

Alcohol and Alcohol-related Deficiencies as Carcinogens¹

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Summary

From the available evidence, alcohol ingestion *per se* does not appear to be carcinogenic. While alcoholism constitutes a major and serious social problem, it is not clear to what extent it constitutes a major health problem. We suggest that excessive alcohol ingestion coupled with a nutritional deficiency or some other insult (e.g., smoking) may be carcinogenic. Alcohol and/or several nutritional deficiencies usually associated with alcoholism have been shown to be immunosuppressive. The relationship between immunoincompetency and neoplasia has long been appreciated, and the exact role that alcohol and/or nutritional insults have in this relationship requires further investigation.

There is no good evidence to support the thesis that alcohol *per se* causes neoplasia in either animals or humans who are well nourished. At present there is a controversy as to whether alcohol ingestion in the well-nourished individual is cytotoxic, hepatotoxic, or biochemically toxic (7). There are, however, those who believe that alcohol is harmful when taken in excessive amounts regardless of the nutritional state. It may be instructive to point out that of the 10 million alcoholics in the United States, only approximately 10% develop cirrhosis. Nevertheless, the association between excessive alcohol intake and liver disease is well established.

In excessive amounts and in subclinically or overtly malnourished individuals, excessive alcohol has been shown to affect the metabolism of various essential nutrients (12). A recent study reports that excessive alcohol ingestion by baboons on a "well-balanced diet" produced alcoholic hepatitis and cirrhosis (7). The validity of this well-balanced diet has been questioned, however, and it has been suggested that these animals were severely malnourished (6).

If indeed alcohol is carcinogenic, it must work in concert with 1 or more other variables. Epidemiological studies

have shown that alcohol and smoking may be responsible for laryngeal cancer or cancer of the oral cavity (14).

Further, a number of nutritional deficiencies may be associated with excessive alcohol ingestion, and whether these deficiencies directly or indirectly affect carcinogenesis is a question that has been raised at this conference (11). Alcohol and the nutritional deficiencies usually associated with its excessive intake have been shown to be immunosuppressive. In addition to being immunosuppressive, alcohol has been shown to have direct cytotoxic effects on various organ systems. One could at this point simply summarize the possible role of alcohol in neoplasia by stating that it can adversely affect 1 or more components of the host-defense system, including tissue integrity and morphology, and that the nutritional deficiencies usually associated with excessive alcohol ingestion also adversely affect the same systems (1-3, 8, 13). Evidence is accumulating that suggests that immunoincompetency is associated not only with the lymphoproliferative diseases but also with solid tumors.

Experimentally, there is no evidence that alcohol ingestion in the well-nourished animal results in carcinoma and/or that a deficiency of any 1 essential nutrient produces cancer. It is known that the combination of excessive alcohol plus a nutritional deficiency results in cirrhosis and hepatoma in experimental animals. On the other hand, the incidence of hepatoma associated with alcoholism is indeed very low and perhaps not a major health problem. However, about 60% of adult patients in the United States with hepatoma have a background of alcohol-associated cirrhosis (5).

Alcohol and Immunocompetency

A number of studies have appeared that indicate that alcohol in moderate to excessive amounts may have adverse effects on peripheral T- and B-lymphocytes. Many of these studies suffer, however, from the fact that they were carried out in patients who were already diseased or who already presented with alcoholic cirrhosis or alcoholic hepatitis. One must distinguish between the effect of alcohol ingestion on T- and B-cell numbers and function and the effect of the disease process itself on these same parameters. Nevertheless, a number of studies have concluded that both T- and B-cells may be reduced in number and function in the patient with alcoholic liver disease and/or cirrhosis (2, 4, 8). The studies of Brayton *et al.* (3) are more significant since they used human volunteers exposed to alcohol to demon-

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strate diminished leukocyte mobilization. However, they also demonstrated that human polymorphonuclear leukocytes obtained after alcohol ingestion or leukocytes exposed to alcohol *in vitro* showed no decrease in their ability to phagocytize or kill ingested bacteria. Still, alcohol may diminish leukocyte mobilization, thus contributing to an increased susceptibility to infection in patients who have been drinking.

Alcohol and Nutrition

A number of vitamin and mineral deficiencies are associated with excessive alcohol ingestion (9, 12). Deficiencies of thiamine, folic acid, magnesium, and iron are often exhibited by chronic alcoholics. Other nutritional deficiencies such as pyridoxine, pantothenic acid, riboflavin, zinc, and copper have also been known to occur. The correlation between alcoholism and vitamin or mineral nutritional deficiencies may be primary or secondary in nature.

There is abundant evidence to suggest that alcohol may produce its deleterious nutritional effects by acting directly on tissues and enzyme systems, principally in the liver, which is the major site for both ethanol metabolism and vitamin storage, rather than by simply reducing nutrient intake. Decreased intake of essential nutrients is undoubtedly associated with excessive alcohol ingestion. However, a diseased organ, either as a result of nutritional deficiencies or a combination of other factors including excessive alcoholism, can exacerbate a dietary deficiency. This exacerbation comes about as a result of altered absorption of nutrients, decreased storage capacity (in terms of both concentration and functional mass), defective activation of vitamins, or metabolic aberrations in the diseased organ. Thus, when alcoholic subjects are not selected on the basis of hepatic or other disease, their nutritional status is not markedly different from subjects in the same economic class not ingesting excessive alcohol (12).

Thiamine (B₁)

One of the more serious diseases of alcoholism is Wernicke's encephalopathy, which is associated with an acute and severe thiamine deficiency (10). Thiamine deficiency or excess has not been implicated in carcinogenesis nor been shown to play any significant role in affecting immunocompetency.

Pyridoxine (B₆)

Vitamin B₆ or pyridoxine deficiency has been associated with alcohol ingestion. While B₆ may cause several clinical disorders, including peripheral neuropathy, convulsions, and sideroblastic anemia, as well as liver disease, it has not been related to production of cancer. On the other hand, in experimental studies, vitamin B₆ has been shown to play a very important role in the production of antibody response to the administration of various antigens (1). However, it

must be stressed that vitamin B₆ deficiency is probably rare and not a serious public health problem. Therefore, it is not a major consideration in understanding carcinogenesis.

Folic Acid

Evidence elucidating the mechanisms of folate deficiency in chronic alcoholism is somewhat equivocal. However, it does appear that folate deficiency is usually secondary in nature, due to liver disease (in terms of increased release of folic acid or possible decreased affinity for folate) and changes in absorption (which are most notable following a concentrated drinking spree), rather than due to a primary dietary deficiency. Other inconclusive evidence suggests that alcohol reversibly suppresses the hematopoietic response to folic acid in anemic folate-deficient patients and that malabsorption of folic acid cannot completely account for the effect (10).

Folic acid deficiency has been shown, however, to interfere with and impair both humoral and cellular immunity (4). Further, the adverse effects of folic acid deficiency on the hematopoietic system as well as on the gastrointestinal tract are well known. Whether these morphological changes associated with folic acid deficiency set the background for chemicals or other carcinogenic agents to become reactive is not known.

Magnesium

Magnesium deficiency is another common deficiency of alcoholic patients, but the signs and symptoms of magnesium deficiency, while they cover a broad range of cardiovascular, renal, and neurological changes, have not been associated with any defects in host-defense systems.

Zinc

Alcohol probably increases the excretion of electrolytes such as zinc and perhaps a number of other trace metals, but their role, if any, in carcinogenesis is certainly obscure.

Iron

Alcoholic patients also may have severe long-standing iron deficiency, and the role of iron in carcinogenesis may be, in fact, very significant. There is an abundance of literature suggesting that iron deficiency without anemia does produce profound defects in cell-mediated immunity (11). Apparently, iron deficiency does not seem to affect the humoral arm. Certainly, chronic prolonged and severe iron deficiency does produce gastric atrophy in rats (10). Recent studies from Colombia and our own laboratory and reports from the National Cancer Institute Epidemiological Section indicate that iron deficiency may have a possible role in the etiology of gastric cancer. There is evidence from our own studies that suggests that chronic severe iron deficiency,

while it may have no other manifestation, does produce atrophy and intestinalization of the stomach, a premalignant lesion (10). In Colombia there is a gastric cancer rate 4 times higher than that seen in the United States.

The question arises as to whether the iron deficiency associated with chronic alcohol ingestion is due to blood loss, decreased absorption, or decreased utilization of iron. Moreover, since iron deficiency has been shown to result in defective folate utilization, it is difficult to delineate the effects of iron deficiency *per se* from the effects it may have on folic acid utilization (9).

In summary, alcohol ingestion *per se* does not, from the available evidence, behave as a potent or even a mild carcinogen. On the other hand, alcohol in combination with nutritional deficiencies may be carcinogenic, and the site in which the cancer is induced may be a function of these other variables. In addition, alcohol may play a role in the conversion of a procarcinogen into a carcinogen, or indeed the distilling process may produce a number of potential carcinogens. Finally, and perhaps most importantly, alcohol may have some role in the pathogenesis of cancer by its effect on the immune system.

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