PATHOGENESIS

Given the varied nature of the conditions that have been associated with NASH, it is not surprising that no common mechanism has been identified yet that can explain the pathogenesis of this condition. This has prompted speculation that NASH may be the end result of several diverse insults, i.e., that its pathogenesis is multifactorial. Several mechanisms have been proposed as causes of NASH, including amino acid imbalance, hyperglycemia (from excess glucose administration or diabetes mellitus), imbalanced anti-ketogenic (anabolic) and ketogenic (catabolic) hormones in portal blood, and endotoxemis (from sepsis or starvation-associated bacterial translocation).

Clearly, each of these processes can shift metabolism to favor net lipogenesis, rather than lipolysis, and they are not mutually exclusive. Although some evidence supports a role for one or more of these mechanisms in steatosis associated with starvation, diabetes, total parenteral nutrition, and jejunoileal bypass surgery, the possibility that some (or all) of them may be sequelae, rather than causes, of NASH has not been excluded. Furthermore, as hepatitis and cirrhosis occur much less often than steatosis, it is conceivable either that only a few causes of steatosis can provoke histologic progression to cirrhosis or that additional insults are necessary to produce this outcome.

If the latter is true, lessons learned from work in alcohol-induced liver disease may be useful to clarify the mechanisms that drive disease progression in NASH. Several lines of evidence suggest that similar mechanisms may be involved in the pathogenesis of alcoholic liver disease and NASH (Table 9). For example, chronic alcohol abuse is known to induce certain microsomal enzymes, such as cytochrome P-450 2E1 (Cyp2E1). Cyp2E1 induction is believed to be important in the pathogenesis of alcoholic liver disease because this enzyme metabolizes ethanol and other substrates to reactive metabolites, which can injure cell membranes and promote hepatocyte death. Of interest, certain fatty acids and ketones are endogenous Cyp2E1 substrates. Hence, it has long been suspected that Cyp2E1 may contribute to the pathogenesis of NASH. This theory is supported by recent evidence that Cyp2E1 expression is increased in rats that develop hepatic steatosis because of choline deficiency, as well as in some patients with NASH.

ROLE OF CYTOKINES

Endotoxin and endotoxin-inducible cytokines, including tumor necrosis factor α (TNFa) and certain TNF-inducible cytokines, such as interleukins-6 and –8 (IL-6, -8), have also been incriminated in the pathogenesis of alcohol-induced steatohepatitis and cirrhosis. Several lines of evidence suggest that these cytokines may also be involved in the progression of liver disease in some patients with NASH. For example, steatohepatitis and cirrhosis occur commonly in patients with obesity-related steatosis who undergo jejunoileal (J-1) bypass surgery, a procedure that is likely to increase portal endotoxemia and stimulate hepatic production of TNFa. TNFa can induce hepatic synthesis of other cytokines, including IL-8, which elicits neutrophil chemotaxis, and, thus, may promote an inflammatory response that results in peroxidative damage to lipid membranes and eventually causes hepatocyte necrosis. In support of the importance of endotoxemia and endotoxin-induced cytokines in the progression of NASH after J-1 bypass, treatment with metronidazole improves liver disease in this and certain other settings (e.g., TPN-associated NASH). Furthermore, recent studies of genetically obese mice and rats demonstrate that these animals develop steatosis and are exquisitely sensitive to endotoxin-mediated liver damage.

Paradoxically, TNFα production is attenuated in these obese animals after endotoxin exposure, suggesting that steatosis, in some way, sensitizes hepatocytes to the toxic actions of TNFα and/or other endotoxin-inducible factors. There is preliminary evidence that such sensitization involves an increased hepatocyte susceptibility to ATP depletion that develops because of mitochondrial adaptations to excessive substrates and/or oxidative stress (K. Chavin and A.M. Diehl, unpublished results). With regard to the latter, there is now strong evidence for macrophage dysfunction in certain obese rodents. Specifically, macrophages from genetically obese (ob/ob) mice produce increased amounts of IL-6, PGE, superoxide, and hydrogen peroxide. This may alter the hepatic microenvironment and provoke phenotypic adaptations in neighboring hepatocytes, including the changes in mitochondrial energy homeostasis mentioned earlier.

CURRENT THERAPY AND FUTURE DIRECTIONS

In order to develop effective treatments for NASH, further work is needed to enhance our understanding of its pathogenesis. Current treatment modalities mainly attempt to eliminate or modify the factors commonly associated with NASH (Table 10). Weight loss, treatment of hyperlipemia and hyperglycemis, and discontinuation of potentially toxic drugs are the mainstays of therapy. Unfortunately, it appears that these efforts cure only a few individuals, and there is some suggestion that rapid weight reduction may even accelerate disease progression. Encouraging results have been reported in a few, highly selected patients that were treated with various agents (e.g., ursodeoxycholic acid, metronidazole, supplemental amino acids, glutamine infusion, or glucagon). However, it is unknown whether these treatments are generally beneficial. Furthermore, many patients with NASH lack known risk factors for the disease, and are therefore not candidates for any of the previously mentioned management recommendations.

While such patient heterogeneity may imply that NASH is the end result of diverse insults, this observation is also consistent with the possibility that NASH is the hepatic manifestation of a metabolic process that variably has other manifestations, including adiposity, diabetes, and hyperlipidemia. If this concept is valid, then NASH may be the type of metabolic liver disease that results, at least partially, from disordered energy homeostasis. Given the recent realization that chronic oxidative stress may be involved in the progression of NASH, future therapies for this disease may attempt to constrain macrophage activation. Indeed, old data support the wisdom of this approach. In 1965, DiLuzio and Costales noted that α-tocopherol, and anti-oxidant, inhibited alcohol and carbon tetrachloride-induced steatosis. For more than two decades, it has been known that supplemental choline, a precursor of the free radical scavenger, reduced glutahione, improves steatosis induced in animal models by nutritional deprivation, ethanol, or certain drugs. These and related treatment strategies (e.g., soluble cytokine receptors and neutralizing anti-cytokine antibodies) are currently being evaluated in patients or experimental animals with alcohol-induced liver disease. Alternatively, treatment efforts could be directed primarily toward protecting hepatocyte ATP stores, which appear particularly vulnerable to depletion in the fatty liver. In addition, since Cyp2E1 may contribute to hepatotoxicity in NASH, strategies that limit the activity of this enzyme may be beneficial. The latter may include dietary modifications that reduce the availability of Cyp2E1 substrates. Carefully controlled trials will be required to determine whether any of these strategies (Table 10) are truly beneficial in patients with NASH.

CONCLUSION

NASH should be considered as an explanation for abnormal transaminases, particularly (but not exclusively) in individuals with identifiable risk factors for steatosis. In patients who deny significant alcohol consumption, negative serologic tests for other congenital and acquired causes of liver disease, coupled with the identification of fatty liver on imaging studies, can suggest the diagnosis of NASH. However, liver biopsy is helpful in establishing the diagnosis and in determining the severity of the disease. The latter provides some insight into patient prognosis. Most NASH patients with simple steatosis are likely to follow an indolent clinical course, but the probability of developing clinically significant complications of liver disease is increased in patients with steatohepatitis, fibrosis or cirrhosis. There is little compelling evidence that any of the current treatments prevent progression to more histologically advanced stages of NASH. The development of more definitive therapies for NASH and selection of patients who are most likely to need treatment will require a better understanding of the pathogenesis and natural history of the disease.

TABLE 9. PATHOGENESIS OF STEATOSIS/STEATOHEPATITIS

Contribution Factor	Alcoholic Liver Disease	NASH

Increased Cyp2E1	+	+
Endotoxin	+	+
Macrophage activation	+	+
Decreased hepatocyte ATP	+	+

TABLE 10. CURRENT MANAGEMENT OF/AND FUTURE THERAPY FOR NASH

Current Management	Potential Future Therapy
Weight loss	Constrain macrophage activation
Treatment of diabetes,	Antioxidants (vitamin E, glutathione
Lipid disorders	pro-drugs)
Avoid EtOH, hepatotoxic	Antibiotics (gut decontamination)
Drugs	Anti-cytokines (anti-TNFα
	Antibodies, soluble receptors)
	Protect hepatocyte ATP stores
	PARP inhibitors
	Minimize Cyp2E1 activity
	Dietary modification (avoid fats)

Seminars in Liver Disease – Vol. 19, No. 2, 1999 ------ Nonalcoholic Steatohepatitis --- Anna Mae Diehl, M.D.

This is the last of Anna Diehl's report…Tomorrow we will start Mohsin Rashid and Eve A. Roberts report on "Nonalcoholic Steatohepatitis in Children"….I am going to post all these reports in a web site so that they can also be accessed by non members there also…I will send the URL as soon as I get them posted….Pam