PROGNOSIS

Major controversy persists concerning the prognosis of NASH. Specifically, it is unknown whether information gathered from studying large numbers of patients with alcohol-induced liver disease (Table 3) can be used to predict the outcome of nonalcoholic patients with histologically similar liver disease. In this regard, it is instructive to recall that although even modest alcohol intake reliably leads to steatosis, cirrhosis is a relatively infrequent complication of alcohol abuse, occurring in only 15 to 20% of individuals who have consumed as much as 180 g ethanol/day for more than a decade. Bouts of alcoholic steatohepatitis are generally believed to increase the likelihood of eventual cirrhosis. However, several studies indicate that cirrhosis is not an inevitable sequella of alcoholic hepatitis, developing in only about one-half of the patients followed for 3 to 5 years after an index episode of alcoholic hepatitis.

Even after alcohol-induced cirrhosis is established, clinical prognosis is extremely variable (Table 4). Cirrhotic patients who are asymptomatic and who have normal serum bilirubin and albumin concentrations at the time of histologic diagnosis have a greater than 80% probability of surviving 5 years. By contrast, only 60% of cirrhotic patients who have developed jaundice, ascites, gastrointestinal bleeding, or hepatic encephalopathy survive 5 years, and their survival probability is reduced to about 30% if they continue to abuse alcohol. Liver-related deaths occur less often in alcoholics without cirrhosis but can occur in patients with “simple” steatosis or steatohepatitis. Thus, experience has shown that histologic progression and clinical outcome are highly variable in patients with alcohol-induced steatosis, steatohepatitis, or cirrhosis.

Given this information, it is curious that many are reluctant to believe that NASH may portend an ominous prognosis, particularly because many small series include a sizeable fraction of patients with histologically advanced disease (Table 5). Severe fibrosis has been noted in 15 to 50% patients, while well-established cirrhosis has been documented in 7 to 16% patients. Relatively few patients with NASH have been followed prospectively to delineate the natural history of the disease. The few follow-up studies that have been reported include small numbers of patients who had various stages of NASH at the time of initial diagnosis. Thus, patient heterogeneity, coupled with relatively short durations of follow-up evaluation, confound interpretation of these studies. Nonetheless, it is clear that at least some patients with NASH do develop progressive liver disease within a decade of diagnosis. What remains unclear is how often the disease evolves to a stage at which clinical sequelae are likely.

Anecdotal reports document the occurrence of liver-related morbidity and mortality in NASH. At least some patients with NASH are known to have developed jaundice, ascites, encephalopathy, gastrointestinal bleeding, or hepatocellular carcinoma. Some transplant centers have also performed liver transplantation for NASH patients with decompensated liver disease. There are even some recent reports that NASH may recur after transplantation, particularly in patients with intact je-junoileal bypasses. On the other hand, NASH appears to be a relatively infrequent indication for liver transplantation. Another argument that has been forwarded to discount the clinical importance of NASH is the apparent discrepancy between the prevalence of steatosis and that of life-threatening cryptogenic cirrhosis. For example, steatosis has been documented in many (at least 40%) of obese patients undergoing elective surgery to induce weight loss. Yet, autopsy series suggest that only about 2% of obese individuals become cirrhotic.

However, these same autopsy series also demonstrate that obesity is the only indentifiable cause of liver disease in 12% cirrhotic patients and that cirrhosis is about six times more prevalent in obese individuals than it is in the general population. The latter observations prompt speculation that steatosis is a risk factor for more progressive liver disease but requires the superimposition of other, ill-defined insults before cirrhosis can develop. This theory is consistent with evidence that both cirrhosis and liver-related mortality occur commonly after patients with obesity-related steatosis undergo jejunoileal bypass surgery.

Final resolution of existing controversies about the clinical implications of NASH will require large epidemiologic studies that track afflicted individuals for several decades. In addition, a better understanding of mechanisms involved in the pathogenesis of NASH should help identify cohorts with steatosis who are at particularly high risk of progressive disease.

TABLE 3. ALCOHOLIC LIVER DISEASE: NATURAL HISTORY

Steatosis
  Almost invariable
Steatohepatitis
  Incidence/prevalence unknown
  About 50% hospitalized patients progress to cirrhosis
  10% hospitalized patients revert to normal histology
Cirrhosis
  Develops in 15-20% patients after a decade or so
  Ultimate consequence of antecedent steatohepatitis

TABLE 4. ALCOHOLIC CIRRHOSIS: 5 YEAR SURVIVAL

Clinically compensated at diagnosis
  Abstinent:> 80%
  Drinking: About 60%
Clinically decompensated at diagnosis
  Abstinent: About 60%
  Drinking: About 30%

TABLE 5. REPORTED PREVALENCE OF HISTOLOGICALLY ADVANCED NASH

Condition	%
Severe Fibrosis	15-50
Cirrhosis	7-16

ETIOLOGY

Many different agents/conditions have been associated with NASH. These may be divided into two broad categories (1) drugs/toxins, and (2) metabolic abnormalities—acquired or congenital. Potential etiologies of NASH are listed in Tables 6 to 8. While it is evident that some or all or the histologic features of NASH have been documented in a wide variety of settings, most published series of NASH emphasize a predisposition for steatohepatitis in middle-aged women with obesity, non-insulin-dependent diabetes mellitus, and/or hyperlipidemia.

TABLE 6. DRUGS/TOXINS ASSOCIATED WITH STEATOSIS

Metals
  Antimony
  Barium salts

- Borates
- Carbon disulfide
- Chromates
- Phosphorus
- Rare earths of low atomic numbers
- Thallium compounds
- Uranium compounds

Cytotoxic/cytostatic drugs
- L-Asparaginase
- Azacytidine
- Azauridine
- Methotrexate

Antibiotics
- Azaserine
- Bleomycin
- Puromycin
- Tetracycline

Other Drugs
- Amiodarone
- Coumadin
- Dichloroethylene
- Ethionine
- Ethyl bromide
- Estrogens
- Flectol H
- Glucocorticoids
- Hydrazine
- Hypoglycin
- Orotate
- Perhexilene maleate
- Safrole

TABLE 7. INBORN ERRORS OF METABOLISM ASSOCIATED WITH STEATOSIS

Abetalipoproteinemia
Familial Hepatosteatosis
Galactosemia
Glycogen storage disease
Hereditary fructose intolerance
Homocystinuria
Systemic carnitine deficiency
Tyrosinemia
Resfum’s disease
Schwachman’s syndrome
Weber-Christian syndrome
Wilson’s Disease

TABLE 8. ACQUIRED METABOLIC DISORDERS ASSOCIATED WITH STEATOSIS

Diabetes mellitus
Inflammatory bowel disease
Jejuno-ileal bypass
Kwashiorkor and marasmus
Obesity
Serum lipid abnormalities
Starvation and cachexia
Severe anemia
Total parenteral nutrition

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Tomorrow we start with Pathogenesis…