

# Nonalcoholic fatty hepatitis: An important clinical condition

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**ABSTRACT:** The entity fatty hepatitis is defined and the literature characterizing the clinical settings in which it develops is reviewed. The pathogenesis is discussed with emphasis on the common denominators shared by the various clinical conditions with which it is associated. The roles of alcohol, obesity and type II diabetes are stressed where inhibition of fatty acid oxidation by the liver is the basic defect in metabolism leading to fatty change, balloon degeneration and Mallory body formation. It is concluded that this important entity is more common than is generally appreciated. *Can J Gastroenterol* 1989;3(5):189-197

**Key Words:** *Diabetes type II, Fatty hepatitis, Mallory bodies, Obesity*

## L'hépatite grasseuse nonalcoolique: Une condition clinique importante

**RESUME:** L'hépatite grasseuse est définie comme entité morbide. La littérature caractérisant les cadres cliniques où cette affection se développe est passée en revue. La pathogenèse est examinée et l'accent est porté sur les dénominateurs communs que partagent les diverses conditions cliniques auxquelles elle est associée. Le rôle de l'alcool, de l'obésité et du diabète de type II est souligné dans les cas où l'inhibition du processus d'oxydation hépatique des acides gras est la déficience principale du métabolisme entraînant l'accumulation de graisses, la dégénérescence grasseuse et la formation de corps de Mallory. On conclut que cette entité importante est plus fréquente qu'on ne l'estime généralement.

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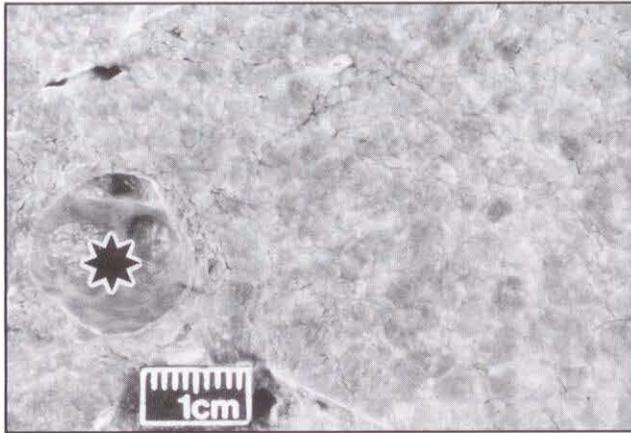
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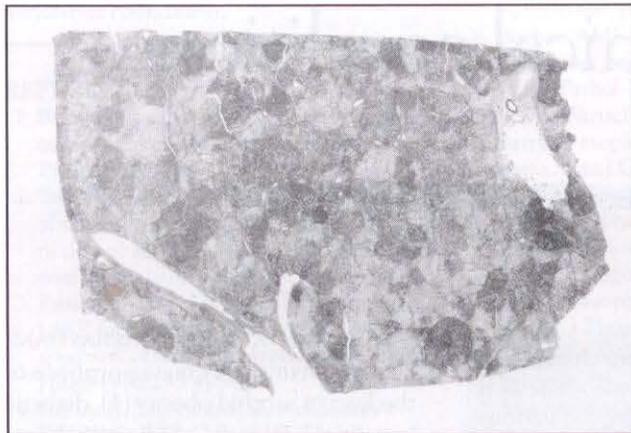
THE TERM FATTY HEPATITIS HAS MANY synonyms: fatty metamorphosis of the liver in morbid obesity (1), diabetic hepatitis (2,3), nonalcoholic steatohepatitis (4,5), fatty liver hepatitis (6), alcohol-like liver disease in nonalcoholics (7), fasting in obesity liver injury with alcoholic hyaline (8), steatonecrosis (9) and non-alcoholic Laennec's (10,11). The term fatty hepatitis is preferred for its simplicity and for the concept that it conveys, one of fatty change with inflammation in the liver. The disease process is important to recognize clinically because it can be mistaken for benign fatty liver or alcoholic hepatitis. Fatty hepatitis is a pernicious disease which may progress to cirrhosis without the physician realizing it unless a liver biopsy is performed (1). The clinical manifestations, associated diseases and pathology are the subject of this review.

## HISTORICAL BACKGROUND

For many years, fatty liver, regardless of its cause, was considered a benign reversible process which did not progress to cirrhosis. This idea was based primar-



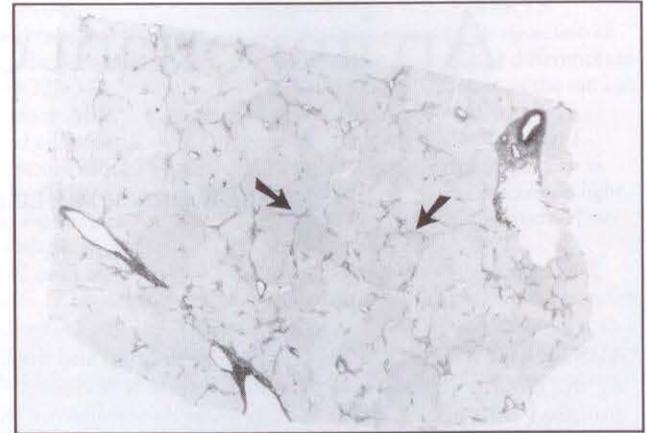
**Figure 1)** Gross photograph of a liver cross section taken at autopsy from an obese patient diagnosed as having fatty hepatitis on liver biopsy. The liver appeared heterogeneous and partly nodular due to an uneven distribution of fat. The light areas are fatty and the dark areas are not. \* Incidental bile duct cyst



**Figure 2)** Low power view of a histologic section from the same liver shown in Figure 1. The pale areas are fatty. The dark areas are nodular analogous to nodular regenerative hyperplasia ( $\times 3$ )



**Figure 3)** High power of Figure 2 showing the junction between 4+ fatty change on the left and minimal fatty change on the right ( $\times 83$ )



**Figure 4)** Same liver as Figures 1 and 2 but stained for collagen with sinus red. Note the central-central bridging fibrosis (arrows). This is incomplete cirrhosis ( $\times 3$ )

ily on the observation that the fatty liver associated with Kwashiorkor in childhood did not progress to cirrhosis. Also, the diabetic fatty liver, unlike the alcoholic fatty liver, did not progress to cirrhosis unless the patients were also alcoholics (12). A similar result was reported in the fatty liver of obesity (13). Fibrosis or cirrhosis was not encountered unless there was also a history of excessive alcohol intake (13). The severity of fatty liver in alcoholics is predictive of cirrhosis (14). However, in the study of fatty liver associated with morbid obesity, a few cases of liver fibrosis or cirrhosis were observed in which alcohol abuse was not a factor (1). Examination of the liver biopsies taken before and after a small bowel bypass operation for morbid obesity showed progression to

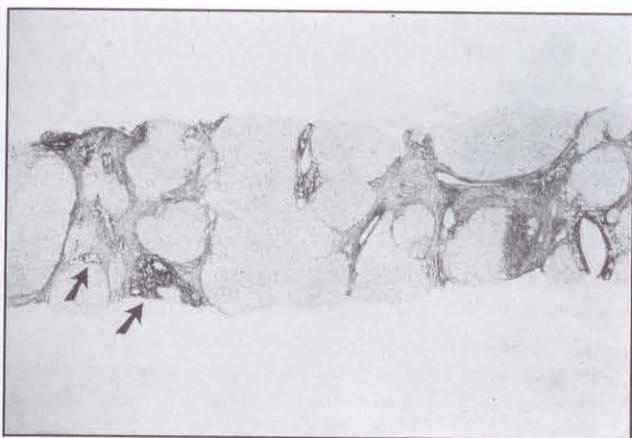
cirrhosis in some (15).

Hepatitis of the fatty liver was first described by Thaler (16), but the entity was not widely appreciated until it became apparent that all of the morphologic features of alcoholic hepatitis, including Mallory body formation and progression to cirrhosis, were sometimes observed in nonalcoholic patients. It has now been found to be associated with diabetes (2-7,9,13,17-21), obesity (3-7,13), morbid obesity with or without intestinal bypass or gastroplasty (1,15,22-36), fasting in obese patients (8,22), massive resection of the small intestine (37,38), bulimia (39) and drug therapy (40-45) (Table 1). Fatty liver with fibrosis or cirrhosis caused by methotrexate may be hard to distinguish morphologically from nonalcoholic fatty hepatitis (46). The

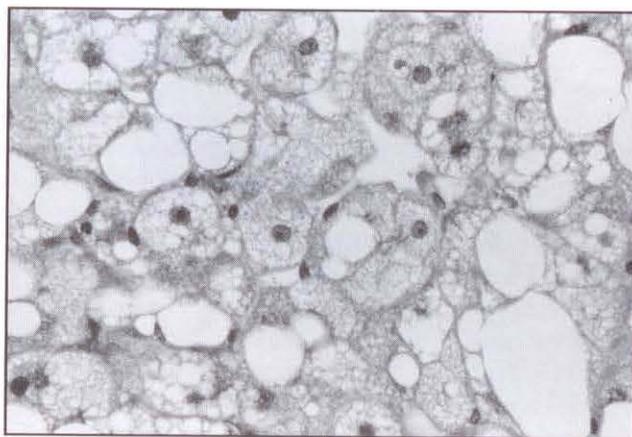
present authors have seen three cases of methotrexate-induced nonalcoholic fatty hepatitis with Mallory body formation, including one case in which typical central sclerosing hyalin necrosis was found in an elderly abstainer.

**TABLE 1**  
**Nonalcoholic fatty hepatitis and fatty cirrhosis: Clinically associated conditions**

Diabetes mellitus (2-7,9,13,17-21)
Obesity (3-7,13)
Morbid obesity with or without intestinal bypass or gastroplasty (1,15,22-36)
Fasting in obese patients (8,22)
Massive resection of small intestine (37-38)
Bulimia (39)
Drug therapy: Glucocorticoids, amiodarone, perhexiline maleate (diuretics, hypoglycemics, cardiac/hypertension, estrogens and thyroid)(40-45)



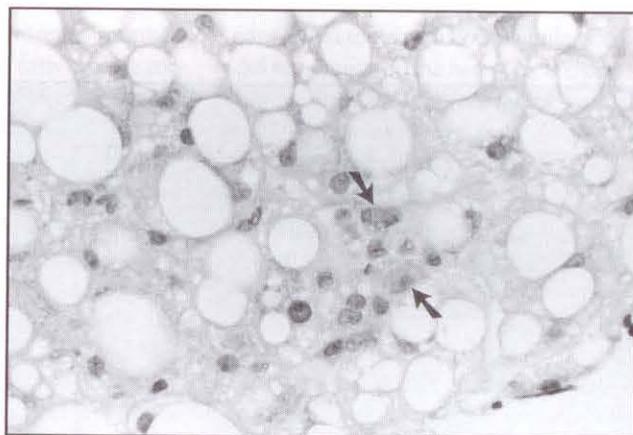
**Figure 5)** Liver biopsy of a patient with morbid obesity and fatty cirrhosis. The bridging fibrosis incorporates central veins and portal tracts (arrow). Sirius red  $\times 17$



**Figure 7)** High power view of a biopsy of fatty hepatitis from a morbidly obese patient. Note both the micro- and macrovesicular fat. The microvesicular fat resembles the foamy degeneration seen in alcoholic hepatitis ( $\times 330$ )



**Figure 6)** View of a portal tract (PT) and centrilobular area (CV) showing both periportal and centrilobular fibrosis. The central fibrosis is pericellular (arrows). This is from a biopsy of fatty hepatitis from an obese patient. Sirius red  $\times 83$



**Figure 8)** High power view of the same liver shown in Figure 6 showing a microfocus of the characteristic macrophage infiltrate seen in the lobule (arrows). The macrophages are identifiable because they contain periodic acid-Schiff positive phagosomes. Digested periodic acid-Schiff reagent  $\times 330$

The frequency of cirrhosis and fibrosis varies with different series, but in a review of 41 papers on liver morphology of 1515 morbidly obese patients, 29% had fibrosis and 3% cirrhosis (34). In a nine month follow-up of 34 cases of jejunoileal bypass for morbid obesity, six developed fibrosis and three cirrhosis (35).

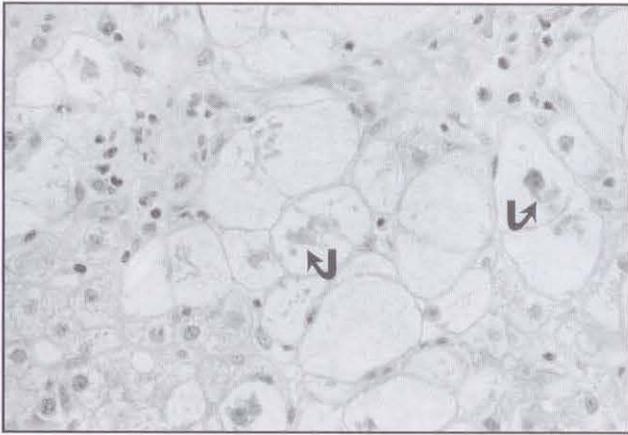
### **PATHOLOGY**

Hepatomegaly is the rule. Grossly, the liver is pale yellow or a mottled yellow and brown, owing to a heterogeneous fatty change (Figure 1). Fibrosis is variable and irregularly distributed unless the liver has progressed to cirrhosis. Microscopically, the fatty change may be diffuse early and more patchy in later stages (Figures 2,3). Scarring is

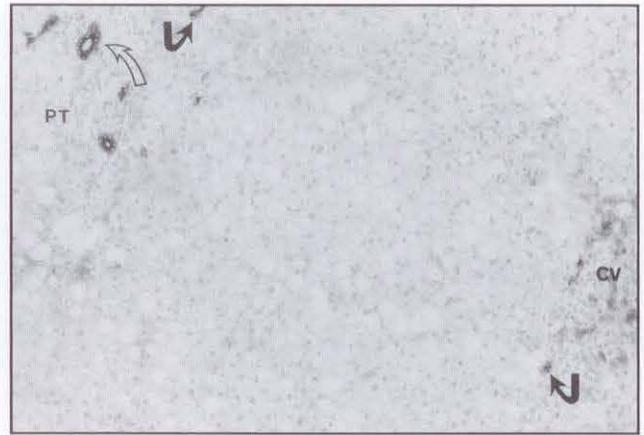
variable, being absent early and progressing to incomplete cirrhosis (Figure 4) or cirrhosis (Figure 5).

Fibrous spurs extend from the portal tracts toward zone 3 of the lobule (Figure 6) whereas scars in zone 3 form fibrous bridges between the terminal hepatic venules (central veins) (Figure 4). The earliest change is fatty change, both microvesicular and macrovesicular (Figure 7). The earliest inflammatory change, which distinguishes fatty liver from fatty hepatitis, is the development of foci of macrophages in the parenchyma (Figure 8). This is followed by balloon degeneration and Mallory body formation in the centrilobular zone (Figure 9). This lesion is accompanied by a mononuclear infiltrate and fibrosis, and is associated with a loss of cytochrome staining in the bal-

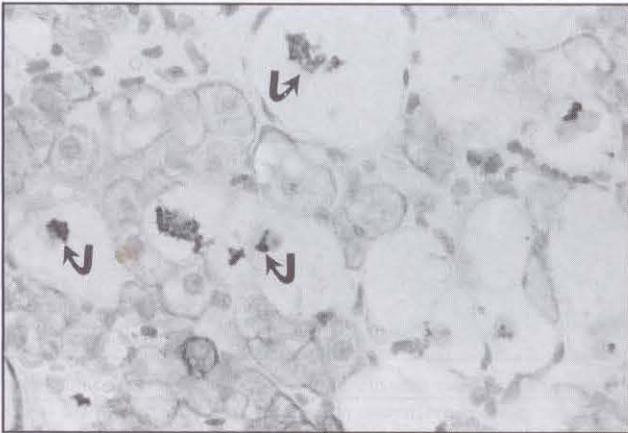
loon cells, and the intense staining of cytochrome in the Mallory bodies (Figure 10), analogous to that seen in alcoholic hepatitis (47). Marked centrilobular bile ductule metaplasia occurs in centrilobular scars (Figures 11,12), as seen in alcoholic hepatitis (48-51). This proliferation of bile ductules induces a desmoplastic response similar to that seen in the periportal areas (Figures 11,12). This phenomenon, in which liver cells express cytochromes which are normally only expressed by bile duct epithelium, is known as bile duct metaplasia of hepatocytes (49). The use of immunoperoxidase in the localization of these bile duct cytochromes is illustrated in Figures 11 and 12. Thus, the evolution of fatty hepatitis to cirrhosis resembles that of alcoholic hepatitis except for one feature.



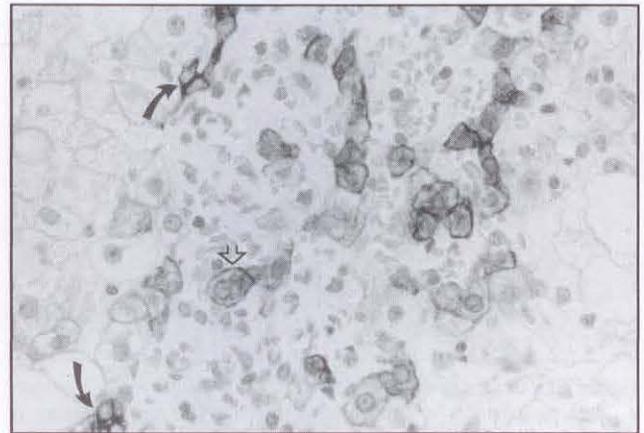
**Figure 9)** Centrilobular balloon degeneration in hepatocytes from a morbidly obese patient. Note the Mallory bodies (arrows) within the ballooning cells. Also, note the absence of polymorphonuclear leukocytes and the foci of mononuclear inflammation and fibrosis ( $\times 330$ )



**Figure 11)** Same liver as in Figures 9 and 10. The bile ductule metaplasia (closed arrows) is illustrated in both the periportal (PT) area and the centrilobular (CV) area. Normal bile ducts (open arrow) also stain positively for cytokeratins. The bile ductules stain positively for cytokeratins like bile ducts even though the bile ductules are transformed liver cells. These metaplastic ductules stimulate periductal fibrosis. Immunoperoxidase  $\times 83$



**Figure 10)** Same liver as Figure 9 stained for normal liver cell cytokeratins. The balloon cells fail to stain positively like the adjacent normal hepatocytes and the Mallory bodies (arrows) which are intensely stained. This failure to stain the cytoplasm with antibodies to liver cell cytokeratin is typical of cells which contain Mallory bodies. Immunoperoxidase  $\times 330$



**Figure 12)** Centrilobular scar shown in Figure 11. It is possible to see that the liver cells first develop increased cytokeratin around the edge of the cell (open arrow). These liver cells seem to become progressively smaller and express cytokeratin throughout the cell. They then form small nests (solid arrows) which resemble bile ductules (bile ductular metaplasia). Immunoperoxidase  $\times 330$

The polymorphonuclear leukocyte infiltrate around hepatocytes that contain Mallory bodies (satellitosis) (52) is missing in fatty hepatitis, although there are exceptions (3,7).

The pathologic changes of fatty hepatitis have been compared in detail with those of alcoholic hepatitis in a study reported by Diehl *et al* (7). They observed no qualitative differences in histology between two groups of patients (39 non-alcoholic and 68 alcoholic hepatitis). There were some differences in the average severity of some of the features. Micro- and macrovesicular fat were more often moderate to marked in severity in the nonalcoholics ( $P < 0.05$ ). Mallory

bodies were identified in 90% of the specimens in both groups. Mallory bodies were very numerous particularly in the alcoholic patients ( $P < 0.05$ ). Intra-acinar inflammation (predominantly neutrophilic) was more prominent in the alcoholics ( $P < 0.005$ ). Centrilobular pericellular fibrosis or cirrhosis was seen in both groups, but severe fibrosis or cirrhosis was present more often in the alcoholic group (63%) compared to the nonalcoholic group (38%). Likewise, the clinical stigmata of portal hypertension were found more often with marked fibrosis or cirrhosis in the alcoholic group.

Another study of hepatic histology involving 320 alcoholics and 348 non-

alcoholics at autopsy established a relationship between the severity of steatosis, Mallory bodies, fibrosis and the degree of obesity in both groups (21). The prevalence of Mallory bodies and fibrosis was higher in type II diabetes. In alcoholic patients who were markedly obese, there was a higher prevalence of Mallory bodies compared to nonobese alcoholics (68 versus 38%,  $P < 0.001$ ).

The frequency of fatty liver in obesity was 48% in a series of 50 patients hospitalized for weight reduction (13). Fatty hepatitis was diagnosed in 26% of non-alcoholics. Fatty fibrosis was found in 8% and cirrhosis in 8%, but in these patients alcohol abuse was a factor. Protein defi-

ciency correlated with steatosis, inflammation and fibrosis. Diabetes mellitus correlated with severe steatosis. Alcohol intake correlated with severe steatosis, fatty hepatitis, fatty fibrosis and fatty cirrhosis in this series.

Diabetes mellitus is sometimes complicated by simple fatty liver and cirrhosis. In a series of 62 patients with type II diabetes, 17 had fatty hepatitis (3). The histology in nine biopsies studied systematically revealed features of alcoholic hepatitis. Fatty change and liver cell ballooning were constant features. Neutrophils in association with Mallory bodies were found in five; mononuclear infiltrate in four; acidophil bodies in five; fat granulomas in seven; pericellular fibrosis was mild. In six cases, there was bridging fibrosis between the portal and central vein, but distortion of the lobular architecture was absent or slight. Cirrhosis was not encountered, although progression was discovered in one case on a subsequent biopsy.

In a series of 29 obese patients without alcohol abuse, fatty liver was seen in seven, fatty hepatitis in eight, fatty fibrosis in seven and fatty cirrhosis in seven (6). Seven cases had Mallory bodies and 12 had central or perisinusoidal fibrosis. There was no correlation between the severity of liver damage and the degree of fatty change. Polymorphonuclear leukocytes were numerous in all of the patients with fatty hepatitis. In these patients, diabetes and lipoprotein abnormalities (mostly type IV) were common. In a second series of 20 cases of nonalcoholic steatohepatitis (5), 90% were obese. Moderate to severe macrovesicular fatty change and lobular inflammation were present in all cases as these were the criteria for case selection. Fat was distributed centrally or diffusely and fat cysts were always present. The inflammatory cells were mixed lymphocytes, mononuclear cells and neutrophils located either centrilobularly or in areas of focal necrosis. Mallory bodies located in zone 3 were present in 70%, Councilman bodies in 25%, perisinusoidal centrilobular or septal fibrosis in 70% and cirrhosis in 15%.

The histopathology of the liver in morbid obesity has been reported by numerous investigators. In a review of 41 articles

in which the liver morphology of a combination of 1515 morbidly obese patients was summarized (34), the liver was normal in 12% of the cases. Fatty change was the most frequent abnormality found (80%). Portal inflammation was seen in 33% and fibrosis, mainly portal or periportal, was seen in 29%, while cirrhosis was seen in 3%. Mallory bodies were rarely found. A few reports describe central or pericellular fibrosis in nonalcoholic patients (34). The same authors (53) studied the livers of 61 cases of morbid obesity (average 82% overweight). The patients' alcohol intake did not exceed a moderate amount and only one patient was diabetic. Seven percent of the biopsies showed a normal liver. Fatty change was the most common abnormality (85%). The degree of fatty change correlated with the presence of lipogranuloma (54%), focal necrosis (33%) and Kupffer cell proliferation (49%). No Mallory bodies or cirrhosis were observed and alcoholic hepatitis was absent. These authors took the view that when Mallory bodies, fibrosis or cirrhosis are encountered in obese patients, it is likely that the patient is abusing alcohol (34,53).

When patients with morbid obesity are treated with a small bowel bypass or gastroplasty, the liver morphology may worsen, implying that malnutrition plays a role in the pathogenesis of fatty hepatitis (29,30,32,35). This idea is strengthened by the observation that a massive small bowel resection can induce fatty hepatitis (37,38) although starvation therapy alone had no injurious effect on the liver of the morbidly obese (30); a mere reduction in fat stores in the liver was observed. Liver biopsies in 88 patients taken one to two years after jejunoileal bypass showed that an increased number of patients had increased fat stores (30). However, portal fibrosis, inflammation or biliary proliferation did not predict progression to alcoholic hepatitis. Only central or pericellular fibrosis predicted progression to alcoholic hepatitis. In 6.8%, central fibrosis progressed to form central-portal bridging fibrosis. One half of these patients developed regenerative cirrhotic nodules. Only one case developed into a morphologic picture resembling alcoholic hepatitis. Mallory bodies were more frequently en-

countered but were apparently periportal in location.

Peters (29) reported serious hepatic disease in 1 to 17% of patients who underwent jejunoileal bypass. Most common was acute hepatic failure two-and-one-half to nine months after the bypass. This failure was associated with a large fatty liver along with fibrosis and hepatocellular necrosis. The fibrosis was both central and portal. The perivenular hepatocytes were hydropic and surrounded by collagen. Mallory bodies were found in these swollen hepatocytes while neutrophils were sparse. The lesion was indistinguishable from alcoholic hepatitis. A similar lesion was encountered after gastroplasty (32). Some of the patients continued to drink alcohol while others did not, however, the histological changes were identical. This indicates that caution must be exercised regarding validity of a negative history of alcohol abuse as the patient may not be candid about drinking habits.

Fatality in patients who underwent small bowel bypass surgery was common. The second least common sequela to bypass was the insidious development of cirrhosis, discovered either accidentally or after the development of ascites. Another important but uncommon complication was the manifestation of tenuous hepatic reserve. In this condition, liver disease developed rather suddenly as a consequence of some other systemic insult, similar to alcoholic liver disease.

The progression of liver disease in 34 patients who underwent jejunoileal bypass for morbid obesity was studied via follow-up biopsy five to nine months postoperatively. Twelve of 15 patients with no or slight steatosis progressed to either moderate to severe steatosis, steatohepatitis or steatofibrosis. The six patients with initial moderate to severe steatosis all progressed to steatohepatitis or steatofibrosis, and one developed septal fibrosis. All of the patients with steatohepatitis (steatosis and a lobular lymphocytic inflammation) progressed to steatofibrosis. Of the five patients with steatofibrosis, three developed bridging fibrosis. Mallory bodies appeared postoperatively in 11 patients (32%), all of whom had had either severe steatosis, steatohepatitis or steatofibrosis preoperatively.

**TABLE 2**  
Clinical features of nonalcoholic fatty hepatitis

	Total number of cases	Number of patients having clinical feature or medication (%)
Diabetes	88	44 (50)
Obesity	88	75 (85)
Hepatomegaly	49	31 (63)
Cholecystectomy	49	14 (29)
Portal hypertension	59	5 (8)
Medications		
Cardiac/hypertension	68	21 (31)
Diuretic	68	19 (28)
Hypoglycemics	68	17 (25)
Thyroid	39	6 (15)
Estrogens	39	5 (13)
Corticosteroids	20	3 (15)

Data are derived from three reports (5-7); most series specifically excluded patients with history of blood transfusion, intravenous drug abuse, positive hepatitis B specific antigen or antimitochondrial antibodies; one series (6) specifically selected for obese patients. The average patient age was 50 years with 21 (24%) males and 67 (76%) females

**TABLE 3**  
Laboratory features of nonalcoholic fatty hepatitis

	Total number of cases	Number of abnormal values (%)
AST/ALT	88	48 (55)
Alkaline phosphatase	49	20 (41)
Bilirubin	59	11 (19)
Hyperlipidemia	49	19 (39)

Data are derived from three reports (5-7). AST Aspartate aminotransferase; ALT Alanine aminotransferase

Only the patients with postoperative steatofibrosis and Mallory bodies developed bridging fibrosis (six patients) or cirrhosis (three patients). The progression of liver disease resembled alcoholic liver disease, ie, increasing steatosis, lobular lymphocytic inflammation, pericellular fibrosis, Mallory bodies and deranged architecture, suggesting that the two diseases have the same mechanisms (35).

One of the features of fatty liver in alcoholics and morbidly obese patients is megamitochondria seen by light microscopy or electron microscopy. The megamitochondria, which are elliptical or cigar-shaped due to intramitochondrial filaments (54), are located in periportal hepatocytes. These are nonspecific, but the globular mitochondria located in centrilobular hepatocytes are a useful marker of both alcoholic liver disease (55-59) and nonalcoholic fatty liver (60,61). There is no prognostic value in the presence of megamitochondria in alcoholic liver disease (59); the prognostic implication of the presence of megamitochondria in fatty hepatitis in nonalcoholics is as yet unknown.

### CLINICAL FEATURES

Tables 2 and 3 summarize the clinical and laboratory features of patients with fatty hepatitis derived from three studies (5-7). The patients are typically obese, female, in their late 40s to early 50s, and taking medication for, or having a variety of, intercurrent conditions. The foremost of these conditions is diabetes; to a lesser extent, heart disease and hypertension are also present. Most of the patients are asymptomatic with respect to liver disease, despite the fact that 15 to 38% have cirrhosis or severe fibrosis. Jaundice, ascites, esophageal varices, encephalopathy and hepatorenal syndrome occurred alone or in combination in only a few patients (12%). The indications for liver biopsy in almost all of the patients were hepatomegaly, abnormal liver function tests, or both. The latter had mostly mild to moderate elevations of aspartate aminotransferase, alanine aminotransferase, bilirubin or alkaline phosphatase. The computerized axial tomography scan and ultrasound of the liver may have a heterogeneous appearance (Figures 13, 14) due to the uneven distribution of the increased fat stores (Figures 1,3).

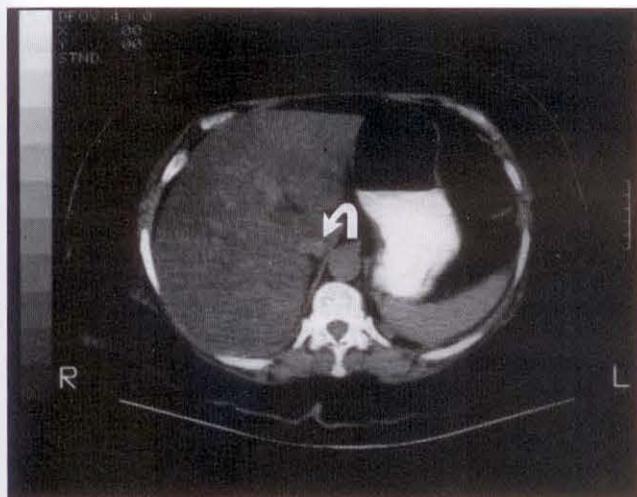
### PATHOGENESIS

A variety of theories regarding the pathogenesis of fatty hepatitis have been proposed, especially as it relates to progression after jejunoileal bypass therapy for morbid obesity. Protein calorie malnutrition has been established four months after bypass, but this reverts toward normal 12 to 36 months postoperatively (62), probably because of intestinal adaptation postoperatively (63). Other factors which may contribute to malnutrition after bypass are bacterial overgrowth in the blind loop and changes in the metabolism of bile acid (63,64). Supporting this theory, Drenick *et al* (65) reported that metronidazole, a drug which suppresses the intestinal growth of anaerobes, prevented the progression of liver disease after bypass.

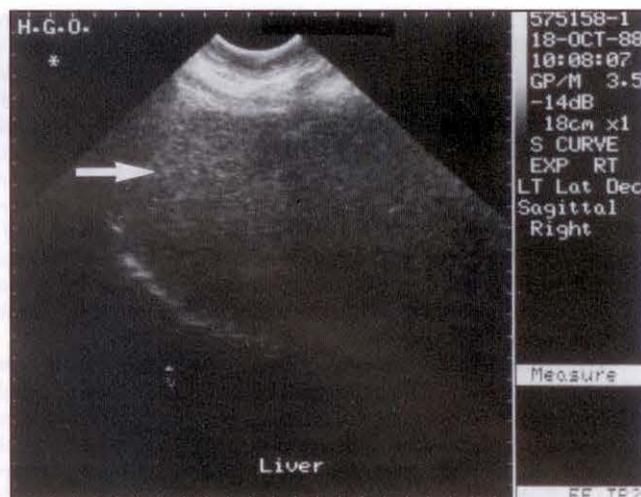
Vyberg *et al* (66) cite evidence that bacteria in the blind loop produce acetaldehyde and suggest that since acetaldehyde is also implicated in the pathogenesis of alcohol liver disease, it may also be the common denominator in the pathogenesis of both nonalcoholic fatty hepatitis and alcoholic liver disease. They argue that since both diseases are similar in their clinical and pathologic features they may have a common etiology and that the common factor could be acetaldehyde-related. Ethanol production through fermentation could be the source of acetaldehyde production; however, alcohol is detected in the blood of only one-third of patients following bypass and only in low concentrations (67).

Hepatic free fatty acids increase in the liver in alcoholic liver disease and in morbid obesity (68). Similar changes occur in liver mitochondria in alloxan diabetes in rats. Thus, it is possible that the common factor responsible for the progression of fatty liver to fatty hepatitis and alcoholic hepatitis may be increased free fatty acids. Fatty acids change the surface tension of membranes and act as detergents to lyse membranes (69,70). However, because free fatty acids increase in proportion to the severity of the disease process, it is difficult to determine which is primary, the disease process or the increase in fatty acids.

Wanless *et al* (21) have reported evidence that supports the hypothesis that the pathogenesis of fatty hepatitis of



**Figure 13)** Computerized axial tomography scan showing heterogeneity in the liver shown in Figures 1 to 3. Note that the density of the liver is focally decreased relative to the blood vessels (arrow)



**Figure 14)** Ultrasound from the liver shown in Figures 1 to 3. Note the typical bright echo of fatty liver (arrow)

morbid obesity with type II diabetes, and fatty hepatitis following jejunoileal bypass surgery for morbid obesity is the same, ie, increased free fatty acids in the liver. They observed steatosis and steatonecrosis with Mallory bodies in the subcapsular liver in patients on peritoneal dialysis with type I diabetes receiving intraperitoneal insulin on a regular basis. They suggested that this localized fatty change was due to insulin and glucose diffusing from the peritoneum into the liver tissue. From this idea they rea-

soned that insulin inhibited fatty acid oxidation in the liver, and that it caused fatty acids to be preferentially esterified and stored as triglycerides, resulting in a fatty liver. Free fatty acids thus accumulated, causing membrane injury, swelling of hepatocytes and steatonecrosis. Generally, when insulin levels are elevated enough to block fatty acid oxidation but not high enough to block free fatty acid mobilization, fatty liver and necrosis may result. Such a clinical situation exists in obesity associated with type

II diabetes and morbid obesity treated with bypass surgery, but not in morbid obesity controlled by diet reduction therapy. This may explain why fatty hepatitis progresses after bypass surgery but reverts to a normal liver when diet calorie restriction without surgery is successful in causing weight loss (30). It is likely that a similar mechanism is involved in alcoholic liver disease with obesity, since the metabolism of alcohol blocks fatty acid oxidation by liver mitochondria (71).

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