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ALCOHOL: Its Metabolism and Interaction With Nutrients

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■ **Abstract** In the past, alcoholic liver disease was attributed exclusively to dietary deficiencies, but experimental and judicious clinical studies have now established alcohol's hepatotoxicity. Despite an adequate diet, it can contribute to the entire spectrum of liver diseases, mainly by generating oxidative stress through its microsomal metabolism via cytochrome P4502E1 (CYP2E1). It also interferes with nutrient activation, resulting in changes in nutritional requirements. This is exemplified by methionine, one of the essential amino acids for humans, which needs to be activated to S-adenosylmethionine (SAMe), a process impaired by liver disease. Thus, SAMe rather than methionine is the compound that must be supplemented in the presence of significant liver disease. In baboons, SAMe attenuated mitochondrial lesions and replenished glutathione; it also significantly reduced mortality in patients with Child A or B cirrhosis. Similarly, decreased phosphatidylethanolamine methyltransferase activity is associated with alcoholic liver disease, resulting in phosphatidylcholine depletion and serious consequences for the integrity of membranes. This can be offset by polyenylphosphatidylcholine (PPC), a mixture of polyunsaturated phosphatidylcholines comprising dilinoleoylphosphatidylcholine (DLPC), which has high bioavailability. PPC (and DLPC) opposes major toxic effects of alcohol, with down-regulation of CYP2E1 and reduction of oxidative stress, deactivation of hepatic stellate cells, and increased collagenase activity, which in baboons, results in prevention of ethanol-induced septal fibrosis and cirrhosis. Corresponding clinical trials are ongoing.

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RESPECTIVE ROLE OF ALCOHOL AND NUTRITION IN ORGAN DAMAGE OF THE ALCOHOLIC

Ethanol is more than a psychoactive drug. In addition to its pharmacologic action, it has considerable energy value (7.1 kcal/g). Therefore, substantial use of alcohol has profound effects on nutritional status (135). Such consumption may cause primary malnutrition, by displacing other nutrients in the diet because of the high-energy content of alcoholic beverages [Figure 1 (see color insert)] or because of associated socioeconomic and medical disorders. Secondary malnutrition may result from either maldigestion or malabsorption of nutrients caused by gastrointestinal complications associated with alcoholism, involving especially the pancreas and the small intestine. These effects include malabsorption of thiamine and folate as well as maldigestion and malabsorption secondary to alcohol-induced pancreatic insufficiency and intestinal lactase deficiency (198). Alcohol also promotes nutrient degradation or impaired activation. Such primary and secondary malnutrition can affect virtually all nutrients (see below). At the tissue level, alcohol replaces various normal substrates, with the liver being the most seriously affected organ and malnutrition being incriminated as a primary etiologic factor of liver dysfunction.

Theories of the exclusively nutritional origin of alcoholic liver disease were supported very strongly by Best et al (18), who wrote that "there is no more evidence of a specific toxic effect of pure ethyl alcohol upon liver cells than there is for one due to sugar." This notion was based largely on experimental work with rats given ethanol in drinking water (18). Under these conditions, no liver lesions developed unless the diet was deficient in proteins, methionine, or choline. Deficiency alone sufficed to produce the liver lesions. However, because rats have an aversion to alcohol, when it is administered in drinking water, ethanol

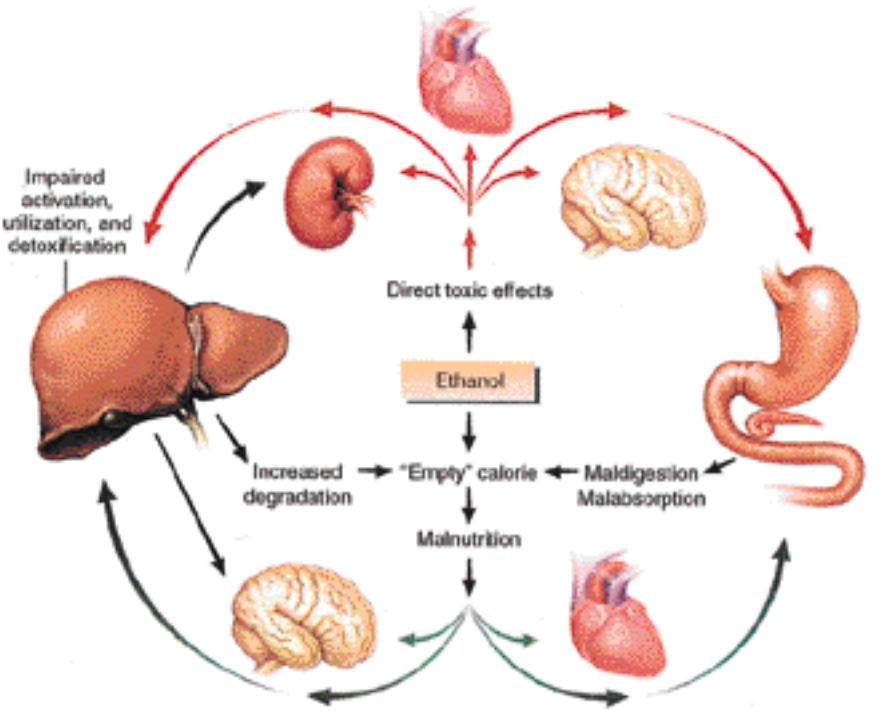

Figure 1 Organ damage in alcoholics. Interaction of direct toxicity of ethanol on various organs with malnutrition secondary to dietary deficiencies, maldigestion, and malabsorption, as well as impaired hepatic activation or increased degradation of nutrients. (From 136.)

consumption usually does not exceed 10–25% of the total energy intake of the animal. Such an amount of alcohol resulted in negligible ethanol concentrations in the blood (149). Thus, administering alcohol to rodents in drinking water is not a suitable model for the human disease. When ethanol was incorporated into a totally liquid diet (149, 150), the aversion for alcohol was overcome because, in order to eat or drink, the animals had no choice but to take the alcohol along with the diet. With this technique, the quantity of ethanol consumed was increased to 36% of total energy, an amount relevant to alcohol intake in humans. It was found that even with nutritionally adequate diets, isoenergetic replacement of sucrose or other carbohydrates by ethanol consistently produced a 5- to 10-fold increase in hepatic triglycerides (39, 149, 150). Furthermore, isoenergetic replacement of carbohydrate by fat instead of ethanol did not produce steatosis (149). With this liquid-diet technique, alcohol was also shown to be capable of producing cirrhosis in nonhuman primates, even when the diet was adequate (145). In addition, the hepatotoxicity of ethanol was established by controlled clinical investigations that showed that even in the absence of dietary deficiencies, alcohol can produce fatty liver and ultrastructural lesions in humans (149, 150).

Some dietary deficiencies were found to exacerbate the effects of alcohol, and judicious supplementations were shown to have beneficial effects. When protein deficiency is present, it may potentiate the effect of ethanol. In rats, a combination of ethanol and a diet deficient in both protein and lipotropic factors leads to more pronounced hepatic steatosis than with either factor alone (158). Indeed, protein deficiency impairs lipoprotein secretion, which can markedly potentiate hepatic lipid accumulation secondarily to the direct effects of alcohol resulting from its metabolism in the liver. However, the effect of protein deficiency has not been clearly delineated in human adults. In children, protein deficiency leads to hepatic steatosis, one of the manifestations of kwashiorkor, but this condition does not progress to cirrhosis. In adolescent baboons, protein restriction to 7% of total energy did not result in conspicuous liver injury (even after 19 months) either by biochemical analysis or by light- and electron-microscopic examination. Significant steatosis was observed only when the protein intake was reduced to 4% of total energy (146). On the other hand, an excess of protein (25% of total energy, or 2.5 times the recommended amount) did not prevent alcohol from producing fat accumulation in human volunteers (156). Thus, in humans, ethanol is capable of producing striking changes in liver lipids, even in the presence of a protein-enriched diet, an effect linked to the metabolism of ethanol.

The hepatocyte contains three main pathways for ethanol metabolism, each located in a different subcellular compartment: (*a*) the alcohol dehydrogenase (ADH) pathway of the cytosol or the soluble fraction of the cell, (*b*) the microsomal ethanol oxidizing system located in the endoplasmic reticulum, and (*c*) catalase located in the peroxisomes (135). Each of these pathways produces specific metabolic and toxic disturbance, and all three result in the production of acetaldehyde, a highly toxic metabolite.

THE ADH PATHWAY AND ASSOCIATED METABOLIC DISORDERS OF CARBOHYDRATES, URIC ACID, AND LIPIDS

ADH Isozymes

ADH has a broad substrate specificity that includes dehydrogenation of steroids, oxidation of the intermediary alcohols of the shunt pathway of mevalonate metabolism, and ω-oxidation of fatty acids (19); these processes may act as the "physiologic" substrates for ADH.

Human liver ADH is a zinc metalloenzyme with five classes of multiple molecular forms that arise from the association of eight different types of subunits—α, $\beta 1$, $\beta 2$, $\beta 3$, $\gamma 1$, $\gamma 2$, π, and χ—into active dimeric molecules. A genetic model accounts for this multiplicity as products of five gene loci, ADH1 through ADH5 (25). There are three types of subunits in class I: α, β, and γ. Polymorphism occurs at two loci, ADH2 and ADH3, which encode the β and γ subunits. Class II isozymes migrate more anodically than class I isozymes, and unlike the latter, which generally have low K_m values for ethanol, class II (or π) ADH has a relatively high K_m (34 mM) and a relative insensitivity to 4-methylpyrazole inhibition. Class III (χ ADH) does not participate in the oxidation of ethanol in the liver because of its very low affinity for that substrate. More recently, a new isoenzyme of ADH has been purified from human stomach, so-called σ- or (class IV) μ-ADH (267, 268).

Metabolic Effects of Excessive ADH-Mediated Hepatic NADH Generation

The oxidation of ethanol via the ADH pathway results in the production of acetaldehyde with loss of H, which reduces NAD to NADH. The large amounts of reducing equivalents generated overwhelm the ability of the hepatocyte to maintain redox homeostasis, and a number of metabolic disorders ensue (Figure 2) (135), including hypoglycemia and hyperlactacidemia. The latter contributes to acidosis and also reduces the capacity of the kidney to excrete uric acid, leading to secondary hyperuricemia, which is aggravated by the alcohol-induced ketosis and acetate-mediated enhanced ATP breakdown and purine generation (47). Hyperuricemia explains, at least in part, the common clinical observation that excessive consumption of alcoholic beverages commonly aggravates or precipitates gouty attacks. The increased NADH also promotes fatty acid synthesis and opposes lipid oxidation, with, as a net result, fat accumulation (157).

The effects of ethanol were reproduced in vitro by an alternate NADH generating system (sorbitol-fructose) and were blocked by a H+ acceptor (methylene blue) (147, 157). The preventive effect of methylene blue against ethanol-induced fat accumulation was recently confirmed (59).

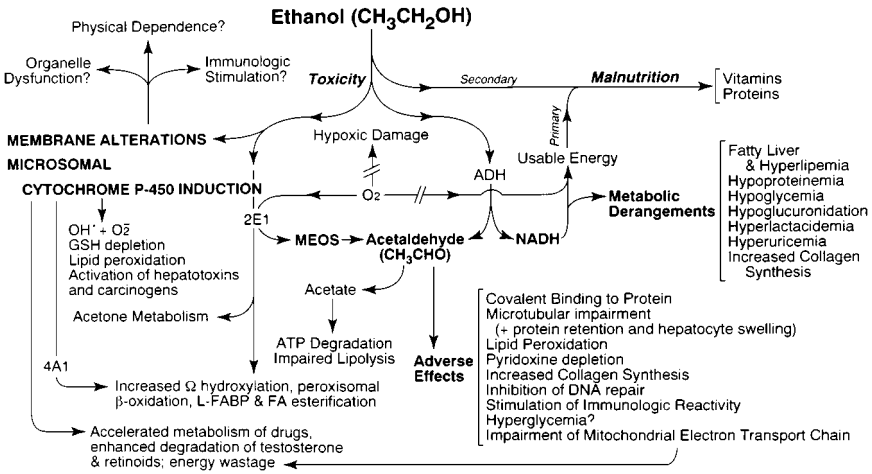

Figure 2 Hepatic, nutritional, and metabolic abnormalities after ethanol abuse. Malnutrition, whether primary or secondary, can be differentiated from metabolic changes or direct toxicity, resulting partly from ADH-mediated redox changes, or effects secondary to microsomal induction, or acetaldehyde production. MEOS, microsomal ethanol oxidizing system; GSH, glutathione. (From 138.)

Extrahepatic ADH

The human gastric mucosa possesses several ADH isoenzymes (77), one of which (class IV ADH or σ ADH) is not present in the liver. This enzyme has now been purified (229), its full length cDNA obtained, the complete amino acid sequence deduced (49, 267), and its gene cloned and localized to chromosome 4 (268). Gastric ADH is responsible for a large portion of ethanol metabolism found in cultured rat (180) and human (70) gastric cells. Its in vivo effect is reflected by the first pass metabolism (FPM) of ethanol, i.e. for a given dose of ethanol, blood levels are usually higher after intravenous than after oral administration (93, 94). Although the relative contribution of gastric and hepatic ethanol metabolism to FPM is still the subject of debate (132, 148, 219), the role of gastric ethanol metabolism in this FPM has been established experimentally (29, 159). Furthermore, FPM is partly lost in the alcoholic (41), together with decreased gastric ADH activity. Moreover, FPM disappears after gastrectomy (30). σ ADH is also absent or markedly decreased in activity in a large percentage of Japanese subjects (15), and their FPM is reduced correspondingly (42), in keeping with a predominant role for σ ADH in human FPM. Thus, the FPM represents some kind of protective barrier against the systemic effects of ethanol, including attenuation of liver damage (16, 88).

Pathogenic Role of ADH Polymorphism

Individual differences in the rate of ethanol metabolism may be genetically controlled. Furthermore, genetic factors influence the severity of alcohol-induced liver

disease. Indeed, the frequency of an alcohol dehydrogenase 3 allele has been found to differ in patients with alcohol-related end-organ damage (including cirrhosis) and matched controls, which suggests that genetically determined differences in alcohol metabolism may explain differences in the susceptibility to alcohol-related disease (possibly through the enhanced generation of toxic metabolites) (37), but this hypothesis has been questioned (201).

MICROSOMAL ETHANOL-OXIDIZING SYSTEM

A new pathway, called the microsomal ethanol-oxidizing system (MEOS) (143, 144), has been the subject of extensive research and is reviewed in detail elsewhere (137, 139). The system was demonstrated in liver microsomes in vitro and was found to be inducible by chronic alcohol feeding in vivo (143).

The key enzyme of the MEOS is the ethanol-inducible cytochrome P4502E1 (CYP2E1), which is increased 4- to 10-fold in liver biopsies of recently drinking subjects (243), with a corresponding rise in mRNA (236). This induction contributes to the metabolic tolerance to ethanol that develops in the alcoholic (in addition to the central nervous tolerance), with other P450 cytochromes (CYP1A2, CYP3A4) possibly also involved (216).

In addition to tolerance to ethanol, alcoholics tend to display tolerance to various other drugs. Indeed, the rate of drug clearance from the blood is enhanced in alcoholics. This could be caused by a variety of factors other than ethanol, such as the nonalcoholic beverage components and the use of other drugs commonly associated with alcoholism. Controlled studies showed, however, that administration of pure ethanol with nondeficient diets to either rats or humans (under metabolic ward conditions) resulted in a striking increase in the rate of blood clearance of meprobamate and pentobarbital (181), and various other drugs (135). The metabolic tolerance persists several days to weeks after cessation of alcohol abuse, and the duration of recovery varies depending on the drug considered (79).

Experimentally, this effect of chronic ethanol consumption is modulated, in part, by the dietary content in carbohydrates (239), lipids (92), and proteins (182). It is now recognized that CYP2E1, in addition to its ethanol-oxidizing activity, catalyzes fatty acid ω-1 and ω-2 hydroxylations (3, 9, 110). Furthermore, acetone is both an inducer and a substrate of CYP2E1 (104, 105, 266) (Figure 3). Excess ketones and fatty acid commonly accompany diabetes and morbid obesity, conditions associated with nonalcoholic steatohepatitis (NASH). Experimentally, obese, overfed rats also exhibit substantially higher microsomal ethanol oxidation, acetaminophen activation, and p-nitrophenol hydroxylation (monooxygenase activities catalyzed by CYP2E1) (206). These diabetic rats are experimental models relevant to NASH, and indeed, the hepatopathology of NASH appears to be due, at least in part, to excess CYP2E1 induction (256).

Clinically, in addition to ethanol oxidation, an important feature of CYP2E1 is its extraordinary capacity to convert many xenobiotics to highly toxic metabolites, which explains the increased vulnerability of the alcoholic. These agents include industrial solvents (e.g. bromobenzene and vinylidene chloride), anesthetic agents

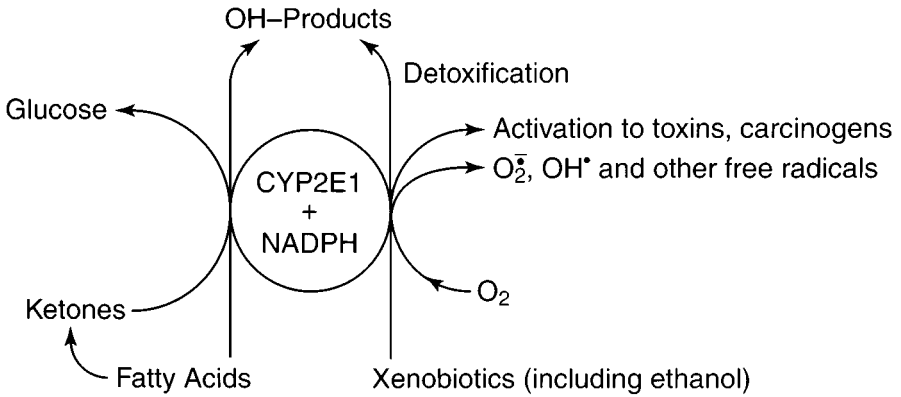

Figure 3 Physiologic and toxic roles of CYP2E1, the main cytochrome P450 of the microsomal ethanol-oxidizing system. Many endogenous and xenobiotic compounds are substrates for CYP2E1 and induce its activity through various mechanisms, resulting in an array of beneficial as well as harmful effects. (From 139.)

[e.g. enflurane (244) and methoxyflurane], commonly used medications (e.g. isoniazid and phenylbutazone), illicit drugs (e.g. cocaine), and over-the-counter analgesics (e.g. acetaminophen) (223), all of which are substrates for, and/or inducers of, CYP2E1. The effects of acetaminophen, ethanol, and fasting are synergistic (259) because all three deplete the level of reduced glutathione, a scavenger of toxic free radicals. Rats fed ethanol chronically have increased rates of glutathione (GSH) turnover (185), and ethanol produces an enhanced loss from the liver (228). The selective loss of the compound from liver mitochondria (81) contributes to the striking alcohol-induced oxidant stress and impairment of this organelle.

CYP2E1 also generates several species of active oxygen (Figures 2 and 3), which, in concert with a decrease in the level of GSH, promote injury by inactivation of enzymes and peroxidation of lipids. In patients with cirrhosis, hepatic depletion of α-tocopherol (129), a major antioxidant, potentiates this effect. GSH offers one of the mechanisms for the scavenging of toxic free radicals. Replenishment of GSH can be achieved by administration of precursors of cysteine (one of the amino acids of this tripeptide), such as acetylcysteine or S-adenosyl-L-methionine (SAMe) (142, 141). Experimentally, CYP2E1 has also been down-regulated by polyenylphosphatidylcholine (7), a potentially beneficial therapeutic approach.

NUTRITIONAL STATUS OF ALCOHOLICS

Overall Assessment

Alcoholics hospitalized for medical complications of alcohol intoxication (such as states of acute intoxication and withdrawal) have the most severe malnutrition. These alcoholics have inadequate dietary protein (197), signs of protein

malnutrition (86, 177), and anthropomorphic measurements indicative of impaired nutrition: Their height-to-weight ratio is low (184), muscle mass estimated by the creatinine-height index is reduced (177, 184), and triceps skin folds are thin (177, 184, 225). Continued drinking results in weight loss, whereas abstinence results in weight gain (261, 262) in patients with and without liver disease (261).

Many patients who drink to excess either are not malnourished or are less malnourished than the hospitalized group. Women drinking one or more drinks per day weighed on average 2.3 kg less than nondrinkers did, and their weight and that of their male counterparts was more stable over the course of 10 years than that of nondrinkers, whose weight rose (163). Other surveys, however, found that alcohol intake, especially when accompanied by high fat intake and sedentary behavior (11), favors truncal obesity, particularly in women (242). Those with moderate alcohol intake (17), even those admitted to the hospital for alcohol rehabilitation rather than for medical problems (187), often differed little nutritionally from control patients (matched for socioeconomic status and health history), except that females had a lower level of thiamin excretion than did control patients following a thiamin load test (187).

The wide range in nutritional status of alcoholics surely reflects, in part, differences in what they eat. Moderate alcohol intake with alcohol accounting for 16% of total calories is associated with slightly increased total energy intake (68).

Although ethanol is rich in energy (7.1 cal/g), chronic consumption does not produce the expected gain in body weight (134). This energy deficit can be attributed, in part, to damaged mitochondria and the resulting poor coupling of oxidation of fat with energy production, as well as to microsomal pathways that oxidize ethanol without conserving chemical energy (Figure 2). Thus, perhaps because of these energy considerations, this group with higher total caloric intake has no weight gain despite physical activity levels comparable to those of the nonalcohol-consuming population. This level of alcohol intake, and even slightly higher levels (23%) (80), is associated with a substitution of alcohol for carbohydrate in the diet. In those individuals consuming more than 30% of total calories as alcohol, significant decreases in protein and fat intake occur, too, and the consumption of vitamins A and C and thiamin may descend below the recommended dietary allowances (68). Calcium, iron, and fiber intake are also lowered (80).

The mechanisms underlying the altered pattern of food intake are under debate. Suppression of appetite has been postulated (257). Depressed consciousness during inebriation, hangover, and gastroduodenitis due to ethanol partly explains the decreased food intake. What contribution the subtle nutritional alterations produced by ethanol makes to the pathogenesis of ethanol-induced or other disease states, including alcoholism, is largely unexamined.

Specific Nutrients

Vitamin C The vitamin C status of alcoholic patients admitted to a hospital is lower than that of nonalcoholics, as measured by serum ascorbic acid, peripheral

leukocyte ascorbic acid, or urinary ascorbic acid after an oral challenge (23). In addition to a lower mean ascorbic acid level, some 25% of patients with Laennec's cirrhosis had serum ascorbic acid levels below the range of healthy controls (23). Ascorbic acid status is low in alcoholic patients with and without liver disease. When alcohol intake exceeds 30% of total calories, vitamin C generally falls below recommended dietary allowances (69). The clinical significance is unknown for patients who have low ascorbic acid levels but who are not clearly scorbutic.

Vitamin D Alcoholics have illnesses related to abnormalities of calcium, phosphorus, and vitamin D homeostasis. They have decreases in bone density (224) and bone mass (61), increased susceptibility to fractures (189), and increased osteonecrosis (226). Low blood calcium, phosphorus, magnesium, and low, normal, and high vitamin D_3 levels have been reported, indicating disturbed calcium metabolism (61). In patients with alcoholic liver disease, vitamin D deficiency probably derives from too little vitamin D substrate, which results from poor dietary intake, malabsorption due to cholestasis or pancreatic insufficiency, and insufficient sunlight.

Vitamin K Vitamin K deficiency in alcoholism may arise when there is an interruption of fat absorption due to pancreatic insufficiency, biliary obstruction, or intestinal mucosal abnormality secondary to folic acid deficiency. Dietary vitamin K inadequacy is not a likely cause of clinical deficiency unless there is concomitant sterilization of the large gut, a reliable source of the vitamin.

Folic Acid Alcoholics tend to have low folic acid status when they are drinking heavily and their folic acid intake is reduced. For example, a group of unselected alcoholics showed a 37.5% incidence of low serum folate levels and a 17.6% incidence of low red blood cell folate levels (261).

In pigs fed ethanol for 11 months, folic acid absorption is normal, but jejunal folate hydrolase, an early enzyme of folate polyglutamate breakdown, is decreased (186, 208). In vitro preparations of rat intestine absorb folate less well when exposed to a variety of alcohols (215). Malnourished alcoholics without liver disease also absorb folic acid less well compared with their better-nourished counterparts (71). Folic acid absorption, usually increased by partial starvation, is less increased in rats when alcohol is ingested (205). It has not been clearly shown, however, that either protein deficiency or alcohol (71, 205) decreases folate absorption in vivo. Thus, it is unclear what aspects of malnutrition adversely affect folate absorption and under what clinical circumstances alcohol may interfere with folate absorption.

Alcohol accelerates the production of megaloblastic anemia in patients with depleted folate stores (161) and suppresses the hematologic response to folic acid in folic acid–depleted patients (234). Alcohol also has other effects on folate metabolism, but their significance is not clear: Alcohol given acutely causes a decrease in serum folate, which is partly explained by increased urinary excretion (214); and alcohol administered chronically to monkeys decreased hepatic folate

levels, partly because of the inability of the liver to retain folate (237), and perhaps partly because of increased urinary and fecal losses (238).

Vitamin B_{12} Alcoholics do not commonly get vitamin B_{12} deficiency. Their serum levels are usually normal even when they are deficient in folate, whether they have cirrhosis (76, 102) or not (71, 205). This is probably due to large body stores of vitamin B_{12}. Pancreatic insufficiency, however, results in decreased vitamin B_{12} absorption, as measured by the Schilling test. In this circumstance, there is insufficient luminal protease activity and alkalinity, which normally serve to release vitamin B_{12} from the "r" protein that is secreted by salivary glands, intestines, and possibly the stomach (78). Alcohol ingestion has also been shown to decrease vitamin B_{12} absorption in volunteers after several weeks of intake (160). The alcohol effect may be in the ileum because coadministration of intrinsic factor or pancreatin does not correct the Schilling test results. It is controversial whether the binding of intrinsic factor-vitamin B_{12} complex to ileal sites is abnormal (162, 50).

Riboflavin When there is a general lack of B vitamin intake, riboflavin deficiency may be encountered (249). In one study, deficiency was found in 50% of a small group of patients with medical complications severe enough to warrant hospital admission (210). Although none of the patients exhibited classic signs of riboflavin deficiency, they had an abnormal activity coefficient that returned to normal 2–7 days after intramuscular replacement with 5 mg of riboflavin daily. Activity coefficient is measured as the ratio of erythrocyte glutathione reductase activity on addition of flavin adenine dinucleotide to the assay, with no other additions. Riboflavin deficiency could be induced readily by alcohol feeding to Syrian hamsters; the most severe deficiency was seen in animals also restricted in riboflavin intake (99). Riboflavin and pyridoxine storage in the liver is adversely affected by alcohol, at least in experimental animals.

Vitamin E and Selenium Vitamin E deficiency is not a recognized complication of alcoholism, although patients with chronic alcoholic pancreatitis have a lower ratio of vitamin E to total plasma lipid (172).

When rodents were fed ethanol repeatedly in one study, their hepatic vitamin E levels, measured as α-tocopherol, were low (20); this was accompanied by increased hepatic lipid peroxidation when alcohol was combined with a low vitamin E diet (97). The mechanism of hepatic vitamin E depletion by ethanol is probably enhanced oxidation of α-tocopherol to α-tocopherol quinone in liver microsomes (97). Alcohol-induced liver injury may be mediated, in part, by stress on cellular antioxidant mechanisms interrelated with vitamin E and selenium. Considering the findings in humans with fat malabsorption or severe cholestasis, and the evidence of vitamin E depletion by chronic alcohol feeding of experimental animals, it would seem that there is great potential for vitamin E deficiency in chronic alcoholics who combine low vitamin E intake with steatorrhea from chronic pancreatitis or prolonged cholestasis.

Magnesium Acute doses of ethanol cause magnesium loss in the urine (174), and alcoholism is associated with magnesium deficiency (54). Alcoholics have low blood magnesium and low body-exchangeable magnesium. Symptoms in alcoholics resemble those in patients with magnesium deficiency from other causes. On withdrawal from alcohol, magnesium balance is positive. Hypocalcemia in alcoholics in the setting of magnesium deficiency has been ascribed, in part, to impaired parathyroid hormone secretion as well as renal and skeletal resistance to parathyroid hormone (1), and the hypocalcemia may be only responsive to magnesium repletion. Hospitalized alcoholics with normal serum total magnesium had significantly lower serum-ionized magnesium (264).

Iron There may be either deficiency or an excess of iron in alcoholics. The iron deficiency may be a result of the gastrointestinal lesions to which alcoholics are prone and that may bleed.

Hepatic iron content was found to be increased in autopsy studies of most patients with early alcoholic cirrhosis (253). In most alcoholics however, the iron content of the liver is normal or only modestly elevated, although there may be stainable iron in reticuloendothelial cells, possibly because of bouts of hemolysis. It is unclear whether increased intestinal absorption of iron because of alcohol (31) or hepatic uptake of iron from plasma in established alcoholic liver disease (32) contributes significantly to increased hepatic iron levels. Using a measure of absolute iron content per gram of liver, with upward adjustments for age, there is usually little difficulty in distinguishing the hepatic iron increases of alcoholic liver disease from the much higher amounts characteristic of genetic hemochromatosis (192). The contribution hepatic iron may make to liver damage via its role in lipid peroxidation (13) (in conjunction with the effects of alcohol) and its possible role in promoting fibrogenesis (34) are of potentially great significance.

Zinc Alcoholic patients have low plasma zinc (248), low liver zinc (247), and increased urinary zinc levels (231, 247). Acute ethanol ingestion, however, does not cause zincuria (232). The low zinc content of chronic alcoholics with cirrhosis is attributed to decreased intake and absorption as well as increased urinary excretion. Many Americans have diets marginal in zinc (170a). Alcoholics fall into the group with marginal intake. It is interesting that zinc absorption has been shown to be low in alcoholic cirrhotics but not in patients with cirrhosis from other causes (246), although cirrhosis of varied etiologies is characterized by low serum zinc (200). Currently, the therapeutic use of zinc in alcoholism is restricted to the treatment of night blindness not responsive to vitamin A.

Copper Hepatic copper content is increased in advanced alcoholic cirrhosis (253). Serum copper content has been reported to be elevated in alcoholics independent of the stage of liver disease (73), but others have reported normal levels (233).

Trace Metals Nickel levels are consistently high in alcoholic liver disease; manganese and chromium are unchanged (253). On acute administration of alcohol, intracellular shifts in trace metals have been described (235). Versieck et al (252) reported increased serum molybdenum in patients with acute liver disease; increased levels were not seen in patients with cirrhosis. The clinical significance of trace metal changes is still obscure, except for the cardiotoxicity ascribed to alcoholic beverages with high cobalt content.

EFFECTS OF ETHANOL ON DIGESTION AND ABSORPTION

Diarrhea frequently occurs in alcoholics. In heavy drinkers, diarrhea may occur for a variety of reasons, including ethanol-exacerbated lactase deficiency, especially in African-Americans (198). Alcohol consumption is also associated with motility changes. In the jejunum, ethanol decreases type I (impeding) waves, whereas in the ileum it increases type III (propulsive) waves. Another major complication is alcoholic pancreatitis. Intestinal malabsorption may also be secondary to folic acid deficiency (234) (see above).

Steatorrhea is commonly due to folic acid deficiency and luminal bile salt deficiency. Intraluminal bile salts are decreased by acute ethanol administration (171). In rodents, long-term ethanol administration delays the half-time excretion of cholic and chenodeoxycholic acids by decreasing the daily excretion and expanding the pool size slightly (111). Alcoholic cirrhotic patients may have bile low in deoxycholic acid, possibly due to impaired conversion of cholate to deoxycholate by bacteria (103).

Hospitalized alcoholics were reported to have impaired thiamin absorption compared with control patients when tested by radioactive thiamin excretion (240), a test also affected by steps not related to absorption. However, folic acid deficiency was not adequately excluded as a cause of thiamin malabsorption in these studies. Refined testing revealed reduced thiamin absorption due to alcohol in a minority of subjects (27). Jejunal perfusion studies did not show an effect of 5% alcohol on thiamin absorption in humans (96). Thus, whereas thiamin absorption may not be affected by alcohol in humans, it is clearly impaired in rodents.

Alcohol also interferes with riboflavin absorption in rodents, but this has not been studied in humans. Alcohol impairs folic acid absorption in malnourished humans, but the mechanism is unclear (234) (see above).

EFFECT OF ALCOHOL ON NUTRIENT ACTIVATION

Thiamine and Pyridoxine

Thiamin deficiency in alcoholics causes Wernicke-Korsakoff syndrome and beriberi heart disease and probably contributes to polyneuropathy. There has been no confirmation of an inborn error of transketolase affinity for its cofactor thiamine pyrophosphate in Wernicke-Korsakoff syndrome, as was once claimed.

Neurologic, hematologic, and dermatologic disorders can be caused in part by pyridoxine deficiency. Pyridoxine deficiency, as measured by low plasma pyridoxal-5′-phosphate (PLP), was reported in over 50% of alcoholics without hematologic findings or abnormal liver function tests (55, 166). Inadequate intake may partly explain low PLP, but increased destruction and reduced formation may also contribute. PLP is more rapidly destroyed in erythrocytes in the presence of acetaldehyde, the product of ethanol oxidation, perhaps by displacement of PLP from protein and consequent exposure to hydrolysis of PLP by cellular phosphatases (166, 167). Studies showed that chronic ethanol feeding lowered hepatic content of PLP by decreasing net synthesis from pyridoxine (168, 196, 250).

Methionine and SAMe

Methionine deficiency has been described and its supplementation has been considered for the treatment of liver diseases, especially the alcoholic variety, but excess methionine was shown to have some adverse effects (52), including a decrease in hepatic ATP (72). Furthermore, whereas in some patients with alcoholic liver disease circulating methionine levels are normal (89), in others elevated levels were observed (53, 87, 183). Moreover, Kinsell et al (100) found a delay in the clearance of plasma methionine after its systemic administration to patients with liver damage. Similarly, after an oral load of this amino acid, the blood clearance of methionine was slowed (85). Because about half the methionine is metabolized by the liver, these observations suggested impaired hepatic metabolism of this amino acid in patients with alcoholic liver disease. Indeed, for most of its functions, methionine must be activated to SAMe and in cirrhotic livers, Duce et al (43) reported a decrease in the activity of SAMe synthetase, the enzyme involved, also called methionine adenosyltransferase (Figure 4). Various mechanisms of inactivation of SAMe synthetase have been reviewed recently (165). One factor that may have contributed to the defect is relative hypoxia, with nitric oxide–mediated inactivation and transcriptional arrest (12). In addition, long-term alcohol consumption was found to be associated with enhanced methionine utilization and depletion (51). As a consequence, SAMe depletion as well as its decreased availability could be expected, and indeed, long-term ethanol consumption under controlled conditions by nonhuman primates was associated with a significant depletion of hepatic SAMe (142). Potentially, such SAMe depletion may have a number of adverse effects. SAMe is the principal methylating agent in various transmethylation reactions, which are important to nucleic acid and protein synthesis. Hirata and coworkers (82, 83) also demonstrated the importance of methylation to cell membrane function with regard to membrane fluidity and the transport of metabolites and transmission of signals across membranes. Thus, depletion of SAMe, by impairing methyltransferase activity, may promote the membrane injury that has been documented in alcohol-induced liver damage (265). Furthermore, SAMe plays a key role in the synthesis of polyamines and provides a source of cysteine for glutathione production (Figure 4). Thus, the deficiency in methionine activation and in SAMe production resulting from the decrease in the activity of the corresponding

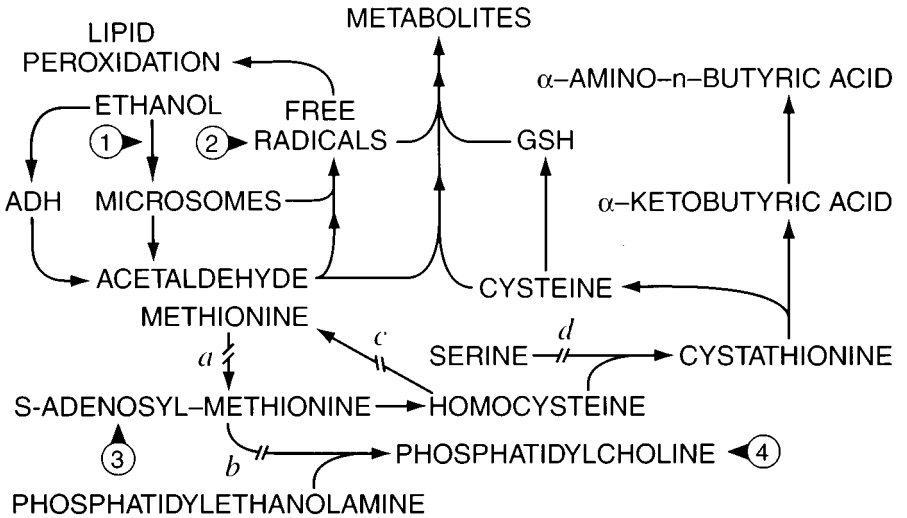

Figure 4 Lipid peroxidation and other consequences of alcoholic liver disease and/or increased free-radical generation and acetaldehyde production by ethanol-induced microsomes, with sites of possible therapeutic interventions. Metabolic blocks caused by liver disease (*a, b*), folate (*c*), B_{12} (*c*), or B_6 (*d*) deficiencies are illustrated, with corresponding depletions in S-adenosylmethionine, phosphatidylcholine, and glutathione (GSH). New therapeutic approaches include (*1*) down-regulation of microsomal enzyme induction, especially of CYP2E1, and (*2*) decrease of free radicals, with antioxidant replenishment of (*3*) S-adenosylmethionine and (*4*) phosphatidylcholine (140).

synthetase results in a number of adverse effects, including inadequate cysteine and GSH production, especially when aggravated by associated folate, B_6, or B_{12} deficiencies (Figure 4). The consequences of this enzymic defect can be alleviated by providing SAMe, the product of the reaction. Blood levels of SAMe increased after oral administration in rodents (230) and in humans (24). It has been claimed that the liver does not take up SAMe from the bloodstream (84), but results in baboons (142) clearly showed hepatic uptake of exogenous SAMe. The effective use of SAMe for transmethylation and transsulfuration has also been demonstrated in vivo (64).

Clinical trials revealed that SAMe treatment is beneficial in intrahepatic cholestasis (63), including recurrent intrahepatic cholestasis and jaundice caused by androgens or estrogens. It was also used successfully in severe cholestasis of pregnancy (57), with few, if any, untoward effects. Oral administration of 1200 mg of SAMe/day for 6 months also resulted in a significant increase of hepatic GSH in patients with alcoholic as well as nonalcoholic liver disease (251).

The most impressive therapeutic success was achieved in a recent long-term, randomized, placebo-controlled, double-blind, multicenter clinical trial of SAMe in patients with alcoholic liver cirrhosis. SAMe significantly improved survival or delayed liver transplantation (173).

Phosphatidylcholine

In the presence of liver disease, the activity of phosphatidylethanolamine methyltransferase is depressed (43), with significant pathologic effects. This enzymatic block can again be bypassed through the administration of the product of that reaction, in this case phosphatidylcholine (154) (Figure 4). This is emerging as a potentially important approach to the treatment of liver disease. Indeed, feeding of a mixture rich in polyenylphosphatidylcholine (PPC), especially dilinoleoylphosphatidylcholine (DLPC), which has a high bioavailability, exerted a remarkable protection against alcohol-induced fibrosis and cirrhosis (155).

PPC contains choline, but choline, in amounts present in PPC, had no protective action against the fibrogenic effects of ethanol in baboons (153). As a dietary nutrient, choline plays a lesser role in primates in general than in rodents, in part because of lesser choline oxidase activity. In fact, choline becomes essential for human nutrition only in severely restricted feeding situations (reviewed in 269). The decreased phospholipid methyltransferase activity in cirrhotic livers (43) is not simply secondary to the cirrhosis but may in fact be a primary defect related to alcohol, as suggested by the observation that the enzyme activity is already decreased prior to the development of cirrhosis (154). Another mechanism whereby ethanol may affect phospholipids is increased lipid peroxidation, as reflected by increased F_2-isoprostanes (153), which could explain the associated decrease of arachidonic acid in phospholipids (10).

One concern was that PPC and DLPC, because of their polyunsaturated nature, may aggravate the oxidative stress, but the opposite was found, both in vitro and in vivo. In alcohol-fed baboons, PPC not only prevented septal fibrosis and cirrhosis (155), it also resulted in a total protection against oxidative stress, as determined by normalization of 4-hydroxynonenal, F_2-isoprostanes, and GSH levels (152). In patients with hepatitis C, PPC improved the transaminase levels, but the effect on liver fibrosis was not assessed (188). However, a clinical trial on alcoholic fibrosis is presently ongoing in the United States.

TOXIC INTERACTION OF ALCOHOL WITH NUTRIENTS

Adverse Interaction with Retinol

In addition to the classic aspects of vitamin A deficiency due to either poor dietary intake or severe liver disease, direct effects of alcohol on vitamin A metabolism, and resulting alterations in hepatic vitamin A levels, have been elucidated (125).

Depletion of Hepatic Vitamin A by Ethanol and Its Mechanism and Pathological Consequences Alcoholic liver disease is associated with severely decreased hepatic vitamin A levels (Figure 5), even when liver injury is moderate (fatty liver) and when blood values of vitamin A, retinol-binding protein, and prealbumin are still unaffected.

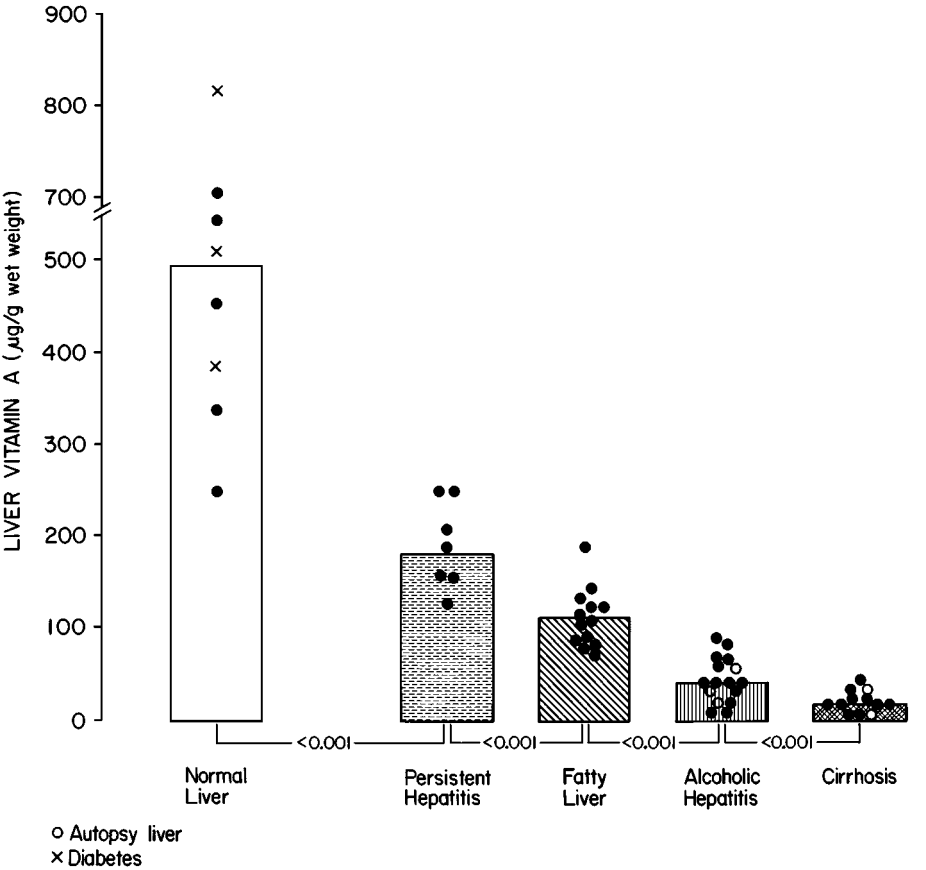

Figure 5 Hepatic vitamin A levels in subjects with normal livers, chronic persistent hepatitis, and various stages of alcoholic injury. (Modified from 119.)

Malnutrition, when present, can of course contribute to hepatic vitamin A depletion, but in a study by Leo & Lieber (119), the patients with low liver vitamin A appeared well nourished, which suggested a more direct effect of alcohol. Under strictly controlled conditions, chronic ethanol consumption was found to decrease hepatic vitamin A in baboons pair fed a nutritionally adequate liquid diet containing 50% of total energy either as ethanol or isocaloric carbohydrate. In these baboons, fatty liver developed after 4 months of ethanol feeding, with a 59% decrease in hepatic vitamin A levels, and fibrosis or cirrhosis appeared after 24–84 months, with a 95% decrease in hepatic vitamin A concentrations (220). Similarly, hepatic vitamin A levels of rats fed ethanol (36% of total energy) were decreased after 3 weeks (by 42%) and continued to decline up to 9 weeks. In contrast, serum vitamin A and retinol-binding protein levels were not significantly changed. When dietary vitamin A was increased fivefold, hepatic vitamin A nevertheless decreased in

ethanol-fed rats relative to the corresponding controls, and sometimes even compared with the rats given five times less vitamin A (without ethanol) (220). To avoid the confounding effect of dietary vitamin A, it was virtually eliminated in some experiments. Under those conditions, the depletion rate of vitamin A from endogenous hepatic storage was observed to be 2.5 times faster in ethanol-fed rats than in control rats. Two possible mechanisms other than malabsorption can be invoked: increased mobilization of vitamin A from the liver, and enhanced catabolism of vitamin A in the liver or in other organs. There is experimental evidence for both (220–222).

Drugs that induce the cytochromes P450 in liver microsomes were shown to result in a depletion of hepatic vitamin A (126). A similar effect was observed after administration of ethanol (119, 220) and other xenobiotics that are known to interact with liver microsomes, including carcinogens (207). The hepatic depletion was strikingly exacerbated when ethanol and drugs were combined (128), which mimics a common clinical occurrence.

Retinoic acid has been shown to be degraded in microsomes of either hamsters (209) or rats (115, 222). In both species, the reported activity was very low compared with the degree of hepatic vitamin A depletion. These observations prompted the search for alternate pathways of retinol metabolism, and two new pathways of retinol metabolism were described: Rat liver microsomes, when fortified with NADPH, converted retinol to polar metabolites, including 4-hydroxyretinol (122). This activity was also demonstrated in a reconstituted monooxygenase system containing purified forms of rat cytochromes P450 (122), including P4502B1 (a phenobarbital-inducible isozyme). More recently, it has been shown that other cytochromes (such as P450 CYP 1A1) also catalyze the conversion of retinal to retinoic acid (241). In addition, a new microsomal NAD^+-dependent retinol dehydrogenase was described (116). The classic pathway for the conversion of retinol to retinal in the liver involves a cytosolic NAD-dependent retinol dehydrogenase, believed to be similar, if not identical, to the liver cytosolic alcohol dehydrogenase (ADH) (alcohol: NAD^- oxidoreductase, EC 1.1.1.1). The observation that a strain of deer mice lacks this enzyme without apparent adverse effects (121) prompted a search for an alternate pathway for the production of retinal, the precursor of retinoic acid. Evidence was obtained for the existence of an NAD-dependent microsomal retinol dehydrogenase (116) that can convert retinol to retinal and retinal to retinol using NAD and NADH, respectively, as cofactors. The activity of the retinol (116) as well as of the retinal (118) dehydrogenases is inducible by chronic alcohol consumption, thereby contributing to hepatic vitamin A depletion. Finally, metabolism of retinol and retinoic acid was also demonstrated with human liver microsomes and purified cytochrome P4502C8 (118).

In patients with severe as well as moderate depletion of hepatic vitamin A, multivesicular lysosome-like organelles were detected in increased numbers (130). That a low hepatic vitamin A concentration contributes to these lesions was also verified experimentally in rats (114).

Hepatic vitamin A depletion plays a key role in hepatic fibrosis, and both hepatocytes and stellate cells are involved. Hepatic stellate cells are the principal

storage site of vitamin A. The activation of stellate cells into myofibroblast-like cells, which then synthesize collagen, is associated with a decrease in vitamin A storage in these cells (36). Retinoic acid, and to a lesser extent retinol, were shown to reduce stellate cell proliferation and collagen production in culture (35, 36, 58). Conversely, lack of retinoids could promote fibrosis in these tissues, especially in the liver, consistent with the associated activation of stellate cells (36). Paradoxically, however, vitamin A excess may also promote fibrosis (see below).

Concomitant ethanol consumption and vitamin A deficiency resulted in an increased severity of squamous metaplasia of the trachea (169, 170). This potentiation of vitamin A deficiency by alcohol may predispose the tracheal epithelium to neoplastic transformation.

A relatively high risk of squamous cell carcinoma of the lung was found in a Norwegian population that drank large amounts of alcohol and had a low dietary intake of vitamin A (108). Furthermore, a positive association of alcohol consumption with lung cancer has been reported in Japanese men in Hawaii (199). In addition, ethanol-induced vitamin A depletion is associated with decreased detoxification of xenobiotics, including carcinogens such as nitrosodimethylamine (127), thereby playing a role in chemical carcinogenesis (see above). Recent data also suggest that functional down-regulation of retinoic acid receptors, by inhibiting biosynthesis of retinoic acid and up-regulating activator protein-1 (c-Jun and c-Fos) gene expression, may be important mechanisms for causing malignant transformation by ethanol (254).

In addition to promoting vitamin A depletion, ethanol may interfere more directly with retinoic acid synthesis because both were shown in vitro to serve as substrates for the same enzymes (46). Specifically, one of the mechanisms by which ethanol induces gastrointestinal cancer may be an inhibition of ADH-catalyzed gastrointestinal retinoic acid synthesis, which is needed for epithelial differentiation. Indeed, class I ADH (ADH-I) and class IV ADH (ADH-IV) that function as retinol dehydrogenases in vitro are abundantly distributed along the gastrointestinal tract (74). Deficiency of retinoic acids can produce birth defects and, as discussed above, ethanol promotes deficiency of retinoids. Duester (44, 46) and Pullarkat (204) implicated competitive inhibition, by ethanol, of the biosynthesis of retinoic acid from retinol, as class I alcohol dehydrogenase (E.C. 1.1.1.1) can contribute to the biosynthesis of retinoic acid from retinol. Indeed, this group identified one human ADH isozyme that exists in the affected embryonic tissues that acts as a retinol dehydrogenase catalyzing the synthesis of retinoic acid. Ethanol did, in fact, reduce retinoic acid levels in cultured mouse embryos (40). However, other results (33) failed to verify, in conceptal tissues, that competitive inhibition of the conversion of retinol to retinoic acid is a significant factor in ethanol-induced embryotoxicity. More recently, Kedishvili et al (98) characterized an ADH enzyme (ADH-F) that oxidize all-*trans*-retinol and steroid alcohols in fetal tissues.

Abnormalities Associated with Excess Vitamin A Vitamin A deficiency promotes carcinogenesis (see above), but paradoxically, vitamin A excess may have a

similar effect: Tuyns et al (245) and DeCarli et al (38) noted that foods providing large amounts of retinol increase the risk of cancer of the esophagus, and in an epidemiologic study, the increased cancer risk associated with the use of cigarettes and alcohol was enhanced on ingestion of foods containing retinol (65). Other food constituents could also play a role in that regard.

The teratogenic potential of excessive intake of retinoid has been clearly demonstrated in experimental animals (227), with corresponding data evolving in humans: Teratogenicity of 13-*cis*-retinoic acid, used to treat cystic acne, has been established in epidemiological studies (109). In addition, among babies born to women who took more than 10,000 IU of preformed vitamin A per day as supplements, $\sim$1 infant in 57 had a malformation (211). However, some caution in the interpretation of these data is still indicated (190). Furthermore, acetaldehyde can cross the placenta (95) and may also contribute to the development of fetal alcohol syndrome, the most prevalent cause of preventable congenital abnormality (1, 2). Therefore, in addition to potentiating the teratogenicity of vitamin A deficiency, alcohol can be expected to aggravate that of vitamin A excess, and this was indeed verified experimentally (258).

An excess of vitamin A is also known to be hepatotoxic (48, 213). The smallest daily supplement of vitamin A reported to be associated with liver cirrhosis is 7500 μg of retinol equivalent (25,000 IU) taken for 6 years (62). These supplements fall well within common therapeutic dosages and amounts used prophylactically with over-the-counter preparations by the population at large.

Potentiation of vitamin A hepatotoxicity by ethanol was first demonstrated in rats fed diets for 2 months with either normal or fivefold increased vitamin A content, both with or without ethanol (113). Although under these conditions ethanol alone produced only modest changes and vitamin A supplementation at the dose used had no adverse effect, the combination resulted in striking lesions, with giant mitochondria containing "paracrystalline" filamentous inclusions and depression of oxygen consumption in state 3 respiration. The potentiation of vitamin A toxicity by ethanol was also seen in patients treated with 10,000 IU of vitamin A per day for sexual dysfunction attributable to excess alcohol consumption (263). In addition to giant mitochondria, filamentous or "crystalline-like" inclusions were seen in the liver mitochondria of patients with hypervitaminosis A (123, 179). The potentiation of vitamin A toxicity by ethanol was most dramatically documented in another study, in which rats were given a combination of vitamin A supplementation and ethanol for up to 9 months (120). There was striking hepatic inflammation and necrosis, accompanied by a rise in the serum level of liver enzymes (glutamic dehydrogenase and aspartate aminotransferase).

Adverse Interactions of Ethanol with β-Carotene

In contrast with retinoids, carotenoids were not known to produce toxic manifestations even when ingested chronically in large amounts (191). Therefore, because β-carotene is an antioxidant, it made sense to assess whether carotenoids may serve

as effective (but less toxic) substitutes for retinol, especially in alcoholic liver injury that has been attributed, in part, to oxidative stress. It was not known, however, whether β-carotene can actually offset alcohol-induced lipid peroxidation.

Effects of Alcohol on β-Carotene Concentrations Studies of humans revealed that for a given β-carotene intake, there is a correlation between alcohol consumption and plasma β-carotene concentration (4). Thus, whereas in general, alcoholics have low plasma β-carotene levels (4, 255), presumably reflecting low intake, alcohol per se might in fact increase blood levels in humans (4). There was also an increase in women who consumed as few as two drinks a day (56). Furthermore, there was an increase in nonhuman primates studied under strictly controlled conditions (117). Indeed, in baboons fed ethanol chronically, liver β-carotene was increased, in contrast with vitamin A, which was depleted. Similarly, plasma β-carotene levels were elevated in these ethanol-fed baboons, with a striking delay in the clearance from the blood after a β-carotene load. Furthermore, whereas β-carotene administration increased hepatic vitamin A in control baboons, this effect was much less evident in alcohol-fed animals. The combination of an increase in β-carotene and a relative lack of a corresponding rise in vitamin A suggests a blockage in the conversion of β-carotene to vitamin A by ethanol.

β-Carotene, Alcohol, Oxidative Stress, and Liver Injury In baboons, the administration of ethanol together with β-carotene resulted in a more striking hepatic injury than with either compound alone (117), with increased activity of liver enzymes in the plasma, an inflammatory response in the liver, and, at the ultrastructural level, striking autophagic vacuoles and alterations of the endoplasmic reticulum and the mitochondria (112). The ethanol-induced oxidative stress, assessed by an increase in hepatic 4-hydroxynonenal and F_2-isoprostanes (measured by gas chromatography-mass spectrometry), was not improved despite a concomitant rise in hepatic antioxidants (β-carotene and vitamin E).

Extra-Hepatic Side Effects Recent results suggest that β-carotene participates as a prooxidant in the oxidative degradation of LDL and that increased LDL β-carotene may cancel the protective qualities of α-tocopherol (26).

In two studies (8, 193), it was noted that in smokers, β-carotene supplementation increased death from coronary heart disease.

Interaction with Cancer Two epidemiologic investigations (8, 193), revealed that β-carotene supplementation increases the incidence of pulmonary cancer in smokers. Because alcohol is known to act as a carcinogen and to exacerbate the carcinogenicity of other xenobiotics, especially those of tobacco smoke (60), and because heavy smokers are commonly heavy drinkers, we raised the possibility that alcohol abuse was contributory (124). Why this cancer should be aggravated by β-carotene is not clear, but β-carotene was found in rat lung to produce a powerful booster effect on phase I carcinogen-bioactivating enzymes, including activators of

polycyclic aromatic hydrocarbons (91,195). In addition, because pulmonary cells are exposed to relative high oxygen pressures, and because β-carotene loses its antioxidant activity and shows an autocatalytic, prooxidant effect at these higher pressures (28), such an interaction is at least plausible. Furthermore, more recent studies showed that the increased incidence of pulmonary cancer was related to the amount of alcohol consumed by the participants (5, 6, 194).

Concentrations of carotenoids, retinoids, and tocopherols were also determined in the homogenate of macroscopically normal appearing oropharygeal mucosa from chronic alcoholics and from control patients. All the alcoholics except one had oropharyngeal cancer. No significant difference was found in tissue levels of carotenoids and tocopherols between alcoholics and control patients. Furthermore, in 7 of 11 control subjects, retinol was undetectable in the oropharyngeal mucosa, whereas in alcoholics, only 2 out of 10 had unmeasurable retinol levels (131). These results did not support the concept that ethanol-associated oropharyngeal carcinogenesis is due, at least in part, to local deficiencies in retinoids, carotenoids, or α-tocopherol.

Contrasting with the investigations showing a lack of beneficial effects of β-carotene supplementation (reviewed above), β-carotene was found to inhibit rat liver chromosomal aberrations and DNA chain break after a single injection of diethylnitrosamine (218). Furthermore, a study of nonmelanocytic skin cancer showed that a high intake of vegetables and other β-carotene–containing foods is protective for nonmelanocytic skin cancers (107). Conversely, Menkes et al (178) showed an association between low levels of serum β-carotene and the risk of squamous-cell carcinoma of the lung. However, the latter two observations do not necessarily prove a causal link because the beneficial effects may be associated with active nutrients other than β-carotene.

Therapeutic Window of Retinoids and Carotenoids Detrimental effects result from deficiency as well as from excess of retinoids and carotenoids, and paradoxically, both have similar adverse effects in terms of fibrosis, carcinogenesis, and possibly embryotoxicity. Treatment efforts, therefore, must carefully respect the resulting narrow therapeutic window, especially in drinkers in whom alcohol narrows this therapeutic window even further by promoting the depletion of retinoids and by potentiating their toxicity.

EFFECTS OF ETHANOL ON THE METABOLISM OF PROTEINS

As reviewed elsewhere (133), ethanol given in single doses causes impaired hepatic amino acids uptake, decreased leucine oxidation (101), increased serum branched chain amino acids, and impaired synthesis of lipoproteins, albumin (90, 202, 203, 212), and fibrinogen (101). Given chronically, ethanol causes impaired protein secretion from the liver, probably related to alterations in microtubles and retention

of proteins in enlarged hepatocytes (14). It promotes protein catabolism in the heart (175) and gastrointestinal tract (67).

EFFECTS OF DIETARY FACTORS ON ETHANOL METABOLISM

Low-protein diets reduce hepatic ADH in rats (22) and lower ethanol oxidation rates in rats (22) and humans (21). Prolonged fasting also decreases ethanol oxidation rates, as shown in isolated rat liver cells. A mechanism for lowered metabolism of ethanol during fasting is the lack of available metabolites to shuttle reducing equivalents from ethanol oxidation into mitochondria (176). For a given alcohol intake, malnourished alcoholics may develop higher blood alcohol levels and sustain them longer than normally nourished individuals (106).

In rats, the microsomal ethanol oxidizing system (MEOS) activity in the liver showed greater induction by alcohol on a normal than on a low-fat diet, although induction of CYP2E1 was the same (151).

NUTRITIONAL THERAPY IN ALCOHOLISM

Individuals consuming over 30% of total calories as alcohol have a high probability of ingesting less than the recommended daily amounts of carbohydrate, protein, fat, vitamins A, C, and B (especially thiamin), and minerals such as calcium and iron (see above). It is sensible to recommend a complete diet comparable to that of nonalcoholics to forestall deficiency syndromes, although this does not suffice to prevent some organ damage due to the direct toxicity of alcohol (e.g. alcoholic liver disease).

Damage due to lack of thiamin is serious but treatable, with a great margin of safety; therefore, thiamin deficiency should be presumed, and if not definitely disproved, parenteral therapy with 50 mg of thiamin per day should be given until similar doses can be taken by mouth. Riboflavin and pyridoxine should be routinely administered at the dosages usually contained in standard multivitamin preparations. Adequate folic acid replacement can be accomplished with the usual hospital diet. Additional replacement is optional unless deficiency is severe. Vitamin A replacement should only be given for well-documented deficiency, and to patients whose abstinence from alcohol is assured.

Zinc replacement is indicated only for night blindness unresponsive to vitamin A replacement. Magnesium replacement is recommended for symptomatic patients with low serum magnesium. Iron deficiency that has been clearly diagnosed may be corrected orally.

The nutritional management of acute and chronic liver disease due to alcoholism should include feeding programs to achieve protein replenishment without promoting hepatic encephalopathy, as reviewed elsewhere (135).

Acute pancreatitis may require withholding oral feeding for prolonged periods, during which time venous alimentation must be given. Chronic pancreatic exocrine insufficiency is treated by dietary manipulation (including decreases in fat), with oral pancreatic enzymes at mealtime. In addition to defining feeding programs to reverse malnutrition, the nutritional management of liver disease due to alcoholism must take into account the fact that because of the alcohol-induced disease process, some of the nutritional requirements change. This is exemplified by methionine, which normally is one of the essential amino acids for humans, but which needs to be activated to S-adenosylmethionine (SAMe), a process impaired by the disease. Thus, SAMe rather than methionine is the compound to be used for supplementation in the presence of significant liver disease, and a resulting prolonged survival has now been documented (173) (see above). Similarly, because of an impairment in phosphatidylethanolamine methyltransferase activity, supplementation with phosphatidylcholine, particularly the highly bioavailable DLPC, may be useful for prevention and treatment (see above).

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