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Fatty Liver

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Steatosis of the liver is a harmless symptom of disturbed lipid metabolism but not a disease. The cause of the steatosis, and not the fat accumulation by itself, produces cirrhosis. There is no evidence so far in man that cirrhosis may be caused by nutritional deficiencies alone. Even cirrhosis after small bowel bypass procedures seems to be result from metabolic rather than nutritional disturbances.

(Key Words: Obesity, Ethanol, Hyperlipoproteinaemia, Malnutrition, Malabsorption)

INTRODUCTION

In the last few years, considerably more attention has been paid to fatty liver than its clinical and pathological importance would warrant.

A connection between fatty liver and cirrhosis was first recognised by Rokitansky (26), the famous Viennese pathologist. He wrote: "Fat accumulation may be the primary affection upon which the granular shaped cirrhosis develops". Rokitansky's finding was confirmed by French clinicians, who distinguished an early stage of 'steatosis' from the late stage of cirrhosis in the liver disease of the chronic alcoholic (37).

The problem attracted interest when Weichselbaum (39) showed that rats given a low casein diet developed severe hepatic injury. However, it remained for Himsworth and Glynn (15) to demonstrate two kinds of experimental nutritional injury: one, acute massive necrosis, the survivors of which developed coarse nodular cirrhosis; the other, a severe fatty infiltration of the liver insidiously progressing to micronodular cirrhosis. The latter condition was also produced experimentally by diets containing only small amounts of protein. The missing factors were shown by Best and Huntsman (2), and Best and Ridout to be choline and methionine. These preventive substances have been termed 'lipotropic factors'.

The experimental fatty liver due to protein deficiency seemed to have its human counterpart in the kwashiorkor of the tropics. Moreover, Himsworth (14) recorded 'successive stages' of the development of micronodular cirrhosis from fatty liver in kwashiorkor. Although the specimens were obtained from different patients, he assumed that the correlation between the two diseases was proven and so did most hepatologists at that time.

The coincidental occurrence of malnutrition, especially protein deficiency, and cirrhosis was assumed not only in tropical countries. After World War II, 13.5 percent of liver cirrhosis in males was estimated to be caused by malnutrition in those prisoners of war who had suffered from

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nutritional oedema ('Heimkehrercirrhose') (18). When Hartroft and Porta (12) finally claimed that alcoholic cirrhosis was not a toxic but a nutritional problem, the supporters of 'nutritional cirrhosis' regarded nutritional abnormalities as the main cause of cirrhosis.

However, after the first enthusiasm for 'nutritional cirrhosis' the pendulum started to swing in the opposite direction. This change of opinion was due to critical and elaborate studies in man. Thus, nutritional cirrhosis is no longer recognised by most scientists.

FATTY LIVER AND ITS CAUSES

Hepatic steatosis is frequent. In 22,995 liver biopsies we were able to find 6,140 fatty livers, i.e., 26.7 percent incidence (35). However, these figures do not reveal the true frequency of steatosis because biopsy material is selective. There are four main causes of fatty change of liver cells (Table 1).

Table 1 Metabolic causes of fatty change of liver cells.

1. Increased influx of fat to the liver
2. Increased synthesis of fat in the liver
3. Reduced breakdown of fat in the liver
4. Reduced removal of fat from the liver

Unquestionably, there is considerable geographic variation in the frequency of fatty liver due to different economic situations, and the habits and vices of the population (Table 2).

In the overpopulated and underdeveloped countries of the tropics, steatosis of the liver from protein deficiency is probably the most frequent type of fatty liver. During and after World War II, malnutrition was also common in Europe, but it became rare after economic recovery took place. At present in the industrialized countries of the world, true malnutrition is limited to patients with severe malabsorption, e.g., due to small bowel resection of following small bowel bypass procedures for control of obesity.

Nowadays, in North America and Europe over-nutrition is probably the most important cause of steatosis of the liver although exact data are not available because obese persons prefer to eat instead of being subjected to biopsy. Obesity is also the usual cause of the so-called diabetic fatty liver.

In biopsy material alcoholism is the most frequent cause of fatty liver because biopsy is the only reliable method of ascertaining the degree of hepatic damage in this condition. The percentage incidence varies geographically. In temperate climates 30 to 50 percent of steatosis confirmed by biopsy is due to ethanol abuse (19); in our Viennese material the figure is 55 percent (36).

Less frequent causes of steatosis are hyperlipoproteinaemia and drugs (e.g., tetracycline and corticoids). Rare causes are glycogen storage disease, galactosaemia or psoriasis. Combinations of several causes are common, such as chronic alcoholism with malnutrition, or chronic alcoholism combined with hyperlipoproteinaemia and overweight.

Table 2 Aetiology and pathogenesis of common types of fatty liver

Cause	Aetiology	Pathogenesis
Malnutrition	Deficiency of protein and vitamins	Reduced lipid removal from the liver, deficiency of carrier protein
	Weight reduction diets	Increased lipid transport to the liver (from fat depot)
Malabsorption	Small bowel bypass, small bowel resection	Increased lipid transport to the liver (from fat depot)
Obesity	Over-nutrition	Enhanced lipid synthesis, increased lipid transport to the liver
Ethanol	Chronic alcoholism	Reduced lipid oxidation in the liver, enhanced lipid synthesis
Hyperlipoproteinaemia	Genetic	Enhanced lipid synthesis, increased lipid transport to the liver
Drugs	e.g.: tetracycline corticoids	Reduced lipid removal from the liver, deficiency of carrier protein, enhanced lipid synthesis, reduced lipid removal from the liver.

RELATION OF STEATOSIS TO CIRRHOSIS

Despite the improved knowledge on metabolism of today, some fatty livers are of unknown origin. We estimate the frequency of these cryptogenetic steatoses to be two to three percent in our material. A very rare but impressive example of cryptogenetic fatty liver is the non-alcoholic giant fatty liver in women (34). This is a good example of severe steatosis followed by cirrhosis. So far we have observed five such cases, all of whom happened to be in the menopause. None of them drinks alcohol. They are moderately obese, diabetic, hyperlipoproteinaemic women who suffer from slight hypertension. After several years of control, in two of these cases a hepatitis with necrosis developed which was indistinguishable from alcoholic hepatitis, and resulted in a micronodular cirrhosis. The change in size and shape of the liver in one of these patients is shown in Fig. 1. The causes of the steatosis, the hepatitis and the cirrhosis remain unknown. Neither a nutritional deficiency nor a malabsorption could be demonstrated. Therefore, the disease seems to be metabolic rather than nutritional.

Hepatic steatosis disappears quickly and completely once the cause is eliminated. In cases of kwashiorkor treated with a diet rich in protein the liver becomes normal after six to 16 days (3). The steatosis in obesity diminishes gradually with weight loss (7). In chronic alcoholics, fatty infiltration of the liver is no longer demonstrable after total abstinence from ethanol for two to four weeks (30). The same applies to drug-induced steatosis after elimination of the pharmacon.

In view of its episodic character steatosis is not a disease but a morphologic

indication of disturbed lipid metabolism. Its pathological importance has doubtless been exaggerated. The condition itself is harmless; only its cause may be dangerous (e.g., alcohol, small intestinal bypass operation).

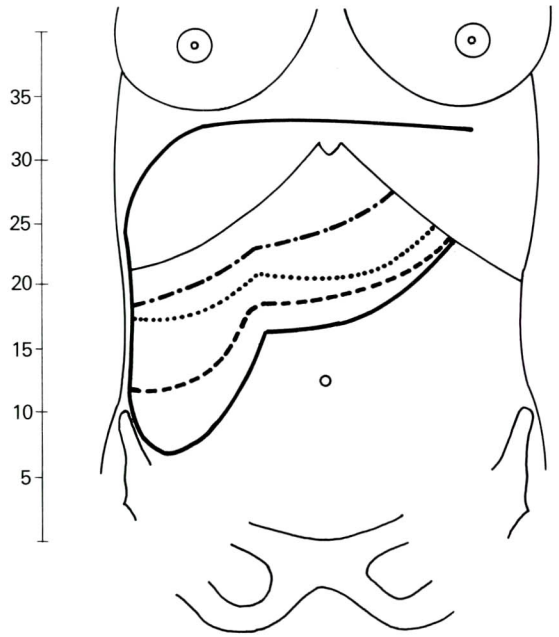

Fig. 1 Non-alcoholic giant fatty liver in a 58-year-old woman. Gradual enlargement of the fatty liver. June 1965 ____.____.; June 1968.....; October 1968---; June 1970____. Reproduced by courtesy of the Editor of *Deutsches Medizinisches Journal* from Thaler (1972).

STEATOSIS AND CIRRHOSIS

Since Rokitansky's (26) work fatty liver and cirrhosis have been regarded as two generations of one disease. On first sight things seem to be easy. However, after careful reevaluation one has to admit that conclusions have been drawn too quickly.

The coincidence of diabetes mellitus, fatty liver and cirrhosis illustrates this problem. Diabetes and liver disease are both common and frequently occur in the same patient. Many statistics prove, however, that this combination occurs more frequently than can be accounted for by statistical chance. In large series, cirrhosis was found in 2.3 to 13.4 percent of non-diabetics and in 5.7 to 21.4 percent of diabetics. The incidence of diabetes in cirrhotic patients varies in clinical and postmortem statistics between 9.6 and 17 percent. If a clear definition of diabetes mellitus is given, its frequency in cirrhotics is surprisingly uniform, between 11.5 and 14 percent, with an average of 12.3 percent. This is significantly higher than in patients with a normal liver (3.3 percent) (6). Therefore, diabetes mellitus and diabetic fatty liver are regarded as important causes of cirrhosis.

In our own material (32) the incidence of overt diabetes in steatosis was 37 percent and the freuqency of fatty liver in diabetes mellitus, 46.7 percent. These figures agree with other statistics (6). Most diabetics with hepatic steatosis suffer from considerable overweight and belong to the maturity-onset type of diabetes. Beringer and Thaler (1) confirmed Joslin's opinion (17) that obesity is a major aetiological factor in both diabetes mellitus and fatty liver. The grade of steatosis in maturity-onset diabetes correlates neither with the duration nor with the serverity of diabetes but with the degree of overweight (Fig. 2). After weight reduction diabetes as well as fatty liver may disappear.

The chronological relationship is important for the appreciation of the cirrhotogenic role of diabetes mellitus. In the well documented series of Creutzfeldt, Frerichs and Sickinger (6) liver disease was present before or detected simultaneously with diabetes in 66 percent, while in only 34 percent, cirrhosis was found after the onset of diabetes. When cirrhosis is the primary disease, diabetes is milder than when it precedes cirrhosis.

The diabetes in cirrhotics can be explained by the instability of carbohydrate metabolism and especially of the B-cell system in liver disease. Naunyn's (21) 'liver diabetes' has been confirmed. The incidence of combined cases, with cirrhosis appearing after diabetes, may be accounted for by the high incidence of viral hepatitis and chronic alcoholism in diabetics. Therefore, we conclude that a diabetic liver disease does not exist.

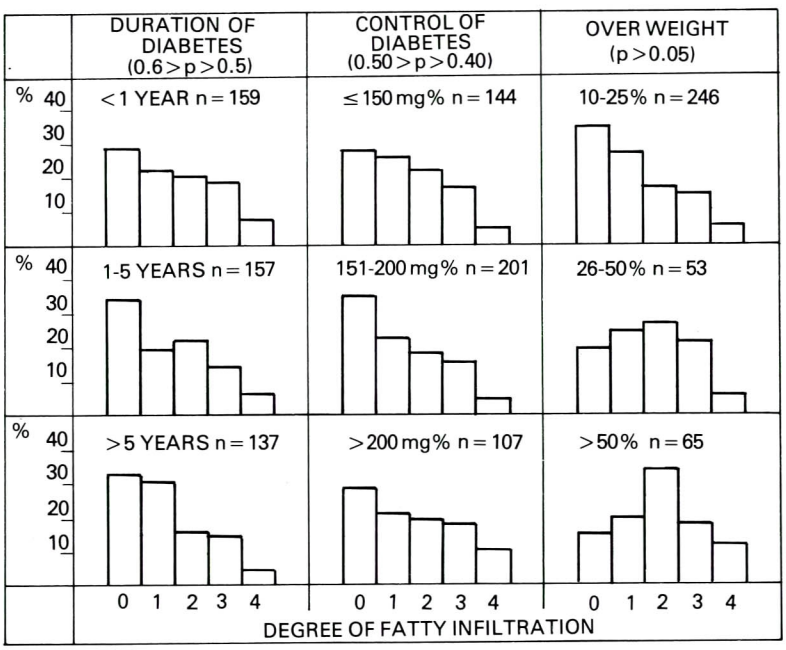

Fig. 2 Frequency of the different degrees of fatty infiltration of the liver compared to the duration and the control of diabetes mellitus and the degree of overweight. Reproduced by courtesy of the Editor of *Deutsche Medizinische Wochenschrift* from Beringer and Thaler (1970).

Our understanding of the other types of cirrhosis previously claimed as nutritional developed in a similar way. Careful follow-up of surviving cases of severe kwashiorkor failed to demonstrate cirrhosis. The disease disappears spontaneously even in untreated cases without important sequelae after the age of six (5, 13). In adults as well, there is no evidence that protein deficiency alone causes cirrhosis (9, 27). The high incidence of cirrhosis in prisoners of war was primarily caused by infections with hepatitis virus B (10), particularly since the hepatic resistence of malnourished patients is decreased (33). Viral hepatitis may then elicit more extensive necroses with subsequent postnecrotic cirrhosis (29). It is not known whether malnourished persons develop chronic hepatitis more easily.

A comprehensive theory on the development of cirrhosis on the basis of steatosis alone was postulated by Hartroft (11). He showed that rats maintained on low choline diets for more than one year develop large fatty cysts in their livers, which are eventually replaced by fibrous tissue. However, cysts of this size do not develop in man.

ALCOHOLIC HEPATITIS AND CIRRHOSIS

After a variable latency period, a very characteristic disease process, alcoholic hepatitis, can occur in the fatty livers of chronic alcoholics. The period of latency depends upon the degree of alcohol abuse and the individual resistance of the alcoholic. On average, it is about 10 years. If alcohol consumption is maintained, alcoholic hepatitis leads to a destruction of the normal architecture and thus to cirrhosis within a matter of weeks, months or even years. If the patients gives up alcohol completely, the liver damage heals within seven to 12 weeks leaving a defect which depends upon the extent of the liver damage obtaining at the time of giving up alcohol consumption. Cases of alcoholic hepatitis unaccompanied by fatty infiltration of liver cells represent an artefact following hospitalisation and they are due to the fact that fatty liver regresses faster than alcoholic hepatitis. The necroses in alcoholic hepatitis are probably due to the hepatotoxic action of acetaldehyde.

Alcoholic hepatitis is the most frequent, but by no means the only necrotizing hepatitis which occurs in fatty livers. Morphologically identical changes are seen in non-alcoholic giant fatty liver in women (34), following small intestine bypass surgery (23) or in infantile cirrhosis in India. For this reason, we have proposed using the general term "fatty liver hepatitis" (31), which should, in particular, always be used when the pathologist has no evidence for alcohol abuse.

Alcoholic hepatitis is not rare. Of 4060 chronic alcoholics we observed 1256 cases, that is in 30.9% of our material (36). Begin and severity of alcoholic hepatitis bears no relationship to the extent of fatty infiltration of the liver cells (30), so that there can be hardly any doubts that we are here dealing with two completely independent processes which, however, are both caused by chronic alcoholism. Hartroft and Porta (12) considered alcoholic hepatitis and alcoholic cirrhosis to be merely a dietary problem and thus included them in the list of nutritional disorders. In the meantime, this opinion has been unequivocally disproved (27).

Edmondson, Peters et al (8) reported that centrilobular (perivenular) sclerosis, a fibrous rim around the central vein, can occur in alcoholic fatty liver in the absence of alcoholic hepatitis. Lieber, DeCarli and Rubin (20) succeeded in the sequential production of fatty liver, hepatitis and cirrhosis in baboons by feeding ethanol with adequate albeit liquid diets. Centrilobular sclerosis was apparent before or even in the absence of alcoholic hepatitis. A similar lesion was observed in fatty livers of chronic alcohlics (38).

The authors consider this sclerosis as a precursor lesion of cirrhosis and regard alcoholic hepatitis as a relatively rare complication of chronic alcoholism. Therefore, Popper (24) claimes a second, slower process of progression to alcoholic cirrhosis, due to the fibrogenetic effect of alcohol. Actually, mild sclerosis may be seen in alcoholic fatty livers which obviously is not caused by a proceeding alcoholic hepatitis. It consists of perivenular sclerosis, centrilobular pericellular fibrosis (chicken-wire fibrosis), and/or the formation of fine porto-portal or centro-portal fibrous septa which may be complete or uncomplete. We observed such a sclerosis in 234 alcoholic fatty livers, 5.8% of all chronic alcoholics or 11.1% of the alcoholic fatty livers. Eight of these cases were followed by serial biopsies. Up to five biopsies were performed. During a maximum control period of six years no progression of sclerosis to cirrhosis was noted despite continuing abuse of alcohol (36).

Based on this findings, it is concluded that alcoholic hepatitis is the usual and probably the inevitable precursor of alcoholic cirrhosis. Theoretically, it cannot be denied with certainty that alcoholic cirrhosis also may develop in fatty liver by simple collagenisation. However, if such an event really occurs it is certainly very rare.

CIRRHOSIS FOLLOWING SMALL INTESTINAL BYPASS

So far, all available data deny the cirrhotogenic potential of malnutrition. Nutritional cirrhosis had been more or less rejected by most hepatologists when its few remaining supporters received unexpected help from surgeons.

The observation that massive resection of the small intestine reduced weight, led Payne, De Wind and Commons (22) to recommend small-intestinal bypass operations for control of severe obesity. In the last decade this operation, either as jejuno-ileal or jejuno-colic shunt has been widely performed especially in the U.S.A. From the first cases operated it became evident that bypass procedures are followed by a marked increase in hepatic steatosis because of mobilisation of depot fat for caloric needs. It was later shown that fatty liver and potential disabling diarrhoea were not the only side-effects. The first fatalities were caused by congestive heart failure and hypocalcaemia. Soon an increasing number of cases was reported which rapidly developed progressive hepatic injury proceeding to cirrhosis. The patients usually died within a year. Histologically, lesions indistinguishable from alcoholic hepatitis are reported, with centrolobular necrosis and alcoholic hyalin in hepatocytes (23). There is moderate focal inflammation. Cholestasis is a frequent finding. The final outcome is micronodular cirrhosis with severe fatty infiltration (7, 25).

The bypass would be an excellent procedure if the small intestine were an organ exclusively involved in the resorption of calories. This being the

case, the shunt operation would give the obese patient the chance to continue his vice without repentance. Unfortunately, things are not so easy. The small intestine has, among other tasks, an important role in electrolyte and bile salt metabolism, which makes the bypass procedure a most unphysiological method, demanding a high price for simple weight reduction.

At this point the usefulness of the operation is of less concern than the question of whether bypass-produced cirrhosis is a unique human model of a 'nutritional' cirrhosis.

Liver injury is most likely to follow jejuno-colic anastomosis (28). As severe steatosis may be well tolerated over many years we are forced to assume that liver injury leading to cirrhosis is caused by missing factors or factors added by the shunt (25). In jejuno-colic shunts the enterohepatic circulation of bile salts is interrupted. Reduced reabsorption increases hepatic synthesis of cholesterol and bile salts, associated with increased smooth endoplasmic reticulum in the hepatocytes. The hypertrophic reticulum might be functionally hypoactive (16), resulting in reduced hydroxylation of bile acids. The dihydroxy bile salt chenodeoxycholate is synthesised in excess instead of trihydroxycholate. Large amounts of bile salts normally absorbed in the terminal ileum are delivered by the intestinal shunt into the colon and exposed to bacterial action. Chenodeoxycholate is reduced to the monohydroxy bile salt lithocholate which causes liver injury, cholestasis and cirrhosis in several animal models (4). Further noxious mechanisms such as the absorption of toxic peptides and the deficiencies of essential fatty acids, vitamin E and electrolytes, especially potassium and calcium (25) may occur.

Although the pathogenesis of the 'blind loop syndrome' is not well understood it is of great importance. Extensive resection of the small intestine in man causes severe fatty infiltration of the liver but no cirrhosis. Similarly, Bondar and Pisesky found startling differences in dog experiments. After the small intestine was bypassed, it was either retained or resected. Animals with resection showed weight loss without complications, whereas animals with either jejuno-ileal or jejuno-colic bypass deteriorated progressively, death occurring within three to five months. Although these findings were not confirmed by Salmon this matter deserves further study.

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