Alcohol and Abnormal Protein Biosynthesis

Biochemical and Clinical

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To Bobby, Roz, and Freda
for all of their past and present
understanding, attention, and assistance

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Preface

REGARDLESS of the etiology, all diseases are accompanied by some alteration in cellular nutrition combined with the specific effects of the disease. Perhaps the most controversial combination has been that of alcohol associated with malnutrition. What roles do these two possibly interrelated stresses play in the development of clinical disease? In the patient or in an experimental animal, the dissection of the effects of specific nutrients or of alcohol or its metabolites is most difficult due to the body's homeostatic mechanisms. Thus, to begin to understand how alcohol and/or altered nutrition affect cellular metabolism, it is necessary to develop specific methods and models so that each entity may be evaluated separately.

In this text we have chosen protein synthesis as the endpoint, for protein synthesis is the ultimate function of all cells. The methods for measuring protein metabolism are evaluated and the effects of alcohol and altered protein intake are examined as they affect the heart, liver, skeletal muscle, and the brain.

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SECTION ONE

Introduction—and Methods

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1

Malnutrition and Alcoholism—An Overview*

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I. INTRODUCTION

The role of malnutrition in the pathogenesis of clinical and laboratory abnormalities in alcoholism has been the subject of much debate. Alcoholics with identical patterns of food and alcohol intake exhibit different biochemical and morphologic lesions, suggesting genetic and constitutional factors are of key importance[1]. This thesis is supported by the remarkably different metabolic effects encountered in individual subjects following (a) total food deprivation for control of obesity[2]; and (b) large intakes of ethanol in the presence of a normal diet[3]. This paper provides an overview of possible interrelationships of nutrient deficits and metabolic or toxic effects of ethanol in development of altered intermediary metabolism and tissue damage in alcoholism (Fig. 1).

II. INTERRELATIONS OF MALNUTRITION AND ETHANOL

Medical complications of alcoholism such as Wernicke's encephalopathy, beriberi heart disease, or macrocytic anemia have been attributed to deficits of specific nutrients, while delirium tremens, gout, or alcoholic gastritis are felt to be

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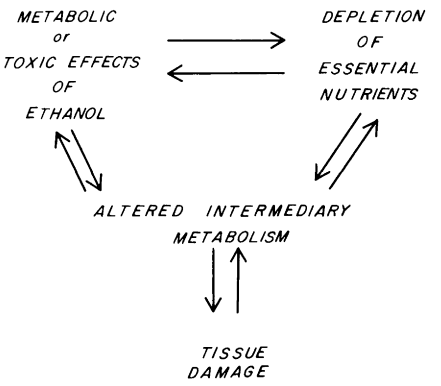

Fig. 1 Possible relationship of nutrient deficits to development of altered intermediary metabolism and tissue damage in the alcoholic.

due to metabolic or toxic effects of ethanol. Opinions remain divided on causative factors in hepatic disorders and pancreatitis (Table 1). Efforts are now underway by many research groups to reevaluate the varying susceptibility to liver disease by alcoholics; similar approaches should be used for other biochemical or morphologic lesions encountered in alcoholism. Thus, ethanol-induced hypoglycemia only occurs in certain alcoholics, suggesting a genetic predisposition [4]; it is due to inhibition of gluconeogenesis resulting from metabolic effects of ethanol [5]; and it may be prevented by changes in nutrient balance following administration of lysine [6], androgenic-anabolic steroids [1], or adrenal steroids [7].

Nutritional and metabolic alterations combine to produce a decrease in cerebral oxidative metabolism in uncomplicated delirium tremens. An increase in the spinal fluid lactate-pyruvate acid ratio, in the absence of change in blood lactate, is characteristic of this state which appears following withdrawal from alcohol or less commonly despite maintained intake of large quantities of ethanol [8]. Deficits of thiamine, magnesium, or phosphate (Fig. 2) contribute directly to the metabolic abnormality; respiratory alkalosis and associated hypoxia independently produce anerobic glycolysis and an accumulation of spinal fluid lactate [9]. Serial studies indicate hallucinations, delirium, hyperkinesis, and elevated spinal fluid lactate

Table 1 Postulated mechanism for tissue injury in the alcoholic.

Nutrient Depletion	Toxicity or Metabolic Effects of Ethanol	Combined Effects
Wernicke's encephalopathy	Delirium tremens	Fatty liver
Beriberi heart disease	Cardiomyopathy	Alcoholic hepatitis
Peripheral neuropathy	Gout	Cirrhosis
Macrocytic anemia	Alcoholic gastritis	Pancreatitis?
	Hypoglycemia	
	Myopathy?	

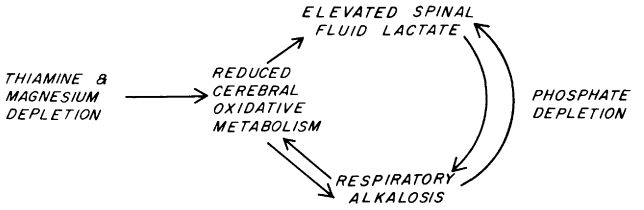

Fig. 2 Possible role of nutrient deficits in pathogenesis of spinal fluid lactic acidosis and reduced cerebral oxidative metabolism in delirium tremens in the alcoholic.

disappear despite persistence of a low spinal fluid magnesium and thiamine, interpreted as evidence that a deficit of these nutrients is not of major importance in pathogenesis of delirium tremens.

In contrast, marked phosphate depletion which occurs in an occasional malnourished alcoholic with delirium tremens may help precipitate this syndrome[10]. Phosphate depletion is characterized by a lower than normal red blood cell 2, 3-DPG which should normally increase with the hypoxia characteristic of delirium tremens (Fig. 3). Tissue hypoxia persists along with symptoms of delirium tremens until phosphate depletion is corrected[11], so that although this syndrome in alcoholics is not due to an identified nutrient deficit, its severity and course is influenced by nutrient imbalance.

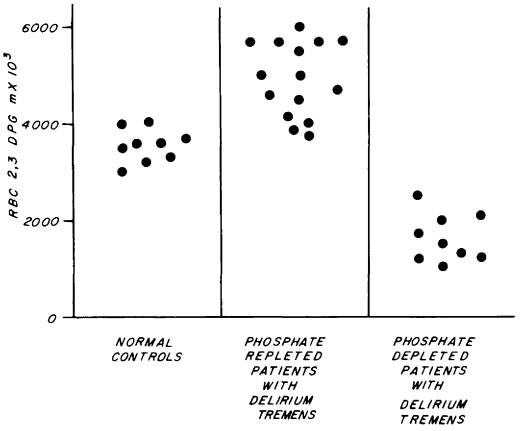

Fig. 3 Influence of phosphate depletion on red blood cell 2, 3-DPG in delirium tremens in the malnourished alcoholic.

III. INCIDENCE OF NUTRIENT DEFICIENCY IN ALCOHOLISM

Persons hospitalized because of complications of alcoholism regularly exhibit clinical and/or laboratory evidence of nutritional deficiency[12]. The common clinical abnormalities are glossitis, nutritional anemia, and peripheral neuropathy; the most frequent laboratory evidence of a deficiency is decreased circulating

levels of B complex vitamins (Fig. 4). A good correlation exists between circulating and tissue levels of vitamins, so that the alcoholic with a reduction in total body vitamin content has a concomitant decrease in vitamins in biological fluids and tissues[13].

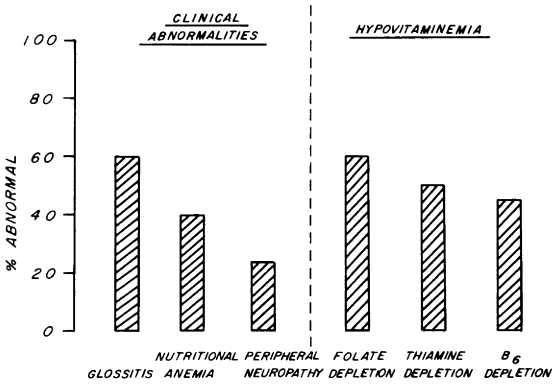

Fig. 4 Common clinical and laboratory evidence of micronutrient deficiency in uncomplicated alcoholism. A lesser frequency of riboflavin, nicotinic acid, pantothenic acid, biotin, vitamin C, vitamin A, vitamin E, and vitamin B_{12} deficiency was encountered.

A cause and effect relationship is not demonstrable between patterns of alcohol and food intake, and stigmata of nutritional deficiency in the alcoholic. More disconcerting is the lack of correlation between clinical and laboratory abnormalities. Thus, glossitis may occur in the absence of laboratory evidence of a deficiency of folic acid, vitamin B_{12}, nicotinic acid, riboflavin, biotin, vitamin B_6, protein or iron, conditions known to cause atrophy of the filliform and fungiform papillae. Low levels of two or more of these constituents is often present, so that combined effects of suboptimum nutriture may produce the biochemical lesion which precedes glossitis[2]. A deficiency of one nutrient often interferes with utilization of other substances to produce encountered clinical or laboratory abnormalities. Thus, riboflavin deficiency inhibits nicotine coenzymes and N^5-methyltetrahydrofolates from catalyzing synthesis of reduced folates in tissues[14].

Molecular events responsible for features of nutrient deficiency have not been identified, however, a variety of biochemical lesions may produce observed stigmata. This is illustrated by studies of Wernicke's encephalopathy, classically attributed to thiamine depletion. Some alcoholic patients with ataxia, confusion, and extraocular nerve palsy, characteristic of this condition, exhibit normal blood thiamine and red blood cell transketolase[15]. Unlike the typical patient with this syndrome who exhibits improvement of ocular palsy within 4 to 6 hours after parenteral thiamine, these patients are refractory to thiamine therapy. Extraocular palsy only responds after providing a nutritious diet for several days or weeks. In depth investigations in three such patients demonstrated a decrease in DNA and RNA synthetic capacity, correction of which was followed by improvement of the neurologic abnormality[16].

IV. MECHANISM OF NUTRIENT DEFICIENCY IN ALCOHOLISM

Reduced intake of essential nutrients due to anorexia or unavailability of food is characteristic of the chronic alcoholic. Nevertheless, a variety of biochemical and morphologic lesions have been produced in volunteers fed alcoholic beverages and a normal diet. It is, therefore, necessary to consider if the so-called "normal diet" is adequate to prevent observed lesions. This is difficult since nutrient deficiency may occur because of ethanol-induced malabsorption or malutilization of nutrients (Table 2). More importantly, once present, whatever its mechanism, deficiency of a single nutrient may lead to other disturbances of body nutriture. Thus, zinc depletion frequently present in the alcoholic because of a combination of reduced intake and increased urinary losses [17] may (a) alter taste and thereby contribute to anorexia and a decrease in intake of other nutrients [18], or (b) interfere with synthesis of enzymes needed for ethanol metabolism, intestinal transport, or utilization of other nutrients [19]

Metabolic or toxic effects of ethanol are responsible for a decrease in intestinal transport of a variety of rate-limited substances including vitamins [20], amino acids [21], and minerals [22]. The chemical nature of the nutrient under consideration is of key importance. Thus, crystalline folic acid is readily absorbed under most circumstances, whereas, nutrient deficiency may prevent absorption of polyglutamates [23]. Studies of thiamine metabolism have provided new insight into the kinetics of ethanol-induced alterations of intestinal transport. Ethanol given orally or parenterally causes a significant decrease in absorption of thiamine hydrochloride [24] whose intestinal transport may be described according to Michaelis Menten kinetics [25]. The absorption defect is increased in the presence of protein [24], or folic acid deficiency [26]; this accounts, in part, for the high incidence of thiamine deficiency and neuropathy in alcoholism.

The untoward influence of ethanol on nutrient utilization deserves special attention. Starvation and ethanol cause identical subcellular changes: disaggrega-

Table 2 Mechanism of nutrient depletion in alcoholics.

A. Decreased intake:
   1. Loss of appetite due to cerebral effects of ethanol.
   2. Decrease in taste attendant to zinc depletion.
   3. Unavailability of nutritious food.

B. Malabsorption:
   1. Toxic injury of intestinal mucosa.
   2. Decreased availability of endogenous substances needed for solubilization or intestinal transport.
   3. Diarrhea or steatorrhea.

C. Malutilization due to decreased conversion of nutrients to their metabolically active form:
   1. Reduced hepatic uptake.
   2. Decreased assimilation.

D. Excess loss.

tion of ribosomes, swelling of mitochondria, and proliferation of smooth endoplasmic reticulum[27, 28]. Physiologic studies, now possible with multiple indicator dilution techniques, reveal liver cells damaged by protein depletion or ethanol exhibit decreased uptake capacity of substances normally sequestered for biotransformation[29]. Both of these mechanisms interfere with assimilation of nutrients. Moreover, ethanol may interfere with the conversion of nutrients into their metabolically active form (Fig. 5).

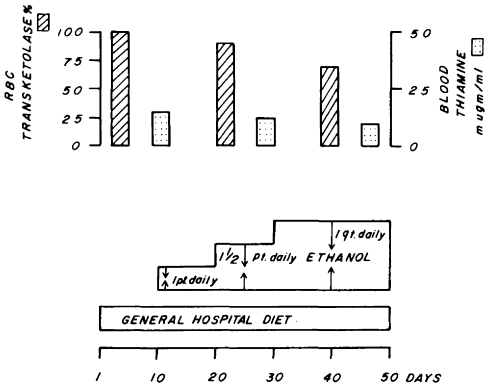

Fig. 5 Influence of ethanol feeding on blood thiamine and red blood cell transketolase activity in a patient who developed alcoholic hepatitis despite a "normal diet." The reduced thiamine was due to malabsorption induced by the ingested ethanol and the low red blood cell transketolase which was refractory to *in vitro* thiamine pyrophosphate was attributed to malutilization of the vitamin.

It is desirable to also evaluate the influence of malnutrition on ethanol metabolism in considering nutrient balance in alcoholism. Both the pellagrin and riboflavin deficient patient are known to be specially predisposed to the untoward effects of ethanol. Hospitalized malnourished alcoholics with aregenerative phases of acute liver injury exhibit a significant increase in activity of alcohol dehydrogenase and microsomal pentobarbital hydroxylase after improvement of body nutriture[30]. A significant increase in microsomal pentobarbital hydroxylase activity occurs when ethanol is given to the folate-repleted alcoholic, whereas, this may not occur with folic acid depletion (Fig. 6).

V. INFLUENCE OF ALCOHOLISM ON INTERMEDIARY METABOLISM

The observation that ethanol alters nutrient utilization, and that nutrient depletion affects ethanol disposal suggests a common pathway may be responsible for the various alterations in intermediary metabolism encountered in alcoholics. We have investigated the influence of ethanol and nutrient deficiency on nucleic acid synthesis in evaluating this concept. The *in vitro* incorporation of tritiated thymidine and uridine into DNA and RNA, respectively, has been studied in lymphocytes, gastric mucosa and liver obtained from patients with a history of chronic alcoholism.