MEDICAL GRAND ROUNDS

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ALCOHOL, THE LIVER, ... AND YOU?

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INTRODUCTION

The association between the excessive consumption of alcohol-containing beverages and the development of liver disease has been recognized from antiquity. Motivated, perhaps, by the vested interest most of us feel in disproving a direct association between the two, a controversy, sometimes heated, has raged until just the last few years as to the importance of alcohol itself in the genesis of the distinctive liver disease observed in alcoholics. Unfortunately, the evidence now rather convincingly indicts the two carbon molecule itself, as the prime factor in the pathogenesis of alcoholic liver disease and relegates to only subsidiary roles the other erstwhile candidates such as dietary deficiencies and the congeners present in the various beverages.

There are three basic histological forms of alcoholic liver disease and, in effect, two different diseases induced in the liver by ethanol.

Histologic Forms of Alcoholic Liver Disease

a. Fatty liver (steatosis)

b. Alcoholic hepatitis

c. Cirrhosis

Each of these histologic forms may occur alone or in combinations in which two or all three may coexist. Alcoholic hepatitis and cirrhosis are manifestations of the *same* process which, in the light of our current ignorance, can be thought of as a disease separate from fatty metamorphosis.

FATTY LIVER

This is a universal, immediate, dose-related, metabolic consequence of the ingestion of excessive quantities of ethanol. Accumulation of hepatic triglyceride can be demonstrated after as little as two days of drinking less than inebriating quantities of alcohol. It is a benign condition in that, while symptoms, signs, and abnormal liver function tests may result, the process is entirely reversible with cessation of consumption of alcohol and permanent structural hepatic damage leading to cirrhosis does *not* develop no matter how long the fat persists.

Pathogenesis: It was argued for many years that fat accumulation in the livers of alcoholics was a manifestation not of a "toxic" effect of alcohol itself but of the dietary deficiencies so prevalent in the alcoholic population. Massive accumulations of fat have been well documented in children subjected to diets deficient in protein (kwashiorkor), in rats deficient in certain lipotropic factors (choline, methionine) and in obese patients who were subjected to an ileal bypass procedure designed to produce severe

malabsorption, and in whom the serum amino acid profile simulates that seen in severe protein deprivation. Recently, however, the prime role played by alcohol *per se* in the genesis of hepatic triglyceride accumulation has been clearly demonstrated by Lieber and Rubin in studies involving both alcoholic and normal volunteers.

In their initial studies five alcoholic patients who had not been drinking for the preceeding 2 to 5 months were fed a high protein (120-140 G/day), low fat (55-70 G) diet in which there was isocaloric replacement of carbohydrate with ethanol in progressively increasing amounts. The final daily alcohol intake reached 140 to 170 G which is equivalent to approximately 1 pint of 86 proof liquor per day. The diet was well supplemented with choline, vitamins, and minerals. Liver biopsies were obtained before and at the end of 18 days on this diet in all patients, after 8 days on the diet in 2 patients and again one month after discontinuing the diet in 2 patients. The tissue was examined histologically and its total lipid and triglyceride content was quantitated chemically.

Subject	Time on Alcohol (days)	Visible Fat (0 - 4+)	Triglyceride (mg/100mg protein)
J.G.	0	0	3.1
	8	2+	6.7
	18	3+	10.4
	1 month after cessation	0	1.7
J.S.	0	1+	1.5
	8	2+	5.9
	18	3+	10.7
F.A.	0	1+	2.5
	8	2+	33.3
	18	2+	13.8
J.K.	0	0	6.7
	18	4+	54.4
	1 month after cessation	0	-
S.J.	0	0	3.2
	18	4+	48.3

(From Lieber and Rubin, Am. J. Med. 44:200, 1968.)

In each instance the addition of alcohol to the patient's diet was followed by an increase, often a striking increase, in the hepatic content of fat. The increase was apparent both chemically and histologically within 8 days, was more marked at 18 days and had completely dissipated within a month of alcohol withdrawal.

To exclude the possibility that this response was a singular one seen only in alcoholics, Lieber and Rubin then conducted a series of similar experiments in 12 normal students, who surprisingly enough, had had very little or even no experience with alcoholic beverages. Diets were either standard (70-90 G protein, 84-104 G fat) or high protein (120-140 G), low fat (55-70 G). Isocaloric replacement of carbohydrate with alcohol was affected as in the previous study and biopsies were obtained before and after this substitution.

Group	Visible Fat (0 - 4+)		Hepatic Triglyceride (mg/100mg protein)	
	Control	After Alcohol	Control	After Alcohol
Alcohol with standard diet	1+	4+	8.8	57.2
	0	3+	5.0	68.1
	0	3+	13.9	67.1
Alcohol with low fat diet	0	2+	3.8	12.7
	0	2+	4.6	7.3
		3+		27.8
Alcohol for 2 days standard diet	0	2+	6.8	11.1
	1+	3+	14.4	32.0
	0	2+	6.8	26.7
Alcohol for 2 days minimal fat diet	1+	1+	11.1	
	1+	1+	7.3	15.3
	1+	2+	8.7	17.8
	0	1+	10.2	19.3

(From Rubin and Lieber, NEJM 278:869, 1968.)

Histological and chemical evidence of fat accumulation was noted in all subjects. The degree of fat accumulation was, however, clearly influenced by the dietary intake of fat and was more dramatic in patients on a standard diet than in patients in whom the fat content was reduced.

Other volunteers were given alcohol for just 2 days but in increased amounts. (1.5 pints 85 proof liquor) Smaller, but finite, increases in hepatic lipids were demonstrated in these subjects too, and again, the quantity of fat was modified, but not eliminated, by the reduction in dietary fat.

These authors concluded:

Ethanol per se leads to fat accumulation.

Dietary effects may modify response.

Fatty change is demonstrable within 2 days.

Quantity of fat increases progressively with time.

Relatively small quantities of alcohol are required.

Effect is totally and rapidly reversible.

Lieber CS, Rubin E: Alcoholic fatty liver in man on high protein and low fat diet. Am J Med 44:200-206, 1968.

Rubin E, Lieber CS: Alcohol-induced hepatic injury in non-alcoholic volunteers. N Engl J Med 278:869-876, 1968.

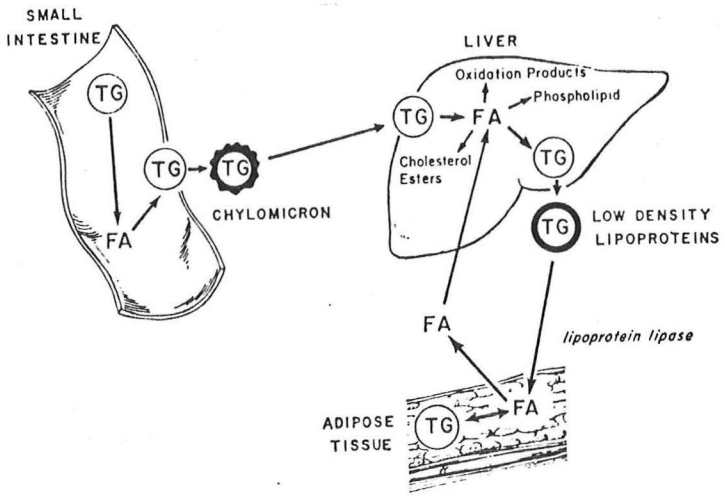
These studies, with others in experimental animals, have established that ethanol *per se* causes accumulation of fat in the liver despite the provision of adequate calories, protein, vitamins and lipotropes. The quantity of accumulated fat may be modified by dietary manipulations, however, and there is no reason to doubt that the known potential of protein malnutrition to lead to lipid accumulation would be additive to the effects of ethanol itself in the alcoholic population. These studies also provide insight into the rapidity with which the fat appears, the relatively small amounts of alcohol necessary for its development and the rapid reversibility of the process when alcohol is withdrawn.

To begin to understand how ethanol might produce these effects we need to review, briefly

a. The normal mechanisms of absorption, disposition, mobilization, and metabolism of lipid and in particular of triglyceride.

b. The metabolic fate of alcohol.

Physiological Disposition of Lipid



(From Alpers and Isselbacher, Diseases of the Liver, Leon Schiff (Ed.) p. 815, 1975.)

Dietary fats consist mostly of triglycerides. Under the influence of pancreatic lipase, these are hydrolyzed in the gut to monoglycerides and fatty acids. The fatty acids are absorbed into the small intestinal mucosa and re-esterified there with glycerol to re-form triglyceride. The triglycerides then interact with protein, phospholipid, and cholesterol to form chylomicra which gain the circulation via the lymph vessels and the thoracic duct. The chylomicra circulate and are presented to the liver where the triglycerides are again hydrolyzed to fatty acids and glycerol. These fatty acids form part of the hepatic pool of fatty acids. Other contributions to this pool come from fatty acids endogenously synthesized in the liver and fatty acids which are released from the depot stores of the adipose tissue and delivered to the liver bound to albumin.

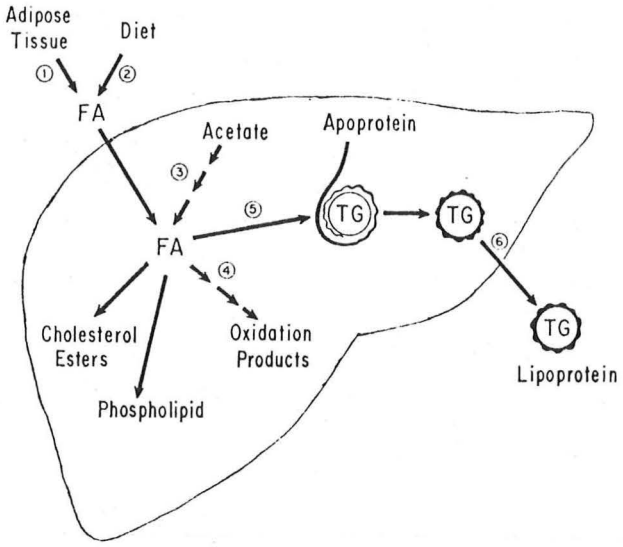
The pool of fatty acids in the liver may be subjected to a number of metabolic fates

a. Oxidation for energy production

b. Resynthesis of triglyceride

c. Synthesis of phospholipid

d. Synthesis of cholesterol esters.



(From Alpers and Isselbacher, Diseases of the Liver, Leon Schiff (ed.) p. 815, 1975)

The newly synthesized lipids (triglycerides plus phospholipid plus cholesterol) are attached to a specific apoprotein, synthesized in the ribosomes of the RER, to form lipoprotein (VLDL) which is then released from the liver cell into the circulation. At peripheral cellular sites the triglycerides are again hydrolyzed under the influence of lipoprotein lipase and the fatty acids thus formed are taken into the adipose cells and re-esterified into triglyceride for storage.

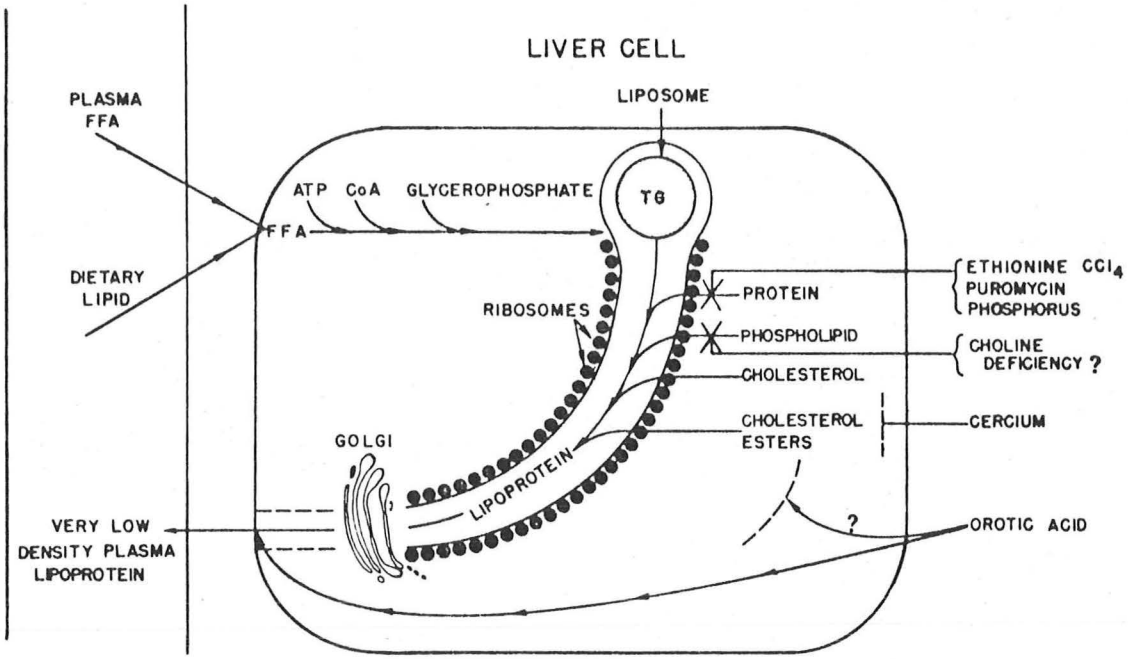
Alpers DH, Isselbacher KJ: Fatty Liver, Biochemical and Clinical Aspects. Diseases of the Liver, 4th Ed. L. Schiff (ed). Philadelphia, Lippincott. 1975, pp 815-832.

Fat, in the form of triglyceride will accumulate in the liver whenever the production of triglyceride exceeds the secretion of triglyceride, as lipoprotein from the liver.

The accumulation of triglyceride is enhanced by:

1. ↑ availability of fatty acids
    a. increased dietary intake (obesity)
    b. mobilization of fat stores (starvation)
    c. increased *de novo* synthesis (adult onset diabetes)
2. ↓ oxidation of fatty acids
3. Impaired secretion of lipoprotein
    a. impaired synthesis of apoprotein (tetracycline)
    b. impaired packaging of lipoprotein (choline deficiency)
    c. interference with actual secretion (orotic acid).

There are many different causes of fatty liver and the mechanisms whereby steatosis develops are equally varied.



(From Farber, Alcoholic Liver Pathology, Khanna, Israel, and Kalant (Ed.) p. 289, 1975.)

Ethanol has been shown to interfere with the physiological pathway in a number of different places. The significance of these effects in the *in vivo* situation is not clear, however, as some of them appear to be dependent on specific experimental conditions. The current consensus locates the major, and pathogenetically most important, influence to be an inhibition of fatty acid oxidation in the mitochondria due to inhibition of the Krebs cycle caused by the change in redox state consequent to the increased $NADH/NAD^+$ which results from the metabolism of ethanol.

Drenick EJ, Simmons F and Murphy TF. Effect on hepatic morphology of treatment of obesity by fasting, reducing diets and small bowel bypass. N Engl J Med 282:829-833, 1970.

Moxley RT, Pozefsky T and Lockwood DH: Protein distribution and liver disease after jejuno ileal bypass for morbid obesity. N Engl J Med 290:921-925, 1974.

Kern WH, Heger AH, Payne JH, DeWind LT: Fatty metamorphosis of the liver in morbid obesity. Arch Pathol 96:342-346, 1973.

Holzbach RT, Wieland RG, Lieber CS et al: Hepatic lipid in morbid obesity. N Engl J Med 290:296-299, 1974.

Camerini-Davalos R, Marble A, Muench H. Liver function in diabetes mellitus. N Engl J Med 266:1349-1354, 1962.

Creutzfeldt W, Fredricks H, Sickinger K: Liver disease and diabetes mellitus. Progress in Liver Diseases Vol 3. H Popper and F Schaffner (ed) Grune & Stratton. New York pp 371-407.

Lieber CS: Alcohol and malnutrition in the pathogenesis of liver disease. J.A.M.A. 233:1077-1082, 1975.

Weber, BL: The liver in kwashiorkor. Arch Pathol 98:400-408, 1974.

Lieber CS, Spritz N and DeCarli LM: Role of dietary, adipose and endogenously synthesized fatty acids in the pathogenesis of the alcoholic fatty liver. J Clin Invest 1:51-62, 1966.

Metabolism of Ethanol

The liver is the major site of ethanol degradation. A very small amount is excreted unchanged by the kidneys or lungs and a fraction is oxidized in extrahepatic sites but approximately 90% of ingested alcohol is dealt with by the liver and, for the most part, this is by oxidation to acetaldehyde and thence to acetate. The acetate, so formed, is not oxidized further in the liver because of inhibition of the citric acid cycle. Most of it enters the circulation and is transported to peripheral sites where it is oxidized to CO_2 and H_2O.

There are at least three postulated mechanisms whereby ethanol is oxidized to acetaldehyde.

Alcohol Dehydrogenase

$$CH_3CH_2OH + NAD^+ \xrightarrow[ADH]{} CH_3CHO + NADH + H^+$$

Microsomal Ethanol Oxidizing System

$$CH_3CH_2OH + NADPH + H^+ + O_2 \xrightarrow[MEOS]{} CH_3CHO + NADP^+ + 2H_2O$$

NADPH Oxidase + Catalase

1. $NADPH + H^+ + O_2 \xrightarrow[\text{oxidase}]{\text{NADPH}} NADP^+ + H_2O_2$

2. $CH_3CH_2OH + H_2O_2 \xrightarrow[\text{catalase}]{} CH_3CHO + 2H_2O$

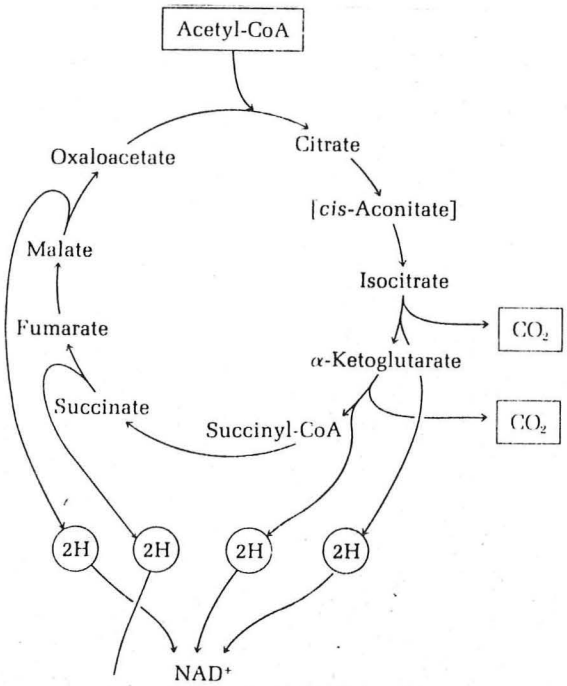
(From Rubin and Lieber, Progress in Liver Diseases, Popper and Schaffner (Ed.), p. 549, 1972.)

There is no argument that, of these, the only pathway of major physiological significance is that mediated by the cytosol enzyme alcohol dehydrogenase. This reaction is coupled to the reduction of NAD^+ to NADH. The acetaldehyde, so formed, then enters the mitochondria where it is further oxidized by acetaldehyde dehydrogenase to acetate. Again this is at the expense of NAD^+ reduction to NADH. Thus, when the liver is presented with a quantity of ethanol large quantities of NADH are produced and there is an increase in the ratio of $NADH/NAD^+$. The availability of NAD^+ in fact becomes the rate limiting step in the metabolism of ethanol. The liver adopts two basic methods to replenish its NAD^+ content. One is to deliver the excess NADH to the respiratory chain within the mitochondria where it will be re-oxidized with the coupled production of high energy phosphate bonds in the form of ATP. The second method is to encourage all chemical reactions which are coupled to the conversion of NADH to NAD^+.

CONSEQUENCES OF ↑ $NADH/NAD^+$ RATIO

Hydroxyacetone Phosphate	+	NADH	+	H^+	⇌	α-GLYCEROPHOSPHATE	+	NAD^+
Oxaloacetate	+	NADH	+	H^+	⇌	MALATE	+	NAD^+
α-Ketoglutarate	+	NADH	+	H^+	⇌	ISOCITRATE	+	NAD^+
Pyruvate	+	NADH	+	H^+	⇌	LACTATE	+	NAD^+
Acetoacetate	+	NADH	+	H^+	⇌	β HYDROXYBUTYRATE	+	NAD^+

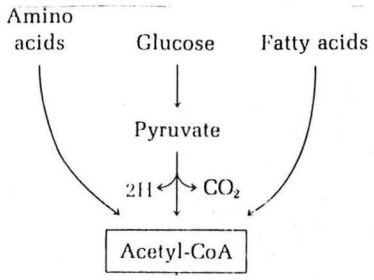
The inhibition of both the conversion of isocitrate to αketoglutarate and of the subsequent oxidation of αketoglutarate to succinate, together with the failure to generate oxaloacetate from malate leads to a marked inhibition of the citric acid cycle.



The tricarboxylic acid cycle

(From Biochemistry, Lehninger (Ed.), p. 443, 1975.)

This cycle is the final common pathway for the oxidation of fatty acids, carbohydrates and the acetate formed from amino acids and even ethanol metabolism itself. Since acetate cannot be oxidized by this cycle it tends to accumulate as acetyl CoA in the liver cell.



(From Biochemistry, Lehninger (ed.), p. 443, 1975.)

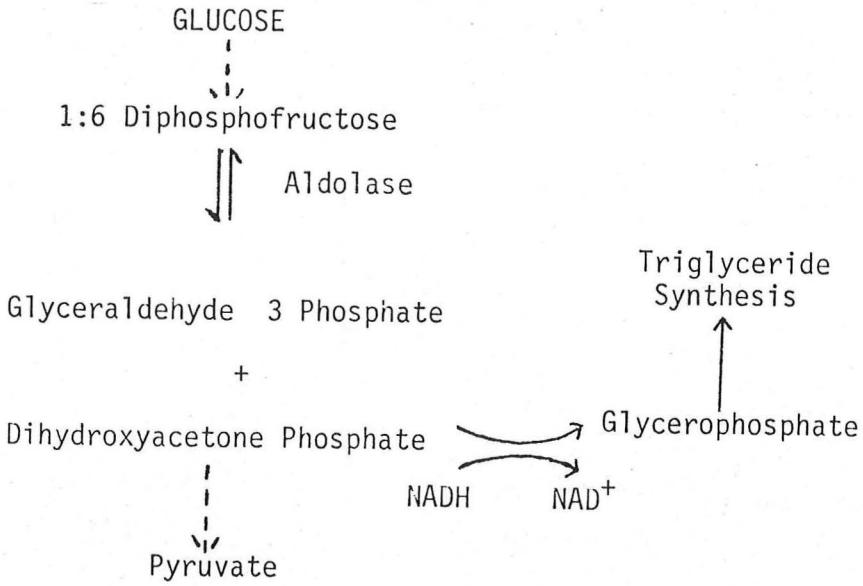
A number of consequences ensue from the inhibition of the citric acid cycle.

a. The tendency to accumulate acetyl CoA leads to an increase in the production of ketone bodies which for the most part exist as β-hydroxybutyrate rather than acetoacetate (this interconversion is also mediated by oxidation of NADH to NAD^+).

b. The synthesis of fatty acids is stimulated by the availability of acetyl CoA and as a means of using the excess reducing equivalents.

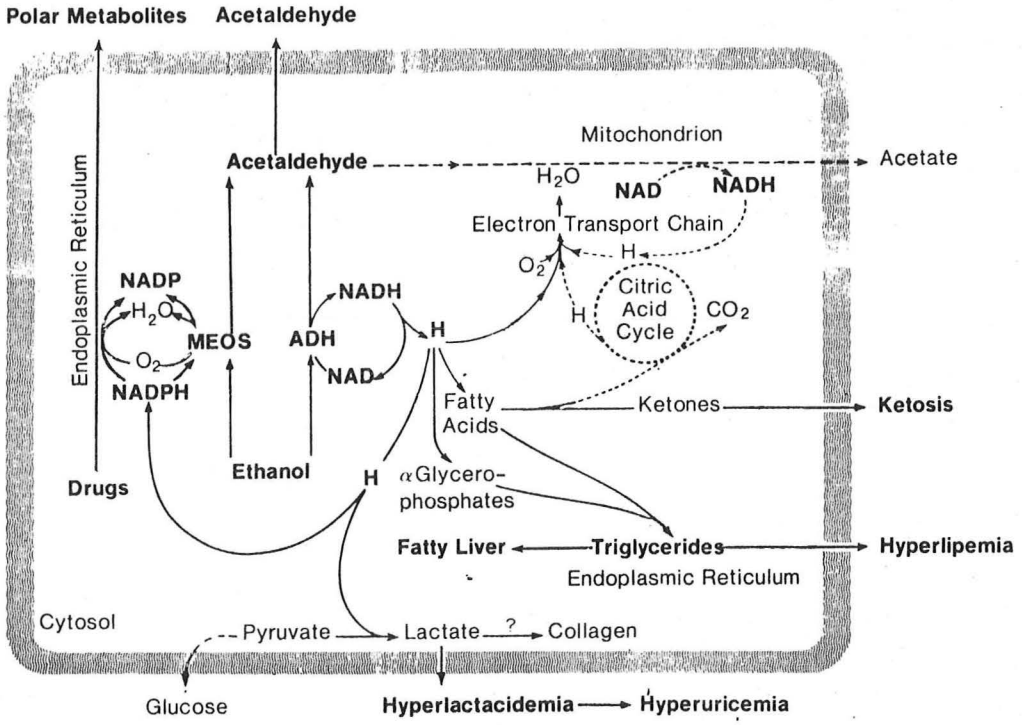
c. There is inhibition of gluconeogenesis and hence the risk of hypoglycemia. This is caused by the deficiency of oxaloacetate and pyruvate.

d. There is stimulation of triglyceride formation by the accumulation of α-glycerophosphate which is the carbohydrate skeleton upon which the fatty acids are joined.



e. The accumulation of lactate contributes to acidosis, interferes with urinary uric acid secretion contributing to hyperuricemia and may be related to stimulation of collagen synthesis.

f. The failure to oxidize fatty acids derived either from the diet, mobilized from fat depots, or endogenously synthesized, encourages their esterification as triglyceride beyond the capacity of lipoprotein formation and secretion to remove them. This, then is the single most important factor causing alcohol-induced fatty liver.

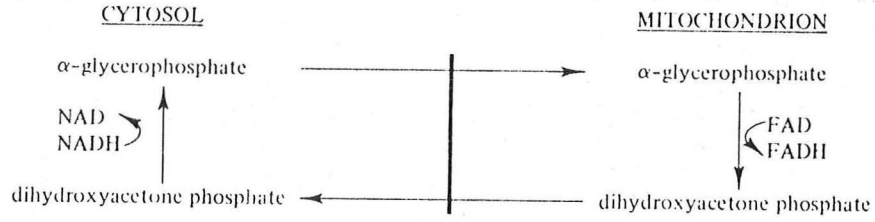


Summary of Metabolic Consequences of Ethanol Metabolism in the Liver

(From Lieber, JAMA 233:1077, 1975.)

These biochemical reactions with their manifold physiological sequelae are of only secondary importance in the re-oxidation of NADH to NAD^+ however. The prime method and eventually the rate-limiting factor in the metabolism of ethanol is by oxidation along the respiratory chain. NADH is unable to diffuse into the mitochondria directly and the transfer of the reduced nucleotide is mediated by one of three major carrier mechanisms.

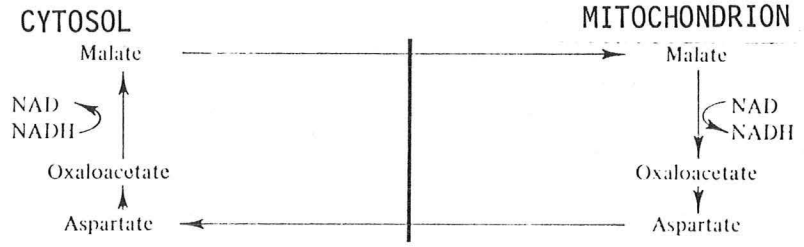
a) *Glycerophosphate-dihydroxyacetonephosphate Shuttle*



(From Rubin and Lieber, Progress in Liver Diseases, Popper and Schaffner (Ed.), p. 549, 1972.)

Glycerophosphate is derived from dihydroxyacetonephosphate in the cytosol with the oxidation of NADH to NAD^+. The glycerophosphate is able to diffuse into the mitochondria where it is reduced to dehydroxyacetone phosphate by an enzyme glycerophosphatase oxidase, with the coincident reduction of FAD^+ to FADH. The dihydroxyacetone phosphate then diffuses back into the cytosol to complete the cycle, during which a reducing equivalent has been transferred from cytosol to mitochondrion where it can enter the respiratory chain.

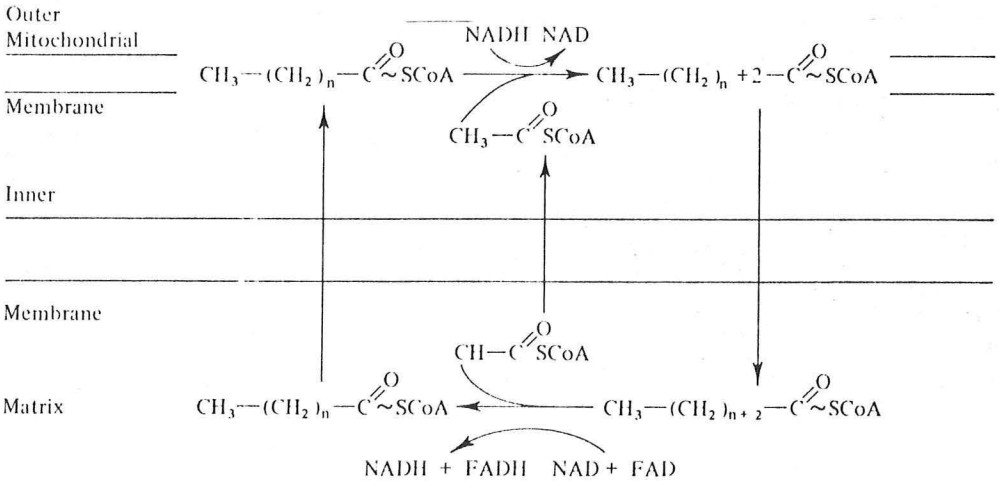
b) Of even more consequence is the *oxaloacetate-malate shuttle.*



(From Rubin and Lieber, Progress in Liver Diseases, Popper and Schaffner (Ed.), p. 549, 1972.)

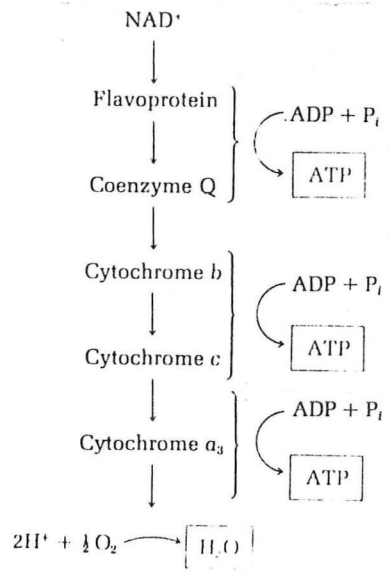
Cytosol oxaloacetate is reduced to malate with the oxidation of $NADH^+$ to NAD^+. Malate then crosses into the mitochondria and is re-oxidized to oxaloacetate accompanied by the reduction of NAD^+ to NADH. Glutamic oxaloacetic transaminase converts oxaloacetate to aspartate which returns to the cytosol and is reconverted to oxaloacetate, completing the cycle. Once again a molecule of NADH (or at lease the reducing equivalents thereon) has been transferred from the cytosol to the mitochondrion and the respiratory chain.

c) The third system utilized in this process is the *fatty acid elongation system* by which fatty acids have an extra 2 carbon fragment added in the cytosol side of the mitochondrial membrane, coupled with the oxidation of $NADH^+$. This elongated fatty acid gains entrance to the mitochondrial matrix via the carnitine carrier and is then subjected to one step of β-oxidation with the loss of the two carbon fragment as acetyl CoA and the reduction of NAD^+ to NADH. The fatty acid and the acetyl CoA are transferred back across the membrane to complete the cycle.



(From Rubin and Lieber, Progress in Liver Diseases, Popper and Schaffner (Ed.), p. 549, 1972.)

The NADH, now in the mitochondria, then donates an electron (in the form of a hydrogen atom) to the respiratory chain (thus becoming oxidized to NAD^+) and the electron is passed along the chain with the liberation of energy which is captured at three sites by the formation of ATP from ADP and P' (coupled oxidative phosphorylation).



Electron transport and oxidative phosphorylation

(From Biochemistry, Lehninger (Ed.), p. 443, 1975.)

The rate of this oxidative process is limited by the availability of ADP because the coupling to phosphorylation is normally very tight. Ultimately any situation which increases the utilization of ATP with the production of ADP will increase the rate at which ethanol can be oxidized. This is considered to be the mechanism by which fructose increases the rate of ethanol metabolism and clearance from the body.

Fructose under these circumstances is converted to glucose with the expenditure of ATP energy and an increase in the supply of ADP at the site of oxidative phosphorylation.

Two other potential mechanisms for ethanol oxidation exist, but, *in vivo*, neither probably play any significant role.

The *Microsomal Ethanol-Oxidizing System (MEOS)* is an aerobic NADPH-dependent system which is located in the endoplasmic reticulum (microsomal fraction) and shares many characteristics of the microsomal drug metabolizing systems including that of induction by exposure to substrate. This reaction yields acetaldehyde but no usable energy and, at best, is thought to only be of significance in the face of very high alcohol concentrations. Under these conditions it could conceivably be important not as a metabolic combustive process but as part of the body's detoxification defences against "toxic" concentrations of ethanol.

Catalase-mediated Oxidation of ethanol is another microsomal system utilizing hydrogen peroxide and has no physiological significance.

Summary of Pathogenetic Mechanisms in Alcoholic Fatty Liver

The significance of the stimulation of fatty acid synthesis which can be shown to occur in ethanol treated livers, of the mobilization of fat depots during an alcohol binge and while fasting, the possibility of interference with the formation and release of lipoproteins and the enhancement of triglyceride esterification consequent to the abundance of α-glycerophosphate has not been established and may well vary from individual to individual. There remains little doubt however that the primary phenomenon leading to alcoholic fatty liver is the inhibition of fatty acid oxidation consequent to the change in redox state evoked by the oxidation of ethanol. That it is the *metabolism* of alcohol that is responsible has been nicely demonstrated by the demonstration that inhibition of ADH with pyrazole prevents the change in redox state and prevents the development of fatty liver.

Lieber, CS: Effects of ethanol upon lipid metabolism. Lipids 9: 103-116, 1974.

Hoyumpa AM, Greene HL, Dunn GD, Schenker S: Fatty Liver: Biochemical and clinical considerations. Dig. Dis. 20:1142-1170, 1975.

Lieber, CS. Hepatic and metabolic effects of alcohol. Gastroenterology 50:119-113, 1966.

Lieber, CS. Hepatic and metabolic effects of alcohol. Gastroenterology 65:821-846, 1973.

Rubin,E, Lieber CS: Ethanol metabolism in the liver. IN Progress in Liver Disease, Vol. IV. H. Popper, F. Schaffner (eds). New York and London, Grune & Stratton, 1972. pp. 549-567.

Lieber, CS and DeCorli, LM. The significance and characterization of hepatic microsomal ethanol oxidation in the liver. Drug. Metab. Disp. 1:428-440, 1973.

Thurman, RG and Scholz R. The role of hydrogen peroxide and catalase in hepatic microsomal ethanol oxidation. Drug Metab. Disp. 1:441-448, 1973.

Isselbacher KJ and Carter EA. Ethanol Metabolism: oxidative and peroxidative mechanisms. Drug. Metab. Disp. 1:449-454, 1973.

Scholz R and Nohl H. Mechanism of the stimulatory effect of fructose on ethanol oxidation in perfused rat liver. Eur. J. Biochem. 63:449-458, 1976.

Meijer AJ, Van Woerkom GM, Williamson JR, Tager JM. Rate-limiting factors in the oxidationof ethanol by isolated rat liver cells. Biochem. J. 150:205-209, 1975.

Pathology of Fatty Liver: The essential morphological change in the liver of patients with fatty metamorphosis is, naturally enough, the presence of fat in the parenchymal cells. Initially this is seen as multiple small vesicles within the cell. As the quantity of fat increases these vesicles coalesce and a single large droplet of fat is observed which continues to increase in size until it has displaced the cell nucleus and the rest of the cytoplasm against the cell membrane. The liver is otherwise histologically normal. The lobular architecture is preserved and there is no inflammation. At times the liver cells become so distended with fat that the cell membranes appear to rupture forming even larger collections of fat which have been called "fatty cysts". Some authors have maintained, however, that these breaks in the cell walls are artifacts of the fixation process and that no fatty cyst equivalent occurs *in vivo*. It is not unusual to notice some increase in the amount of fibrous tissue present in the livers of patients with fatty liver. This is often explained away as being the legacy of previous episodes of acute liver disease either alcohol related or not alcohol related. Recent studies have shown however that, in experimental animals, the alcoholic fatty liver is associated with increased formation and accumulation of hepatic collagen and enhanced activity of collagen proline hydroxylase.

It is possible then that some increase in fibrosis may be part and parcel of the pathology of alcohol fatty liver without any intervening hepatitis. Other investigators have not confirmed these findings in the fatty liver in man but *have* shown these chemical changes in alcoholic hepatitis.

Feinman L, Lieber CS: Hepatic collagen metabolism: Effect of alcohol consumption in rats and baboons. Science 176:795, 1972.

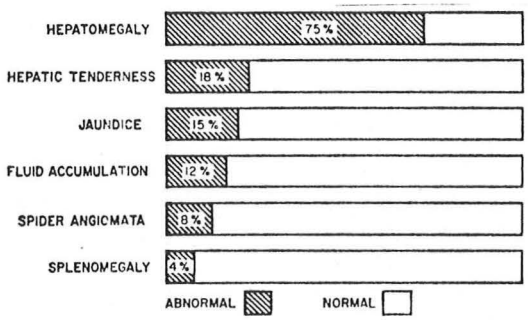
Chen TSN and Leevy CM: Collagen biosynthesis in liver disease of the alcoholic. J Lab Clin Med 85:103-112, 1975.

Galambos JT and Shapira R: Natural History of Alcoholic Hepatitis. IV. Glycosaminoglycuronans and collagen in the hepatic connective tissue. J Clin Invest 52:2952-2962, 1973.

Mezey E, Potter JJ and Maddrey WC: Hepatic collagen proline hydroxylase activity in alcoholic liver disease. Clin Chim Acta 68:313-320, 1976.

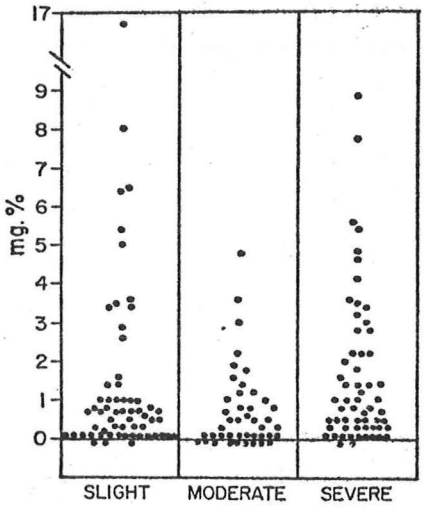
Clinical Features:

Despite what may appear to be the total replacement of the hepatic parenchyma with lipid lacunae the clinical expression of fatty liver is in most part very mild. Hepatomegaly is, of course, very common and may be associated with RUQ pain and tenderness from distension of the liver capsule. It is the result of the accumulation of not only fat but also of protein. Jaundice is not common and the degree of hyperbilirubinemia is, in most patients, quite mild (< 5 mg%) and is accompanied by only modest elevations of SAP and SGOT. Such patients are more likely to be admitted to County Hospitals for complications of alcoholism unrelated to the liver although at times an acute cholestatic picture may be seen in these patients with more marked jaundice, pruritus, and more markedly elevated enzyme activities.



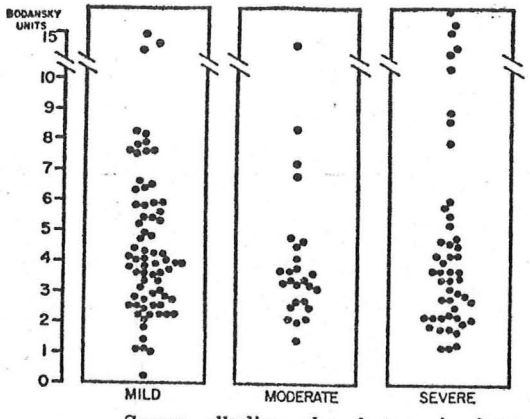
Clinical features of fatty liver.

(From Leevy, Medicine 41:249, 1962.)



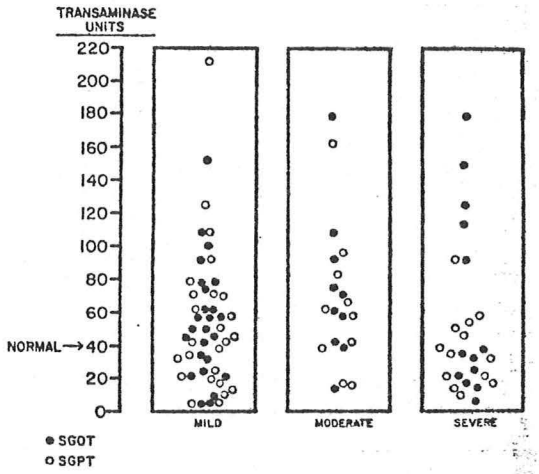
Serum bilirubin in fatty liver.

(From Leevy, Medicine 41:249, 1962.)



Serum alkaline phosphatase in fatty liver. Normal upper level 5 Bodansky units.

(From Leevy, Medicine 41:249, 1962)



Serum transaminases in fatty liver.

(From Leevy, Medicine 41:249, 1962.)

The prognosis of this condition is very good. If the patient ceases drinking his liver will quickly return to normal. If he continues to drink, the fat will persist, may become more marked, and he runs the risk of eventually developing acute alcoholic hepatitis and then of course the risk of progression to an irreversible form of alcoholic liver disease. Severe fatty liver of the alcoholic may not be as benign a condition as we have been want to believe however. Kramer et al have recently drawn attention to the occurrence of sudden death in a group of relatively young alcoholics in whom autopsies have not disclosed any particular abnormalities other than severe fatty metamorphosis of the liver. The cause of these sudden deaths is not known although hypotheses such as fat embolism, hypoglycemia, acute electrolyte disturbances and acute cardiomyopathy have been suggested.

Baraona E, Leo MA, Borowsky S and Lieber CS: Alcoholic Hepatomegaly: Accumulation of protein in the liver. Science 190:794-795, 1975.

Bradus S, Korn RJ, Chomet B, West M and Zimmerman HJ: Hepatic function and serum enzyme levels in association with fatty metamorphosis of the liver. Amer J Med Sci 246:36-41, 1963.

Hilden M, Tuttle E, Thomsen AC and Christoffersen P: Fatty liver persisting for up to 33 years. Acta Med Scand 194:485-489, 1973.

Leevy CM, Zinke MR, White TJ and Gnassi AM: Clinical observations on the fatty liver. Arch Int Med 92:527-541, 1953.

Leevy CM: Fatty Liver: A study of 270 patients with biopsy-proven fatty liver and a review of the literature. Medicine (Baltimore) 41: 249-276, 1962.

Kramer K, Kuller L and Fisher R: The increasing mortality attributed to cirrhosis and fatty liver in Baltimore (1957-1966). Ann Int Med. 69:273-282, 1968.

ALCOHOLIC HEPATITIS AND CIRRHOSIS

Pathogenesis:

The distinction between alcoholic hepatitis and acute fatty liver to be stressed is the presence in the former of actual *cell necrosis*. The mechanism producing this injury is not known but it is presumed to be different from the mechanisms that result in fatty liver. Alcoholic hepatitis is associated with active fibrogenesis as measured by proline hydroxylase activity and by the incorporation of radiolabelled proline and hydroxyproline into collagen. It is believed that this stimulation of collagen synthesis is an active process and not just the consequence of tissue healing following cell necrosis. Alcoholic hepatitis is considered to be a *necessary intermediate* in the development of cirrhosis in the alcoholic but it does not inevitably progress to this end. It is *NOT* a universal consequence of the prolonged and excessive abuse of alcoholic beverages and while the reported incidence of alcoholic hepatitis and, cirrhosis have varied quite widely, it seems clear that more than half of the alcoholics in the community will not develope any changes other than fatty liver irrespective of how much or how long they drink. It has been observed repeatedly that only approximately 10% of people, considered to have chronically abused alcohol, will have cirrhosis at autopsy but these figures probably underestimate the danger in particular groups of patients and tend to obscure what Lelbach has shown quite dramatically in recent years and that is the rather direct association between the life time volume of alcohol ingested and the presence of cirrhosis.

During the late 1960, Lelbach studied 526 male alcoholics admitted for withdrawal therapy to a sanitorium in West Germany. 320 of these patients were subjected to liver biopsy and 39 (12%) were found to have established micronodular cirrhosis. Very detailed histories of alcohol consumption were obtained by two different persons at different times and checked with information derived from family, friends and social agencies. All 39 patients with cirrhosis were found to have a mean daily intake of more than 160 G of alcohol per day giving the presence of cirrhosis a prevalence of 25% in this group of drinkers. It is noteworthy that the calculated mean capacity for ethanol metabolism in man is approximately 160 G/day.

Incidence of Cirrhosis on Liver Biopsy

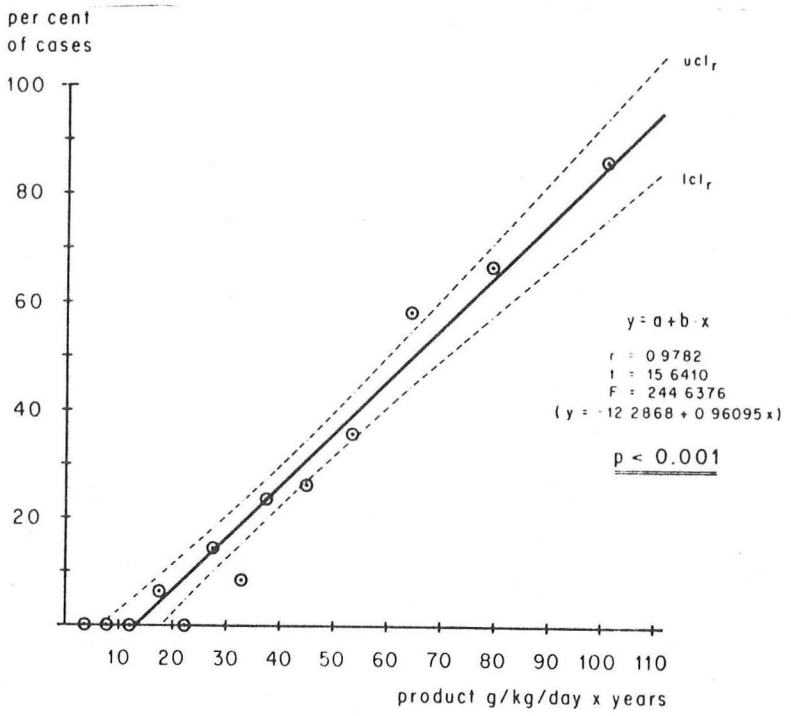
	No. with cirrhosis	% of sample	Years of alcohol abuse (mean)
Intake > 160 gm/day (n = 157)	39	25%	11.4
Intake < 160 gm/day (n = 163)	0	0%	7.4
Total	39	12%	9.9

It was also noted that the cirrhotic group had been drinking for a longer period of time than the others so this aspect was analyzed separately.

Influence of Duration of Drinking on Cirrhosis

Years of drinking (mean)	No.	% with cirrhosis	Mean daily consumption (gm/day)
3.6	73	0%	163
8.3	129	8%	177
12.9	81	21%	192
21.6	51	51%	227

The duration and quantity of alcohol excess could not be disassociated in this study. The longer patients drank, the greater was their daily consumption. This analysis, however, did identify a group of very heavy drinkers who had been drinking for approximately 20 years in whom the prevalence of cirrhosis was 50%. This suggested that the determining factor may have been the absolute volume of alcohol consumed in a lifetime.



(From Lelbach, Progress in Liver Diseases V, Popper and Schaffner (Ed.), p. 494, 1976.)

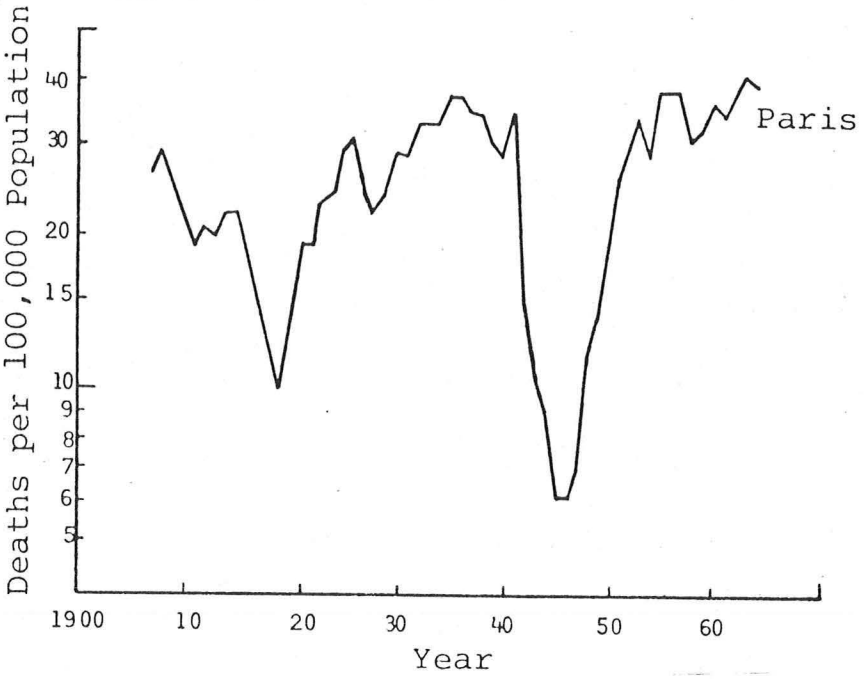
When the product of alcohol consumed and duration of drinking were plotted against the prevalence of cirrhosis a surprisingly direct relationship was observed.

Other epidemiological facts which have been established, or at least strongly suggested, by a variety of workers include

1. Cirrhosis is related to the volume of alcohol consumed.
2. Cirrhosis is related to the duration of drinking.
3. Cirrhosis is more common in continuous than periodic drinkers.
4. The type of alcoholic beverage is irrelevant.
5. Nutritional status is not a determinant.
6. There are no racial determinants (other than volume).
7. Women appear to be more susceptible than men.

Nutrition

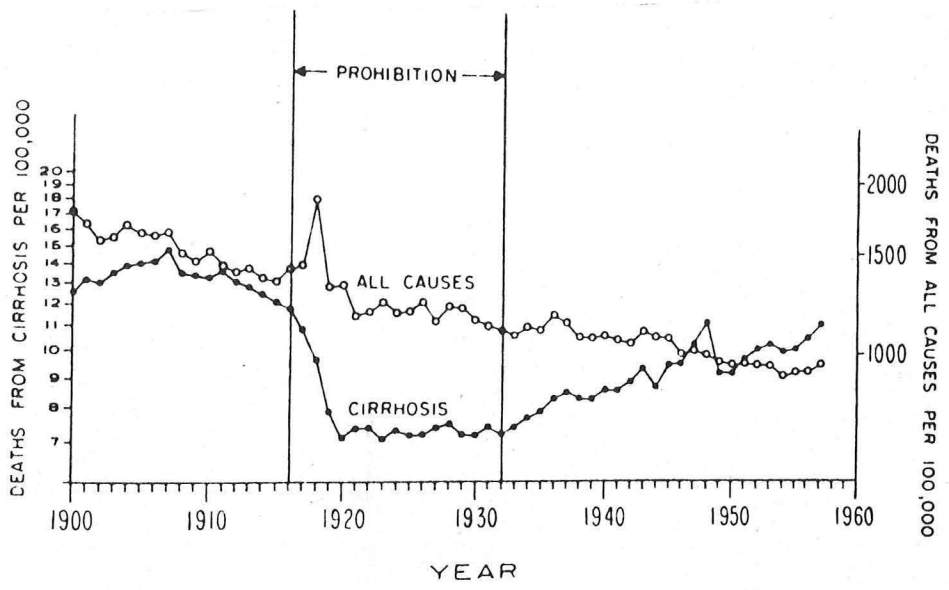
The question of the contribution of nutritional deficiencies to the development of alcoholic cirrhosis has been a vexed one. Cirrhotic lesions can be produced in rats by the addition of alcohol to a choline deficient diet and prevented by the provision of supplemental choline. All of the epidemiological data reported in man, however, have refuted the concept that dietary deficiencies make a significant contribution to the disease in alcoholic man. Moreover, it has been shown that the rodent is particularly susceptible to choline deprivation, a state which has little effect on mammalian liver. Epidemiologists have pointed to data derived from death rates from cirrhosis over the past 60 years to stress the importance of *alcohol* rather than dietary factors in the genesis of chronic alcoholic liver disease. For example, in Paris there have been two periods when the death rate from cirrhosis has decreased dramatically. Both occurred during war years when there was a sharp and sudden drop in alcohol consumption and when dietary deficiencies were at their peak. The cirrhotic death rate returned to its previous levels when the per capita alcohol consumption returned to its prewar rates and at a time when the nutritional status of the citizenry had recovered to its normal level.



Death Rates, Cirrhosis of the Liver, Paris, 1900-1964

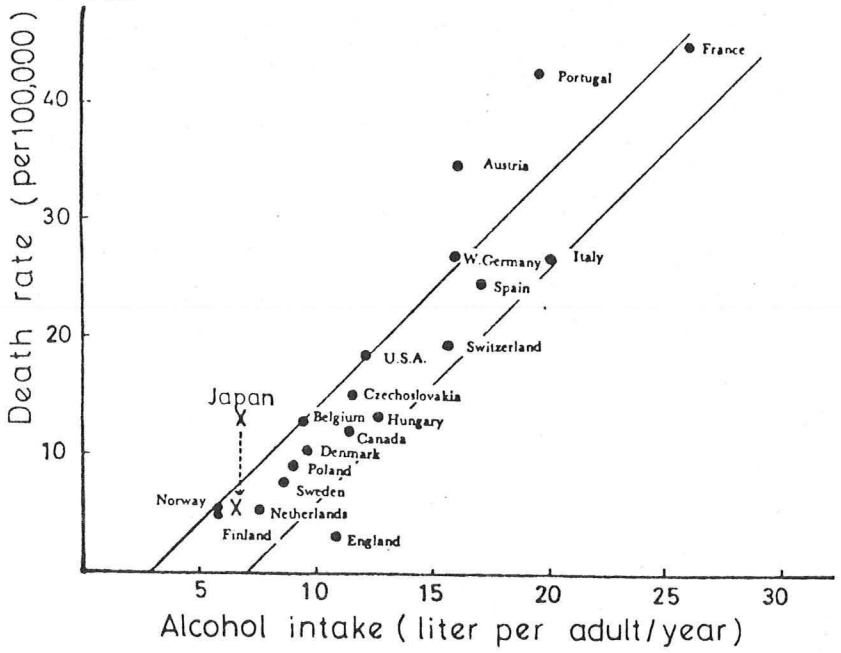
(From Schmidt, Alcoholic Liver Pathology, Khanna, Israel, and Kalant (Ed.), p. 19, 1975.)

Similar associations with the per capita consumption of alcohol and cirrhotic death rates can be seen during the prohibition years in the U.S.



(From Lelbach, Progress in Liver Diseases V, Popper and Schaffner (Ed.), p. 494, 1976.)

At an international level there is a direct association between the reported death rates from cirrhosis and mean per capita consumption of alcohol.

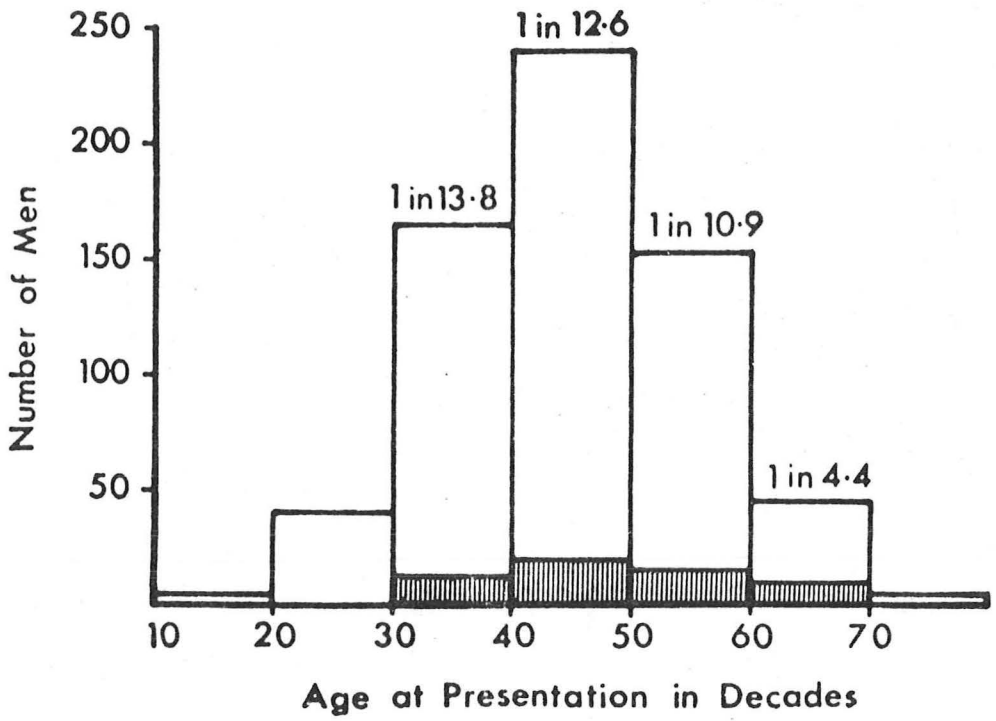


Correlation between death rates from cirrhosis and alcohol intake in various countries.

(From Takeuchi and Takada, Alcoholic Liver Pathology, Khanna, Israel, and Kalant (Ed.), p. 199, 1975.)

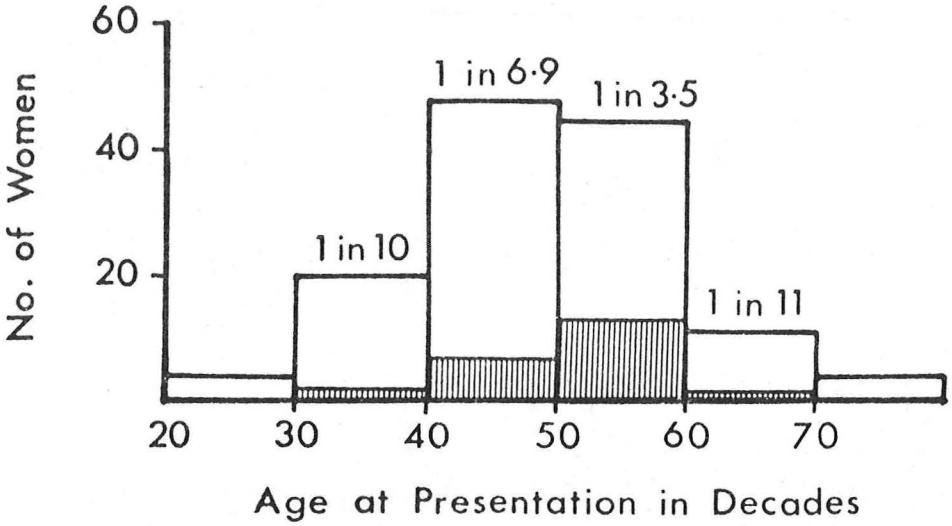
Sex:

In view of the known susceptibility of women to such liver diseases as cryptogenic cirrhosis, primary biliary cirrhosis and chronic active hepatitis, it is of interest that cirrhosis occurs about twice as commonly in alcoholic women as it does in alcoholic men.



Prevalence of cirrhosis in alcoholic men (cirrhotic patients shown hatched).

(From Rankin et al., Alcoholic Liver Pathology, Khanna, Israel, and Kalant (Ed.), p. 31, 1975.)



Prevalence of cirrhosis in alcoholic women (cirrhotic patients shown hatched).

(From Rankin et al., Alcoholic Liver Pathology, Khanna, Israel, and Kalant (Ed.), p. 31, 1975.)

It has also been observed that alcoholic women develop cirrhosis at a lower level of consumption and after a shorter period of excessive drinking than do alcoholic men.

Direct Role of Ethanol

While the actual mechanism whereby ethanol results in hepatic cell necrosis, and hence alcoholic hepatitis, remains entirely unknown, recent studies have provided *direct* confirmation of the view, supported by the above *indirect* epidemiological evidence, that it is ethanol itself that is the prime agent in the genesis of the disease.

This evidence has come from the demonstration by Rubin and Lieber that the whole constellation of pathological changes which are seen in alcoholic hepatitis can be reproduced in baboons fed large amounts of ethanol for as short a period as 9 months. These animals received ethanol in doses ranging between 50 and 70 G/day as part of a diet which was adequate in calories and protein and which was liberally supplemented with vitamins and minerals. Biopsies obtained after 9 months showed fat accumulation with focal areas of cell necrosis and a predominantly polymorphonuclear inflammation scattered throughout the liver but most marked in the central zones. Mallory bodies were also seen and early deposition of collagen, most marked in the central zones, mimicked the entity of central hyaline sclerosis. Further follow up of these animals, still receiving the alcohol enriched diet for as long as 4 years, showed the subsequent development of micronodular cirrhosis.

This convincing evidence of the direct hepatotoxicity of ethanol leaves many questions unanswer. At this time not even a working hypothesis has been presented which adequately answers all of the questions arising from this remarkable effect of prolonged and excessive ethanol ingestion.

Questions which must be satisfied by such an Hypothesis include

a. Why does this manifestation of ethanol injury only develope in a proportion of people who abuse ethanol?

b. Why is there a latent period of, at the very least, some months and more usually of years of heavy drinking before the onset of the lesion?

c. Why is it possible for the alcoholic hepatitis lesion to resolve with essentially normal histology in some people and yet progress to cirrhosis in others even in the absence of further alcohol ingestion?

d. Why does the recurrence of alcoholic hepatitis not require the same long latent period as the initial episode?

e. Why does the severity of the cell necrosis and hence the clinical expression of the illness vary so much in people consuming equivalent amounts of alcohol?

f. What provokes the active fibrogenesis in this disease?

It is of great interest that of the 13 baboons subjected by Rubin and Lieber to the ethanol enriched diet, *all* developed fatty livers but only 4 showed evidence of alcoholic hepatitis and of these, only 2 progressed to cirrhosis during the 4 years in which the animals were followed. These findings suggest that this baboon model will prove to be very useful (if time consuming) in finding the solution to the enigma of the mechanisms involved in ethanol mediated cell necrosis.

Lelbach WK: Quantitative Aspects of Drinking in Alcoholic Liver Disease. In Alcoholic Liver Pathology. Khanna JM, Israel Y, and Kalant H (eds). Addiction Research Foundation of Ontario, pp. 1-18.

Rankin JG et al: Epidemiology of Alcoholic Liver Disease. In Alcoholic Liver Pathology. Khanna JM, Israel, Y and Kalant H (eds). Addiction Research Foundation of Ontario. pp 31-42.

Henley KS, Clancy PE, Laughrey EG, Lyra LG. Nitrogen metabolism in the perfused cirrhotic liver of the rat. J Lab Clin Med 85:273-280, 1975.

Rubin E and Lieber CS: Fatty liver, alcoholic hepatitis and cirrhosis produced by alcohol in the primate. N. Engl J Med 290:128-135, 1974.

Rubin E and Lieber CS: Experimental alcoholic hepatitis: A new primate model. Science 182:712-714, 1973.

Clinical Features:

The clinical manifestations of alcoholic hepatitis vary widely and may present in an asymptomatic patient with a normal physical examination and very mild disturbances of his liver function tests or as an acute fulminant disease in which there may be deep icterus, with severe symptoms of right upper abdominal pain, anorexia, vomiting and diarrhea with fever and leukocytosis. This may be followed by the development of edema and ascites with marked disturbances of the plasma proteins and coagulation factors and terminate with hepatic coma and death. Any clinical picture between these two extremes may be seen in patients who have alcoholic hepatitis as the sole or major form of alcohol-related liver injury. The frequency with which various clinical features or laboratory abnormalities are noted depends upon the population being studied. Hospitalized patients are much more likely to show evidence of severe liver disease than are patients who are examined in an outpatient addiction-control setting. It is important to realize however that the prognostic significance of alcoholic hepatitis is not diminished by what is, clinically, benign disease and that many such people progress to cirrhosis and irreversible disease without manifesting any dramatic symptoms or signs in the interim. It is quite impossible to distinguish between fatty liver and acute alcoholic hepatitis by clinical or chemical criteria in a patient with only mild disturbances of liver function. The difference in prognosis between these two entities underlines the importance of making the distinction and is the basis for the widespread performance of liver biopsies in alcoholics with evidence of hepatic dysfunction.

THE AVERAGE INCIDENCE OF THE MOST COMMON
SYMPTOMS OF ALCOHOLIC HEPATITIS
IN 6 REPORTED SERIES OF PATIENTS

	%
Anorexia	70
Weight loss	55
Abdominal pain	50
Nausea and vomiting	40

(From Galambos, Alcoholic Liver Pathology, Khanna, Israel, and Kalant (Ed.), p. 97, 1975.)

THE AVERAGE INCIDENCE OF THE MOST COMMON
SIGNS OF ALCOHOLIC HEPATITIS
IN 8 REPORTED SERIES OF PATIENTS

	%
Hepatomegaly	90
Jaundice	50
Fever	45
Ascites	40
Splenomegaly	30
Encephalopathy	15

(From Galambos, Alcoholic Liver Pathology, Khanna, Israel, and Kalant (Ed.), p. 97, 1975.)

THE AVERAGE INCIDENCE OF THE MOST COMMON
LABORATORY ABNORMALITIES OF ALCOHOLIC HEPATITIS
IN 5 REPORTED SERIES OF PATIENTS

	%
Anemia	70
Leukocytosis	45
SGOT – normal	20
< 500 U	99
< 300 U	95
Alkaline phosphatase	
(< X 3 elevation)	70
Bilirubin	75

(From Galambos, Alcoholic Liver Pathology, Khanna, Israel, and Kalant (Ed.), p. 97, 1975.)

The presence of cirrhosis contributes very little, directly, to the patient's hepatic symptoms, signs or laboratory disturbances. It is more likely to draw attention to its presence by virtue of the complications which it causes (e.g. portal hypertension, hypersplenism, fluid retention, encephalopathy, etc.).

A patient with inactive cirrhosis (i.e. no acute parenchymal disease) is usually anicteric. There may be peripheral stigmata of chronic liver disease (vascular and endocrinological), and the liver may be enlarged or of normal size. Signs of the various complications may be present. The serum bilirubin, if elevated at all, will probably be largely unconjugated reflecting hemolysis from hypersplenism, the serum alkaline phosphatase activity may be normal or increased, reflecting foci of intrahepatic biliary obstruction by scar tissue, but the SGOT activity will be normal or only minimally elevated. There is usually hyper-gammaglobulinemia, the consequence of the access to the systemic circulation of colonic antigens normally sequestered by the liver, and there may be chronic hypo-albuminemia and coagulopathy reflected by a prolonged prothrombin time secondary to the protein synthetic failure of the diminished liver cell mass.

If fatty liver or alcoholic hepatitis co-exist, the clinical findings and laboratory abnormalities induced by these acute diseases will be superimposed upon the features of cirrhosis.

Green J, Mistillis S, Shiff L: Acute alcoholic hepatitis. A clinical study of fifty cases. Arch Intern Med 112:67-78, 1963.

Lesesne HR, Fallon HJ: Alcoholic liver disease. Postgrad Med 53:101-106, 1973.

Lischner MW, Alexander JF, Galambos JT. The natural history of alcoholic hepatitis. I. The acute disease. Am J Dig Dis 16:481-494, 1971.

Galambos JT. The Course of Alcoholic Hepatitis. In Alcoholic Liver Pathology. Khanna JM, Israel Y, Klaant H (eds) Addiction Research Foundation of Ontario. pp 97-112.

Triger DR, Alp MH, Wright R: Bacterial and dietary antibodies in liver disease. Lancet I: 60-63, 1972.

PATHOLOGY

The essential histologic distinction between acute fatty liver and acute alcoholic hepatitis is the presence, in the latter, of cell necrosis with its attendant inflammatory response. Characteristically, this inflammation is predominantly polymorphonuclear and is present in both the portal triads and in foci of cell degeneration. The cell necrosis in alcoholic hepatitis is usually most severe in the central zones and it may be associated there with the deposition of collagen which forms a reticular pattern around the central veins. This histologic pattern has been called *central hyaline sclerosis* and has been associated with a rapid progression

to cirrhosis. The parenchymal cells undergoing necrosis in alcoholic hepatitis most frequently appear as swollen cells undergoing balloon-degeneration but eosinophilic degeneration with Councilman-body formation also occurs. Within the swollen hydropic cells may be seen irregular strands of deeply eosinophilic hyaline material which was first observed in 1911 by Mallory and which is now known as *Mallory's alcoholic hyaline* or a *Mallory body*. The Mallory body occurs within the cytoplasm of the cell and appears as a condensation of *part* of the cytoplasm. It is to be distinguished from the Councilman body which is in effect a *whole* cell which has become dehydrated, shrunken and eosinophilic and appears to lie free in the sinusoid. Under the electron microscope the Mallory body is seen to be composed of masses of fibrils and chemical assays have demonstrated that it consists of basic and poorly soluble protein. Dispute persists over the origin of this hyaline material. The original view that it is formed by degeneration of intracellular organelles has more recently given ground to the view that this is newly formed protein, synthesized on the ribosomes. This new protein accumulates either because of increased synthesis in response to injury or because there is interference with the normal distribution and dispersal mechanisms in the damaged cell. Cells containing hyaline frequently are surrounded by polymorphonuclear cells which ultimately phagocytose both the cell and the Mallory body.

While the presence of Mallory bodies is not confined to alcoholic hepatitis, the other conditions in which it has been described seldom pose differential diagnostic difficulties so that the finding of Mallory's hyaline may be a very useful diagnostic marker of alcohol-induced injury. In alcoholic hepatitis the hyaline is frequently present in the central zones while in all the other causes of this phenomenon apart from the liver disease of jejuno-ileal bypass, the hyaline is found only periportally or besides fibrous bands.

Conditions Associated with Mallory Bodies

Alcoholic hepatitis.

Jejuno-ileal bypass liver disease.

Primary biliary cirrhosis.

Hepatoma.

Wilson's disease.

Indian childhood cirrhosis.

Chronic extrahepatic biliary obstruction.

Asbestosis (pulmonary).

Confusion can sometimes be created by the occurrence in liver cells of giant mitochondria. These, too, stain intensely with eosin and are frequently seen in alcoholic liver disease. They form discrete globular masses however and can usually be distinguished from the irregular skein-like strands of Mallory's hyaline.

Cirrhosis is defined as the presence of bands of fibrous tissue in the liver, with nodular regeneration leading to a distortion of the lobular architecture. The cirrhosis of alcoholic liver disease is usually micro-nodular in type. That is to say that the regenerating nodules in this form of cirrhosis are smaller than the normal lobule and arise from parts of a single lobule. Often, however, much larger regenerative nodules may be seen and occasionally the cirrhosis is macronodular and indistinguishable from what has been called post-necrotic cirrhosis.

Galambos JT: Natural history of alcoholic hepatitis. III Histological changes. Gastroenterology 63:1026-1035, 1972.

French SW and Davies PL: The Mallory Body in the Pathogenesis of Alcoholic Liver Disease. In Alcoholic Liver Pathology. Khanna JM, Israel Y, Kalant H (eds). Addiction Research Foundation of Ontario. PP 113-144.

Kuhn C, Kuo TT: Cytoplasmic hyalin in asbestosis. Arch Path 95:190-194, 1973.

Prognosis of Alcoholic Hepatitis:

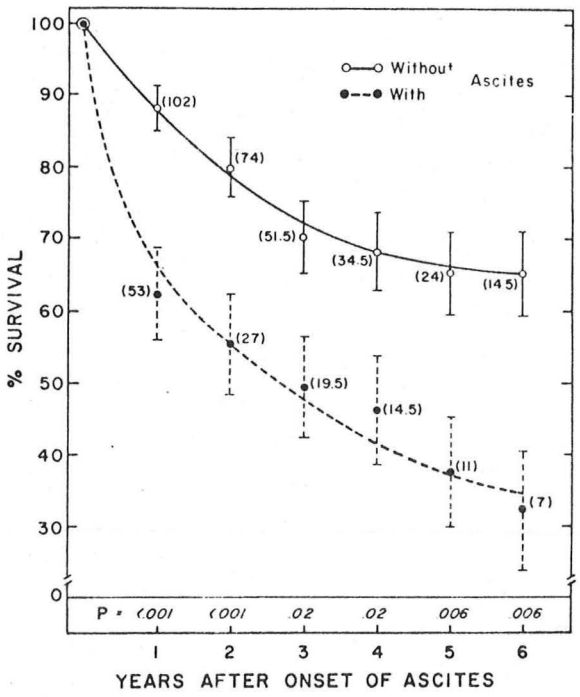
In 1974 Alexander and his colleagues reported their findings with respect to the long term prognosis of 164 patients with biopsy proven alcoholic hepatitis. The overall 5 year survival rate was approximately 50%. The features that were found to be significant determinants of outcome included

PROGNOSIS OF ALCOHOLIC HEPATITIS

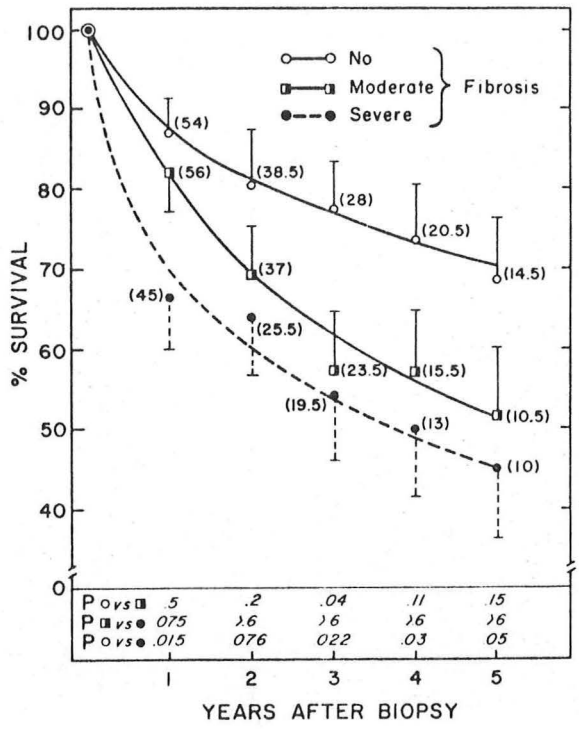
(Alexander et al. 1971)

Factors Affecting Outcome

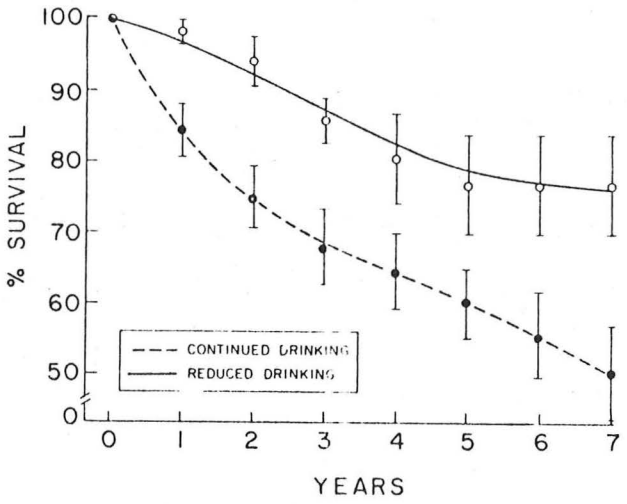
1. Presence of cirrhosis.
2. Presence of ascites.
3. Marked reduction in alcohol consumption.



(From Galambos, Progress in Liver Diseases, Popper and Schaffner (Ed.), p. 567, 1972.)



(From Galambos, Progress in Liver Diseases, Popper and Schaffner (Ed.), p. 567, 1972.)



Survival rates from liver biopsy of 59 patients who either stopped drinking or demonstrated clear-cut changes in their living habits as evidence for meaningful reduction of drinking compared to 98 patients who apparently continued to drink.

(From Galambos, Progress in Liver Diseases, Popper and Schaffner (Ed.), p. 567, 1972.)

Features that did not affect the prognosis in these patients included

PROGNOSIS OF ALCOHOLIC HEPATITIS (CONT)

Factors Without Effect

Histological severity of hepatitis

Presence of hyaline

Severity of steatosis

Bilirubin > 2 mg %

Liver function tests

Encephalopathy

Varices

The number of patients involved with varices and encephalopathy was really too small for valid conclusions to have been drawn. Not surprisingly other authors have found these two factors to have been prognostically significant and have also identified a serum bilirubin level of > 5 mg% as being a bad prognostic sign.

The importance of alcohol abstinance in patients with alcoholic hepatitis and/or cirrhosis in influencing outcome has been demonstrated repeatedly.

5 YEAR SURVIVAL OF ALCOHOLIC LIVER DISEASE

		Drinking		
	No.	Excessive %	Stop/Mild %	Entire group %
London	123	34	69	50
New Haven (cirrhosis)	283	41	63	48
Boston (varices)	146	42	61	55
Atlanta (alcoholic hepatitis)	164	60	77	63
Atlanta (cirrhosis)	46	—	—	61

(From Galambos, Alcoholic Liver Pathology, Khanna, Israel, and Kalant (Ed.), p. 97, 1975.)

A recent study from Boston however in patients with cirrhosis and unequivocal esophagogastric varices failed to show an improvement in survival among those patients who stopped drinking. The time, then, obviously is reached when the outcome is determined more by the established disease than by the inciting event.

Brunt PW, Kew MC, Scheuer PJ, sherlock S: Studies in alcoholic liver disease in Britain. Gut 15:52-58, 1974.

Alexander TF, Lischner MW, Galambos JT: Natural History of Alcoholic Hepatitis. II Long term prognosis. Am J Gastroenterol 56:515-525, 1971.

Soterakis J, Resnick RH, Iber FL: Effect of alcohol abstinence on cirrhotic portal hypertension. Lancet ii:65-67, 1973.

Powell WJ, Klatskin G: Duration of survival in patients with Laennec's cirrhosis. Am J Med 44:406-420, 1968.

Rankin JR, Wilkinson P, Santamaria JN: Factors influencing the prognosis of the alcoholic patient with cirrhosis. Aust Ann Med 3:232-239, 1970.

Treatment of Alcoholic Hepatitis and Cirrhosis

Apart from encouraging the abstinance from alcohol, the provision of adequate nutrition, and the correction of any associated complications of alcoholism in general or of alcoholic liver disease in particular, the treatment of alcoholic hepatitis is expectant. Much attention has been

directed recently to the place of corticosteroid therapy in severe alcoholic hepatitis. Prospective trials have been performed in at least three centers with conflicting results. Two studies have shown no benefit to accrue from such therapy while one study in only 15 patients showed decided benefit. However, since the acute mortality of the control group in this study was 100% (a result not claimed by many centers) it is questionable whether the apparent benefit from steroid therapy is real.

Fallon HJ: The management of alcoholic hepatitis. Hosp. Pract Feb 1974 pp 115-121.

Porter HP, Simon FR, Pipe CE, Volwiler W, Fenster LF: Corticosteroid therapy in severe alcoholic hepatitis. N Engl J Med 284:1350-1355, 1971.

Campra JL et al: Prednisone therapy of acute alcoholic hepatitis. Ann Int Med 79:625-631, 1973.