

# Alcohol and the Liver:

## Metabolism of Alcohol and Its Role in Hepatic and Extrahepatic Diseases

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### Abstract

Dr. Charles S. Lieber has conducted clinical and experimental studies for more than four decades (three at Mount Sinai and the Bronx VA Medical Centers) with emphasis on liver, nutrition and GI pathophysiology. His major contributions include elucidation of the pathogenesis of alcoholic liver disease, by demonstrating the toxic role of alcohol and describing associated metabolic disorders. This was achieved through judicious clinical studies and newly developed rodent and primate models with the administration of ethanol in liquid diets. The mechanisms of various pathological and metabolic effects of ethanol were clarified, including hyperlipemia (with the rise in HDL), hyperuricemia, the role of acetaldehyde toxicity and alcohol-induced oxidative stress. The latter, including glutathione depletion, was corrected by S-adenosyl-1-methionine given to alcohol-fed baboons; the compound is now being used successfully for the treatment of patients with alcoholic liver disease in Europe. Alcoholic cirrhosis was produced for the first time in nonhuman primates and shown to be fully prevented by polyenylphosphatidylcholine, which is now being tested in a multicenter clinical trial. Lieber also discovered a new (microsomal) pathway of ethanol metabolism, responsible for the tolerance to ethanol and for several clinically important toxic interactions with other drugs (e.g., acetaminophen), anesthetics, industrial solvents, carcinogens, as well as retinol and  $\beta$ -carotene, with narrowing of their therapeutic window. His work defined the role of the stomach in ethanol metabolism, description of corresponding gender differences, cloning (for the first time) of the gene for sigma ADH (a newly recognized gastric alcohol dehydrogenase isozyme) with its chromosomal localization, and the discovery of the effects of commonly used medications (e.g.,  $H_2$  blockers and aspirin) on the activities of the enzyme and on blood alcohol levels in social drinkers. Lieber was among the first to use antibiotics for the elimination of gastric bacterial urease and its ammonia production in man, thereby alleviating chronic gastritis and hypoacidity, with attenuation of hepatic encephalopathy in cirrhotics. He promoted early detection and treatment of heavy drinkers before their social or medical disintegration, by defining precirrhotic lesions and markers of alcohol consumption.

**Conclusions:** The research of Dr. Lieber and his group has yielded a better understanding of the pathogenesis of common hepatic, gastric and nutritional disorders, with elucidation and prevention of serious toxic alcohol-drug interactions and the development of methods for early recognition and more effective approaches to prevent and treat liver and gastrointestinal diseases.

**Key Words:** Ethanol, liver, cirrhosis, drugs, nutrition.

### A. Alcohol and Nutrition

ETHANOL IS A PSYCHOACTIVE DRUG, but, besides its pharmacologic action, it has a substantial energy value (7.1 kcal/g). In the heavy drinker, alcohol represents, on the average, 50% of the total dietary energy intake. As a consequence, alcohol displaces many normal nutrients of the diet, resulting in primary malnutrition and associated symptomatology (Fig. 1). Alcohol also

impairs the activation and utilization of nutrients, and secondary malnutrition may result from either maldigestion or malabsorption caused by gastrointestinal complications associated with alcoholism. Originally, it was believed that liver disease in the alcoholic was due exclusively to malnutrition. This dogma was primarily based on the experiments of Best and Hartroft, who had observed that in rats given alcohol as part of their liquid diet, no liver damage resulted when the diet was adequate. The first stage of liver disease, namely fatty liver, only developed when the diet was deficient. From their experiments, Best et al. (1) concluded that "there is no more evidence of a specific toxic effect of pure ethyl alcohol upon

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**Fig. 1.** Interaction of direct toxicity of ethanol on liver and gut with malnutrition secondary to dietary deficiencies, maldigestion, and malabsorption, as well as impaired hepatic activation or increased degradation of nutrients (154).

liver cells than there is for one due to sugar.” Lieber et al. confirmed these experiments but added the observation that under those conditions, blood alcohol levels were negligible. Indeed, rats have a natural aversion for alcohol that was overcome by giving alcohol in totally liquid diets (2). This diet also allowed perfect pair feeding of controls and, using such a diet, it was established for the first time that alcohol, even in the absence of nutritional deficiencies, can cause the first stage of alcoholic liver disease, namely a fatty liver, a finding confirmed in human volunteers (2, 3). The question still remained of the pathogenesis of the more severe stages of alcoholic liver disease, culminating in cirrhosis, which is responsible for the high rate of mortality in the heavy drinker. This issue was addressed by extending the liquid diet technique to an experimental animal more closely related to man, namely nonhuman primates (4). The latter studies were conducted after Dr. Lieber and his team had moved from Harvard and Cornell to the Bronx Veterans Affairs (VA) Medical Center and the newly created Mount Sinai School of Medicine in 1968. There, it was shown for the first time that alcohol can cause cirrhosis of the liver, even in the absence of nutritional deficiencies (4, 5).

This realization had profound consequences on the preventive as well as therapeutic approaches to the medical disorders of alcoholism. The major therapeutic efforts shifted from the mere correction of nutritional deficiencies to the moderation of alcohol consumption and the development of new therapeutic modalities by a better understanding of the mechanism of hepatotoxicity. The latter was investigated by a systematic study of the biochemical pathways through which the body rids itself of the alcohol.

## B. Alcohol Metabolism and Associated Toxicity

Alcohol is oxidized primarily in the liver and the main pathway involves alcohol dehydrogenase.

### 1. Metabolic Disorders Associated with Alcohol Oxidation by Alcohol Dehydrogenase

#### a. Hepatic effects

The oxidation of ethanol via the alcohol dehydrogenase pathway results in the production of acetaldehyde with loss of H. Nicotinamide adenine dinucleotide (NAD) is reduced to NADH. The large amounts of reducing equivalents generated overwhelm the hepatocyte's ability to maintain redox homeostasis, and it was shown that a number of metabolic disorders ensue (Fig. 2), including hyperuricemia (6) and hyperlipemia (2), with a rise in HDL (7) popularized more recently in conjunction with some apparently beneficial effects of moderate drinking on coronary arteries. It was also found that the increased NADH opposes lipid oxidation and promotes fatty acid synthesis with, as a net result, hepatic fat accumulation (8). The perivenular exaggeration of this redox change (because of the relative perivenular hypoxia) was found to be responsible for the exacerbation of the alcohol-induced injury (including steatosis) in the perivenular zone of the hepatic lobule (9). The respective roles of the amount of dietary fat (10) and dietary deficiencies (11) were elucidated. An associated metabolic disorder, namely ketoacidosis, was discovered and defined (12). In addition to the raised NADH, microsomal induction (*vide infra*) was incriminated through increased activity of enzymes involved in lipogenesis (13, 14) which was found to be associated with enhanced production of low and very low density lipoproteins (LDL and VLDL) (15). LDL and VLDL, in addition to alterations in cholesterol turnover (16), were shown to play a role in the alcohol-induced hyperlipemia (17–19). The latter was observed to involve the high density lipoproteins (HDL). Their increase was described by Baraona and Lieber (7), and has gained much attention in recent years. Ethanol was also found to affect the lipids, the microviscosity (20) and the structure of plasma membranes, as demonstrated by scanning electron microscopy (21). Thus, the hypothesis that the NADH generated by alcohol dehydrogenase (ADH)-mediated ethanol oxidation may play a major role in alcohol-induced disorders (22) was shown indeed to explain a vast array of associated metabolic abnormalities, including the steatosis (Fig. 2).

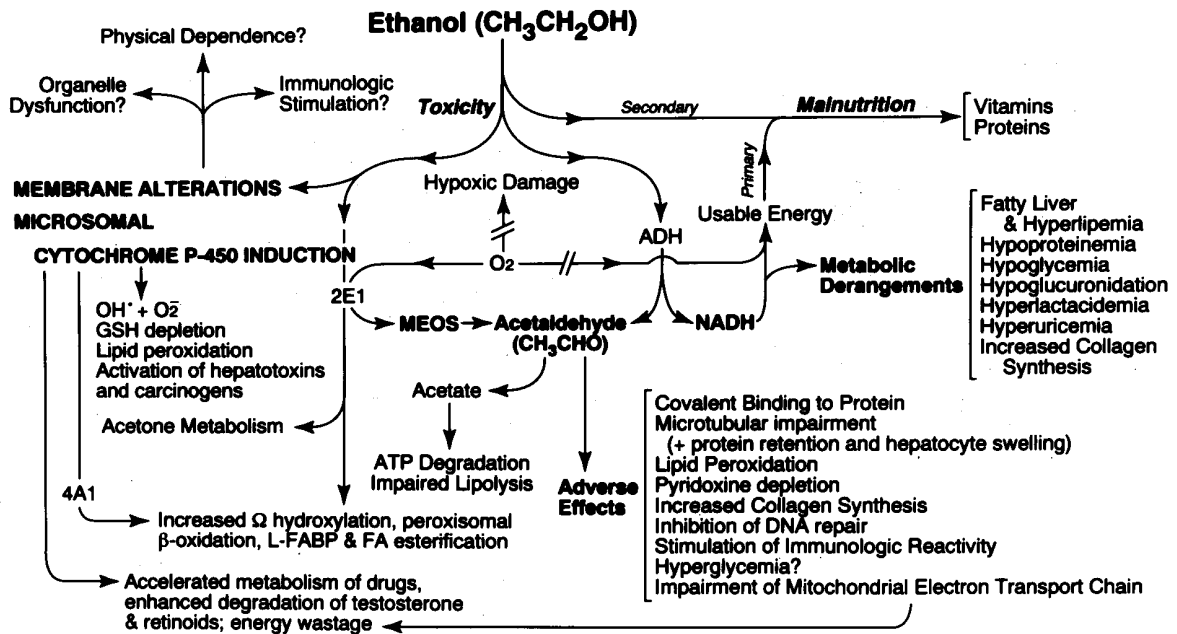


Fig. 2. Hepatic, nutritional and metabolic abnormalities after ethanol abuse. Malnutrition, whether primary or secondary, can be differentiated from metabolic changes or direct toxicity, resulting partly from redox changes, or effects secondary to microsomal induction, including increased acetaldehyde production (155).

## b. Gastric effects

### 1. Gastric ethanol metabolism and interactions with other drugs

Chronic ethanol consumption was found to produce a significant decrease in gastric alcohol dehydrogenase (ADH) activities (23), associated with greater bioavailability (lesser first pass metabolism) of ethanol (23, 24). Significant ethanol metabolism was also observed in cultured rat (25) and human (26) gastric cells. Women were found to have a lower gastric ethanol metabolism than men, which explains, at least in part, their greater susceptibility to the effects of ethanol (27). Commonly used drugs, e.g., aspirin (28) and H<sub>2</sub> receptor antagonists, e.g., cimetidine (29), were discovered to inhibit gastric ADH activity and to enhance the bioavailability of ethanol, with a resulting increase in blood ethanol levels (30). This effect was shown to be particularly important for social drinkers who commonly take several small drinks, with a cumulative effect on blood alcohol levels, strikingly exaggerated by various drugs (Fig. 3), either because of an inhibition of gastric ADH (*vide supra*) and/or an acceleration of gastric emptying (31).

At least three different forms of ADH were observed in the human stomach, with either high or low  $K_m$ 's for ethanol (32), including a newly recognized gastric isozyme, now called class IV or sigma ADH. A deficiency of this gastric ADH was uncovered in Asians (33), and the lower

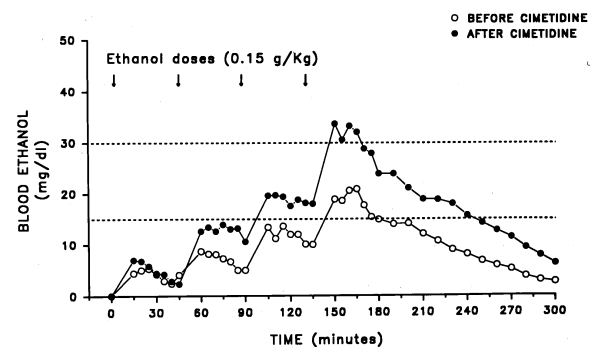


Fig. 3. Effects of cimetidine (400 mg twice a day for 7 days) on average blood levels after oral consumption of ethanol in nine subjects. Four small doses of ethanol (150 mg/kg) were imbibed at 45-min intervals, before and after administration of cimetidine. The effect of cimetidine on repeated drinking was significant ( $p < 0.01$  by two-way analysis of variance for repeated measures). (Modified from ref. 156).

ADH activity was found to be associated with a lesser first pass metabolism of ethanol (34), in keeping with a predominant role for ADH in human first pass metabolism. The full length cDNA of sigma ADH was determined and the complete amino acid sequence deduced (35). The corresponding ADH<sub>7</sub> gene in Caucasian and Japanese subjects was compared (36), including the upstream structure and the organ distribution of its expression (37) with, for the first time, molecular cloning and chromosomal localization of the gene (38). These studies not only established

the role of gastric ADH in ethanol metabolism, but they also delineated corresponding differences at a molecular level and opened a new approach to explain differences in the handling of ethanol and possibly of other dietary xenobiotics, such as gastric carcinogens.

## 2. Gastritis in the alcoholic

The product of ethanol metabolism is acetaldehyde, a toxic compound (*vide infra*) which may contribute to the chronic gastritis which is common in the alcoholic. An additional pathogenic factor is *Helicobacter pylori* infection (HP). Indeed it was found that this chronic gastritis generally resolves with the eradication of the microbe (39). The role of the gastric microbial flora in converting urea into  $\text{NH}_3$  was first recognized by the successful elimination of gastric  $\text{NH}_3$  using antibiotics in man (40, 41). These studies were completed at Mount Sinai (42). Adverse effects of  $\text{NH}_3$  included hypoacidity and gastritis, especially in the alcoholic (41). Gastric  $\text{NH}_3$  was shown to correlate with the severity of gastritis (39), and its measurement is now the basis for an accurate, yet simple, method for the detection of HP (43). The infection has its most striking impact in patients with uremia (40, 41) and in those with cirrhosis whose encephalopathy was improved with the antibiotic therapy (44).

Other gastrointestinal effects of ethanol that were elucidated comprised significant intestinal lesions in the rat (45), confirmed in man (46). These alterations included  $\text{B}_{12}$  malabsorption (47) and decrease of intestinal lactase (46).

## 2. Microsomal Ethanol Oxidizing System (MEOS)

### a. Ethanol metabolism

A toxicological breakthrough was achieved with the discovery of a microsomal ethanol oxidizing system and its interactions with xenobiotics (48, 49). This second pathway for alcohol metabolism was separate from that of alcohol dehydrogenase and catalase (49, 50) and characterized (51) and reconstituted by a semi-purified preparation of cytochrome P-450 (52). The role of the microsomes in ethanol metabolism and its increase after chronic ethanol consumption was demonstrated in rats (53), nonhuman primates (54, 55), acatalasemic mice (56), and deermice lacking alcohol dehydrogenase (57–62). It was quantitated using, in part, deuterium isotope effects (61). An ethanol-inducible form of cytochrome P-450 was discovered (52) and was subsequently purified by various groups from the livers of different species, including rats (63) and humans (64); it is now called 2E1. Unlike ADH,

MEOS was found to be strikingly inducible by chronic ethanol consumption, with its key component, namely 2E1, increased 4- to 10-fold in liver biopsies of recently drinking subjects (65), with a corresponding rise in mRNA in hamsters (66), rats (67) and man (68). P4502E1 induction was demonstrated with normal, as well as low-fat diets (69). It was shown in hepatocytes and in nonparenchymal cells of the liver (70), and also in extrahepatic tissues (71).

### b. Other microsomal effects

Microsomal induction was found to have an impact on sex hormones in normal men (72), and to enhance fatty acid  $\omega$ -oxidation (73). Induction of 2E1 contributes to the tolerance that develops to ethanol in the alcoholic and other drugs that are microsomal substrates. The tolerance of the alcoholic to various psychoactive drugs had generally been attributed to central nervous system adaptation, but metabolic adaptation now had to be considered, because the clearance rate of many drugs from the blood was found to be enhanced in alcoholics (74). Indeed, controlled studies have shown that chronic administration of pure ethanol with nondeficient diets either to rats or man (under metabolic ward conditions) results in a striking increase in the rate of blood clearance of ethanol (75), meprobamate and pentobarbital (74) as well as other drugs.

Contrasting the effect of chronic ethanol consumption, which results in microsomal induction and tolerance to a number of drugs, the presence of ethanol may slow down disposition of some drugs and enhance their pharmacologic effects by competing for some common component(s) of the microsomal degradation process. This was shown for meprobamate (76), acetaminophen (77, 78) as well as methadone (79).

### c. Activation of hepatotoxins

One of the most important consequences of the discovery of this new microsomal pathway of ethanol metabolism was the realization that the ethanol-inducible cytochrome P4502E1 not only catalyzes ethanol oxidation, but is also capable of activating various other compounds to highly toxic metabolites. This pertains to analgesics, such as acetaminophen (80), anesthetics (81), hepatotoxins (82), industrial solvents (83), as well as carcinogens (e.g., nitrosodimethylamine [NDMA]) (84). Activation of the latter was achieved at concentrations significantly lower than those required after the administration of other inducers (84), in part because the ethanol-inducible P4502E1, including the human variety (64), has a high affinity for NDMA. Increased activation of carcinogens was also demonstrated

in the alimentary tract and the lungs (85). Thus, this inducible microsomal ethanol oxidizing system explains not only the metabolic tolerance to ethanol that develops in the heavy drinker, but also the concomitant increased vulnerability to ubiquitous xenobiotics. Furthermore, the proliferation of the endoplasmic reticulum (86) associated with P4502E1 induction is also accompanied by enhanced activity of other cytochrome P-450s, resulting in accelerated metabolism and tolerance to other drugs, as well as increased degradation of retinol and its hepatic depletion.

#### d. Interactions with retinoids and carotenoids

Liver microsomes were also found to harbor hitherto unrecognized pathways for retinol metabolism (87, 88) which were found to play a role in the homeostatic control of hepatic vitamin A levels (89). Using purified cytochrome P-450 isozymes, including the human P4502C8 (90), retinol (87, 90) and retinoic acid (90, 91), metabolizing systems were reconstituted; chronic ethanol or drug administration was shown to result in increased microsomal degradation of retinoic acid (92) and retinol (93). This provided a possible mechanism for the striking hepatic vitamin A depletion which was discovered to result from chronic ethanol consumption in rats (94), nonhuman primates (94), and man (95) (Fig. 4). This hepatic vitamin A depletion was associated with striking lysosomal lesions (96). Potentiation of the deleterious effects of vitamin A depletion

by ethanol was also found in other tissues, including a profound loss of the ciliated epithelium in the lining of the respiratory tract and the exacerbation of squamous metaplasia, a precancerous lesion (97). Hepatic depletion of vitamin A was also demonstrated after administration of other drugs (98); the combination of ethanol with drugs or food additives (such as butylated hydroxytoluene) resulted in a striking potentiation of the depletion, with almost all of the vitamin A disappearing from the liver (99).

Thus, vitamin A requirements had to be revised for the large segment of our population that chronically abuses ethanol and/or other drugs. The practical limits of vitamin A supplementation, however, were delineated by the demonstration that vitamin A toxicity can be markedly exacerbated by chronic ethanol consumption, with development of mitochondrial injury (100), necrosis and fibrosis (101). Indeed, amounts of ethanol and vitamin A which, by themselves, did not produce fibrosis, when combined, resulted in necrosis and fibrosis in the liver (101), with development of severe mitochondrial injury (100). Furthermore, it was discovered that alcohol interferes with the clearance of  $\beta$ -carotene, possibly by impairing its conversion to vitamin A, resulting in enhanced hepatic and blood levels in baboons (102) and also in man (103), with associated potentiation of hepatotoxicity (102) possibly due, in part, to the beadlets used as carrier for  $\beta$ -carotene (104). In addition, carotenoids were found to undergo significant biliary excretion in man (105) and are therefore affected by liver pathology. The recognition of a narrowed therapeutic window for vitamin A and  $\beta$ -carotene in the alcoholic has prompted a redefinition of the optimal conditions for their use in nutritional repletion and therapy.

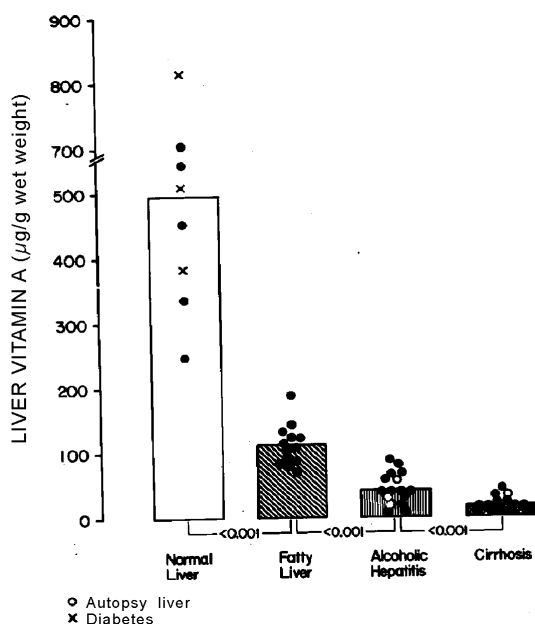


Fig. 4. Hepatic vitamin A levels in subjects with normal livers and various stages of alcoholic liver injury. Figures below the graph denote P values (95).

#### C. Acetaldehyde Toxicity and Mitochondrial Impairment

Ethanol oxidation, whether by the ADH or the microsomal pathway, results in acetaldehyde, which may cause ubiquitous damage, including in the mitochondria. Indeed, the ethanol-induced ultrastructural lesions of the mitochondria (86) were found to be associated with functional abnormalities, including decreased oxidation of fatty acids (106) and acetaldehyde (107, 108). The latter, together with the increased production by the induced microsomes (109), explains the elevated blood level of acetaldehyde observed in alcoholics (110). Using improved analytical methods (111), the high acetaldehyde levels were found to be reversible upon alcohol withdrawal

(112), and exaggerated by pregnancy and lactation (113). The human placenta was shown to be capable both of transferring acetaldehyde from the mother to the fetus and of converting ethanol to acetaldehyde (114), which may thus play a role in the pathogenesis of the fetal alcohol syndrome, the most common preventable cause of congenital abnormalities.

Administration of ethanol, particularly at high levels and in animals fed alcohol chronically, was accompanied by a 10-fold increase in splanchnic acetaldehyde release in the hepatic vein (115), associated with a striking leakage of the mitochondrial enzyme glutamic dehydrogenase into the hepatic venous blood. There was also an inappropriately low oxygen utilization by the liver. The flow-independent  $O_2$  extraction ( $VO_2$ ) was measured by reflectance spectroscopy with a probe placed on the liver surface through a peritoneoscope:  $VO_2$  significantly decreased after the high ethanol dose in the alcohol-treated baboons (115). This impaired  $O_2$  utilization was associated with a marked shift in the mitochondrial redox level (measured by the  $\beta$ -hydroxybutyrate / acetoacetate ratio). A "vicious cycle" was thus recognized, with chronic ethanol consumption inducing increased acetaldehyde formation leading to mitochondrial toxicity, including an associated decreased capacity of the mitochondria to oxidize acetaldehyde. As a consequence, acetaldehyde rises even further, and perpetuates and aggravates the toxicity.

The morphologic (116) and functional (117) impairment of the mitochondria after chronic ethanol consumption was accompanied by a significant decrease in cytochrome oxidase activity associated with the depletion of mitochondrial phosphatidylcholine, whereas restoration of cytochrome oxidative activity was achieved by replenishment of the phosphatidylcholine *in vitro* (117). This observation was one of the factors that led to the supplementation of phosphatidylcholine *in vivo* (using delinoleoylphosphatidylcholine), which resulted in the discovery of its spectacular beneficial effects, including the prevention of liver fibrosis and cirrhosis (*vide infra*). The uncoupling of oxidation with phosphorylation associated with mitochondrial impairment, together with the net loss of chemical energy that accompanies the operation of the induced microsomes explained, at least in part, the startling observation that "alcohol calories do not fully count" and why many alcoholics do not maintain an adequate body weight despite a large caloric intake (118).

One mechanism for the hepatotoxicity of acetaldehyde is its high chemical reactivity and

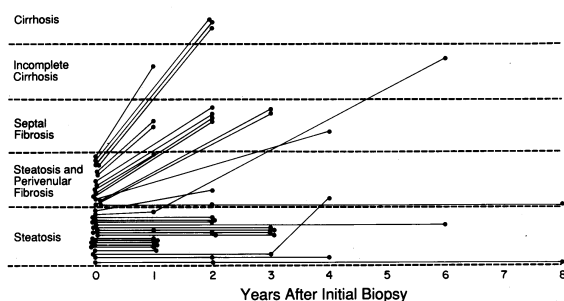
formation of adducts with various proteins. Indeed, it was discovered that acetaldehyde binds to microsomal proteins (119) and forms adducts *in vivo* with P4502E1 (120), collagen (121–122), as well as VLDL and LDL (123). Acetaldehyde adducts also elicit an immune response with increased circulating antibodies in alcoholics (124). The appearance of antibodies against acetaldehyde-protein adducts was found to reflect the severity of liver disease, both in alcoholics and non-alcoholics (125). Furthermore, even in non-alcoholic liver disease, hepatic acetaldehyde was found to be increased to a potentially toxic level (126). Moreover, acetaldehyde toxicity was shown to interfere with the repair of alkylated nucleo-proteins; human and rat O6 methylguanine transferase was inhibited *in vitro* by minute concentrations of acetaldehyde (as low as 0.01  $\mu$ M) (127). Acetaldehyde binding was also shown to impair microtubule polymerization and hepatic protein secretion (128, 129) which, together with an increase in constituent proteins (130), resulted in protein accumulation and hepatocyte swelling, thereby explaining the ballooning of the hepatocyte and the hepatomegaly, two characteristic features of alcohol-induced liver injury.

Acetaldehyde also contributes to depletion of glutathione and its potentiation of lipid peroxidation (131), verified in human liver biopsies (132). These effects were found to be attenuated by S-adenosyl-L-methionine (133), which has now been introduced in Europe for the treatment of liver disease. The oxidative stress was exacerbated by a low vitamin E diet, and ethanol was found to aggravate hepatic vitamin E depletion, in part by promoting conversion of  $\alpha$  tocopherol to  $\alpha$  tocopheryl-quinone (134), probably by free radical reaction. Allopurinol partially prevented the ethanol-induced lipid peroxidation (135), most likely through inhibition of purine degradation (enhanced by ethanol) and the associated free radical generation.

#### **D. Fibrosis and Cirrhosis of the Liver: Pathogenesis and Prevention**

Traditionally, fibrosis and cirrhosis were viewed as a "scarring" response to the necrosis and inflammation associated with liver injury, most clearly demonstrated in alcoholic hepatitis. However, the observation that chronic alcohol administration (under controlled dietary conditions) stimulated fibrogenesis (136) and produced cirrhosis in the baboon (4) without an obvious stage of alcoholic hepatitis (137) but with evidence for increased collagen production, including enhanced type I procollagen mRNA (138),

raised the hypothesis of a more direct effect of alcohol on fibrogenesis. Indeed, in baboons fed alcohol (139) as well as in man (140), perivenular fibrosis was identified as a precirrhotic lesion and shown to be useful for the early detection of subjects prone to rapidly develop cirrhosis, even in the absence of alcoholic hepatitis (141) (Fig. 5). Scanning electron microscopy also revealed significant changes of the endothelial fenestrations of the liver sinusoids (142), a finding of obvious implications for the exchange of nutrients and metabolites between the hepatocytes and the blood. Efforts were then directed to define the cell(s) involved. Myofibroblasts were identified in normal liver (139) and were discovered to proliferate after chronic alcohol consumption (139, 140). Furthermore, stellate cells (also called lipocytes or fat-storing cells) were found to be transformed or activated to "transitional" myofibroblast-like cells (143), associated with active fibrogenesis. Lipocytes and myofibroblasts were isolated from the liver and cultured, and acetaldehyde was shown to stimulate collagen production *in vitro* (144, 145), with an associated increase in mRNA for collagen (146). The acetaldehyde-induced increase in collagen accumulation was prevented by polyunsaturated phosphatidylcholine (PPC) extracted from soybeans (147) and by its main phosphatidylcholine species, namely dilinoleophosphatidylcholine (DLPC) (148), selected because of its high bioavailability. Several modes of action were elucidated: increased collagen breakdown (148), a significant decrease in the number of lipocytes activated to myofibroblast-like cells (148, 149), correction of the ethanol-induced depletion in phosphatidylcholine (148), as well as an attenuation of some of the associated enzyme deficiencies, including that of phosphatidylethanolamine methyltransferase (150). More recently, PPC was also found



**Fig. 5.** Progression of fibrosis in alcoholics without hepatitis followed up to eight years after initial biopsy. The presence of perivenular fibrosis on the initial biopsy specimen was found to be a harbinger of rapid development of fibrosis to more severe stages, including cirrhosis (141).

to prevent alcohol-induced steatosis and hyperlipemia (151) and to exert an unexpected but potent antioxidant effect (152) of possible relevance to the fibrosis, since the latter is known to be stimulated by products of lipid peroxidation. Furthermore, PPC prevented or attenuated non-alcoholic cirrhosis produced by either  $\text{CCl}_4$  or heterologous albumin in the rat and accelerated the regression of preexisting cirrhosis (153). PPC is now being tested in man.

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