry tests. An initial MEDLINE literature search under the subject headings *Liver, Chemistry, Function, and Test* revealed over 14,000 references, with over 6000 references published since 1990. Thus, it is essential to adopt a selective approach to the literature, analyzing data investigating specific liver biochemistries in both asymptomatic and symptomatic patients. Data from abstracts will not routinely be used, and when they are used, it will be explicitly stated that the data are published solely in abstract form. Finally, although there are no arbitrary dates of publication used for studies included for analysis

in this document, medical advances over the past two decades (identification of hepatitis C virus, genetic testing methodologies, etc.) may make older studies obsolete. Emphasis is placed on a critical analysis of more recent literature and any limitations in cited studies resulting from subsequent advances in medical diagnosis and treatment are explicitly stated.

Interpretation of Abnormal Liver Chemistry Values

Normal laboratory values are defined as the mean of the distribution \pm 2 standard deviations of the "normal" population.³ Therefore, by definition, 5% of normal patients will have abnormalities of any given test (2.5% are above and 2.5% are below the 2 standard deviation level). Although low liver chemistry values are not typically associated with disease states, 2.5% of "normal" individuals will have mild elevations of a given serum liver chemistry test. In addition, the "normal" population may not be reflective of normal values for a given patient. Normal laboratory chemistry values may vary according to age, gender, blood group, and postprandial state as well as other factors. In fact, "normal physiologic" states such as pregnancy may result in markedly elevated levels of the serum alkaline phosphatase.^{4,5} Thus, all laboratory abnormalities must be interpreted within the clinical context of the patient.

One may also falsely assume that a normal laboratory value excludes disease. In fact, any population of patients with a given disease also has a distribution of laboratory values, and some affected individuals may have laboratory values extending into the "normal" range.³ Thus, if a liver chemistry test is normal, it does not ensure that the patient is free of liver disease. If a laboratory error is

Abbreviations used in this paper: bilirubin-UGT, bilirubin UDP-glucuronosyltransferase; HH, hereditary hemochromatosis; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis.

© 2002 by the American Gastroenterological Association

0016-5085/02/\$35.00

doi:10.1053/gast.2002.36061

suspected, the laboratory test should be repeated. However, a repeated value in the normal range does not ensure that the initial value was truly erroneous and may reflect a fluctuating biochemical value. Aminotransferase levels typically may fluctuate in liver diseases such as hepatitis C virus (HCV), including serum alanine aminotransferase (ALT) levels that may intermittently be in the normal range and may not correlate well with liver histology.⁶ Finally, differing laboratories may use alternative methodologies for a respective assay, which can result in differing normal laboratory values.

The clinical significance of any liver chemistry test abnormality must be interpreted in the context of the clinical situation. Patients with marked abnormalities of liver chemistry tests, or with signs and symptoms of chronic liver disease or hepatic decompensation (i.e., ascites, encephalopathy, coagulopathy, or portal hypertension), should be evaluated and treated in a more expeditious manner than asymptomatic individuals with minimal chronic liver test abnormalities and normal physical examinations. Thus, the initial evaluation of laboratory tests must involve an assessment of the patient's symptoms, risk factors for liver disease, concomitant conditions, medications or drug use, history and physical examination findings, and even the consideration that there may potentially be a laboratory error.

Based on the pattern of the serum liver chemistry abnormalities, serum liver chemistry tests can be classified to provide a practical approach for the evaluation and diagnosis of hepatobiliary diseases. For the purpose of this document, we have classified the analysis of liver chemistry abnormalities to the interpretation of serum ALT and aspartate aminotransferase (AST) abnormalities (hepatocellular injury) and serum alkaline phosphatase and bilirubin abnormalities (cholestatic pattern). Although it is important to emphasize that liver chemistry test abnormalities frequently occur in overlapping patterns, presenting an obvious limitation to this type of categorized analysis, the division of liver chemistry test abnormalities into "hepatocellular injury" and "cholestatic" patterns allows a commonly used, simplified approach for the interpretation of serum liver chemistries. In addition, elevations of the hepatic alkaline phosphatase with minimal or no elevations of the serum ALT, AST, or bilirubin also may be indicative of "infiltrative" diseases of the hepatic parenchyma. Blood tests such as serum albumin and prothrombin time are also important determinants of hepatic synthetic function, but are not specific for hepatic disease. Nonetheless, these tests have

Table 1. Common Serum Liver Chemistry Tests

Liver chemistry test	Clinical implication of abnormality
Alanine aminotransferase	Hepatocellular damage
Aspartate aminotransferase	Hepatocellular damage
Bilirubin	Cholestasis, impaired conjugation, or biliary obstruction
Alkaline phosphatase	Cholestasis, infiltrative disease, or biliary obstruction
Prothrombin time	Synthetic function
Albumin	Synthetic function
γ -glutamyltransferase	Cholestasis or biliary obstruction
Bile acids	Cholestasis or biliary obstruction
5'-Nucleotidase	Cholestasis or biliary obstruction
Lactate dehydrogenase	Hepatocellular damage, not specific for hepatic disease

an essential role in the evaluation of the hepatic function of patients with acute or chronic liver diseases.

Biological Basis of Liver Chemistries

The term "liver chemistry tests" is a frequently used but poorly defined phrase that encompasses the numerous serum chemistries that can be assayed to assess hepatic function and/or injury (Table 1). Although these also are often termed liver function tests, this term is a misnomer because standard liver chemistry tests do not effectively assess the actual function of the liver. The term liver chemistry tests also implies that the biochemical tests are solely of hepatic origin, but in fact, liver chemistry tests are not always specific for the liver and may encompass numerous biochemical assays that reflect hepatocellular injury, intra- or extrahepatic cholestasis, infiltrating diseases of the liver, impairment of hepatic synthesis, and alterations in liver metabolism.

In 1955, elevations of the serum AST were reported in viral hepatitis as well as other hepatic diseases and subsequently, concomitant ALT elevations were found in similar disorders.⁷⁻⁹ The AST and ALT are abundant hepatic enzymes that catalyze the transfer of amino groups to form the hepatic metabolites pyruvate and oxaloacetate, respectively. The ALT is found in the cytosol of liver, whereas two AST isoenzymes are located in the cytosol and mitochondria, respectively. Both the ALT and AST are released from damaged hepatocytes into the blood after hepatocellular injury or death. The AST also is abundantly expressed in several nonhepatic tissues including heart, skeletal muscle, and blood. The ALT is found in low concentrations in tissues other than liver, so it is frequently considered specific for hepatocellular injury. However, this specificity is not absolute because serum ALT elevations can occur in nonhepatic

conditions such as myopathic diseases.^{10,11} In addition, the serum ALT has diurnal variation, may vary day-to-day, and may be affected by exercise; the serum AST may be 15% higher in African-American males, in addition to varying day-to-day or with exercise.¹²⁻¹⁵ Nonetheless, both the ratio and absolute elevation of the AST and ALT can provide important information regarding the extent and etiology of liver disease. The ratio of mitochondrial to cytoplasmic AST may be useful in the diagnosis of specific liver diseases; however, because isoenzyme activity is not assayed routinely in clinical practice, these data will not be evaluated further.

Bilirubin is a normal heme degradation product that is excreted from the body predominately via secretion into bile. Bilirubin is insoluble in water and requires conjugation (glucuronidation) into the water-soluble bilirubin mono- and di-glucuronide forms before biliary secretion. In the second decade of the twentieth century, van den Bergh and Muller¹⁶ used Ehrlich's diazo reagent to determine that two types of bilirubin were present in the serum of jaundiced patients: one that reacted directly with the reagent (direct bilirubin) and a second form that required the addition of alcohol for color development (indirect bilirubin). Four decades later, independent work by Billing and Schmid demonstrated that unconjugated bilirubin was the indirect form, whereas the direct form was a combination of the bilirubin mono- and di-glucuronides (conjugated bilirubin).¹⁷ Although the methodologies in serum bilirubin determination have advanced since this time, the terminology of direct and indirect bilirubin have remained virtually synonymous with conjugated and unconjugated bilirubin, respectively.

To secrete bilirubin into bile, unconjugated bilirubin must be taken up into the hepatocyte and conjugated into the glucuronide form by the endoplasmic reticulum enzyme bilirubin UDP-glucuronyltransferase (bilirubin-UGT), and the water-soluble bilirubin glucuronides must be secreted across the canalicular membrane into bile. The molecular mechanisms of these processes recently have been delineated and reviewed¹⁸⁻²⁰ but are beyond the scope of this document.

Bilirubin-UGT, the enzyme that conjugates bilirubin, is expressed shortly after birth. However, once enzyme expression occurs, it continues to be highly expressed and active even in severe liver disease and cirrhosis.^{21,22} Diminished expression of this enzyme is one of the defects causing Gilbert's syndrome, a benign, unconjugated hyperbilirubinemia occurring in up to 5% of the normal population.²³⁻²⁷ Unconjugated hyperbilirubinemia also

may result from hemolysis (increased heme breakdown) or in rare genetic diseases such as the Crigler-Najjar syndrome.^{27,28} After the neonatal period, most hepatic conditions that result in a conjugated hyperbilirubinemia are caused by either extrahepatic obstruction of bile flow, intrahepatic cholestasis, hepatitis, or cirrhosis, with a resultant impairment of hepatocellular bilirubin secretion into bile. Because bilirubin-UGT expression and bilirubin conjugation typically are well preserved, these pathophysiological states usually result in a conjugated hyperbilirubinemia. When conjugated hyperbilirubinemia occurs, significant amounts of bilirubin may also be excreted via the urine.

The alkaline phosphatase family of enzymes are zinc metalloenzymes that are present in nearly all tissues. In liver, the enzyme has been immunolocalized to the microvilli of the bile canaliculus. Under normal conditions, serum alkaline phosphatase predominantly is caused by liver and bone isoenzymes, with intestinal enzymes contributing up to 20% of total activity. The normal reference range is dependent on a host of factors including the method of determination, patient age and gender, and the postprandial state.²⁹ During normal pregnancy, alkaline phosphatase activity begins to rise by the late first trimester (because of placental isoenzymes), may reach levels of twice normal by term, and can remain elevated for several weeks after delivery.^{4,5} Serum alkaline phosphatase levels can be elevated by cholestatic or infiltrative diseases of the liver and by diseases causing obstruction to the biliary system, as well as by bone diseases, numerous medications, and tumors of hepatic and nonhepatic origin. When evaluating serum liver chemistries, the important clinical issue is the determination of whether the alkaline phosphatase abnormality is of hepatobiliary or nonhepatic origin. Liver alkaline phosphatase is more heat stable than bone, and isoenzyme determination can be made based on heat sensitivity; however, this assay may be subject to considerable inaccuracy and therefore its clinical use may be "laboratory-specific." Other isoenzyme determination methodologies may include assays using monoclonal antibodies or wheat germ lectin precipitation.^{30,31}

Serum assays of 5'-nucleotidase or γ -glutamyltransferase activity can be used to confirm the liver-specific origin for an elevation of the alkaline phosphatase. The alkaline phosphatase 5'-nucleotidase acts on phosphate groups at the 5' position of the pentose. It is present in many tissues, but serum levels become significantly elevated only in liver diseases. Highest levels are found in cholestatic conditions, but elevations also can occur dur-

ing hepatitis, cirrhosis, or other hepatocellular conditions. The glycoprotein γ -glutamyltransferase is located on membranes of cells with high secretory or absorptive activities. It is abundant in liver, kidney, pancreas, intestine, and prostate, but not in bone. Thus, serum levels may be clinically useful for determining whether an alkaline phosphatase elevation is of liver or bone origin.³² Serum levels also may be elevated after alcohol consumption (presumably because of enzyme induction) and in almost all types of liver disease.^{33,34} Elevations of this enzyme are therefore less useful for determining the cause of liver disease.

Initial Approach to the Evaluation of Abnormal Liver Chemistries Tests

When a patient is identified as having an asymptomatic elevation of one or more liver chemistry test, the physician must decide what initial additional evaluation, if any, is clinically indicated. This will be based, at least in part, on the findings of the history and physical examination. Unfortunately, significant data are lacking on the cost-effectiveness of evaluating patients with asymptomatic abnormalities of liver chemistry tests; nor are there long-term prospective studies to define the natural history of the potential liver disease in these patients. However, given the high prevalence of asymptomatic liver chemistry abnormalities in the United States and the significant costs of an extensive serologic, radiologic, and pathologic evaluation, rational choices must be made based on available data.

In a study of 19,877 presumably healthy Air Force recruits, 99 (0.5%) had confirmed ALT elevations. Of these 99 individuals, only 12% had identifiable causes (4 hepatitis B virus [HBV], 4 HCV, 2 autoimmune hepatitis, 1 cholelithiasis, 1 gastrointestinal infection). Although this study had a low rate of ALT abnormalities and was performed with less sensitive HCV testing methodology than is available today, it suggests that the majority of asymptomatic individuals with serum ALT abnormalities may not have demonstrable liver disease.² In a Scandinavian study of 151 consecutive patients who were referred for mild to moderately elevated serum aminotransferase levels (42–300 U/L) continuing for more than 6 months and who subsequently underwent liver biopsy, identifiable causes of liver disease were more common.³⁵ Chronic HCV was diagnosed in 15.3% of patients, presumed alcoholic liver disease in 8%, autoimmune hepatitis, hepatitis, and primary biliary cirrhosis (PBC) in 1.3% each, α -1-antitrypsin deficiency in

0.7%, and non-alcoholic steatohepatitis and/or steatosis in 42% (the study began before the availability of HCV serologic testing; thus, the HCV group may be underestimated). In addition, 36 (24%) patients had chronic hepatitis of unknown origin, with 11 having bridging fibrosis and 16 having moderate fibrosis on liver biopsy. Cryptogenic cirrhosis was diagnosed in only 1 (0.7%) patient. The significant differences between these two studies may be due to the fact that the latter study involved patients with durations of ALT elevations in excess of 6 months, or due to referral bias because these individuals were referred to an academic center. The data from similar studies from the pre-HCV era are difficult to assess, given that the prevalence of HCV infection could not be ascertained. In addition, a study of 92 asymptomatic blood donors with elevated serum ALT levels who were followed for 6 months revealed that ALT elevations were persistent or recurrent in two thirds of the patients (28% persistent, 36% intermittent) and occurred as an isolated elevation in only 33% of patients. There was no identifiable cause for the ALT elevation in 22 of these 92 patients, although several may have had HCV infection, because testing was not available at the time of this study.³⁶ Finally, the incidence of hepatic disease in selective high-risk populations is, not surprisingly, significantly higher than in screening populations. In a large, multicenter screening study for viral hepatitis, the prevalence of HBV or HCV infection was 24.8%³⁷ and asymptomatic liver chemistry abnormalities occurred in over three quarters of patients taking anticonvulsant medication.³⁸ Thus, a decision to observe an asymptomatic patient closely and repeat a liver chemistry test, versus proceeding with an additional evaluation, must be made in the context of the clinical scenario.

Although a decision regarding the evaluation of abnormalities of liver chemistries must be made based on clinical criteria, the costs of these serologic, radiologic, and pathologic evaluations can be significant. In the absence of definitive cost-effectiveness data regarding the appropriate evaluation, the physician must assess both the benefit and costs (nonfiscal and fiscal) associated with further evaluating these laboratory abnormalities. Table 2 lists fiscal charges and estimated Medicaid reimbursements of selective tests that may be considered in the evaluation of a patient with liver chemistry test abnormalities. These probably represent an extreme range of costs because charges for many laboratory tests may not be fully reimbursed, yet Medicaid reimbursement rates tend to be relatively low compared with many other reimbursement plans. Nonetheless, these may be useful

Table 2. Financial Costs of Selective Serologic Tests for Assessing Hepatic Diseases

Laboratory test	Fiscal charges (U.S. dollars, 2001)	Medicaid/Medicare reimbursement (U.S. dollars, 2001)
ALT, AST, alkaline phosphatase, bilirubin	60–104	51
ALT	28–58	7
AST	28–58	18
Alkaline phosphatase	27–60	7
Bilirubin	26–104	7
Albumin	27–49	6
Prothrombin time	29–44	5
Complete blood count	41–82	8
γ-glutamyltransferase	28–65	8
5'-Nucleotidase	36–54	8
Alpha-Fetoprotein	83–130	23
Hepatitis A-IgM	79–111	6–56
HBsAg	55–58	14
Hepatitis Bc-IgM	85–111	16
Hepatitis A/B profile	108	37
Hepatitis Bc-Total	40–107	17
Hepatitis Bs antibody	86–111	15
Hepatitis Be Ag/Ab	32–81	26
Hepatitis B-DNA	250–300	49
Hepatitis C antibody ELISA	92–104	18
Hepatitis C-RNA qualitative	250–276	49
Hepatitis C-RNA quantitative	327–340	59
Hepatitis C genotype	578–590	70
Iron	29–57	9
Ferritin	69–120	10
Total iron-binding capacity	40–57	12
Hemochromatosis genetic analysis	263–520	N/A
Anti-nuclear antibody	58–113	17
Anti-smooth muscle antibody	73–117	8–23
Anti-liver-kidney microsomal antibody	136–205	9
Anti-mitochondrial antibody	73–179	8–23
Alpha-1-antitrypsin	83–99	12
Ceruloplasmin	65–78	12
Copper, serum	77–83	16
Copper, urine	82–83	16
Abdominal ultrasonography	600	80
Liver biopsy U/S-directed (total cost)	≈1500	63–113

NOTE. Cost data in U.S. dollars is based on the year 2001–2002 laboratory fee schedule and approximate financial reimbursement from Medicaid or Medicare at 2 inner-city, university-affiliated outpatient facilities.

for the clinician to assess the potential financial implications of various approaches to evaluating serum liver chemistry tests. The cost of repeating the serum ALT can be performed for less than \$30; in contrast, an extensive serologic evaluation, abdominal ultrasonography, and percutaneous liver biopsy would cost over \$3000. An initial evaluation to assess common causes of a chronically elevated ALT (e.g., repeat liver chemistries, hepatitis B surface antigen [HBsAg], HCV-Ab, iron, total iron binding capacity, ferritin) can be performed for approximately \$350, or for 2–3 times this cost if an abdominal ultrasonography is obtained.

Thus, the initial decision to evaluate an abnormal liver chemistry further and the choice of testing desired should be dictated by the clinical scenario. The physician

must realize that all liver chemistry abnormalities are not indicative of progressive chronic liver disease, yet must also appreciate that the prompt diagnosis and therapy of many common liver diseases can prevent progression to end-stage liver disease.^{39–41} Given the high incidence of abnormal liver chemistries in asymptomatic individuals, decisions to evaluate these abnormalities by ordering a large number of tests will be quite costly, both in fiscal and nonfiscal (i.e., false-positive tests, complications of liver biopsy, etc.) terms. Therefore, a decision regarding the need to perform additional testing, and/or the choice of the appropriate additional evaluations required to determine the potential cause of the liver disease should be individualized and based on historical and physical examination findings. If an observational approach is

deemed appropriate (with close clinical observation and repeating serial liver chemistries), the physician must continue to re-evaluate the need for additional testing, realizing that a significant number of patients with persistent liver chemistry abnormalities may develop progressive liver disease.

Evaluation of Abnormalities of the Serum ALT and AST Levels

There are numerous causes of increased serum ALT and AST levels in both symptomatic and asymptomatic patients. As previously mentioned, ALT and AST are enzymes released from damaged hepatocytes into the blood following hepatocellular injury or death, although they can originate from other tissues. Historical information and the physical examination are essential for the initial evaluation to determine whether the liver injury is acute or chronic, the underlying etiology, and associated systemic illnesses. The initial management may include repeating the laboratory value if a laboratory error is strongly suspected or if the ALT and AST elevation is minimal. Elevations of both the AST and ALT may rarely be caused by nonhepatic conditions, and although the ALT is considered a "liver-specific" enzyme, this is not always true.^{10,11}

Both the magnitude and relative level of elevation of the ALT and AST may be useful in narrowing the differential diagnosis for the cause of the liver injury, especially when the level of elevation is either mild or severe. Therefore, a useful paradigm to categorize elevated serum ALT and AST levels involves ALT and AST elevations of less than 5 times normal, with either a predominant ALT or AST elevation; and ALT and AST elevations greater than 15 times normal. ALT and AST elevations in an intermediate range may be caused by numerous disease processes that fall into both of the above categories and thus are less useful for limiting the differential diagnosis.

Aminotransferase elevations of up to 5 times normal may be seen in numerous chronic liver diseases as well as in acute hepatic processes. Transaminase elevations usually imply liver cell injury and death, which may or may not be associated with cholestasis. The initial evaluation of all abnormal ALT and AST levels involves a detailed history and physical examination to determine potential causes and chronicity of the liver disease. Lifestyle modifications including discontinuation of medications and alcohol, weight loss, and dietary changes can be recommended. The patient should be evaluated initially for common causes of liver injury (Table 3), and, therefore,

Table 3. Etiology of Mild ALT or AST Elevations: Less Than 5 Times Normal

Hepatic: ALT-predominant
Chronic hepatitis C
Chronic hepatitis B
Acute viral hepatitis (A-E, EBV, CMV)
Steatosis/steatohepatitis
Hemochromatosis
Medications/toxins
Autoimmune hepatitis
Alpha ₁ -antitrypsin deficiency
Wilson's disease
Celiac disease
Hepatic: AST-predominant
Alcohol-related liver injury
Steatosis/steatohepatitis
Cirrhosis
Nonhepatic
Hemolysis
Myopathy
Thyroid disease
Strenuous exercise
Macro-AST

knowledge of the prevalence of specific causes of liver disease may be useful in guiding the initial diagnostic management. However, in patients who have been previously identified as having an abnormal serum liver chemistry test, the probability of having any given type of liver disease is much higher than in the general population with normal liver chemistry tests. If the initial evaluation is unrevealing and if the patients are asymptomatic, appropriate management options include additional diagnostic evaluations versus lifestyle changes and close clinical observation with serial serum liver chemistry testing.

Etiology of Mild ALT and AST Elevations (Less Than 5 Times the Upper Limit of Normal): ALT-Predominant Elevation

Chronic viral hepatitis remains one of the most common causes of abnormal liver chemistries. HCV infection is a highly prevalent disease and a common cause of elevated liver enzymes, affecting nearly 2% of the American population.⁴² All patients with abnormal serum aminotransferases should be questioned for risk factors for HCV acquisition, including a history of intravenous or intranasal drug use, blood transfusion, exposure to unsterile needles (nosocomial, body piercing, tattoo placement), and sexual exposure to an infected individual. The presence of HCV can be diagnosed serologically by obtaining a positive HCV antibody test, and viremia can be confirmed with HCV-RNA measurement

via the reverse-transcription polymerase chain reaction or signal amplification techniques such as branched DNA assay. In patients with elevated aminotransferases and HCV-RNA positivity, ultrasonography (or other imaging modalities) may be useful to visualize the liver parenchyma, but ultrasonography cannot assess the histologic stage of disease. If the presence of chronic HCV infection (6 or more months' duration) is confirmed serologically, liver biopsy should be considered to histologically assess the degree of inflammation and the presence of fibrosis or cirrhosis; this may be important prognostically and in the assessment of response to antiviral therapy.⁴³⁻⁴⁵ Assessing the histologic stage of disease may be particularly important in patients with suspected concomitant hepatic diseases (iron overload, alcohol liver injury), with suspected cirrhosis, or who have failed antiviral therapy. The need to perform an initial liver biopsy or serial liver biopsies routinely for chronic HCV remains controversial.⁴⁶ However, the performance of a liver biopsy should be considered as part of the evaluation of patients with chronic hepatitis C, albeit with the recognition that the decision to perform the procedure must be individualized to the specific patient and clinical scenario.

Chronic HBV is a highly prevalent infection and is a significant cause of serum ALT and AST elevations throughout the world. The prevalence of HBsAg-carrier rate is 0.1%–2% in the United States, Australia, and Western Europe, but is as high as 10%–20% in Southeast Asia and Sub-Sahara Africa.⁴⁷ Risk factors for HBV acquisition are similar to those discussed for hepatitis C, although with a higher risk of transmission vertically at the time of birth and with sexual contact.^{48,49} The presence of a detectable hepatitis B surface antigen or the immunoglobulin (Ig) M-fraction of the hepatitis B core antibody indicates that an individual is infected and chronic infection is defined by HBV positivity for at least 6 months. The natural history of HBV infection is quite variable and depends on the patient's immunologic status and age of acquisition. Additional evaluation including hepatitis B e antigen and antibody, hepatitis Delta virus antibodies, and quantitative HBV-DNA can be obtained if clinically indicated. Ultrasonography may be useful to visualize the liver parenchyma, and liver biopsy should be strongly considered in patients with chronic hepatitis B and elevated transaminases, particularly if a decision regarding treatment is dependent on the pathologic findings.

Most medications have been reported to be associated with serum liver enzyme elevations, although certain

Table 4. Medications, Herbs, and Toxins That Can Cause Elevations of Aminotransferases

Medications and drugs	
Acetaminophen	Herbs/Alternative medications
Alpha-methyl dopa	Chaparral leaf
Amoxicillin-clavulanic acid	Ephedra
Amiodarone	Gentian
Carbamazepine	Germander
Dantrolene	Jin Bu Huan
Disulfiram	Senna, Kavakava
Etretinate	Scutellaria (skullcap)
Fluconazole	Shark cartilage
Glyburide	Vitamin A
Halothane	
Heparin	
HMG-Co A reductase inhibitors	Illicit drugs
Isoniazid	Anabolic steroids
Ketoconazole	Cocaine
Labetolol	Ecstasy (MDMA)
Nicotinic acid	Phencyclidine (PCP)
Nitrofurantoin	
Nonsteroidal anti-inflammatory drugs	Toxins
Phenylbutazone	Carbon tetrachloride
Phenytoin	Chloroform
Propylthiouricil	Dimethylformamide
Protease inhibitors	Hydrazine
Sulfonamides	Hydrochlorofluorocarbons
Trazadone	2-Nitropropane
Troglidazone	Trichloroethylene
Valproic acid	Toluene
Zafirlukast	

medications cause elevated serum aminotransferase levels more frequently than others (Table 4). Over-the-counter medications and herbal preparations are frequent causes of elevated liver enzymes and even hepatic failure. Thus, when evaluating abnormal liver chemistry tests, a careful history must be taken to determine all medications (including all over-the-counter or herbal/alternative medications) that the patient is taking and when therapy was initiated. Although hepatotoxicity often occurs within 1–2 months of when a medication is initiated, this is not universally true. In the presence of abnormal serum liver chemistries, all nonessential medications should be discontinued and the liver chemistry tests should be monitored. Similarly, if suspect medications are administered for clear-cut clinical benefit, alternative medications should be sought. With many medications, liver enzyme elevations are mild and essential medications must be continued. It should be noted that data on the long-term effects of chronic, medication-induced hepatotoxicity are lacking for many drugs because long-term follow-up of large patient cohorts often is limited. If liver enzyme elevations continue to rise, the suspect medication should be stopped because liver failure potentially can occur. Finally, occupational or other toxin exposure can

cause mild to severe elevation of the serum aminotransferases.^{50–52}

Hepatic steatosis/steatohepatitis, or fatty infiltration of the liver with or without associated inflammation, may be the most common cause of mild liver enzyme elevations. However, the actual prevalence in the general population has not been definitively defined,⁵³ in part because nonalcoholic steatohepatitis (NASH) is asymptomatic in 48%–100% of patients. In an autopsy series of 351 unselected obese and nonobese patients, the prevalence of NASH was 6.3%, yet other studies indicate that it occurs in 6%–26% of obese patients.^{53,54} Historical factors such as obesity, weight gain, hyperlipidemias, or diabetes mellitus may be helpful, but risk factors are absent in some patients with this disease.⁵⁵ Because no available blood tests can confirm the diagnosis, the initial evaluation of abnormal serum aminotransferases in patients with suspected steatosis/steatohepatitis includes a serologic evaluation to exclude other forms of liver diseases. Liver ultrasonography, abdominal computerized tomography scanning, or magnetic resonance imaging can be suggestive of the diagnosis. Liver biopsy can confirm the diagnosis and allow assessment of the degree of inflammation and/or fibrosis, thus providing important prognostic information. In asymptomatic individuals suspected of having steatosis/steatohepatitis, appropriate management strategies include modification of lifestyle and risk factors (i.e., weight loss, exercise, discontinuing hepatotoxic medications, control of diabetes and hyperlipidemias) and close clinical follow-up to assess whether the transaminases normalize,⁵⁶ or the performance of a liver biopsy in selective patients. If the transaminases remain abnormal over 6–12 months, or if the patient's ALT remains elevated despite successful lifestyle modifications, liver biopsy should be further considered to confirm the diagnosis and assess for the presence of fibrosis or cirrhosis.⁵⁷

Hereditary hemochromatosis (HH) is one of the most common genetic diseases, and thus should be considered initially in patients presenting with mildly elevated ALT or AST levels.^{58,59} HFE-associated hemochromatosis occurs with a homozygote frequency of 1:200 to 1:400, although the phenotypic expression of the disease may be lower. The disease has an autosomal recessive inheritance, so when a homozygote proband is identified, 25% of the patient's siblings will possess the homozygote genotype, and each parent has at least 1:20 chance of being a homozygote. Important historical information includes the family history and symptoms of weakness, fatigue, abdominal pain, arthralgias, and impotence. Congestive

heart failure, diabetes mellitus, or darkening of skin pigmentation can occur, but these extrahepatic manifestations are relatively late findings in the natural history of the disease. In patients with serum ALT elevations without obvious origin, serum ferritin levels, serum iron, and total iron binding capacity should be measured so that the iron saturation (serum iron/iron binding capacity) can be calculated. These tests, however, are not specific for hemochromatosis and the specificity of these tests is particularly low in patients with other forms of liver disease. Abnormalities of serum tests assaying iron metabolism are age-dependent and can be abnormal in the heterozygote state and in many other conditions.⁶⁰ The genotype typically found in individuals of Northern European descent can be diagnosed with a high degree of accuracy by detection of mutations of the HFE gene. The C282Y/C282Y homozygote is most likely to manifest the disease phenotype, whereas a minority of genotype C282Y/H63D (compound heterozygotes) individuals may also develop the disease.^{61,62} Hemochromatosis may occur in the absence of these mutations, especially in individuals who are not of Northern European descent, presumably because of other known or unknown genetic mutations.^{63,64} Liver biopsy for histology and quantitative iron determination has been used extensively in the past for diagnosing this disease and still has a diagnostic role in patients who present with iron overload and have normal HFE analysis. C282Y homozygote or compound heterozygote individuals under the age of 40 years who manifest an iron overload phenotype and have normal liver enzyme levels, serum ferritin levels less than 1000 ng/mL, and are without hepatomegaly do not routinely require liver biopsy before initiation of phlebotomy.^{61,62} However, the recommendation to avoid performing a liver biopsy cannot be applied to patients who are being evaluated for abnormalities of their serum liver chemistry tests. In addition, although detection of the HFE C282Y/C282Y mutation by genetic testing may obviate the need for liver biopsy in many patients, the absence of the above HFE mutations does not rule out the disease. Non-HFE-related forms of iron overload disease exist, and liver biopsy should be considered in evaluating individuals with abnormal transaminases of unknown origin and evidence of serum ferritin elevations or iron saturations in excess of 50%.⁶⁵ In addition, because the presence of cirrhosis in patients with hemochromatosis confers a high risk for the development of hepatocellular carcinoma, when cirrhosis is suspected, liver biopsy is essential to assess the histologic state of the liver.⁶⁶

Finally, all first-degree relatives of affected patients should be screened for HH (even in the presence of normal serum liver chemistries, because normal values typically are present in young individuals with hemochromatosis). In young probands with children, it is reasonable to perform HFE mutational analysis on the spouse in order to determine whether the children are at risk for having an HH genotype. If the spouse has either a C282Y or H63D mutation, HFE analysis of the offspring should be considered. If a C282Y homozygote or C282Y/H63D compound heterozygote state is identified, the children (especially adult children) should be followed with serum iron indices to determine if therapeutic phlebotomy (or potentially liver biopsy) is required.⁶¹

Chronic autoimmune hepatitis also can cause mildly elevated liver enzymes.^{67,68} Autoimmune hepatitis has a female gender predisposition, and occurs with a prevalence of approximately 1:6000 to 1:7000 individuals.^{69,70} It is often associated with thyroid disease and other autoimmune disorders. Patients with suspected autoimmune hepatitis and abnormal ALT levels should have serum serologic markers measured (anti-nuclear antibodies, anti-smooth muscle antibodies, and potentially liver-kidney microsomal antibodies) and serum studies to exclude other forms of liver disease. Elevated gamma globulin levels (IgG fraction) may occur but are not specific. The criteria for making the diagnosis of autoimmune hepatitis have been defined and include liver histology.⁷¹ Liver biopsy is recommended for patients with abnormal transaminases in whom autoimmune hepatitis is suspected, both for diagnostic criteria and to determine the presence of fibrosis or cirrhosis.

In patients with abnormal ALT levels of unknown origin, serum ceruloplasmin and alpha-1-antitrypsin levels can be measured to screen for Wilson's disease and alpha-1-antitrypsin deficiency, respectively. The homozygote frequency for Wilson's disease is 1:30,000 to 1:300,000,⁷² whereas the homozygote state for alpha-1-antitrypsin is more common, occurring with a frequency of 1:1500 to 1:7600 in North American white individuals.⁷³ The serum ceruloplasmin may increase as a result of hepatic inflammation but generally is lower than normal in patients with Wilson's disease. The further diagnostic evaluation for these autosomal recessive diseases involves additional tests of copper metabolism (serum and urinary copper levels), slit-lamp examination for Kayser-Fleischer rings, and liver biopsy for quantitative copper measurement to diagnose Wilson's disease; and a

protease inhibitor phenotype analysis (P_i-type) and confirmatory liver biopsy for alpha-1-antitrypsin deficiency.^{74,75} A family history of affected siblings should raise strong suspicions for either of these disorders, as do neuro-psychiatric or ophthalmologic manifestations suggestive of Wilson's disease.^{76,77}

Celiac disease may also cause abnormal transaminases, and antiendomysial and antigliadin antibodies may be useful for screening for this entity.⁷⁸⁻⁸² Other diseases associated with mildly elevated transaminase levels are listed in Table 3, and these etiologies of hepatic disease should be sought in the appropriate clinical settings.

Acute viral hepatitis A, B, C, D, or E, Epstein-Barr virus or cytomegalovirus, can cause variable elevations of the serum ALT, which may exceed a level of 5 times normal. The diagnosis of acute hepatitis A, D, or E can be made by virus-specific IgM antibody assays, and acute HBV infection can be diagnosed by obtaining a detectable HBsAg and Hep B core IgM antibody. Acute HCV infection may be diagnosed by measuring the serum HCV-RNA, which can become detectable prior to the development of a positive serum HCV antibody (Table 5).^{83,84} Similarly, the diagnosis of other hepatotropic viruses (Epstein-Barr virus, cytomegalovirus, herpes, adenovirus) can be made by serologic measurement of antibody titers or by the detection of viral antigen in the

Table 5. Commonly Performed Serologic Tests for Viral Hepatitis

Virologic test	Usual clinical implication of a positive test
Hepatitis A-IgM	Positive in acute hepatitis A
Hepatitis A-IgG	Positive in response to previous hepatitis A infection or vaccination
Hepatitis B surface antigen	Positive during active hepatitis B infection
Hepatitis B surface antibody	Positive in response to previous hepatitis B infection or vaccination
Hepatitis B core antibody-IgM	Positive during active hepatitis B infection
Hepatitis B core antibody-IgG	Positive in response to current or prior hepatitis B infection
HBV-DNA	Positive during active hepatitis B infection
Hepatitis B e antigen	Positive tests indicates replicative state of wild-type hepatitis B infection
Hepatitis B e antibody	Positive after replicative state of wild-type hepatitis B infection
HCV-antibody ELISA	Positive during or after hepatitis C infection
HCV-RIBA	Positive during or after hepatitis C infection
HCV-RNA	Positive during hepatitis C infection

ELISA, enzyme-linked immunosorbent assay.

serum and, if clinically indicated, tissue involvement can be verified by liver biopsy.

Etiology of Mild ALT and AST Elevations (ALT and AST Elevations Less Than 5 Times the Upper Limit of Normal): AST-Predominant Elevation

Alcohol use is a common cause of an elevated serum AST and is a cofactor for hepatic injury due to viral hepatitis and metabolic liver diseases.^{85,86} Accurate and detailed assessment of alcohol intake must be elicited by interviewing patients and often other family members because accurate historical information is essential for making the diagnosis of alcohol-related liver injury. The quantity of alcohol and the length of time that alcohol has been consumed are important factors for the development of disease. Alcohol-related liver injury includes hepatic steatosis, hepatitis, and cirrhosis, which may occur in 90%–100%, 10%–35%, and 8%–20% of heavy drinkers, respectively.⁸⁷ Alcoholic hepatitis is commonly associated with an AST:ALT ratio of approximately 2:1, and the AST rarely exceeds 300 IU/dL. If significantly higher enzymes are noted, the presence of an additional cause of liver injury should be sought (acetaminophen use, viral hepatitis, etc.). An appropriate history of alcohol consumption, the serologic exclusion of other forms of liver disease, exclusion of hepatotoxic drugs, and a characteristic pattern of AST and ALT elevation are usually sufficient to make a presumptive diagnosis. Liver biopsy can provide histologic evidence to support the diagnosis of alcoholic hepatitis (and may demonstrate the presence of fibrosis or cirrhosis), although no biopsy findings are pathognomonic.⁸⁸ NASH may present similarly to alcohol-related liver injury, and biopsy findings often are similar in both diseases.⁸⁹ This further emphasizes the importance of obtaining an accurate history of alcohol consumption from all patients with liver disease. AST elevations often predominate in patients with cirrhosis, even in liver diseases that typically have an ALT predominance.⁹⁰

Nonhepatic diseases can present with mild elevations of the serum AST or, less commonly, ALT elevations (Table 3). Hemolysis studies (hemoglobin, peripheral blood smear, reticulocyte count, haptoglobin, Coombs' test, etc.), aldolase, creatine phosphokinase, and macro-AST levels can be used to exclude nonhepatic causes.^{10,11,91–93} The differential diagnosis of an isolated, elevated AST includes alcohol-related or drug-induced liver injury, NASH, hemolysis, myopathic processes, and macro-AST.

AST levels may be reduced in the presence of renal failure.⁹⁴

The differential diagnosis of moderately elevated liver aminotransferases (5–15 times the upper limit of normal) encompasses a wide range of hepatic diseases, and ALT and AST elevations in this range may therefore be less useful in determining likely causes of liver disease. Disease entities that can present in this manner include virtually the entire spectrum of hepatic diseases that may cause either mild or severe aminotransferase elevations.

Etiology of Severe ALT and AST Elevations (Greater Than 15 Times the Upper Limit of Normal)

The differential diagnosis for severe elevations of liver transaminases often differs from etiologies causing lesser elevations of the aminotransferases and is relatively limited (Table 6).^{95,96} Liver enzyme elevations in this range typically indicate more marked hepatocellular injury or necrosis, although transient elevations to this degree may also occur with the passing of gallstones via the common bile duct into the gut.^{97,98} Drug-induced hepatotoxicity can present with marked liver enzyme elevation, thus a careful medication history including over-the-counter medications should be sought. Acetaminophen overdose is the most common cause of drug-induced fulminant hepatic failure,⁹⁹ and patients with significant alcohol consumption may be particularly susceptible.^{100,101} Exposures to occupational, environmental, or other toxins also can cause acute hepatocellular necrosis with marked liver enzyme elevations (Table 4).

Any of the primary hepatotropic hepatitis viruses (A–E) can cause acute hepatitis characterized by marked liver enzyme elevations and can be diagnosed with serologic markers. Initial HCV antibody testing may be negative during acute viral hepatitis C.^{83,84} Serum liver biochemistry levels must be interpreted in light of information obtained from the medical history, including recent travel. Hepatitis A virus (HAV) may be acquired from oral-fecal contact, often in an institutional setting,

Table 6. Etiology of Severe ALT and AST Elevations: Greater Than 15 Times Normal

Acute viral hepatitis (A–E, herpes)
Medications/toxins
Ischemic hepatitis
Autoimmune hepatitis
Wilson's disease
Acute bile duct obstruction
Acute Budd-Chiari syndrome
Hepatic artery ligation

from contaminated food, and HAV is particularly prevalent in many third-world nations. Risk factors for acquisition of hepatitis B and C have been discussed previously. Hepatitis D occurs due to blood-blood contact in concert with hepatitis B, either as a coinfection or subsequent superinfection, whereas hepatitis E is acquired by contaminated food or water in endemic areas, and may be particularly fulminant in pregnant females.¹⁰² Autoimmune hepatitis or Wilson's disease can also present with severe ALT and AST elevations.¹⁰³

Ischemic hepatitis causes marked elevations in liver enzymes and should be considered in the appropriate clinical setting.^{104,105} A low-flow hemodynamic state typically occurs (hypotension, sepsis, cardiac arrhythmia, myocardial infarction, hemorrhage), followed by an acute and rapid rise of liver enzymes. On occasion, acute bile duct obstruction can present with marked, transient elevation in liver enzymes.^{97,98,106} Patients frequently have right upper quadrant pain and nausea, and abdominal ultrasonography may reveal biliary ductal dilatation and cholelithiasis. Liver enzymes typically decline rapidly when a stone passes out of the biliary system. Finally, acute vascular events such as acute Budd-Chiari syndrome, or surgical ligation or thrombosis of the hepatic artery, can present with marked elevation of liver enzymes.¹⁰⁷ Budd-Chiari frequently is characterized by the development of ascites and jaundice and is diagnosed by imaging the hepatic vein and parenchyma; it may be further confirmed by liver biopsy. Accidental ligation or thrombosis of the hepatic artery can occur after surgical procedures of the biliary tree or liver and may be visualized by Doppler evaluation or angiography.

Evaluation of Abnormalities of the Serum Bilirubin and Alkaline Phosphatase Levels

Hyperbilirubinemia and serum elevations of hepatic alkaline phosphatase may be associated with cholestatic conditions. Cholestatic diseases can be categorized as either anatomic obstructions to bile flow (extrahepatic cholestasis) or as functional impairments of bile formation by the hepatocyte (intrahepatic cholestasis). Disorders causing hyperbilirubinemia, however, may not always be associated with abnormalities of the serum alkaline phosphatase or other serum liver chemistries. In fact, hyperbilirubinemia is relatively common with many forms of liver disease and does not necessarily imply the presence of either cholestatic or hepatocellular liver disease, nor even indicate that hepatic disease is present (especially unconjugated hyperbilirubinemias

due to Gilbert's syndrome). The initial evaluation of an elevated isolated serum bilirubin level is, thus, a determination of whether the bilirubin elevation is caused by conjugated (direct) or unconjugated (indirect) bilirubin.

As previously mentioned, alkaline phosphatase elevations may be caused by diseases in organ systems outside the hepatobiliary system. In addition, the cost-effectiveness of evaluating a single, isolated mildly elevated alkaline phosphatase in an asymptomatic individual may be low¹⁰⁸ and therefore, an initial observational approach may be appropriate for many individuals.¹⁰⁹ The initial approach to evaluate an elevated serum alkaline phosphatase is a determination of whether it is of hepatic or nonhepatic origin. This determination can be based on clinical criteria (such as in a patient with known or suspected hepatobiliary diseases) or the concomitant elevation of other serum liver chemistries. However, in asymptomatic patients or in individuals without known liver diseases, confirmation of the hepatic origin of the serum alkaline phosphatase may require the detection of elevated serum levels of the γ -glutamyltransferase, 5'-nucleotidase or hepatic alkaline phosphatase isoenzyme.

Isolated Unconjugated Hyperbilirubinemia

The screening of asymptomatic patients for serum liver biochemistries will identify a large number of individuals with elevated serum unconjugated bilirubin levels. In fact, up to 5% of the population has Gilbert's syndrome, a benign condition of unconjugated hyperbilirubinemia with otherwise normal liver chemistries.²⁴ Given the high prevalence and benign nature of this syndrome, it may be considered a normal variant of the population rather than a disease state. Gilbert's syndrome is caused, in part, by a polymorphism in the TATA box of the gene encoding bilirubin UDP-GT. This results in diminished bilirubin UGT protein expression and enzyme activity, with a resultant impaired ability to conjugate bilirubin. Hyperbilirubinemia may become more prominent during fasting states, systemic illnesses, hemolysis, or with some medications. Although fasting, modified diets, nicotinic acid administration test, and analysis of the UGT1*1 TATA box can be used to diagnose this entity,^{110,111} these measures are not required routinely. In asymptomatic, healthy individuals who have mild (<4 mg/dL) unconjugated hyperbilirubinemia, evaluation should include exclusion of medications that cause hyperbilirubinemia, exclusion of hemolysis (hemoglobin, reticulocyte count, haptoglobin, etc.), and confirmation of normal serum transaminase and al-

Table 7. Causes of an Isolated Unconjugated Hyperbilirubinemia

Gilbert's syndrome
Neonatal jaundice
Hemolysis
Blood transfusion (hemolysis)
Resorption of a large hematoma
Shunt hyperbilirubinemia
Crigler-Najjar syndrome
Ineffective erythropoiesis

kaline phosphatase levels. A presumptive diagnosis of Gilbert's syndrome can be made and the provocative tests cited above are thus not routinely required. Severe unconjugated hyperbilirubinemia can also occur with Crigler-Najjar disease, a rare genetic disease that presents shortly after birth, characterized by a severe or total impairment of bilirubin conjugation by the liver. Unconjugated hyperbilirubinemia, occurring in the absence of primary hepatic disease, may also be caused by entities that increase bilirubin production, impair uptake of bilirubin into the hepatocyte (such as shunt hyperbilirubinemia), or are associated with diminished bilirubin conjugation (Table 7).

Conjugated Hyperbilirubinemia and Elevated Hepatic Alkaline Phosphatase

Cholestatic conditions may cause a conjugated hyperbilirubinemia, and elevated serum bilirubin levels may occur before the development of frank jaundice. Although the Dubin-Johnson and Rotor syndrome are rare genetic diseases caused by an impaired hepatocellular secretion of bilirubin glucuronides into the bile,^{112,113} conjugated hyperbilirubinemias are more typically caused by hepatocellular diseases, biliary obstruction, toxins, or drugs (Table 8). These cholestatic conditions also typically have elevations of hepatic alkaline phos-

Table 8. Causes of Conjugated Hyperbilirubinemia

Bile duct obstruction
Hepatitis
Cirrhosis
Medications/toxins
Primary biliary cirrhosis
Primary sclerosing cholangitis
Sepsis
Total parenteral nutrition
Intrahepatic cholestasis of pregnancy
Benign recurrent cholestasis
Vanishing bile duct syndromes
Dubin-Johnson syndrome
Rotor syndrome

Table 9. Medications That Can Cause Elevations of the Serum Bilirubin or Alkaline Phosphatase

Anabolic steroids	Gold salts
Allopurinol	Imipramine
Amoxicillin-clavulanic acid	Indinivir
Captopril	Iprindole
Carbamazepine	Nevirapine
Chlorpropamide	Methyltestosterone
Cyproheptadine	Methylenedioxymethamphetamine
Diltiazem	Oxaprozin
Erythromycin	Pizotyline
Estrogens	Quinidine
Floxuridine	Tolbutamide
Flucloxacillin	Total parenteral hyperalimentation
Fluphenazine	Trimethoprim-sulfamethoxazole

phatase and, to a lesser degree, liver transaminases. In fact, although data regarding the temporal rise of bilirubin and alkaline phosphatase are lacking for many hepatobiliary diseases, in some chronic cholestatic diseases (primary biliary cirrhosis, primary sclerosing cholangitis), bilirubin elevations and jaundice develop late in the natural history of the disease and may be indicative of impending hepatic failure or malignancy.¹¹⁴⁻¹¹⁶ Isolated hepatic alkaline phosphatase isoenzyme elevations may be the sole abnormality in PBC or other cholestatic diseases, or with infiltrative diseases of the liver.

When a serum alkaline phosphatase elevation is detected, it must be interpreted in the clinical setting of the patient's historical findings and physical examination. Initial management may involve repeating the serum chemistry or confirming the hepatic origin by obtaining a serum γ -glutamyltransferase (or 5'-nucleotidase, alkaline phosphatase isoenzyme) level. If medications are suspected, the initial evaluation may involve discontinuation of medications and repetition of the serum liver chemistries (Table 9). However, patients with persistently elevated serum alkaline phosphatase levels of hepatic origin must be evaluated for cholestatic and infiltrative liver diseases (granulomatous diseases including sarcoidosis, lymphoma, metastatic disease) and for biliary obstruction (Tables 10 and 11). Several infiltrative diseases of the hepatic parenchyma frequently present with a mildly or markedly elevated serum alkaline phosphatase, often with minimal or no elevation of the serum bilirubin, ALT, or AST. The initial evaluation should include ultrasonography to assess the hepatic parenchyma and biliary system. If additional abdominal imaging is clinically indicated, an abdominal computerized tomography scan or abdominal magnetic resonance imaging/magnetic resonance cholangiopancreatography can be obtained. If extrahepatic obstruction is evident, an

Table 10. Causes of Elevated Serum Alkaline Phosphatase

Hepatobiliary
Bile duct obstruction
Primary biliary cirrhosis
Primary sclerosing cholangitis
Medications
Infiltrating diseases of the liver
Hepatic metastasis
Hepatitis
Cirrhosis
Vanishing bile duct syndromes
Benign recurrent cholestasis
Nonhepatic
Bone disease
Pregnancy
Chronic renal failure
Lymphoma and other malignancies
Congestive heart failure
Childhood growth
Infection/inflammation

endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography typically should be performed. Recent data indicate that magnetic resonance cholangiography is effective in diagnosing both PSC and other biliary diseases, although it remains slightly less sensitive than endoscopic retrograde cholangiopancreatography.¹¹⁷ Data published in abstract form indicate that magnetic resonance cholangiography may be more cost-effective than invasive cholangiography in this setting, largely due to the lower complication rate.¹¹⁸ If extrahepatic obstruction is not evident, an antimitochondrial antibody should be obtained. Because potentially treatable cholestatic and infiltrative liver diseases (i.e., PBC, sarcoidosis, primary sclerosing cholangitis, etc.) may have long asymptomatic periods characterized solely by mild, asymptomatic elevations of the serum alkaline phosphatase, the continued presence of persistent hepatic alkaline phosphatase elevations (typically greater than 6 months' duration) of unknown origin typically warrants further evaluation, often with imaging of the biliary tree and liver biopsy.

Serum Albumin and Prothrombin Time

The serum albumin and prothrombin time are commonly obtained serum tests that may be essential in the evaluation of hepatic function, although neither test is specific for evaluating liver function. Albumin levels may be diminished due to poor nutritional status, severe illness with protein catabolism, nephrosis, malabsorption, and other abnormalities of the gastrointestinal tract, whereas serum prothrombin time elevations may

occur with malabsorption and with several acquired or genetic hematologic abnormalities. Nonetheless, in the proper clinical scenario these tests may be important indicators of hepatic synthetic function.¹¹⁹ The liver synthesizes both albumin and many of the blood coagulation factors that are required to be in adequate concentrations in order for the prothrombin time to be normal. Thus, in the absence of other nonhepatic etiologies for abnormalities in the albumin or prothrombin time, these laboratory tests can be useful in assaying hepatic synthetic function. The half-life of serum albumin normally is 19–21 days, whereas the half-life of blood coagulation factors may be less than a day, so these tests often can be used in tandem to assess both acute and chronic components of hepatic function or impairment. The prothrombin time may be a better indicator of coagulation in liver diseases than the international normalization ratio.^{120–122} Unlike serum liver chemistry tests like the serum ALT, AST, and alkaline phosphatase (which are not true indicators of hepatic function), serum albumin levels and prothrombin time, along with physical examination findings such as encephalopathy, are important clinical parameters of hepatic function that are essential in the context of interpreting abnormal serum liver chemistry tests, especially in clinical scenarios of impending hepatic failure.^{123,124}

Evaluation of the Clinical Indication for Performing a Liver Biopsy

When evaluating a patient with abnormal serum liver chemistries, a common diagnostic decision facing the gastroenterologist is whether to perform a percutaneous liver biopsy. Liver biopsy can provide important prognostic and diagnostic information regarding the cause of the liver disease but should be performed only if the expected benefit exceeds the small risks of the procedure. Outpatient percutaneous liver biopsy can be performed safely in most patients, although complications requiring hospitalization may occur in 1.4%–4% of patients.^{125–129} A large series of 68,276 percutaneous

Table 11. Infiltrating Diseases of the Liver That Can Cause Elevations of the Serum Alkaline Phosphatase

Sarcoidosis
Tuberculosis
Fungal infection
Other granulomatous diseases
Amyloidosis
Lymphoma
Metastatic malignancy
Hepatocellular carcinoma

liver biopsies revealed a severe complication rate (i.e., death, severe hemorrhage, pneumothorax, bile peritonitis) of 0.1%–0.3% and a mortality rate of 9/100,000, with deaths occurring in patients with malignant disease or cirrhosis.¹²⁵ Because this study was performed before the routine use of transjugular liver biopsy techniques, it probably includes higher-risk patients who would not currently undergo percutaneous liver biopsy. Thus, it may report a complication rate that potentially is higher than one would expect in the era when transjugular liver biopsy is available. Transjugular liver biopsy can be performed successfully in the majority of patients with contraindications (i.e., coagulation disorders, ascites) to percutaneous biopsy and is relatively safe, although complications have been reported in this high-risk patient population.^{130,131}

Recent studies from the post-HCV era indicate that when liver biopsies are performed for abnormal serum liver chemistries with an unremarkable serologic evaluation, the most likely diagnosis is steatosis and steatohepatitis, occasionally associated with fibrosis.⁴⁶ In one study, the postbiopsy diagnosis differed from the prebiopsy diagnosis in 14% of patients, although recommendations for treatment (excluding investigational therapies) were altered in a smaller number of individuals as a result of the procedure.¹³²

Liver biopsy can be performed with a low complication rate and may provide useful prognostic and diagnostic information in patients with chronically (greater than 6 months) elevated, marker-negative serum liver chemistries, and thus should be considered. The decision to perform a biopsy, however, must be individualized to the patient's age, lifestyle, liver chemistry abnormalities, desire for prognostic information, and associated comorbid conditions.

Conclusion

This review of the medical literature on the evaluation of liver chemistry tests indicates, at least to the authors, that a reliable literature to make unequivocal recommendations for the diagnostic evaluation of patients with abnormal liver chemistry tests is lacking. There are no large, double-blinded, prospective studies and few uncontrolled studies addressing this issue. Several review articles have been published on the evaluation of liver chemistry tests, although the recommendations often reflected the authors' opinions based on the imperfect data available in the medical literature, and on their expertise in the management of liver diseases.^{133–136}

As previously described, the normal range of serum laboratory test values is defined such that 2.5% of the normal population will have abnormally elevated laboratory values for a given test. In addition, normal serum liver chemistry values do not definitively exclude the presence of disease. Compounding this problem, common hepatic diseases such as HCV may have fluctuating serum liver chemistry tests, which can be intermittently normal. However, given the common clinical practices of screening asymptomatic individuals and patients with suspected liver disorders with serum liver biochemistry tests, the appropriate interpretation and evaluation of these tests has important patient care, public health, and economic implications.

The initial evaluation of a serum liver chemistry value must be assessed in the clinical context of the patient, based on the findings of a detailed history and physical examination. Patient symptoms (or lack of symptoms), risk factors for acquisition of hepatitis, family history of genetic liver disease, alcohol and illicit drug use, medications, age, gender, the patient's psychological state, comorbid diseases, and pertinent physical examination findings of liver disease should be assessed initially. Lifestyle modifications should be recommended when appropriate and any nonessential medications discontinued. If a laboratory error is suspected, the serum test may be repeated, albeit with the realization that a normal value does not eliminate the possibility that liver disease is present. A decision regarding further diagnostic evaluation or close clinical follow-up and serial evaluation of repeat liver chemistry testing can then be made.

It seems prudent that in symptomatic individuals, and certainly in patients with evidence of decompensated or chronic liver disease, an expeditious and complete diagnostic evaluation is warranted. In fact, further diagnostic evaluation may also be appropriate for the majority of asymptomatic individuals. Noninvasive tests to exclude common hepatobiliary diseases should be performed initially. In stable patients with elevated ALT levels, serologic assessment of viral hepatitis markers and iron studies should be obtained. If these are negative, further evaluation to exclude autoimmune, metabolic, and other less common causes of liver injury should be considered. Ultrasonography to assess the hepatic parenchyma and biliary tree may also be appropriate. Similarly, in a patient with evidence of cholestatic liver disease, ultrasonography to exclude biliary dilatation and, potentially, antimitochondrial antibody testing are warranted. The pattern of liver chemistry test abnormalities may not be so clear-cut, and additional serologic or radiologic tests

may be required. Finally, in patients with nondiagnostic evaluations of their abnormal serum liver chemistries who have evidence of impaired hepatic function or chronic liver chemistry test abnormalities, liver biopsy seems warranted for both diagnostic evaluation and prognostication.

RICHARD M. GREEN

STEVEN FLAMM

Division of Hepatology

*Northwestern University Feinberg School of Medicine
Chicago, Illinois*

References

- Hultcrantz R, Glaumann H, Lindberg G, Nilsson LH. Liver investigation in 149 asymptomatic patients with moderately elevated activities of serum aminotransferases. *Scand J Gastroenterol* 1986;21:106-113.
- Kundrotas LW, Clement DJ. Serum alanine aminotransferase (ALT) elevation in asymptomatic US Air Force basic trainee blood donors. *Dig Dis Sci* 1993;38:2145-2150.
- Sox HC, Blatt MA, Higgins MC, Marton KI. Medical decision making. Boston: Butterworth-Heinemann, 1988.
- Fishman WH, Bardawil WA, Habib HG, Anstiss CL, Green S. The placental isoenzymes of alkaline phosphatase in sera of normal pregnancy. *Am J Clin Pathol* 1972;57:65-74.
- Romslo I, Sagen N, Haram K. Serum alkaline phosphatase in pregnancy. I. A comparative study of total, L-phenylalanine-sensitive and heat-stable alkaline phosphatase at 56 degrees C and 65 degrees C in normal pregnancy. *Acta Obstet Gynecol Scand* 1975;54:437-442.
- Haber MM, West AB, Haber AD, Reuben A. Relationship of aminotransferases to liver histological status in chronic hepatitis C. *Am J Gastroenterol* 1995;90:1250-1257.
- De Ritis F. Biochemical laboratory tests in viral hepatitis and other hepatic diseases. *Bull World Health Organ* 1965;32:59.
- Wroblewski F. The clinical significance of transaminase activities in serum. *Am J Med* 1959;27:911.
- Wilkinson JH. Blood enzymes in diagnosis. In: London University (Br Post Grad Med Fed). Lectures on the scientific basis of medicine. London: Athlone Press, 1958.
- Scola RH, Werneck LC, Prevedello DM, Toderke EL, Iwamoto FM. Diagnosis of dermatomyositis and polymyositis: a study of 102 cases. *Arq Neuropsiquiatr* 2000;58:789-799.
- Lin YC, Lee WT, Huang SF, Young C, Wang PJ, Shen YZ. Persistent hypertransaminasemia as the presenting findings of muscular dystrophy in childhood. *Taiwan Erh Ko I Hsueh Hui Tsa Chih* 1999;40:424-429.
- Siest G, Schiele F, Galteau M-M, et al. Aspartate aminotransferase and alanine aminotransferase activities in plasma: statistical distributions, individual variations, and reference values. *Clin Chem* 1975;21:1077-1087.
- Cordoba J, O'Riordan K, Dupuis J, Borensztajn J, Blei AT. Diurnal variation of serum alanine transaminase activity in chronic liver disease. *Hepatology* 1999;28:1724-1725.
- Nuttall FQ, Jones B. Creatine kinase and glutamic oxalacetic transaminase activity in serum: kinetics of change with exercise and effect of physical conditioning. *J Lab Clin Med* 1968;51:257-261.
- Dufour DR. Effects of habitual exercise on routine laboratory tests. *Clin Chem* 1998;44:136.
- Hijmans van den Bergh AA. Der gallenfarbstoff im blute. Leipzig: Berth, 1918.
- Billing BH. Twenty-five years of progress in bilirubin metabolism (1952-1977). *Gut* 1978;19:481-491.
- Trauner M, Meier PJ, Boyer JL. Molecular regulation of hepatocellular transport systems in cholestasis. *J Hepatol* 1999;31:165-178.
- Jansen PL, Muller M. Genetic cholestasis: lessons from the molecular physiology of bile formation. *Can J Gastroenterol* 2000;14:233-238.
- Paulusma C, Oude Elferink RPJ. The canalicular multispecific organic anion transporter and conjugated hyperbilirubinemia in rat and man. *J Mol Med* 1997;75:420-428.
- Debinski HS, Lee CS, Danks JA, Mackenzie PI, Desmond PV. Localization of uridine 5'-diphosphate-glucuronosyltransferase in human liver injury. *Gastroenterology* 1995;108:1464-1469.
- Debinski HS, Mackenzie PI, Lee CS, et al. UDP glucuronosyltransferase in the cirrhotic rat liver. *J Gastroenterol Hepatol* 1996;11:373-379.
- Beutler E, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? *Proc Natl Acad Sci U S A* 1998;95:8170-8174.
- Monaghan G, Ryan M, Seddon R, Hume R, Burchell B. Genetic variation in bilirubin UDP-glucuronosyltransferase gene promoter and Gilbert's syndrome. *Lancet* 1996;347:578-581.
- Bosma PJ, Chowdhury JR, Bakker C, et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. *N Engl J Med* 1995;333:1171-1175.
- Rudenski AS, Halsall DJ. Genetic testing for Gilbert's syndrome: how useful is it in determining the cause of jaundice? *Clin Chem* 1998;44:1604-1609.
- Tukey RH, Strassburg CP. Human UDP-glucuronosyltransferases: metabolism, expression, and disease. *Annu Rev Pharmacol Toxicol* 2000;40:581-616.
- Tiribelli C, Ostrow JD. New concepts in bilirubin and jaundice: report of the Third International Bilirubin Workshop, April 6-8, 1995, Trieste, Italy. *Hepatology* 1996;24:1296-1311.
- Langman MJ, Leuthold E, Robson EB, Harris J, Luffman JE, Harris H. Influence of diet on the "intestinal" component of serum alkaline phosphatase in people of different ABO blood groups and secretor status. *Nature* 1966;212:41-43.
- Sorensen S. Wheat-germ agglutinin method for measuring bone and liver isoenzymes of alkaline phosphatase assessed in postmenopausal osteoporosis. *Clin Chem* 1988;34:1636-1640.
- Seabrook RN, Bailyes EM, Price CP, Siddle K, Luzio JP. The distinction of bone and liver isoenzymes of alkaline phosphatase in serum using a monoclonal antibody. *Clin Chim Acta* 1988;172:261-266.
- Whitfield JB, Pounder RE, Neale G, Moss DW. Serum-glutamyl transpeptidase activity in liver disease. *Gut* 1972;13:702-708.
- Zein M, Discombe G. Serum gamma-glutamyl transpeptidase as a diagnostic aid. *Lancet* 1970;2:748-750.
- Penn R, Worthington DJ. Is serum gamma-glutamyltransferase a misleading test? *BMJ* 1983;286:531-535.
- Mathiesen UL, Franzen LE, Fryden A, Foberg U, Bodemar G. The clinical significance of slightly to moderately increased liver transaminase values in asymptomatic patients. *Scand J Gastroenterol* 1999;34:85-91.
- Friedman LS, Dienstag JL, Wadkins E, et al. Evaluation of blood donors with elevated serum alanine aminotransferase levels. *Ann Intern Med* 1987;107:137-144.
- Kaur S, Rybicki L, Bacon BR, Gollan JL, Rustgi VK, Carey WD. Performance characteristics and results of a large-scale screening program for viral hepatitis and risk factors associated with exposure to viral hepatitis B and C. National Hepatitis Surveillance Group. *Hepatology* 1996;24:979-986.

38. Wall M, Baird-Lambert J, Buchanan N, Farrell G. Liver function tests in persons receiving anticonvulsant medications. *Seizure* 1992;3:187-190.
39. Kamath PS. Clinical approach to the patient with abnormal liver test results. *Mayo Clin Proc* 1996;71:1089-1095.
40. Goddard CJR, Warnes TW. Raised liver enzymes in asymptomatic patients: investigation and outcome. *Dig Dis Sci* 1992;10:218-226.
41. Craxi A, Almasio P. Diagnostic approach to liver enzyme elevation. *J Hepatol* 1996;25(suppl 1):47-51.
42. Management of hepatitis C. National Institutes of Health Consensus Development Conference, 1997.
43. Saadeh S, Cammell G, Carey WD, Younossi Z, Barnes D, Easley K. The role of liver biopsy in chronic hepatitis C. *Hepatology* 2001;33:196-200.
44. Perrillo RP. The role of liver biopsy in hepatitis C. *Hepatology* 1997;26(suppl 1):57S-61S.
45. Ahmed A, Keeffe EB. Treatment strategies for chronic hepatitis C: update since the 1997 National Institutes of Health Consensus Development Conference. *J Gastroenterol Hepatol* 1999;14(suppl):S12-S18.
46. Wong JB, Koff RS. Watchful waiting with periodic liver biopsy versus immediate empirical therapy for histologically mild chronic hepatitis C. A cost-effectiveness analysis. *Ann Intern Med* 2000;133:665-675.
47. Schiff ER, Sorrell MF, Maddrey WC. *Hepatitis B. Schiff's diseases of the liver*. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 1999:757-758.
48. Michielsen PP, Van Damme P. Viral hepatitis and pregnancy. *Acta Gastroenterol Belg* 1999;62:21-29.
49. Alter MJ, Mast EE. The epidemiology of viral hepatitis in the United States. *Gastroenterol Clin North Am* 1994;23:437-455.
50. Redlich CA, Beckett WS, Sparer J, et al. Liver disease associated with occupational exposure to the solvent dimethylformamide. *Ann Intern Med* 1988;108:680-686.
51. Petersen P, Bredahl E, Lauritsen O, Laursen T. Examination of the liver in personnel working with liquid rocket propellant. *Br J Ind Med* 1970;27:141-146.
52. Hoet P, Graf ML, Bourdi M, et al. Epidemic of liver disease caused by hydrochlorofluorocarbons used as ozone-sparing substitutes of chlorofluorocarbons. *Lancet* 1997;350:556-559.
53. Reid AE. Nonalcoholic steatohepatitis. *Gastroenterology* 2001;121:710-723.
54. Ballew C, Bowman BA, Russell RM, Sowell AL, Gillespie C. Serum retinyl esters are not associated with biochemical markers of liver dysfunction in adult participants in the third National Health and Nutrition Examination Survey (NHANES III), 1988-1994. *Am J Clin Nutr* 2001;73:934-940.
55. Bacon BR, Farahvash MJ, Janney CG, et al. Non-alcoholic steatohepatitis: an expanded clinical entity. *Gastroenterology* 1994;107:1103-1109.
56. Palmer M, Schaffner F. Effective weight reduction on hepatic abnormalities in overweight patients. *Gastroenterology* 1990;99:1403-1408.
57. Daniel S, Ben-Menachem T, Vasudevan G, Ma CK, Blumenkehl M. Prospective evaluation of unexplained chronic liver transaminase abnormalities in asymptomatic and symptomatic patients. *Am J Gastroenterol* 1999;94:3010-3014.
58. Adams PC, Kertesz AE, Valberg LS. Clinical presentation of hemochromatosis: a changing scene. *Am J Med* 1991;90:445-449.
59. Powell LW, George DK, McDonnell SM, Kowdley KD. Diagnosis of hemochromatosis. *Ann Intern Med* 1998;129:925-931.
60. Bassett ML, Halliday JW, Ferris RA, et al. Diagnosis of hemochromatosis in young subjects: predictive accuracy of biochemical screening tests. *Gastroenterology* 1984;87:628-633.
61. Bacon BR. Hemochromatosis: diagnosis and management. *Gastroenterology* 2001;120:718-725.
62. Tavill AS. Diagnosis and management of hemochromatosis. *Hepatology* 2001;33:1321-1328.
63. Pietrangelo A, Montosi G, Totaro A, et al. Hereditary hemochromatosis in adults without pathogenic mutations in the hemochromatosis gene. *N Engl J Med* 1999;341:725-732.
64. Camaschella C, Roetto A, Cali A, et al. The gene TFR2 is mutated in a new type of haemochromatosis mapping to 7q22. *Nat Med Nat Genet* 2000;25:14-15.
65. Summers KM, Halliday JW, Powell LW. Identification of homozygous hemochromatosis subjects by measurement of hepatic iron index. *Hepatology* 1990;12:20-25.
66. Fargion S, Fracanzani AL, Piperno A, et al. Prognostic factors for hepatocellular carcinoma in genetic hemochromatosis. *Hepatology* 1994;20:1426-1431.
67. Czaja AJ. Autoimmune hepatitis: evolving concepts and treatment strategies. *Dig Dis Sci* 1995;40:435-456.
68. Krawitt EL. Autoimmune hepatitis. *N Engl J Med* 1996;334:897-903.
69. Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. *Scand J Gastroenterol* 1998;33:99-103.
70. Berdal JE, Ebbesen J, Rydning A. Incidence and prevalence of autoimmune liver diseases. *Tidsskr Nor Laegeforen* 1998;118:4517-4519.
71. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999;31:929-938.
72. Olsson C, Waldenstrom E, Westermarck K, Landegre U, Syvanen AC. Determination of the frequencies of ten allelic variants of the Wilson disease gene ATP7B, in pooled DNA samples. *Eur J Genet* 2000;12:933-938.
73. Cox DW, Mansfield T. Prenatal diagnosis of α 1-antitrypsin deficiency and estimates of fetal risk of disease. *J Med Genet* 1987;24:52-59.
74. Crystal RG. Alpha-1 antitrypsin deficiency, emphysema, and liver disease: genetic basis and strategies for therapy. *J Clin Invest* 1990;85:1343-1352.
75. Ludwig J, Moyer TP, Rakela J. The liver biopsy diagnosis of Wilson's disease. *Methods in pathology*. *Am J Clin Pathol* 1994;102:443-446.
76. Brewer GJ, Yuzbasiyan-Gurkan V. Wilson's disease. *Medicine* 1992;71:139-164.
77. Loudianos G, Gitlin JD. Wilson's disease. *Semin Liver Dis* 2000;20:353-364.
78. Yuce A, Demir H, Kocak N, Gurakan F, Ozen H. Antiendomysium and anti gliadin antibodies for the diagnosis of celiac disease. *Am J Gastroenterol* 2000;95:1366-1367.
79. Mugica F, Aranzadi MJ, Recasens M, et al. Adult celiac disease and hypertransaminasemia. *Rev Esp Enferm Dig* 2000;92:78-85.
80. Naschitz JE, Yeshurun D, Zuckerman E, Arad E, Boss JH. Massive hepatic steatosis complicating adult celiac disease: report of a case and review of the literature. *Am J Gastroenterol* 1987;82:1186-1189.
81. Volta U, DeFranceschi L, Lari F, et al. Coeliac disease hidden by cryptogenic hypertransaminasaemia. *Lancet* 1998;352:26-29.
82. Bardella MT, Vecchi M, Conte D, et al. Chronic unexplained hypertransaminasemia may be caused by occult celiac disease. *Hepatology* 1999;29:654-657.
83. Krajden M. Hepatitis C virus diagnosis and testing. *Can J Public Health* 2000;91(suppl 1):S34-S39.
84. Tanaka E, Kiyosawa K. Natural history of acute hepatitis C. *J Gastroenterol Hepatol* 2000;15(suppl):E97-E104.

85. Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology* 1998;28:805–809.
86. Fletcher LM, Halliday JW, Powell LW. Interrelationships of alcohol and iron in liver disease with particular reference to the iron-binding proteins, ferritin and transferrin. *J Gastroenterol Hepatol* 1999;14:202–214.
87. Schiff ER, Sorrell MF, Maddrey WC. Hepatitis B. Schiff's diseases of the liver. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 1999:942.
88. Pinto HC, Baptista A, Camilo ME, Valente A, Saragoca A, de Moura MC. Nonalcoholic steatohepatitis. Clinicopathological comparison with alcoholic hepatitis in ambulatory and hospitalized patients. *Dig Dis Sci* 1996;41:172–179.
89. Sorbi D, Boynton J, Lindor KD. The ratio of aspartate aminotransferase to alanine aminotransferase: potential value in differentiating nonalcoholic steatohepatitis from alcoholic liver disease. *Am J Gastroenterol* 1999;94:1018–1022.
90. Sheth SG, Flamm SL, Gordon FD, Chopra S. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. *Am J Gastroenterol* 1998;93:44–48.
91. Litin SC, O'Brien JF, Pruett S, et al. Macroenzyme as a cause of unexplained elevation of aspartate aminotransferase. *Mayo Clin Proc* 1987;62:681–687.
92. Remaley AT, Wilding P. Macroenzymes: biochemical characterization, clinical significance, and laboratory detection. *Clin Chem* 1989;35:2261–2270.
93. Galasso PJ, Litin SC, O'Brien JF. The macroenzymes: a clinical review. *Mayo Clin Proc* 1993;68:349–354.
94. Cohen GA, Goffinet JA, Donabedian RK, Conn HO. Observations on decreased serum glutamic oxalacetic transaminase (SGOT) activity in azotemic patients. *Ann Intern Med* 1976;84:275–280.
95. Johnson RD, O'Connor ML, Kerr RM. Extreme serum elevations of aspartate aminotransferase. *Am J Gastroenterol* 1995;90:1244–1245.
96. Whitehead MW, Hawkes ND, Hainsworth I, Kingham JG. A prospective study of the causes of notably raised aspartate aminotransferase of liver origin. *Gut* 1999;45:129–133.
97. Anciaux ML, Pelletier AG, Attali P, Meduri B, Liguory C, Etienne JP. Prospective study of clinical and biochemical features of symptomatic choledocholithiasis. *Dig Dis Sci* 1986;31:449–453.
98. Fortson WC, Tedesco FJ, Starnes EC, Shaw CT. Marked elevation of serum transaminase activity associated with extrahepatic biliary tract disease. *J Clin Gastroenterol* 1985;7:502–505.
99. Makin AJ, Williams R. Acetaminophen-induced hepatotoxicity: predisposing factors and treatments. *Adv Intern Med* 1997;42:453–483.
100. Seeff LB, Cuccherini BA, Zimmerman HJ, et al. Acetaminophen hepatotoxicity in alcoholics. *Ann Intern Med* 1986;104:399.
101. Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instance of therapeutic misadventure. *Hepatology* 1995;22:767–773.
102. Acharya SK, Panda SK, Saxena A, Gupta SD. Acute hepatic failure in India: a perspective from the East. *J Gastroenterol Hepatol* 2000;15:473–479.
103. Reich DJ, Fiel I, Guarrera JV, et al. Liver transplantation for autoimmune hepatitis. *Hepatology* 2000;32:693–700.
104. Bynum TE, Boitnott JK, Maddrey WC. Ischemic hepatitis. *Dig Dis Sci* 1979;24:129–135.
105. Gitlin N, Serio KM. Ischemic hepatitis: widening horizons. *Am J Gastroenterol* 1992;87:831–836.
106. Patwardhan RV, Smith OJ, Farmelant MH. Serum transaminase levels and cholescintigraphic abnormalities in acute biliary tract obstruction. *Arch Intern Med* 1987;147:1249–1253.
107. Lee YT. Liver chemistry tests after ligation of hepatic artery. *J Surg Oncol* 1978;10:305–320.
108. Amberg JM, Schneiderman LJ, Berry CC, Zettner A. The abnormal outpatient chemistry panel serum alkaline phosphatase: analysis of physician response, outcome, cost and health effectiveness. *J Chronic Dis* 1982;35:81–88.
109. Lieberman D, Phillips D. "Isolated" elevation of alkaline phosphatase: significance in hospitalized patients. *J Clin Gastroenterol* 1990;12:415–419.
110. Dickey W, McAleer JJ, Callender ME. The nicotinic acid provocation test and unconjugated hyperbilirubinaemia. *Ulster Med J* 1991;60:49–52.
111. Whitmer DI, Gollan JL. Mechanisms and significance of fasting and dietary hyperbilirubinemia. *Semin Liver Dis* 1983;3:42–51.
112. Tsujii H, Konig J, Rost D, Stockel B, Leuschner U, Keppler D. Exon-intron organization of the human multidrug-resistance protein 2. (MRP2) gene mutated in Dubin-Johnson syndrome. *Gastroenterology* 1999;117:653–660.
113. Paulusma CC, Bosma PJ, Zaman GJ, et al. Congenital jaundice in rats with a mutation in a multidrug resistance-associated protein gene. *Science* 1996;271:1126–1128.
114. Bonnand AM, Heathcote EJ, Lindor KD, Poupon RE. Clinical significance of serum bilirubin levels under ursodeoxycholic acid therapy in patients with primary biliary cirrhosis. *Hepatology* 1999;29:39–43.
115. Kim WR, Thorneau TM, Wiesner RH, et al. A revised natural history model for primary sclerosing cholangitis. *Mayo Clin Proc* 2000;75:688–694.
116. Grambsch PM, Dickson ER, Wiesner RH, Langworthy A. Application of the Mayo primary biliary cirrhosis survival model to Mayo liver transplant patients. *Mayo Clin Proc* 1989;64:699–704.
117. Angulo P, Pearce DH, Johnson CD, et al. Magnetic resonance cholangiography in patients with biliary disease: its role in primary sclerosing cholangitis. *J Hepatol* 2000;33:520–527.
118. Talwalkar JA, Angulo P, Johnson CD, Peterson BT, Lindor KD. Cost-minimization analysis of MRC vs ERCP in patients with biliary disease: its role in primary sclerosing cholangitis (PSC) (abstr). *Hepatology* 2000;32:175A.
119. Doumas BT, Peters T. Serum and urine albumin: a progress report on their measurement and clinical significance. *Clin Chim Acta* 1997;258:3–20.
120. Ts'ao C, Swedlund J, Neofotistos D. Implications of use of low international sensitivity index thromboplastins in prothrombin time testing. *Arch Pathol Lab Med* 1994;118:1183–1187.
121. Kovacs MJ, Wong A, MacKinnon K, et al. Assessment of the validity of the INR system for patients with liver impairment. *Thromb Haemost* 1994;71:727–730.
122. Robert A, Chazouilleres O. Prothrombin time in liver failure: time, ratio, activity percentage, or international normalized ratio? *Hepatology* 1996;24:1392–1394.
123. Lee WM. Acute liver failure. *N Engl J Med* 1993;329:1862–1872.
124. Harrison PM, O'Grady, Keays RT, Alexander GJ, Williams R. Serial prothrombin time as prognostic indicator in paracetamol induced fulminant hepatic failure. *BMJ* 1990;301:964–966.
125. Piccinino F, Sagnelli E, Pasquale G, Giusti G. Complications following percutaneous liver biopsy. A multicentre retrospective study on 68,276 biopsies. *J Hepatol* 1986;2:165–173.
126. Lindor KD, Bru C, Jorgensen RA, et al. The role of ultrasonography and automatic-needle biopsy in outpatient percutaneous liver biopsy. *Hepatology* 1996;23:1079–1083.
127. McGill DB, Rakela J, Zinsmeister AR, Ott BJ. A 21-year experi-

- ence with major hemorrhage after percutaneous liver biopsy. *Gastroenterology* 1990;99:1396–1400.
128. Janes CH, Lindor KD. Outcome of patients hospitalized for complications after outpatient liver biopsy. *Ann Intern Med* 1993;118:96–98.
129. Gilmore IT, Burroughs A, Murray-Lyon IM, Williams R, Jenkins D, Hopkins A. Indications, methods, and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and the Royal College of Physicians of London. *Gut* 1995;36:437–441.
130. Corr P, Beningfield SJ, Davey N. Transjugular liver biopsy: a review of 200 biopsies. *Clin Radiol* 1992;45:238–239.
131. Gamble P, Colapinto RF, Stronell RD, Colman JC, Blendis L. Transjugular liver biopsy: a review of 461 biopsies. *Radiology* 1985;157:589–593.
132. Sorbi D, McGill DB, Thistle JL, Therneau TM, Henry J, Lindor KD. An assessment of the role of liver biopsies in asymptomatic patients with chronic liver test abnormalities. *Am J Gastroenterol* 2000;95:3206–3210.
133. Keeffe EB. Diagnostic approaches to mild elevation of liver enzyme levels. *Gastrointest Dis Today* 1994;3:1–9.
134. Younossi ZM. Evaluating asymptomatic patients with mildly elevated liver enzymes. *Cleve Clin J Med* 1998;65:150–158.
135. Moseley RH. Evaluation of abnormal liver chemistry tests. *Med Clin North Am* 1996;80:887–906.
136. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Engl J Med* 2000;342:1266–1271.

Address requests for reprints to: Gary R. Lichtenstein, M.D., Chair, Clinical Practice Committee, AGA National Office, c/o Membership Department, 7910 Woodmont Avenue, 7th Floor, Bethesda, Maryland 20814. Fax: (301) 654-5920.

The Clinical Practice Committee acknowledges the following individuals whose critiques of this review paper provided valuable guidance to the authors: William D. Carey, M.D., Richard H. Moseley, M.D., Karen Eun-Young Kim, M.D., and Giles Richard Locke III, M.D.