TABLE 364-1 ALTERNATIVE CAUSES OF HEPATIC STEATOSIS

- Alcoholic liver disease
- Hepatitis C (particularly genotype 3)
- Inborn errors of metabolism
  - Abetalipoproteinemia
  - Cholesterol ester storage disease
  - Galactosemia
  - Glycogen storage disease
  - Hereditary fructose intolerance
  - Homocystinuria
  - Systemic carnitine deficiency
  - Tyrosinemia
  - Weber-Christian syndrome
  - Wilson's disease
  - Wolman's disease
- Medications (see **Table 364–2**)
- Miscellaneous
  - Industrial exposure to petrochemical
  - Inflammatory bowel disease
  - Lipodystrophy
  - Bacterial overgrowth
  - Starvation
  - Parenteral nutrition
- Surgical procedures
  - Bilopancreatic diversion
  - Extensive small-bowel resection
  - Gastric bypass
  - Jejunoileal bypass
- Reye's syndrome
- Acute fatty liver of pregnancy
- HELLP syndrome (*h*emolytic anemia, *e*levated *l*iver enzymes, *l*ow *p*latelet count)

factors for pediatric NAFLD. Thus, the rising incidence and prevalence of childhood obesity suggests that NAFLD is likely to become an even greater contributor to society's burden of liver disease in the future.

PATHOGENESIS

The mechanisms underlying the pathogenesis and progression of NAFLD are not entirely clear. The best-understood mechanisms pertain to hepatic steatosis. This is proven to result when hepatocyte mechanisms for triglyceride synthesis (e.g., lipid uptake and de novo lipogenesis) overwhelm mechanisms for triglyceride disposal (e.g., degradative metabolism and lipoprotein export), leading to accumulation of fat (i.e., triglyceride) within hepatocytes. Obesity stimulates hepatocyte triglyceride accumulation by altering the intestinal microbiota to enhance both energy harvest from dietary sources and intestinal permeability. Reduced intestinal barrier function increases hepatic exposure to gut-derived products, which stimulate liver cells to generate inflammatory mediators that inhibit insulin actions. Obese adipose depots also produce excessive soluble factors (adipokines) that inhibit tissue insulin sensitivity. Insulin resistance promotes hyperglycemia. This drives the pancreas to produce more insulin to maintain glucose homeostasis. However, hyperinsulinemia also promotes lipid uptake, fat synthesis, and fat storage. The net result is hepatic triglyceride accumulation (i.e., steatosis).

Triglyceride per se is not hepatotoxic. However, its precursors (e.g., fatty acids and diacylglycerols) and metabolic by-products (e.g., reactive oxygen species) may damage hepatocytes, leading to hepatocyte lipotoxicity. Lipotoxicity also triggers the generation of other factors (e.g., inflammatory cytokines, hormonal mediators) that deregulate systems that normally maintain hepatocyte viability. The net result is increased hepatocyte death. Dying hepatocytes, in turn, release various factors that trigger wound healing responses that aim to replace (regenerate) lost hepatocytes. Such repair involves transient expansion of other cell types, such as myofibroblasts and progenitor cells, that make and degrade matrix, remodel the vasculature, and generate replacement hepatocytes, as well as the recruitment of immune cells that release factors that modulate liver injury and repair. NASH is the morphologic manifestation of lipotoxicity and resultant wound healing responses. Because the severity and duration of lipotoxic liver injury dictate the intensity and duration of repair, the histologic features and outcomes of NASH are variable. Cirrhosis and liver cancer are potential outcomes of chronic NASH. Cirrhosis results from futile repair, i.e., progressive accumulation of wound healing cells, fibrous matrix, and abnormal vasculature (scarring), rather than efficient reconstruction/regeneration of healthy hepatic parenchyma. Primary liver cancers develop when malignantly transformed liver cells escape mechanisms that normally control regenerative growth. The mechanisms responsible for futile repair (cirrhosis) and liver carcinogenesis are not well understood. Because normal liver regeneration is a very complex process, there are multiple opportunities for deregulation and, thus, pathogenic heterogeneity. To date, this heterogeneity has confounded development of both diagnostic tests and treatments for defective/deregulated liver repair (i.e., cirrhosis and cancer). Hence, current strategies focus on circumventing misrepair by preventing and/or reducing lipotoxic liver injury.

DIAGNOSIS

Diagnosing NAFLD requires demonstration of increased liver fat in the absence of hazardous levels of alcohol consumption. Thresholds for potentially dangerous alcohol ingestion have been set at more than one drink per day in women and two drinks per day in men based on epidemiologic evidence that the prevalence of serum aminotransferase elevations increases when alcohol consumption habitually exceeds these levels. In those studies, one drink was defined as having 10 g of ethanol and, thus, is equivalent to one can of beer, 4 ounces of wine, or 1.5 ounces (one shot) of distilled spirits. Other causes of liver fat accumulation (particularly exposure to certain drugs; **Table 364-2**) and liver injury (e.g., viral hepatitis, autoimmune liver disease, iron or copper overload, α_1 antitrypsin deficiency) must also be excluded. Thus, establishing the diagnosis of NAFLD does not require invasive testing: it can be accomplished by history and physical examination, liver imaging (ultrasound is an acceptable first-line test; computed tomography [CT] or magnetic resonance imaging [MRI] enhances sensitivity for liver fat detection but adds expense), and blood tests to exclude other liver diseases. It is important to emphasize that the liver may not be enlarged, and serum aminotransferases and liver function tests (e.g., bilirubin, albumin, prothrombin time) may be completely normal, in individuals with NAFLD. Because there is yet no one specific blood test for NAFLD, confidence in the diagnosis of NAFLD is increased by identification of NAFLD risk factors. The latter include increased body mass index, insulin resistance/type 2 diabetes mellitus, and other parameters indicative of the metabolic syndrome (e.g., systemic hypertension, dyslipidemia, hyperuricemia/gout, cardiovascular disease; **Chap. 422**) in the patient or family members.

Establishing the severity of NAFLD-related liver injury and related scarring (i.e., staging NAFLD) is more difficult than simply diagnosing NAFLD. Staging is critically important, however, because it is necessary to define prognosis and thereby determine treatment recommendations. The goal of staging is to distinguish patients with NASH from those with simple steatosis and to identify which of the NASH patients have advanced fibrosis. The 10-year probability of developing liver-related morbidity or mortality in steatosis is negligible, and hence, this subgroup of NAFLD patients tends to be managed conservatively (see below). In contrast, more intensive follow-up and therapy are justified in NASH patients, and the subgroup with advanced fibrosis merits the most intensive scrutiny and intervention because their 10-year risk of liver-related morbidity and mortality is clearly increased.

Staging approaches can be separated into noninvasive testing (i.e., blood testing, physical examination, and imaging) and invasive approaches (i.e., liver biopsy). Blood test evidence of hepatic dysfunction (e.g., hyperbilirubinemia, hypoalbuminemia, prothrombin time