Alcohol, malnutrition, and alcoholic cirrhosis

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ABSTRACT The relative importance of malnutrition and alcohol toxicity in the pathogenesis of cirrhosis has been controversial. In epidemiological studies, the incidence of cirrhosis can be correlated with the duration and amount of alcohol imbibed. The importance of nutrition has been discounted. In these studies, few analyses of dietary intake were included. Diets of patients with alcoholic cirrhosis characteristically are poor. Furthermore, alcohol toxicity impairs nutrition by interfering with absorption, transport, and utilization of essential nutrients. Patients with cirrhosis respond favorably to nutritious diets despite the concurrent intake of alcohol, although in lesser amount than their usual intakes. In long-term studies, highly nutritious diets have protected rats against cirrhosis from alcohol. However, in acute experiments with "loading" doses, there was evidence of direct hepatotoxicity in animals and man. Recently, cirrhosis has been produced in baboons with alcohol and a diet considered adequate. The findings are important, but there is some question whether dietary factors (imbalance) may have played a role. Also of recent interest has been the occurrence of lesions simulating alcoholic hepatitis and cirrhosis after jejunoileal bypass surgery. The evidence suggests that malnutrition may have been a major factor in this disease.

The roles of alcohol toxicity and of malnutrition in the pathogenesis of cirrhosis are not fully understood. Further studies are needed to clarify these relationships.
duration and amount of alcohol imbibed (10-12). Cirrhosis occurred in 25 to 50% of persons imbibing over 160 g of alcohol daily for 15 to 25 years. The large majority consumed over 200 g daily. There was no apparent relation to dietary intake in these reports. Others have discerned no differences in dietary intakes between cirrhotic and noncirrhotic alcoholics whether derived from middle (13) or lower economic class (14). In these reports analyses of dietary intake were not presented with one exception. In one report (10) protein intakes averaged 90 to 114 g. This is remarkably high when compared to the usual experience in the United States, and one wonders whether it is peculiar to wine drinkers, who characterized this series.

Thus, the relation of human nutrition to liver disease has been questioned. In one study (9), for example, 21 Germans who had subsisted on a low-protein, low-caloric intake for a year were grossly undernourished and had substantial loss of weight. There were no clinical signs of hepatic disease and no important histological changes in the liver.

The findings, however, may reflect the basic difference between undernutrition (starvation) and malnutrition. Malnutrition is seen chiefly where sufficient calories are provided by relatively nonnutritious foods or by alcohol, so as to create imbalance. The authors point out the limitations of their study: "Correlation of our results with recent reports of malnutrition in the Far East and elsewhere, and in experimental animals, is extremely difficult. The present report refers only to the effects of undernutrition in one group of Europeans in one town in Germany at one particular time, namely, August 1946" (9).

Dietary intakes should be documented by professional dieticians with the same expertise and care that other scientific data require to be of value. Towards this end a study was made of 304 chronic alcoholics (15). It was impossible to carry out a prospective study in a disease that evolves over a period of many years. Dietary intakes therefore were assessed for a period of at least 2 years before the presenting illness, in order to avoid changes of diet that might result from liver disease. Whenever possible patients were interviewed a second time. Confirmation of alcohol and food intakes were obtained from the family in 67%. In unconfirmed cases the patients were living alone. The mean duration of alcohol excess was 20 years; the mean daily intake of alcohol was 180 to 200 gm. Alcohol comprised 50 to 55% of total calories. On dividing this population between cirrhotic, precirrhotic, and noncirrhotic patients there were no significant differences in the amounts or duration of alcohol imbibed. In all groups the protein intakes were low. However, the cirrhotics consumed 15% less protein and 15% less food calories than the noncirrhotic patients prior to onset of clinical disease. The differences were statistically significant ($P < 0.05$).

Although there is a close time-dose correlation between intake of alcohol and frequency of cirrhosis there are as many subjects who fail to develop the disease after alcohol excess of like degree and duration. This implies that other factors may be involved in the pathogenesis of cirrhosis, factors that could be either constitutional or environmental in nature. Indeed one of the epidemiologists previously cited cautioned that "any additional enhancing factor, such as nutritional imbalance will increase the risk of cirrhosis in the alcoholic to an unpredictable extent" (12).

**Experimental clinical studies**

Although the response to dietary therapy cited (6, 7) favored recovery from cirrhosis of the liver it did not necessarily throw light on pathogenesis, in as much as a noxious agent, alcohol, was removed. To explore this further several studies were undertaken in which alcohol was administered to patients under controlled hospital conditions.

In one study (6) four volunteer subjects with signs of gross malnutrition and decompensated cirrhosis were placed on a nutritious, high protein diet and alcohol. After their conditions had improved and stabilized 9 ounces of 40% ethanol were administered in divided doses daily for 6, 6, 14, and 18 months, respectively. Improvement continued in clinical signs and laboratory tests. Follow-up ranged from 1 to 4 years after discharge from the hospital.

In another study (16) 21 patients who had partially recovered from liver failure were placed in three dietary groups: one group of 15 patients was fed a diet containing protein...
(P) 100 to 120 g, carbohydrate (C) 300 g, fat (F) 80 g, cal 2400. A second group of four patients was fed a diet containing P 25 to 30 g, C 260 g, F 80 g, cal 1480. To eliminate several variables a third group of two patients was placed first on the above high-protein diet for two months, and then on the low-protein diet for 2 months but with the caloric content increased to that of the high protein diet. (30 g, C 350 g, F 90 g, cal 2330.) Ethanol was administered to all groups in like amounts. Absolute alcohol was diluted with unsweetened fruit juice so that the mixture contained 55% alcohol. This was served four times daily in 90-ml doses, equivalent to 154 g absolute alcohol. The study extended over 60 days for the first two groups and 120 days for the third group. Needle biopsy of the liver was performed before and after each 2-month period. In those fed the high-protein diet there was steady clinical improvement except for one case. Laboratory tests reflected clinical changes. Histological findings after 2 months showed slight increase in fatty infiltration, slight decrease in focal necrosis and in inflammatory reaction, no apparent change in fibrosis. Of four patients fed the low-protein diet and ethanol the trend was either toward no change or toward deterioration in clinical state, laboratory tests, and histological findings. In the two patients placed first on a high-protein intake for 2 months and then on a low-protein intake for 2 months the findings corroborated the results in the previous groups.

In a third study (17) similar findings were reported: one group of 13 patients entered the hospital with signs of decompensated cirrhosis. After 1 to 3 weeks they were in a relatively stable condition and were placed on a nutritious diet plus ethanol. The diet contained 55 to 75 g protein. Calories were approximately 2000. Ethanol was mixed with fruit juice and 10% protein hydrolysate. Total dosage was 3 ml 95% ethanol per kilogram (equivalent to 156 g/70 kg subject).

A second group of 10 patients received doses ranging from 140 to 210 g ethanol daily, and a third group of four patients received doses ranging from 200 to 300 g ethanol daily. All groups showed clinical and laboratory signs of improvement. Biopsies at the end of the study period (approximately 10 weeks) showed little or no fatty changes. In three patients with serial biopsies there was progressive decrease in fat.

Two other studies (18, 19) with smaller numbers of patients indicated that alcohol in moderate dosage did not impede recovery from alcoholic liver disease.

In contrast to the above studies are two more recent reports which suggest that alcohol exerts direct hepatotoxic effects independently of dietary intake. The first study (20) comprised five alcoholics who had abstained for periods ranging from 1 month to 2 years. Previous liver biopsies had disclosed fatty changes but biopsies obtained before this study showed normal morphology. The patients were fed a nutritious diet, expressed in percentage of total calories as P 16%, C 48%, F 36%, cal 2300. This is equivalent to P 92 g, C 276 g, F 92, cal 2300. Ethanol was added to the diet of two subjects and was substituted for carbohydrate in two other subjects. It was administered as blended whiskey in divided doses. Four subjects received about 150 g of alcohol daily and a fifth received up to 300 g. Biopsies of liver obtained after 8 to 21 days showed increased fat. There were no significant functional changes. It was concluded that alcohol exerted a direct hepatotoxic effect (fatty liver) independent of nutritional deficiency.

Since the above study was performed on subjects with alcoholic backgrounds a second study (21) was undertaken with 12 healthy, nonalcoholic volunteers. As in the previous study the caloric intake was approximately 2300. Dietary constituents were expressed in percentage of total calories. There were 4 groups: group 1 received the standard control diet with P 16%, C 48%, F 36%, expressed as percentage of total calories. Group 2 received a high-protein control diet. In both groups alcohol was then substituted for carbohydrate up to 40% of total calories. Groups 3 and 4 received similar control diets to which alcohol was then added in like amount. Experimental periods ranged from 2 to 14 days. Liver biopsies showed consistent increases in fat. There also were ultrastructural changes in mitochondria and endoplasmic reticulum. The latter changes were more marked when alcohol was substituted for carbohydrate than when it was added to the control diet.
There is no reason to challenge the findings. Assuming the changes to be manifestations of hepatic injury due to alcohol it is difficult to reconcile them with the previous findings cited, in which alcohol was administered with relative impunity to a cirrhotic population that might be considered more vulnerable. Moreover, alcohol was administered over greater periods of time and in comparable dosage. It seems likely that the differences observed were related to methodology.

Experimental studies on animals

An experimental animal may be more resistant or more susceptible than man to deficiency of a particular nutrient or to a toxic agent such as alcohol. There always is this handicap in the application of animal experiments to human disease. Attempts to reproduce cirrhosis experimentally have been made for years. Animals fed diets deficient in choline and protein develop fatty livers and cirrhosis resembling alcoholic cirrhosis. These effects have been produced readily in the rat (22, 23), less readily in the dog (24) and primate (25, 26). However, certain features of alcoholic cirrhosis were lacking, notably the acute inflammatory changes of alcoholic hepatitis.

When alcohol was added to diets marginally deficient in choline hepatic fibrosis developed in the rat (22). It was suggested that alcohol increased the choline requirements of the animals (27). Other studies in rats have shown that high-protein diets can protect against hepatic injury from alcohol even when alcohol constituted 30 to 45% of caloric intake for many months (28–31).

The importance of the experimental model is in establishing the concept of nutritional cirrhosis. There is no solid evidence that alcoholic cirrhosis in man results from dietary deficiency alone, whether it be choline or protein. However, there is evidence that alcohol can exert an adverse effect on the biosynthesis of phosphatidyl choline (lecithin) which is the major phospholipid of cell membranes (32). It is conceivable that alcohol toxicity may thus impair availability or utilization of choline in man.

The loading effect of alcohol may be important with regard to alcoholic hepatitis. It is well known that a large, loading dose or bolus of alcohol, in either man or experimental animal, is less well tolerated than the same amount of alcohol administered over a longer period of time. The effect probably is due to the higher blood alcohol level achieved. This loading effect may have relevance to the development of acute alcoholic hepatitis. In rats fed a marginal diet or a commercial chow diet hepatic changes resembling alcoholic hepatitis were produced when weekly acute intoxicating doses were superimposed on the chronic administration of alcohol. These were seen in all of five rats on a protein and choline-deficient diet and in two of five rats on a chow diet. Changes in the latter group were minimal. The numbers were very small, but they suggest that in sufficient dosage acute alcohol toxicity can override a protective effect of diet (33). Confirmation of these studies has not yet appeared.

Of particular interest is the recent report of lesions produced in baboons closely resembling those of human alcoholic cirrhosis (34). The animals received liquid diets. A control group received a diet considered adequate for normal nutritional needs of this species. The test animals received a similar diet in which alcohol was substituted for sucrose in isocaloric amounts as shown in Table 1.

The diets were isocaloric and were considered to be nutritionally equivalent. It was concluded, therefore, that the hepatic changes were due to alcohol hepatotoxicity alone. The observations are important but more data are needed to interpret the findings. It is possible that a diet which is adequate under normal conditions may not be adequate when alcohol, comprising 50% of total calories, is substituted for carbohydrate. In fact, it has been suggested that calories derived from alcohol

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are “empty” calories, devoid of nutritional value.

In making this substitution the study follows a familiar experimental model but to an extreme degree. The effects of the dietary imbalance thus created are not fully known. One could speculate on several possibilities.

A sharp decrease in carbohydrate intake would limit glycogen reserves and gluconeogenesis; it could impair a protein sparing effect of carbohydrate; the high fat to carbohydrate ratio might cause problems related to the oxidation of alcohol and to fat metabolism.

The question remains whether dietary factors play a significant role in the pathogenesis of alcoholic cirrhosis. In order to answer this question the comparison of three experimental diets would be informative: 1) a substandard, low-protein, low-caloric diet, which is commonplace with chronic alcoholics; 2) a diet similar to the control diet in Table 1, which is considered to meet normal nutritional needs in the baboon; 3) a highly nutritious diet, rich in protein, low in fat, supplemented with folate, vitamin B complex, and essential minerals in excess of usual requirements. By increasing the protein and decreasing the fat this diet could be made isocaloric with diet no. 2.

It would be important to test several levels of alcohol intake as well. On the basis of clinical and experimental data cited it seems likely that there is a range of alcohol intake that is tolerated without liver damage under optimal dietary conditions. However, it is also likely that there is a threshold of alcohol toxicity beyond which no protection is afforded by dietary manipulation.

Metabolic derangements associated with alcohol

The studies cited thus far have been directed largely at dietary intake. Possibly they were simplistic in view of later developments. It has become evident that alcohol toxicity can cause metabolic changes with far reaching effects upon nutrition. These may be summarized briefly: 1) it interferes with the absorption of nutrients including thiamin, folate, vitamin B12, amino acids, and calcium. It impairs the absorption of water and electrolytes and glucose; 2) it interferes with the absorption of fat; 3) it exerts multiple effects on carbohydrate metabolism; 4) it impedes the synthesis of albumin in the liver and leads to a defect in hepatic protein export; 5) it impedes the conversion of vitamins from their inactive to active forms where they serve as cofactors (notably in vitamin A, thiamin, riboflavin, and pyridoxin metabolism); 6) it induces catabolic loss of zinc, calcium, and magnesium; 7) it causes gastritis; in others, pancreatitis and its related malabsorption. Thus, alcohol-associated malnutrition is caused by poor intake and by impaired absorption, transport, and utilization of nutrients.

It has been estimated that in the oxidation of alcohol roughly 80% is mediated by alcohol dehydrogenase and 20% by microsomal ethanol oxidizing systems. The rate of oxidation is sharply reduced by a low-protein intake. Indeed, the rate may decrease 30 to 50% when dietary protein is reduced from 120 to 20 g in the same subject.

Jejunoileal bypass

Ideally, as Pope said, “The proper study of mankind is man.” However, a long-term controlled study with alcohol in man is not feasible. Recently a human experiment bearing on the subject was performed unwittingly in patients subjected to jejunoileal bypass surgery for extreme obesity.

This procedure often is followed by severe diarrhea, malabsorption syndrome, hypoproteinemia, depletion of essential nutrients, and a sharp fall in weight. The livers have marked fatty changes. A significant number of patients develop lesions simulating alcoholic liver disease.

Several etiologies have been suggested. These include altered bile metabolism, blind loop syndrome with bacterial endotoxin, and protein-calorie malnutrition. None of these hypotheses can fully explain the features. The presence of toxic circulating bile acids has been noted but their relation to the observed hepatic changes is not evident. Bacterial overgrowth in the blind loops has been reported as a common phenomenon in dogs but has been an uncommon finding in human cases. The pathological changes produced by bile acids or bacterial invasion
do not resemble the hepatitis and cirrhosis produced by the bypass procedure. "The 2 to 6 month lag period that regularly occurs between by-pass procedure and the onset of hepatic dysfunction favors a pathogenesis that is not a simple direct toxic effect." (65) In protein-calorie malnutrition (kwashiorkor) fatty infiltration and mild hepatocellular degeneration are the rule, and only a few progress to cirrhosis. In obese patients subjected to starvation to achieve weight reduction, liver fat tends to decrease and mild hepatocellular degenerative changes are occasionally seen (72). However, patients with jejunooileal bypass have far more acute and severe nutritional derangement. There is depletion of essential and nonessential amino acids, potassium, calcium, zinc, magnesium, and other nutrients (69, 73). In a comparison of biopsies obtained from 235 patients preoperatively and 234 postoperatively there was an impressive increase in lesions simulating alcoholic liver disease. In addition to fatty metamorphosis there were acute inflammatory changes, "alcoholic" hyalin, zonal necrosis, and increased fibrosis (66). These changes may regress with time (66, 69, 74). However, in a survey of the literature 3 to 6% of cases showed progressive hepatic deterioration, some leading to frank cirrhosis and failure (67). In one series of 75 patients (69) four developed cirrhosis postoperatively.

Arrest, improvement, and at least partial recovery have been achieved by restoration of intestinal continuity or by parenteral hyperalimentation (66-68, 75, 76). Emphasis has been placed on supplements of amino acids, vitamins, minerals, and potassium. In one report (74) oral supplementation of amino acids failed to check postoperative deterioration. However, the authors had seen two patients who made substantial improvement after intravenous administration of amino acids. Another report (75) on three patients with severe fatty metamorphosis of the liver showed prompt decrease in liver size and in hepatic steatosis after intravenous infusions of these supplements. A third report (67) cites five patients who developed jaundice and progressive worsening of liver function tests 5 to 11 months postoperatively. Four of the five showed increased liver damage on biopsy when compared to preoperative biopsies. All were placed on intravenous hyperalimentation. Four of five improved within 2 weeks. Improvement was maintained in all even with the shunt intact.

Admittedly, experience with parenteral alimentation thus far is limited, but it has been consistent. The histological features and the clinical response to therapy suggest that malnutrition is a major factor in the pathogenesis of the disease. This does not exclude the possibility that other factors mentioned may play a contributory part.

Direct hepatotoxic effects of alcohol

Toxicity of alcohol in body tissues is closely related to the duration of exposure and the blood-alcohol concentration. This in turn depends upon the amount and rate of administration of alcohol and the rate of oxidation of alcohol. The evidence presented suggests that alcohol is tolerated up to a threshold beyond which toxic effects develop. In the experimental animal alcohol comprising 36% of the caloric intake has been tolerated. However, at levels exceeding 45% of total calories signs of hepatotoxicity may ensue both in experimental animals and man. Hepatotoxicity from alcohol varies with different animal species. Doubtless there are individual differences in susceptibility as well.

Evidence of hepatotoxicity is manifested by clinical and laboratory tests, but these are relatively slow in appearing when compared to histological changes. Although the earliest signs are fatty changes these lack specificity. Ultrastructural changes seem to be early, sensitive markers of hepatotoxicity. In livers of rats on protein-deficient diets (without alcohol) (77) and in patients with protein-calorie malnutrition (78) changes in mitochondria and endoplasmic reticulum have been described. The alterations, however, appear to be less striking than those reported after exposure to alcohol in experimental animals (79) and man (21, 80).

Conclusions

The mechanism by which alcohol excess leads to cirrhosis is not fully understood. The question whether alcohol is directly hepatotoxic or whether it is indirectly hepatotoxic by interfering with nutrition and metabolic processes is not yet answered.
Probably both mechanisms are involved. They are not mutually exclusive. Malnutrition may result from inadequate diet, malabsorption, impaired transport, and faulty utilization of nutrients. These in turn appear to render the liver more susceptible to alcohol toxicity. However, the crucial steps leading to cirrhosis need further clarification.2

References


2 In the following Reference section only a few selected references are cited from the extensive literature. References 35, 40-43, 46, and 57 are review articles.


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72. Rozenthal, P., C. Biava, H. Spencer and H. J.


