The manifestations of alcoholic cirrhosis are similar to those of other forms of cirrhosis. Laboratory findings reflect hepatic dysfunction, with elevated serum aminotransferases, hyperbilirubinemia, variable elevation of serum alkaline phosphatase, hypoproteinemia (globulins, albumin, and clotting factors), and anemia. In some instances, liver biopsy may be indicated, since in about 10% to 20% of cases of presumed alcoholic cirrhosis, another disease process is found. Finally, cirrhosis may be clinically silent, discovered only at autopsy or when stress such as infection or trauma tips the balance toward hepatic insufficiency.

The long-term outlook for alcoholics with liver disease is variable. Five-year survival approaches 90% in abstainers who are free of jaundice, ascites, or hematemesis; it drops to 50% to 60% in those who continue to imbibe. In the end-stage alcoholic the proximate causes of death are (1) hepatic coma, (2) massive gastrointestinal hemorrhage, (3) intercurrent infection (to which these patients are predisposed), (4) hepatorenal syndrome following a bout of alcoholic hepatitis, and (5) hepatocellular carcinoma (the risk of developing this tumor in alcoholic cirrhosis is 1% to 6% of cases annually).

KEY CONCEPTS

Alcoholic Liver Disease

- Alcoholic liver disease is a chronic disorder that can give rise to steatosis, alcoholic hepatitis, progressive steatofibrosis and marked derangement of vascular perfusion leading eventually to cirrhosis.
- Consumption of 80 gm/day of alcohol is considered to be the threshold for the development of alcoholic liver disease.
- It may take 10 to 15 years of drinking for the development of cirrhosis, which occurs only in a small proportion of chronic alcoholics.
- The multiple pathologic effects of alcohol include changes in lipid metabolism, decreased export of lipoproteins, and cell injury caused by reactive oxygen species and cytokines.

Metabolic Liver Disease

A distinct group of liver diseases is attributable to disorders of metabolism, either acquired or inherited. The most common acquired metabolic disorder is non-alcoholic fatty liver disease. Among inherited metabolic diseases, hemochromatosis, Wilson disease, and α_1-antitrypsin deficiency are most prominent. Also included among liver metabolic diseases is neonatal hepatitis, a broad disease category encompassing rare inherited diseases and neonatal infections.

Nonalcoholic Fatty Liver Disease (NAFLD)

NAFLD represents a spectrum of disorders that have in common the presence of hepatic steatosis (fatty liver) in individuals who do not consume alcohol or do so in very small quantities (less than 20 g of ethanol/week). NAFLD has become the most common cause of chronic liver disease in the United States and in its various forms probably affects 3 to 5% of the population. However, these estimates are approximate, because fatty liver without other complications may not be detected clinically. The term "nonalcoholic steatohepatitis" (or its common acronym *NASH*) is often used to denote overt clinical features of liver injury, such as elevated serum transaminases, but the designation NAFLD is preferred, with *steatohepatitis* reserved for histologic features of hepatocyte injury already described in the section on alcoholic liver disease.

Table 18-6 World Health Organization Criteria for the Metabolic Syndrome

One of	Diabetes mellitus *or* impaired glucose tolerance *or* impaired fasting glucose *or* insulin resistance
and two of:	Blood pressure: ≥ 140/90 mm Hg Dyslipidemia: triglycerides (TG): ≥ 1.695 mmol/L and high-density lipoprotein cholesterol (HDL-C) ≤ 0.9 mmol/L (male), ≤ 1 mmol/L (female) Central obesity: waist-hip ratio > 0.90 (male); > 0.85 (female), or body mass index > 30 kg/m^2 Microalbuminuria: urinary albumin excretion rate of ≥ 20 μg/min or albumin-to-creatinine ratio ≥ 30 mg/gm

The histologic hallmarks of NAFLD are most consistently associated with the *metabolic syndrome* (Table 18-6). The epidemic of obesity in the United States and, and its overall, dramatic global increase, has resulted in increasing rates of NAFLD. Prevalence in children has also registered a steady rise. NAFLD contributes to the progression of other liver diseases such as HCV and HBV infection. Increasingly, NAFLD is found to increase the risk for hepatocellular carcinoma, although, unlike in chronic viral hepatitis and alcoholic liver disease, it may often do so in the absence of significant scarring.

The prevalence of NAFLD varies among ethnic groups and probably relates, at least in part, to genetic differences. For example, in the United States, Hispanics have the highest prevalence of NAFLD/NASH, followed by African Americans and Caucasians.

Pathogenesis. Currently available data suggests a two hit model for NAFLD.

- Insulin resistance gives rise to hepatic steatosis.
- Hepatocellular oxidative injury resulting in liver cell necrosis and the inflammatory reactions to it.

The interplay of these two factors is discussed below.

Hepatic steatosis, like obesity in general, arises from an overabundance of calorie rich food, diminished exercise, and genetic/epigenetic mechanisms. Data indicate that individuals with NAFLD eat more fast food and exercise less. High fructose corn syrup, a nearly ubiquitous, inexpensive sweetener in manufactured foods, also appears to promote insulin resistance.

In individuals with established insulin resistance and metabolic syndrome, the visceral adipose tissue not only increases, but also becomes dysfunctional, with reduced production of the lipid hormone,adiponectin, and increased