Nonalcoholic Steatohepatitis

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Nonalcoholic steatohepatitis (NASH) is a liver disease that, until recently, has been under-recognized as a common cause of elevated liver enzymes. This distinct clinical entity is characterized by liver biopsy findings similar to those seen in alcoholic hepatitis but in the absence of alcohol consumption sufficient to cause such changes. Patients with NASH are often middle-aged and obese, with coexisting diabetes or hyperlipidemia, but NASH also occurs in younger lean, otherwise healthy individuals and even in children. Although NASH is generally a benign disorder, it may be progressive, leading to cirrhosis and complications

Nonalcoholic steatohepatitis (NASH) is a common but under-appreciated liver disease. The reasons for low-level awareness are the relatively recent coining of the term "NASH" in 1980, the requirement of a liver biopsy for definitive diagnosis, the relatively indolent nature of the disease in most patients, and the lack of a consensus regarding histological diagnosis and management. However, this is likely to change as NASH becomes recognized as a common liver disease that may affect otherwise lean, healthy patients and may result in cirrhosis, sometimes necessitating liver transplantation.

The term "NASH" was first used in 1980 by Ludwig et al at the Mayo Clinic in describing 20 nonalcoholic patients with liver biopsy changes compatible with alcoholic hepatitis. NASH is part of the spectrum of nonalcoholic fatty liver disease that ranges from simple fatty liver to cirrhosis. It is characterized by fatty change with lobular inflammation, hepatocellular injury, and Mallory hyalin, with or without fibrosis, in the absence of excessive alcohol consumption. In contrast, simple fatty liver is characterized histologically by hepatic steatosis without inflammation, ballooning degeneration, necrosis, fibrosis, or cirrhosis.

EPIDEMIOLOGY AND ASSOCIATIONS

The true prevalence of NASH is unknown because of the inherent selection bias in patients scheduled for liver biopsy. NASH has been reported in 1% to 9% of patients undergoing liver biopsy.[2] A Wanless and Lentz[5] reported the autopsy prevalence of NASH in 22 (6%) of 351 apparently nonalcoholic patients. The prevalence ranged from 2.7% of those who were not overweight to 18.5% of those who were greater than 40% above their ideal body weight. NASH has been described most frequently in obese females who are diabetic or hyperlipidemic (Table 1); however, it has also been described in male patients who are non-obese, non-diabetic, and normolipidemic.[10] Bacon et al[10] reported a higher occurrence of NASH in males than previously recognized. NASH also occurs in children.

The single most consistent association with NASH is obesity, with a reported prevalence of 40% to l00%. Most patients with NASH are either overweight (body mass index [BMI] >25 kg/m^2) or obese (BMI > 30 kg/m^2). A high degree of correlation between severity of hepatic steatosis and fibrosis and total fat mass, as estimated by the BMI, has been reported,[13] and weight loss has been shown to result in biochemical and histological improvement in patients with NASH. 14 Some observers have demonstrated a relationship between fatty liver and the regional body distribution of adipose tissue. Kral et a1[15] showed that the abdominal distribution of fat, which is reflected by an elevated waist-hip ratio, is a predictor of hepatic steatosis, an effect independent of body weight or total body fat. Type 2 diabetes mellitus and glucose intolerance have been reported in 21% to 75% of patients with NASH.[15-'0] Hyperlipidemia is also a common association, with a reported prevalence of 21% to 83%. The role of diabetes and hyperlipidemia in the pathogenesis of NASH is still unclear, although the presence of diabetes has been found to correlate with the degree of fibrosis. [13]

Table 1. Selected Major Series of Patients With Nonalcoholic Steatohepatitis*

Reference	No. of patients	Females (%)	Obesity (%)	Diabetes mellitus (%)	Hyper lipidemia (%)
Ludwig et al	**20**	**65**	**90**	50	67
Itoh et al	16	75	100	5	63
Diehl et al[7]	39	81	71	55	20
Lees.	49	78	95	51	NR

Powell et al[9]	42	83	95	36	81
Bacon et al[10]	33	42	39	21	21
Laurin et al[1]	40	73	70	28	NR
Pinto et al[12]	32	75	47	34	28

***There is wide variability among these studies regarding definitions used (especially for obesity and diabetes), population sampled, etc, and this greatly limits comparability among studies. NR = not reported.**

NASH IN CHILDREN

Neither NASH nor obesity is solely an adult disorder. Baldridge et al[16] reported NASH in 14 of 32 children with hepatic steatosis, all of whom were obese, and 10 had bridging fibrosis. Among 299 obese children, Kinugasa et a1[17] noted that 12% had elevated aminotransferase levels, and NASH was diagnosed in 73% of those who underwent liver biopsy. In a recent series of 36 children with NASH, fibrosis was noted in 71% of those who underwent liver biopsy, and 1 had established cirrhosis at diagnosis; 83% were obese, and 18 of 20 patients studied had hyperlipidemia.[18] Thus, NASH may not be rare in children, especially in obese children, and severe fibrosis may be found at any early age. Therefore, NASH should be considered in obese children with elevated aminotransferase levels.

The elevated serum aminotransferase levels in such children have been demonstrated to decrease or normalize with weight [1055.14,18] Whether weight loss also results in improvement in liver histology is unknown. The effect maturation has on NASH in children is also unknown. Substantial improvement in aminotransferase levels has been noted with consumption of vitamin E, an antioxidant, in children with NASH.[19] Long-term follow-up observations on the efficacy of vitamin E are awaited. As in adults, the pathogenesis of NASH in children is still unclear. However, the common epidemiological associations among adult and pediatric patients with NASH suggest similar pathogenic mechanisms.

PATHOLOGY

Liver histology in NASH is characterized by fatty change and hepatocyte injury (inflammation, Mallory hyalin, or necrosis) with or without fibrosis (Table 2). The spectrum of histological changes varies from mild steatohepatitis to bridging fibrosis and cirrhosis. Hepatic steatosis in NASH is macrovesicular and primarily centrilobular (zone 3), although it may be diffuse in severe forms of the disease. Inflammation, which must be present for the diagnosis of NASH, is usually low grade, lobular, and mixed neutrophilic and mononuclear. Of note is the absence of severe portal or periportal inflammation, and the presence of severe portal inflammation suggests an alternative diagnosis. Mallory hyalin, if present, is usually less prominent than that in alcoholic hepatitis. Fibrosis, which is initially perisinusoidal (pericellular), may progress to cirrhosis. The reported prevalence of fibrosis in NASH on the initial biopsy specimen ranges from 15% to 100%, with cirrhosis noted in up to 15% of specimens.[2,9] Compared to hepatic histological findings in alcoholic hepatitis, the steatosis in NASH is more often severe, and glycogenation of nuclei is more prominent.[6,7] A difficult problem in interpreting liver histological findings in suspected NASH is variation of the criteria used by pathologists for the diagnosis.

Table 2.
Histological Features of
Nonalcoholic Steatohepatitis

Macrovesicular steatosis
- Mild to severe, primarily in zone 3; in severe cases, zones 2 and 1

Inflammation
- Usually mild, lobular, mixed neutrophilic and mononuclear; no severe portal or periportal inflammation

Hepatocyte degeneration
- Mallory hyalin-less prominent than in alcoholic hepatitis; acidophilic (Councilman) bodies

Fibrosis
- Initially pericellular; cirrhosis in 10% to 15% on initial biopsy

PATHOGENESIS

The pathogenesis of NASH is poorly defined. The factor responsible for the transition of a liver with excess triglyceride levels (i.e., fatty liver) to one with an ongoing inflammatory process (i.e., NASH) is unclear. The major hypotheses center around the roles of oxidative stress, lipid peroxidation, and cytokine release.

Investigators have proposed that the development of steatohepatitis from simple steatosis requires a second process that tends to overcome the normal cellular defenses by increasing the normal mild level of oxidative stress that is constitutively present.[20] Potential sources of increased oxidative stress include increased expression of the cytochrome P-450 (CYP) 2E1, which generates superoxide, hydroxyl, and hydroxyethyl radicals, and peroxisomal β-oxidation of free fatty acids, which generates hydrogen peroxide. In hepatic steatosis, excess triglyceride levels may be present as substrate for peroxidation. Hepatic lipid peroxidation may lead to formation of cytotoxic intermediates, which may cause cellular injury directly or by initiating an inflammatory response. Free fatty acids, which are thought to be a key initiating factor in NASH pathogenesis, can induce cytochrome P-450 2E1, an outcome resulting in increased generation of reactive oxygen species and lipid peroxidation leading to damage to biological membranes. These hypothesized, important intracellular disturbances may result in propagation of inflammation and cell injury.

Interindividual differences in the severity of NASH might be explained by the magnitude of the oxidative stress or may be determined genetically (such as having a more readily inducible form of CYP 2E1) or by environmental factors such as dietary intake of antioxidants or exposure to pro-oxidant stresses.

In alcohol-induced liver disease, CYP 2E 1 seems to have an important role in the generation of free radicals, resulting in lipid peroxidation and hepatocyte damage.[21] Increased hepatic CYP 2E1 is the first potential pathophysiologic defect to be demonstrated in humans with NASH.[22] Increased CYP 2E1 in NASH has been demonstrated by immunostaining, and the distribution corresponded to that of steatosis, with extension into zones 2 and 1 in severe cases. The increased CYP 2E1 noted was independent of associated obesity, diabetes, or hyperlipidemia. Therefore, there is increasing evidence that CYP 2E1 has an important role in the pathogenesis of NASH in humans.

As in alcoholic steatohepatitis, endotoxins and certain endotoxin-inducible cytokines, such as tumor necrosis factor Q, are also thought to have a role in NASH.[23] This is supported by the fact that patients undergoing jejunoileal bypass surgery, which is likely to increase portal endotoxemia, are more prone to developing steatohepatitis. By
facilitating neutrophil chemotaxis, these cytokines promote an inflammatory response that results in cellular degeneration and progression of NASH. Animal models have shown that obesity increases sensitivity to endotoxinmediated liver damage 24

Insulin resistance and hyperinsulinemia have been shown to be associated with nonalcoholic fatty liver disease.[25] A recent study found that insulin resistance and hyperinsulinemia are associated with fatty liver, regardless of BMI or fat distribution, suggesting that insulin resistance may be the primary phenomenon, with obesity and splanchnic fat distribution being the effects of insulin resistance rather than being directly involved in the pathogenesis of hepatic steatosis.[25] Additionally, investigators have shown that postprandial serum insulin levels are higher in patients with NASH.[26] Resistance to peripheral action of insulin (characteristic of type 2 diabetes) facilitates lipolysis, resulting in increased production of free fatty acids. These free fatty acids, apart from serving as substrates for triglyceride synthesis and thus leading to steatosis, may directly increase cellular oxidative stress via peroxisomal ~-oxidation of free fatty acids and increasing expression of CYP 2E1.

ROLE OF HEPATIC IRON

The role of hepatic iron in the progression of NASH remains controversial, but in some patients, iron may have a role in the pathogenesis of NASH by promoting oxidative stress. Iron is a potent catalyst of oxidative stress and may act synergistically with other promoters of lipid peroxidation by catalyzing these reactions. Thon overload can also directly cause lipid peroxidation, and one of the subsequent products, malondialdehyde, has been shown to activate hepatic stellate cells in vitro, the maj6r source of fibrogenesis in liver injury.[27] George et al[28] reported a higher prevalence of the Cys282Tyr mutation of the *HEE* gene in patients with NASH, although there was no difference in the frequency of the His63Asp mutation. The presence of the Cys282Tyr mutation was associated with increased hepatic iron staining and hepatic iron concentration, and the increased hepatic iron correlated with the severity of fibrosis. Bonkovsky et al[29] also reported a significantly higher prevalence of heterozygosity for either mutation in patients with NASH.

The effect of heterozygosity for the HFE gene on hepatic fibrosis is not specific for NASH, and its importance is still uncertain. Patients with chronic hepatitis C virus who are heterozygous for the HFE gene have more fibrosis on biopsy specimens, an effect independent of hepatitis C virus RNA levels or degree of inflammation.[30] In a recent series, Younossi et al found no significant iron accumulation in patients. with nonalcoholic fatty liver and no association between hepatic iron and aggressive histological or clinical outcome. Additionally, another recent report[3] found no association between increased transferrin saturation and degree of fibrosis in NASH.

SYMPTOMS, SIGNS, AND LABORATORY STUDIES

Most patients with NASH are asymptomatic, although some may have fatigue, malaise, or right upper quadrant discomfort. Often the only clinical sign is hepatomegaly, which may not be present in all patients. Few patients have cutaneous signs of chronic liver disease, but the presence of ascites, splenomegaly, spider angiomas, and palmar erythema suggests underlying cirrhosis with portal hypertension.

Laboratory studies for NASH are non-diagnostic but essential for excluding other potential causes of liver disease. There are no reliable distinguishing laboratory features of NASH vs simple fatty liver or NASH vs alcoholic steatohepatitis. Generally, modest elevations of aminotransferase levels are noted (in the 2- to 3-fold range), and unlike alcoholic hepatitis, elevation of alanine ami-

notransferase (ALT) levels may exceed that of aspartate aminotransferase (AST) levels. Of note, a recent study identified an AST/ALT ratio greater than 1 as an independent predictor of liver fibrosis in patients with NASH.[13] However, some patients with NASH may have normal aminotransferase levels. Less than one half of patients have an elevated alkaline phosphatase level, which is almost always modest, and only 10% to 15% have elevated serum conjugated bilirubin levels. The serum albumin level and prothrombin time are typically normal in the absence of cirrhosis.

EVALUATION OF A PATIENT WITH SUSPECTED NASH

As with other liver diseases, the diagnostic evaluation of suspected NASH begins with a history and physical examination of the patient, with attention to factors like alcohol consumption, medications, and concurrent systemic disorders. NASH can be diagnosed only after excessive alcohol consumption has been excluded, although the threshold for defining excessive alcohol consumption is uncertain.

As previously mentioned, the laboratory features of NASH are non-diagnostic. A reasonable evaluation to exclude other potentially treatable causes of liver disease must be performed and may include serologic testing for hepatitis C and B, serum iron studies, testing for presence of antinuclear antibodies as well as anti-smooth muscle and anti-mitochondrial antibodies, and determination of serum ceruloplasmin and α_1-antitrypsin levels. If drug-induced liver injury is suspected, a trial of drug withdrawal may be warranted.

If the alkaline phosphatase level is elevated (which is not typical in NASH), imaging of the liver and biliary tree should be performed to rule out biliary obstruction. Imaging modalities such as ultrasonography, computed tomography, or magnetic resonance imaging may suggest the presence of hepatic steatosis but do not reliably distinguish between simple fatty liver and NASH. Ultrasonography generally shows a diffusely echogenic liver. When imaging modalities suggest steatosis in the presence of elevated aminotransferase levels with no other known causes of fatty liver, liver biopsy may be indicated to confirm the diagnosis. Liver biopsy remains the gold standard for diagnosing NASH, - and the diagnosis is suggested by typical pathologic findings. However, because of the generally indolent nature of the disease and the lack of proven treatment, many clinicians do not recommend liver biopsy.

CLINICAL COURSE AND NATURAL HISTORY

Although simple fatty liver is probably not progressive, patients with NASH can develop progressive fibrosis. Prospective studies of the natural history of NASH are lacking. The major series reporting follow-up with liver histological studies have each been retrospective, with a total of only 28 patients undergoing serial liver biopsies over a 1- to 7-year period.[8-10] Among these 28 patients, 1 experienced improvement, no change was evident in 15, and 12 (43%) had histological progression, 4 of whom developed cirrhosis. Therefore, the available data suggest that, although NASH generally has an indolent clinical course, a substantial proportion of patients may develop progressive fibrosis that leads to cirrhosis and subsequent complications from portal hypertension.[8-10] As yet, no clinical, laboratory, or histological findings have been noted that might identify the subset of patients at risk of progression, except perhaps for those with fibrosis on the initial biopsy specimen. In a recent series, older age, obesity, diabetes mellitus, and an AST/ALT ratio greater than 1 were found to be independent predictors of liver fibrosis in NASH.[13] This may help identify the subset of patients at risk of progression, and thus more aggressive therapy can be attempted. An increased risk of fibrosis has been reported in Patients with NASH who have mildly increased hepatic iron stores.[28]

Some evidence shows that NASH may evolve into inactive non-fatty cirrhosis after several years, and this condition may have been termed "cryptogenic" if an index biopsy had not been performed. In a recent series, many patients with cryptogenic cirrhosis had characteristics similar to those in patients with NASH.[32] Thus, NASH is probably an under-recognized cause of cirrhosis. The absence of steatosis and inflammation as NASH progresses has been observed sporadically and needs further study.

The incidence of hepatocellular carcinoma in NASH is completely unknown, although sporadic cases have been reported.

TREATMENT

Currently, no available therapy is known to alter the course of NASH. A single treatment option may be infeasible because of the probable multiple mechanisms involved and perhaps different predominant mechanisms in various patients (such as lean vs obese patients). If NASH- is diagnosed, the degree of fibrosis present, if any, could be of importance in tailoring the aggressiveness of therapy. Because no absolute correlation exists between serum test

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As most patients with NASH are obese, weight loss is commonly recommended, although weight reduction has not been studied systematically and prospectively. Modest gradual, sustained weight loss has been shown to result in improvement of serum aminotransferase levels and in liver histology. **14.33**

Since many of the presumed pathophysiologic mechanisms involved in alcoholic and nonalcoholic steatohepatitis are similar, a reasonable strategy may be to restrict all alcohol intake in patients with NASH, especially in those with fibrosis on a biopsy specimen. However, the effect of small amounts of alcohol intake on the progression of NASH~ remains unknown.

When diabetes coexists with NASH, treatment of the diabetes is a standard recommendation, although no evidence shows that control of diabetes affects the activity or progression of NASH. Nonetheless, good glycemic control in such patients seems reasonable.

Similar to treatment of diabetes, therapy for any hyperlipidemia present in NASH has not been shown to decrease disease activity, but this approach seems to be reasonable. In a pilot study, no significant clinical, biochemical, or histological improvement was noted after 1 year of therapy with clofibrate.[11] However, preliminary results suggest possible benefit with gemfibrozil; significant improvement in mean ALT and AST levels was noted after 4 weeks of therapy with gemfibrozil. There have been no reported clinical trials of use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in patients with NASH.

In a pilot study of ursodeoxycholic acid (UDCA) in the treatment of NASH, significant improvement in levels of ALT, alkaline phosphatase, and γ-glutamyl transpeptidase and grade of hepatic steatosis was noted in most patients after 1 year of therapy, suggesting a possible role for UDCA in the treatment of NASH." However, there was no significant change in the histological grade of inflammation or fibrosis. Although the precise mechanism of action of UDCA is unclear, its cytoprotective action is thought to have a role. Randomized controlled trials are under way to confirm the possible beneficial effect of UDCA in NASH.

Because an increase in hepatic iron has been found to correlate with severity of fibrosis,[28] phlebotomy to remove excess iron may potentially have a beneficial effect in preventing the progression of fibrosis. Desai and Chiorean[35] reported significant improvement in mean ALT levels after phlebotomy in 8 patients, all of who had 1+ or lower iron staining on biopsy. However, the effect of phlebotomy on liver histology in NASH must be evaluated further.

NASH AND LIVER TRANSPLANTATION

Cirrhosis due to NASH may eventuate in liver transplantation. Orthotopic liver transplantation (OLT) is an alternative for patients with end-stage liver disease due to cirrhosis and complications of portal hypertension. However, NASH can recur after OLT, especially in patients who had previously undergone jejunoileal bypass surgery.[3~] Kim et al[37] reported recurrent steatosis in 6 of 8 patients who underwent transplantation because of NASH, 3 of whom had evidence of recurrent NASH. In 5 of the 6 patients, fatty infiltration occurred within 4 months of OLT. Another report found that, of 5 patients with NASH who underwent transplantation not associated with gastrointestinal bypass surgery, NASH recurred in 2 patients at 4 and 6 weeks post-transplantation. One of these patients required re-transplantation, and NASH recurred again at 3 weeks.[38] These cases support the concept that a systemic derangement of fat metabolism that is not "cured" by liver transplantation is responsible for NASH.

CONCLUSION

NASH is a metabolic disease that is probably caused by multifaceted disturbances of hepatic lipid homeostasis, the prevalence of which is higher than previously thought. It should be considered in the differential diagnosis of asymptomatic patients with persistently elevated liver enzymes, particularly in the presence of other risk factors (obesity, diabetes, hyperlipidemia). However, it should also be considered in lean, otherwise healthy patients with elevated aminotransferase levels. Liver biopsy is essential to confirm the diagnosis of NASH, and findings vary from mild steatohepatitis to severe fibrosis and cirrhosis. The course of NASH is highly variable but is probably underestimated as a cause of cirrhosis. Although no proven therapy exists,

gradual sustained weight loss and UDCA may have a beneficial effect. NASH may recur after liver transplantation if the underlying pathophysiologic disturbances are not addressed.

REFERENCES

1. Ludwig 3, Viggiano TR, McGill DB, Ott BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc. 1980;55:434A38.*
2. Sheth SG, Gordon FD, Chopra S. Nonalcoholic steatohepatitis [published erratum appears in *Ann Intern Med.* 1997;127:658]. *Ann Intern Med.* l997;l26:137-145.
3. Nasrallah SM, Wills CE Jr, Galambos JT. Hepatic morphology in obesity. *Dig Dis Sci.* l981;26:325-327.
4. Andersen T, Gluud C. Liver morphology in morbid obesity: a literature study. *IntJ Obes.* 1984;8:97-106.
5. Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology.* 1990;12:1106-lll0.
6. Itoh S, Yougel T, Kawagoc K. Comparison between nonalcoholic steatohepatitis& and alcoholic hepatitis. *An' J Gastroenterol.* 1987, 82:650-654.
7. Diehi AM, Goodmati Z, Ishak KG. Alcohol like liver disease in nonalcoholics: a clinical and histologic comparison with alcohol-induced liver injury. *Gastroenterology.* l988;95:1056-1062.
8. Lee RO. Nonalcoholic steatohepatitis: a study of 49 patients. *Hum Pathol.* 1989;20:594-598.
9. Powell EE, Cooksley WO, Hanson R, Searie 3, Halliday - *JW,* Powell LW. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. *Hepatology.* 1990; 11:74-80.
10. Bacon BR, Farahvash MJ, Janney CG, Neuschwander-Tetti BA. Nonalcoholic steatohepatitis: an expanded clinical entity. *Gastro-enterology.* 1994; 107:1103-1109.
11. Laurin 3, Lindor KD, Crippin 35, Ct al. Ursoileoxycholic acid or dofibrate in the treatment of non-alcohol-induced steatohepatitis: a pilot study. *Hepatology.* 1996;23: 1464-1467.
12. Pinto HC, Baptists A, Camilo MB, 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.
13. Angulo P, Keach 3C, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology.* 1999;30:1356-l362.
14. Vajro P, Fontanella A, Perna C, Orso G, Tedesco M,- Dc Vincenzo A. Persistent hyperarninotransferaseniia resolving after weight re-duction in obese children. *Jpediatr.* 1994;125:239-241.
15. Kral JG, Schaffner F, Pierson RN Jr, Wang 3. Body fat topography as an independent predictor of fatty liver. *Metabolism.* 1993;42: 548-551.
16. Baldridge AD, Perez-Atayde AR, Graeme-Cook F, Higgins L, Lavine JE. Idiopathic steatohepatitis in childhood: a multicenter retrospective study. J *Pediatr.* 1995; 127:700-704.
17. Kinugasa A, Tsunamoto K, Furukawa N, Sawada T, Kusunolci T, Shimada N. Fatty liver and its fibrous changes found in simple obesity Of children. *JPediatr GastroenterolNutr.* 1984;3:408-414.
18. Rashid M, Robents BA. Nonalcoholic steatohepatitis in children. J *Fediatr Gastroenterol Wutr.* 2000;30:48-53;
19. Levine JE. Treatment of obesity-induced steatohepatitis with vitamin B [abstract]. *Gastroenterology.* 1998; 1 14:A1284-A1285. Abstract 1,0356.
20. Day CP, James OFW. Steatohepatitis: a tale of two "hits"? [editorial]. *Gastroenterology.* 1998;l 14:842-845.
21. Albano E, Clot P, Morimoto M, Tomasi A, Ingelman-Sundberg M, French SW. Role of cytochrome P4502B 1-dependent formation of hydroxyethyl free radical in the development of liver damage in rats intragastrically fed with ethanol. *Hepatology.* 1996;23:155-163.
22. Weltman MD, Farrell GC, Hall P, lngelman-Sundberg M, Liddle C. Hepatic cytochrome P450 2E1 is increased in patients with nonalcoholic steatohepatitis. *Hepatology.* 1998;27: 128-133.
23. McClain C, Hill D, Sclsrnidt 3, Diehl AM. Cytokines and alcoholic liver disease. *Semin Liver Dis.* 1993; 13:170482.
24. Yang SQ, Lin HZ, Lane MD, Clemens M, Diehl AM. Obesity increases sensitivity to endotoxin liver injury: implications for the pathogenesis of steatohepatitis. *Proc Nati Acad Sci U S A.* 1997; 94:2557-2562.
25. Marchesini G, Bnzi M, Morselli-Labate AM, Ct al. Association of nonalcoholic fatty liver disease with insulin resistance. *Am J Med.* 1999;107:450-455.
26. Tankurt B, Biberoglu S, Bliidokuz B, Ct al. Hyperinsulinemia and insulin resistance in non-alcoholic steatohepatitis [letter]. J *Hepatol.* 1999;31:963.
27. Lee KS, Buck M, Houglum K, Chojkier M. Activation of hepatic stellate cells by TGFa and collagen type l is mediated by oxidative stress through *c-myb* expression. J Clin *Invest.* 1995;96:2461-2468.
28. George DK, Goldwurm S, MacDonald GA, Ct al. Increased hepatic iron concentration in nonalcoholic steatohepatitis is associated with increased fibrosis. *Gasnoenterology.* 1998; 114:311-318.
29. Bonkovsky HL, Jawaid Q' Tortorelli K, et al. Non-alcoholic steatohepatitis and iron: increased prevalence of mutations of the HFB gene in non alcoholic steatohepatitis. J *Hepatol.* l999;31: 421429. al. Heterozygosity for hereditary
30. Smith BC, Gorve J, Guzall MA, Ct hemochromatosis is associated with more fibrosis in chronic hepatitis C. *Hepatology.* 1998;27: 1695-1699.
31. Younossi ZM, Gramlich T, Bacon BR, Ct al. Hepatic iron and nonalcoholic fatty liver disease. *Hepatology.* 1999;30:847-850.
32. Oelsner DH, CaIdwell SH, Hespenheide EB, Driscoll CJ. Cryptogenic cirrhosis: a disease largely of mild to moderately obese, mildly diabetic older females [abstract]. *Hepatology.* [199]7;26(program issue):357A. Abstract 914.
33. Briksson S, Briksson KF, Bondesson L. Nonalcoholic steatohepatitis in obesity: a reversible condition. *Acta Med Scand.* 1986,220: 83-88.
34. Basaranoglu M, Sonsuz A, Bilir M, et al. A controlled trial of gemfibrozil in the treatment of nonalcoholic steatohepatitis [abstract]. *Hepatology.* 1998;28(suppl):166A. Abstract 15.
35. Desal TK, Chiorean M. Phlebotomy reduces transaminase levels in patients with chronic non-alcoholic steatohepatitis [abstract]. Gas-*troenrerology.* 1998;l 14:A1233. Abstract Lo141. -

36. Requarth JA, Burchard KW, Colacchio TA, et al. Long-term morbidity following jejunoileal bypass: the continuing potential need for surgical reversal. *Arch Surg.* 1995;130:318-325.
37. Kim WR, Poterucha J3, Porayko MK, Dickson BR, Steers JL, Wiesner RH. Recurrence of nonalcoholic steatohepatitis following liver transplantation. *Danspiantation.* 1996;62: 1802-1805.
38. Weston S, Charlton MR, Lindor KD. Liver transplantation for nonalcoholic steatohepatitis [abstract]. *Gasfroenterology.* 1998; 114:A1364. Abstract L0681.

Questions About NASH

1. Which one of the following is not a typical histological finding in NASH?

   a. Mallory hyalin
   b. Macrovesicular steatosis
   c. Lobular inflammation
   d. Severe portal or periportal inflammation
   e. Pericellular fibrosis

2. Which one of the following statements best describes the natural history of NASH?

   a. NASH is a benign disorder and is not progressive
   b. NASH is progressive only in obese patients
   c. Patients with NASH can develop progressive fibrosis, resulting in cirrhosis in some patients
   d. NASH in children has a benign prognosis
   e. Laboratory studies can accurately identify patients at risk of progression

3. Which one of the following statements regarding the diagnosis of NASH is true?

   a. Laboratory studies are diagnostic
   b. Imaging studies can accurately diagnose NASH
   c. Liver biopsy is the only means of accurately diagnosing NASH
   d. The most common laboratory abnormality is elevation of the alkaline phosphatase level
   e. Elevation of the ALT level never exceeds that of AST

4. Which *one* of the following statements concerning the treatment of NASH is *correct*?

   a. Strict control of associated diabetes can arrest the progression of NASH
   b. Weight l6ss has been shown to result in improvement in aminotransferase levels
   c. Hypolipidemic agents have been shown to improve liver histology in NASH
   d. UDCA has been shown to reverse fibrosis
   e. Liver transplantation cures the metabolic disturbances that cause NASH

5. Which one of the following statements regarding the pathogenesis of NASH is true?

   a. Hepatic iron has no role in the progression of NASH
   b. Decreased CYP 2E1 is among the first pathophysiologic defects demonstrated in humans with NASH
   c. Endotoxins and endotoxin-inducible cytokines may have a role in NASH
   d. Antioxidants have a proven therapeutic role in NASH
   e. Insulin sensitivity has been shown to be associated with NASH

Correct answers:
l.d, 2.c, 3.c, 4.b, 5.c