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Mechanisms of Vitamin Deficiencies in Alcoholism

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Chronic alcoholic patients are frequently deficient in one or more vitamins. The deficiencies commonly involve folate, vitamin B_6, thiamine, and vitamin A. Although inadequate dietary intake is a major cause of the vitamin deficiency, other possible mechanisms may also be involved. Alcoholism can affect the absorption, storage, metabolism, and activation of many of these vitamins. Possible factors which cause alterations in the absorption, storage, and metabolism of these vitamins are discussed. Suggestions for management of vitamin deficiencies in chronic alcoholics are also discussed.

CHRONIC ALCOHOLIC patients are frequently deficient in one or more vitamins.[1] The deficiencies commonly involve folate, vitamin B_6, thiamine, and vitamin A. No doubt inadequate dietary intake is a major cause of the vitamin deficiency, but other possible mechanisms may be also involved. For lack of space, the present discussion will be limited to these vitamins and will focus on factors that may affect their absorption, storage, metabolism, and excretion.

FOLATE

This water-soluble vitamin is essential for purine and pyrimidine metabolism, DNA synthesis, and cell replication. In nature folate occurs predominantly as methyltetrahydrofolate polyglutamate. Following ingestion (Fig. 1), the vitamin undergoes initial hydrolysis by folate conjugates to the monoglutamate form prior to or during absorption from the upper small intestine. Absorption is accomplished by a pH and sodium-dependent, carrier-mediated, active process at concentrations below 10 μM and predominantly by passive transport at higher concentrations.[2-6] During intestinal absorption of physiologic concentrations of folate monoglutamate (pteroylmonoglutamate or $PteGlu_1$), reduction, methylation, and formylation may occur. Absorbed folate, circulating predominantly as methyltetrahydrofolate monoglutamate ($CH_3H_4PteGlu_1$), is rapidly carried to various tissues, including the liver, where it is taken up also by active and passive mechanisms.[7] Certain organs, the liver among them, tend to accumulate folate. Once in the tissues methyltetrahydrofolate monoglutamate participates in a number of reactions involved in amino acid and DNA synthesis.[8] In the rat liver, radio-labeled methyltetrahydrofolate monoglutamate is quickly excreted into bile and not incorporated into the pentaglutamate pool (Glu_5).[9] In contrast, a major portion of the nonmethylated folate monoglutamate ($PteGlu_1$) is rapidly reduced and methylated by the liver to form methyltetrahydrofolate monoglutamate ($CH_3H_4PteGlu_1$). In addition, a smaller portion of the pteroylmonoglutamate is converted to pentaglutamate, the predominant form of hepatic polyglutamates. These polyglutamates are tightly bound to proteins.[10-12] The remainder of pteroylmonoglutamate is then excreted into bile, either as methyl- or formyltetrahydrofolate monoglutamate, for recirculation through the gut to complete the enterohepatic circulation, an important component of folate homeostasis. The mechanisms of folate homeostasis has been presented in detail elsewhere.[8]

Lack of folate leads to megaloblastic anemia and impaired enterocyte function. In alcoholic patients, particularly those with liver disease, folate deficiency is the most common form of hypovitaminosis.[1] That ethanol can induce folate deficiency is apparent from several lines of evidence. Ethanol can abort the hematologic response to folic acid in patients with folate deficiency anemia.[13] In patients on low folate diet, the onset of megaloblastic anemia is hastened by ethanol[14]; in such patients the serum folate levels that may decline gradually over 3 weeks without ethanol drops precipitously within 2-3 days with added ethanol.[15,16] Finally, the intravenous infusion of ethanol produces a dramatic fall in serum folate that is quickly reversible upon discontinuation of ethanol.[15] Alcohol ingestion can adversely affect folate metabolism at various sites as indicated by the numbers in Fig. 1.

Intestinal Malabsorption

Aside from inadequate dietary intake (site I), alcoholism may be associated with impaired intestinal absorption of folate (site 2). Indeed, in vitro studies in animals demonstrate that acute exposure to ethanol curtails the transmural flux of folate.[17] In addition, the jejunal uptake of folic acid in hospitalized alcoholic patients is depressed on admission, but improves after an adequate diet and abstinence from alcohol.[18] In abstinent patients on adequate hospital diet, daily ingestion of ethanol (192 g) for 2 weeks, fails to alter folate absorption, suggesting that poor nutrition is more important than ethanol consumption.[18] Sub-

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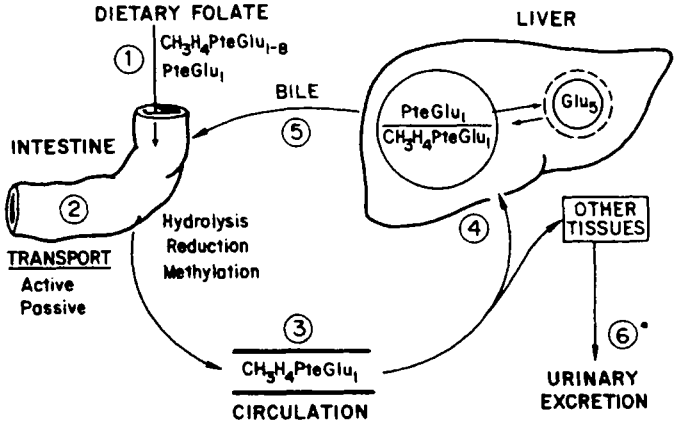

Fig. 1. Folate transport, metabolism, and excretion. Numbers indicate sites at which ethanol may act to disrupt folate homeostasis. For discussion see text. More detailed presentation of folate metabolism is given in Ref. 8.

sequent studies, however, show that chronic ethanol drinking causes a significant folate malabsorption in monkeys[19] and in humans.[20] Thus, a cycle is perpetuated in which ethanol ingestion leads to folate deficiency that in turn causes further depletion of the vitamin. Such a potential chain of events, however, may be partly alleviated in alcoholic patients with chronic pancreatic insufficiency.[21] This is because folate absorption, which is pH-dependent, proceeds maximally at pH 6.3 and becomes less efficient at a higher pH. With the decreased bicarbonate secretion in patients with chronic pancreatitis, the intestinal pH may fall off, facilitating folate absorption.

Plasma Protein Binding

In the plasma (site 3), methyltetrahydrofolate is bound nonspecifically to a variety of proteins and specifically to β-globulin. The specific binding protein is normally saturated, but in patients with alcoholic cirrhosis, binding is decreased by 32%, a change that may promote a greater urinary excretion of unbound folates particularly when binding to tissues is also compromised (see below).

Hepatic Uptake

The effect of ethanol on the hepatic uptake (site 4) of folate has been studied in vitro.[22] Acute exposure of isolated hepatocytes to ethanol inhibits the uptake of folic acid and methotrexate,[22] but increases the hepatocyte accumulation of methyltetrahydrofolate by 30%,[22] consistent with the concept of separate mechanisms for the cellular transport of these compounds. The addition of pyrazole, an inhibitor of ethanol oxidation, either alone or with ethanol, abolishes the stimulatory effect of ethanol. This finding suggests that the enhanced uptake of methyltetrahydrofolate is the consequence of events related to ethanol metabolism. Further studies indicate that this phenomenon is not caused by acetaldehyde, the product of ethanol oxidation, but rather by the attendant increased NADH/NAD ratio. Other studies indicate that the hepatic retention of folates may be due to impaired release of labeled methyltetrahydrofolate monoglutamate from liver cells into bile.[23]

Interruption of Enterohepatic Folate Circulation

Furthermore, studies by Hillman et al.,[9,16] indicate that short term ethanol administration interferes with the enterohepatic cycling of folate (Fig. 1, site 5). The evidence is presented in Fig. 2 which shows the distribution of ^3H marker in folate pools 6 hr after the intravenous injection of [^{3}H]$PteGlu_1$ to control animals and to animals on folate-deficient diet given ethanol. As shown in the left and middle panels, hepatic monoglutamates and polyglutamates are increased in the alcohol-treated animals, while as indicated in the right panel the concentrations of methyl and formyl folates in bile are decreased. From these observations it is postulated that ethanol exposure leads to a major shunting of folate into the pentaglutamate pool with a consequent fall in biliary excretion of folate. Expansion of the pentaglutamate pool (Glu_5) is indicated by the broken circle around Glu_5 in Fig. 1. Further support of this concept is provided by the finding that in animals with subcutaneous fibrosarcoma implants more labeled folate is converted into polyglutamates in the implants of ethanol-treated animals than in controls[24] and by the observation that contrary to a previous report[25] ethanol administration stimulates methionine synthetase activity in the liver[26]; such an increase in methionine synthetase would be consistent with increased polyglutamate synthesis. In contrast to these findings, studies in monkeys placed on an alcohol diet for 2 years show no change in the synthesis of polyglutamates,[27] although total hepatic folate was reduced, as a consequence of decreased intestinal absorption and increased urinary excretion of the vitamin. The reduction, methylation, and formylation of reduced folate are not affected. After 4 years of ethanol feeding in these monkeys, there is a further decrease in total hepatic

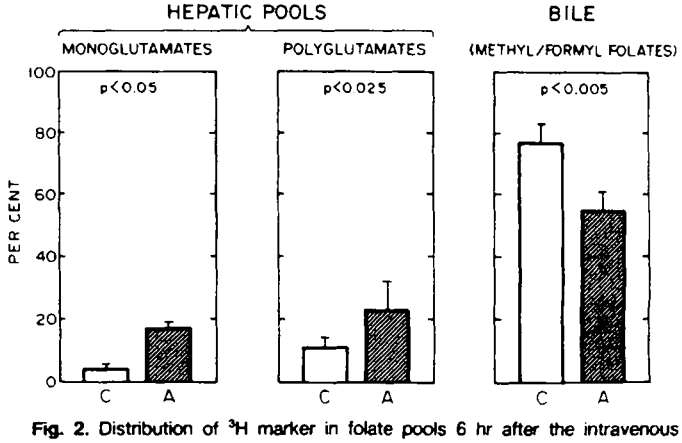

Fig. 2. Distribution of ^3H marker in folate pools 6 hr after the intravenous injection of [^{3}H]PteGlu to control animals (C) and rats given alcohol (A) for 3 days. Monoglutamates and polyglutamates accumulated in the hepatic pools, but there was a decrease in the concentration of methyl/formyl folates in bile. (Drawn from the data of Hillman RS, McGuffin R, Campbell C: Trans Assoc Am Physicians 90:145–156, 1977.)

folates, while normal serum and red cell folate levels are maintained.[28] Recently, it has been pointed out also that the original study of Hillman et al. (Fig. 2) did not include alcohol-treated but folate-replete animals. When such a group is included in a similar study, ethanol administration has no effect on the biliary excretion of folate.[26] Thus, the precise influence of ethanol on folate enterohepatic circulation is still open to question.

Tissue Binding and Urinary Excretion

Hepatic levels of folate may be decreased in patients with alcoholic liver disease,[29] in rats,[25] and in monkeys on chronic ethanol feeding.[27,28] These findings may be due, at least partly, to the reduced ability of the cirrhotic liver to bind and retain folate, and to the subsequent increased urinary excretion of the vitamin (Fig. 1, site 6). A similar increase in the urinary excretion of folate has been noted in acute viral hepatitis,[30] but whether an analogous change also occurs in acute liver injury from ethanol is not known. Acute ethanol administration has been shown to increase the urinary excretion of folate in rats[30a] and in humans. Thus, alcoholism may cause abnormal folate absorption, metabolism, hepatic storage, and urinary excretion, either as a direct or an indirect effect of ethanol ingestion. These abnormalities may help account for the frequency of folate deficiency in alcoholic patients.

VITAMIN B_6

This vitamin exists as pyridoxine in plants as well as pyridoxal and pyridoxamine in animal tissues. These substances can also exist in their respective phosphorylated forms and can be converted, primarily in the liver, to pyridoxal 5′-phosphate (PLP), the active cofactor that is essential to a number of enzymatic reactions. A deficiency of vitamin B_6 may be manifested by neuromuscular irritability, peripheral neuropathy, dermatitis, stomatitis, cheilosis, depression of the immune system, and sideroblastic anemia.

The plasma PLP values is low (<5 ng/ml) in 57% of alcoholic patients with no evident hepatic or hematologic manifestations,[31] but the incidence of vitamin B_6 deficiency is higher and may be 80–100% in alcoholic patients with liver disease. Curiously the serum transaminase values (serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase) in patients with alcoholic liver disease tend to be low or seldom rises above 300 units, despite severe liver injury.[32,33] This may be because these enzymes require PLP, the active metabolite of vitamin B_6. Vitamin B_6 deficiency is associated particularly with decreased hepatic and serum glutamic-pyruvic transaminase activity more so than serum glutamic-oxaloacetic transaminase activity. Similar low transaminase values may be observed also in patients with chronic renal failure[34] who may be deficient in vitamin B_6 as well. These observations have important clinical implications. A serum glutamic-oxaloacetic transaminase/serum glutamic-pyruvic transaminase ratio of 2 or more would suggest alcoholic liver disease, and in the patient with chronic renal failure the presence of viral hepatitis may be missed or not fully appreciated as it may not be heralded by the expected marked elevation of transaminase values.

Because low serum PLP levels tend to occur when the alcohol abuse is prolonged and severe and they tend to correlate with other evidence of malnutrition, it is probable that inadequate dietary vitamin B_6 intake is a major reason for the disorder. However, other mechanisms may be involved as discussed below.

Intestinal Absorption

Under normal circumstances, the intestinal transport of pyridoxine, unlike that of folate, is nonsaturable over a wide range of concentrations, suggesting a passive process.[35–38] Passive mechanism also characterizes pyridoxal and pyridoxamine absorption.[39,40] The hydrolysis of PLP prior to its absorption is dependent on its binding to protein and on lumenal pH.[41] Direct in vitro exposure of the jejunum to 1% ethanol has no effect on pyridoxine intestinal uptake, but 4% ethanol increases uptake by 30% due to mucosal injury manifested by villous blebs and clefts.[42] Both abnormalities in transport and morphology are reversible upon cessation of exposure to ethanol. In contrast, chronic ethanol administration does not change pyridoxine uptake, intestinal PLP concentration, or the rate of pyridoxine phosphorylation.[42]

Hepatic Metabolism

Since the liver is the sole source of PLP, the influence of liver disease on PLP dynamics has been examined by intravenously injecting the PLP precursor, pyridoxine, to normal volunteers, patients with alcoholic cirrhosis, viral hepatitis, or biliary obstruction, and monitoring plasma PLP. As shown in Fig. 3, patients with the above hepatobiliary disorders display a blunted PLP response to the administration of pyridoxine,[43] either because of decreased hepatic PLP generation or because of accelerated PLP degradation and elimination.[43,44] To investigate the second possibility, the systemic clearance of PLP was measured in another study after the intravenous infusion of PLP itself, rather than its precursor. PLP clearance was greater in patients with cirrhosis, hepatitis, or biliary obstruction than in normal controls.[43] The mechanism for the accelerated PLP clearance in hepatobiliary disorders remains to be established, but may possibly involve enhanced degradation of PLP by exposure to increased alkaline phosphatase activity found in hepatobiliary disorders.[43,45]

The acute administration of ethanol also causes a derangement of PLP dynamics after pyridoxine injection as shown in dogs.[46] To elucidate the mechanism of ethanol action on vitamin B_6 metabolism, the effect of ethanol on

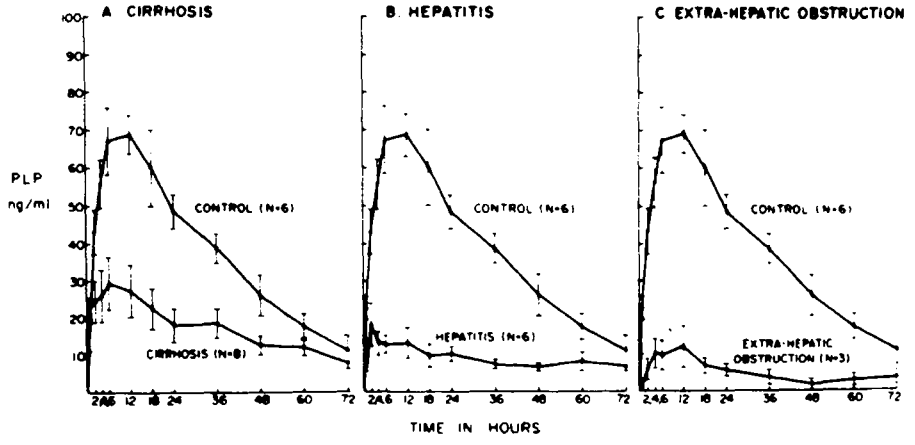

Fig. 3. Plasma concentration/time profile (area under the curve) for pyridoxal 5'-phosphate after intravenous injection of pyridoxine to control subjects and to patients with alcoholic cirrhosis (A), hepatitis (B), and extrahepatic biliary obstruction (C). The area under the curve for each patient group is much smaller than controls. Reproduced with permission.[45]

PLP content in perfused rat livers has been determined after pyridoxine administration.[46] Ethanol greatly impairs the accumulation of PLP (Fig. 4). The inhibitory effect is prevented by pyrazole, suggesting action by a product of ethanol metabolism.[47] Indeed, acetaldehyde has been shown to promote PLP degradation, by facilitating the dissociation of PLP from protein binding.[48-50] However, whether these in vitro findings apply to in vivo situations remains to be seen.

Tissue Affinity/Urinary Excretion

In addition to increased PLP clearance, ethanol may also induce the release of increased quantitities of pyridoxine.[51] Furthermore, ethanol may stimulate the urinary excretion of nonphosphorylated vitamin B_6 compounds. The combined effect of these factors, then, is to diminish hepatic storage of vitamin B_6.

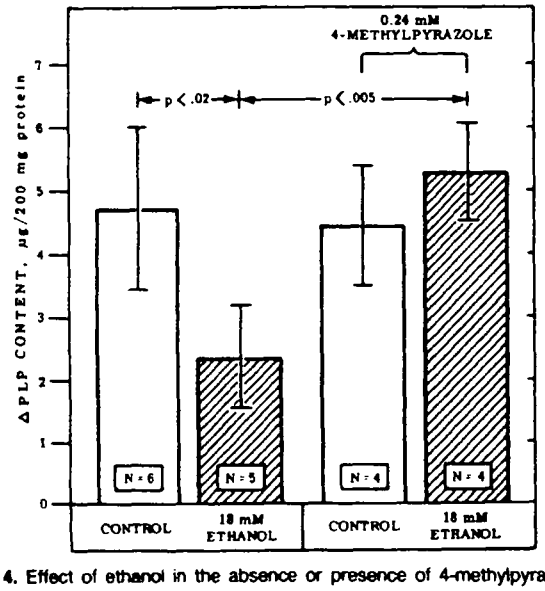

Fig. 4. Effect of ethanol in the absence or presence of 4-methylpyrazole on hepatic PLP content of isolated perfused livers from vitamin B_6-deficient rats. Reproduced with permission.[47]

THIAMINE

The first member of the vitamin B complex to be chemically identified, thiamine (vitamin B_1) is converted in the presence of ATP to thiamine pyrophosphate which serves as an essential coenzyme in carbohydrate metabolism. A deficiency of thiamine leads to the accumulation of pyruvate and α-ketoglutarate and a decrease in transketolase activity. It is clinically manifested by neurologic and cardiovascular disturbances that give rise to Wernicke-Korsakoff syndrome, peripheral neuropathy, beriberi, and heart disease. In underdeveloped countries, thiamine deficiency is usually the consequence of poor dietary practices, but in developed countries, it is often related to chronic alcoholism. The possible mechanisms are discussed below.

Intestinal Transport

Normal Mechanisms. The absorption of thiamine in healthy animals and humans is a dual process that is most efficient in the upper small intestine. At physiologic intraluminal thiamine concentrations (<2.0 μM), transport is mainly a saturable, carrier-mediated process requiring energy,[52-54] although the initial movement across the brush-border may be nonmediated.[55] Once in the cell, thiamine is phosphorylated, in the presence of ATP, into thiamine mono-, di, and triphosphate. Thiamine diphosphate (thiamine pyrophosphate) is the active coenzyme. Of thiamine in the cell, 60–80% is phosphorylated, but it is evidently dephosphorylated as it leaves the cell and appears as free thiamine in the serosal compartment. Energy for transport may well be provided by (Na-K)-ATPase located in the basolateral membrane. In contrast, the transport of thiamine in high or pharmacologic concentrations (>2.0 μM) is predominantly passive. Transport by paracellular pathways has not been evaluated.

Acute Effect of Ethanol. In addition to inadequate intake of the vitamin, thiamine deficiency in chronic alcholism may be also related to thiamine malabsorption.[56-58] Studies in rats indicate that ethanol significantly reduces the absorption of thiamine by inhibiting in a

reversible manner the active, but not the passive, component of the dual transport process.[59] Furthermore, ethanol appears to allow the initial uptake of thiamine across the brush-border membrane of the enterocyte, but impairs the subsequent movement of the vitamin across the basolateral membrane into the serosal compartment.[59] The fall in the rate of cellular thiamine exit is associated with inhibition of basolateral membrane (Na-K)-ATPase activity.[60]

Chronic Effect of Ethanol. The relevance of these observations, obtained with single doses of ethanol given to normal rats, to the pathogenesis of human thiamine deficiency in chronic alcoholism is uncertain. Therefore, the effect of chronic ethanol exposure on thiamine intestinal transport was determined. Unlike the earlier studies with acute doses, chronic ethanol feeding for 6–8 weeks failed to alter thiamine transport or (Na-K)-ATPase activity in rats.[61] At the time of the in vitro transport measurements, however, the ethanol concentrations in the blood and intestinal lumen were low, 40 mg/dl or less. Recently, thiamine transport was studied by constant intestinal perfusion in chronic alcoholic patients. The addition of ethanol to the perfusion solution in these patients also failed to significantly inhibit the active transport of thiamine.[62] As in the rat study above, the plasma ethanol levels reached in these patients were relatively low (<55 mg/dl). Although rats on chronic ethanol diet did not demonstrate any defect in thiamine transport when the lumenal and systemic ethanol concentrations were low, the addition of a single dose of ethanol to achieve higher ethanol concentrations (185 and 318 mg/dl in the gut and blood, respectively) produced a significant fall in thiamine transport and a depression of (Na-K)-ATPase activity.[61] These data suggest that in rats on chronic ethanol feeding, inhibition of thiamine transport is dependent more on the ethanol concentration bathing the basolateral membrane of the enterocyte rather than on the duration of exposure, and that thiamine malabsorption in this animal model may be intermittent. This possibility may be relevant with respect to binge drinkers, and one clinical study suggests that thiamine malabsorption is the most important factor in inducng thiamine deficiency in some alcoholic patients.[63]

Effect of Membrane Fluidity. Since (Na-K)-ATPase is a membrane-bound protein, the effect of ethanol on the physical state of the membrane microenvironment was investigated by determining membrane "fluidity" (or its reciprocal "viscosity"). As shown in Fig. 5, acute exposure of both the brush-border and the basolateral membranes of the rat enterocyte to ethanol (0.1–1.5 M), in vitro, produced a decrease in membrane "viscosity" in a dose-dependent, although nonlinear manner.[64] In contrast, chronic ethanol feeding for 12 weeks slightly increased viscosity. Analysis of the membrane lipid composition revealed a fall in phospholipid content and a rise in cholesterol/phospholipid ratio which may account for the small but significant increase in membrane viscosity. When an acute dose of ethanol was added in vitro to membrane preparations obtained from rats that were chronically fed ethanol, the membrane viscosity which had been slightly raised, decreased significantly in response to increasing doses of ethanol.[65]

These findings suggest that the previously observed abnormalities in membrane permeability, enzyme activity, and intestinal transport may be associated with alterations in membrane fluidity (viscosity) and lipid composition. But whether these changes are directly related to one another still remains to be established. Some investigators believe that they are only associated phenomena. On the other hand, chronic ethanol exposure may evoke adaptive changes in basolateral membrane lipid composition and physical state but does not affect the responsiveness of the membrane to the fluidizing effect of ethanol.

Storage of Thiamine

The hepatic content of thiamine in patients with severe alcoholic fatty liver is shown in Table 1. In severe hepatic steatosis, thiamine content is greatly reduced.[66] Hepatic storage of the vitamin may be low because of a smaller parenchymal cell mass, impaired hepatocyte uptake, or increased release of thiamine.[51] At present there is no evidence to indicate that thiamine transport into hepatocytes is impaired[67] unless high concentrations of ethanol are used.[68] Measurement of hepatic thiamine content after chronic ethanol ingestion is difficult to interpret in view of the known effect of ethanol on intestinal thiamine absorption.

Activation/Utilization of Thiamine

Studies with isolated hepatocytes show that *acute* ethanol exposure, in vitro, does not affect the transformation of thiamine to the active coenzyme.[67] On the other hand, the data of *chronic* ethanol exposure are conflicting. Some studies indicate a fall in hepatic transketolase activity suggesting lowering of thiamine pyrophosphate activity. Most other investigators, however, find no change in the thiamine or thiamine pyrophosphate content of the liver, brain, gut, and heart[58,61,69] although one group of workers notes a drop in hepatic thiamine.[70]

A transketolase abnormality has been observed in patients with Wernicke-Korsakoff syndrome.[71] The transketolase obtained from cultured skin fibroblasts of these patients bind thiamine pyrophosphate less avidly than that from control cell lines. Thus, K_m is considerably higher in the Wernicke-Korsakoff cell line than in controls. More recently a pattern of erythrocyte transketolase isoenzyme that is distinct from normal controls has been noted in a group of Wernicke-Korsakoff patients.[72] Since the transketolase abnormality appears to be genetic rather than acquired, such genetically predisposed individuals may be expected to manifest thiamine deficiency early,

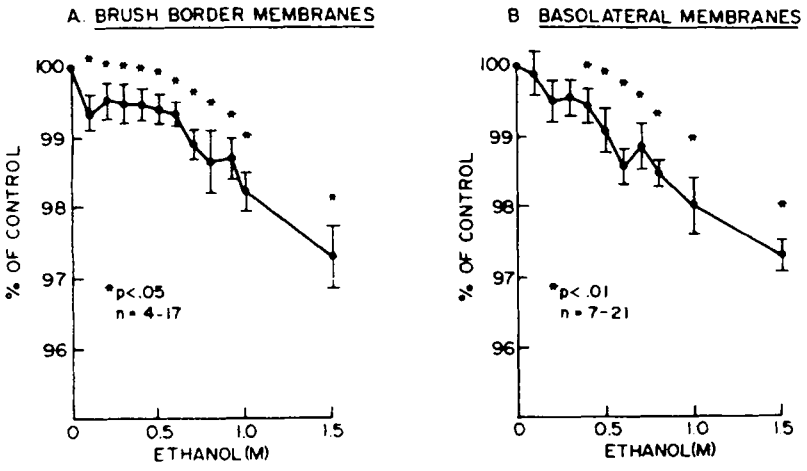

Fig. 5. Effect of acute ethanol exposure in vitro on the viscosity of brush-border (A) and basolateral membrane (B) of rat enterocytes as assessed by electron paragmagnetic resonance.

Table 1. Hepatic Thiamine Content in Severe Alcoholic Fatty Liver

	Normal controls	Severe alcoholic fatty liver
	pg/μg	
Weight	11.5	1.6
Total fat	111.0	3.0
DNA-phosphorus	1690.0	530.0
Total N_2	120.0	31.0

From Frank O, Luisada-Oper A, Sorrell MF, Thomson AD, Baker H: Exp Mol Pathol 15:191–197, 1971.

especially if intake of the vitamin is marginal or when they are exposed to alcohol.

Urinary Excretion

With respect to thiamine urinary excretion, no direct studies seem available. However, the urinary excretion of thiamine depends on the amount of intake and the tissue stores. When intake is low or tissue stores are depleted, little or no thiamine is excreted in the urine. In chronic alcoholic patients, the urinary excretion of thiamine is reduced,[56] probably secondary to intestinal malabsorption and depleted tissue stores of the vitamin. No direct measurements of the renal handling of thiamine are available.

VITAMIN A

This fat-soluble vitamin is essential for growth and differentiation of epithelial tissues. A deficiency of vitamin A may be manifested not only by keratosis and keratomalacia, but also by night blindness and impaired spermatogenesis in males. In females, it may lead to resorption of fetus, abortion, and fetal malformation.

Ingested vitamin A is absorbed from the small intestine by a saturable nonenergy-dependent system and transported with chylomicrons to the liver where it is stored in the ester form. Retinol ester hydrolases release vitamin A from its storage in the form of retinol that is bound to retinol-binding protein. In this form, it is secreted from the liver and joined by prealbumin in the circulation. At the end organ (eye or testis), retinol is released and either utilized directly or metabolized to its active form, retinal. In the eye, retinal becomes a component of rhodopsin, the photosensitive pigment in the rods of the retina. Since the rods are concerned with dark adaptation, vitamin A deficiency results in night blindness. In the testis, spermatogenesis is impaired. The conversion of retinol to retinal requires the action of alcohol dehydrogenase, a zinc-dependent enzyme. Ethanol may inhibit the activation of retinol by competing for alcohol dehydrogenase. Thus, night blindness and hypogonadism in the alcoholic patient may be related to zinc deficiency (a common feature of alcoholism) and alcohol inhibition of retinol activation, in addition to deficient intake of these substances.[73,74] The inadequate intake of vitamin A is readily reflected in the significantly low serum concentrations of this vitamin and of the retinol-binding protein in alcoholic patients with cirrhosis.[74] In addition to inadequate intake of vitamin A however, hypovitaminosis A may be brought about by other factors.

Absorption

Malabsorption of the vitamin probably does not contribute to this state, since acute ethanol administration fails to change the serum levels of retinol, retinyl esters, or retinyl binding protein following oral vitamin A.[75] The effect of chronic ethanol ingestion has not been carefully assessed.

Hepatic Storge and Metabolism

On the other hand, studies by Lieber and his associates indicate that the hepatic vitamin A stores are reduced in patients with liver disease.[76] The reduction in hepatic vitamin A concentration is greater in alcoholic fatty liver than in persistent hepatitis, although the degree of morphologic damage may be comparable in both conditions. The change in vitamin A levels becomes apparent even though blood concentrations of vitamin A, retinol-binding protein, and prealbumin are still normal. Thus, plasma vitamin A may not accurately reflect tissue stores of the vitamin. With the greater damage present in alcoholic hepatitis and in cirrhosis, however, a more severe deple-

tion of hepatic vitamin A develops. In animals, chronic ethanol feeding produces a steady depletion of hepatic vitamin A.[77,78] Depletion of hepatic vitamin A itself leads to abnormal hepatic morphology with the appearance of multivesicular lysosomes,[79] a change that is made worse by ethanol. The possible mechanisms[80] for the decreased hepatic stores of vitamin A from chronic alcohol ingestion include (a) decreased uptake of the vitamin by the diseased liver, (b) greater mobilization of vitamin A from the liver to other tissues, such as the kidneys, and (c) increased metabolism of vitamin A to retinoic acid and other metabolites. A similar decrease in hepatic vitamin A after the administration of phenobarbital and methylcholanthrene, which like ethanol induce microsomal enzymes, tend to support this last possibility.[81]

Table 2 summarizes the effects of ethanol on the disposition of the vitamins discussed.

MANAGEMENT

The approach to the treatment of vitamin deficiency is straightforward and consists principally of preventive measures, improvement of the patient's general nutrition, and replacement therapy. Preventive measures, including social, psychologic, and legislative forces designed to induce the patient to stop drinking, have been tried with variable and frequently disappointing results. Fortification of alcoholic beverages with vitamins, particularly thiamine in pharmacologic amounts, has been advocated as cost-effective, but it remains controversial and, so far, has not been implemented. Another approach that has been suggested is the use of thiamine propyl disulfide. Unlike thiamine hydrochloride, this form of thiamine is absorbed passively[82] and may not be affected by ethanol.

Improving the patient's general nutrition is important, because a specific vitamin deficiency may be associated with, or may lead to, other secondary nutritional disorders. For instance, folate deficiency may decrease the absorption of glucose, water, sodium, alanine, and thiamine. Similarly, lack of B_6 may lead to secondary thiamine deficiency.

Replacement therapy, therefore, may involve not only the primary vitamin but also other nutrients. Thus, zinc therapy may be needed along with vitamin A replacement,[83] since low zinc levels can potentiate the visual and gonadal dysfunction due to vitamin A deficiency. Finally, the potential of vitamin A toxicity from excessive doses should be kept in mind, especially in alcoholic patients. Harmful effects have been noted in a patient who took only 2 capsules of 25,000 IU vitamin A for about 2 years.[84] Chronic alcohol ingestion may potentiate vitamin A toxicity even when the vitamin dose is below the ordinary toxic range.[85] This may be particularly true in the presence of protein deficiency that may impair the mobilization of vitamin A from the liver.[86] Pyridoxine toxicity also occurs. Thus, although vitamins are generally well tolerated and safe, their use nevertheless must be restrained.

Table 2. Effect of Ethanol on Vitamin Disposition

	Folate	B_6	B_1	A
Absorption	●	○	●	○
Storage	●	●	●	●
Metabolism/activation	●	●	○	●
Urinary excretion	●	●	●	

●, abnormal; ○, normal.

REFERENCES

1. Leevy CM, Baker H, Ten Hove W, Frank O, Cherrick GR: B-complex vitamins in liver disease of the alcoholic. Am J Clin Nutr 16:339–346, 1965
2. Smith ME, Matty AJ, Blair JA: The transport of pteroylglutamic acid across the small intestine. Biochim Biophys Acta 219:37–46, 1970
3. Halsted CH, Bhanthumnavin K, Mezey E: Jejunal uptake of tritiated folic acid in the rat studied by in vivo perfusion. J Nutr 104:1674–1680, 1974
4. Eilam Y, Ariel M, Jablonska M, Grossowicz N: On the mechanism of folate transport in isolated intestinal epithelial cells. Am J Physiol 240:G170–G175, 1981
5. Selhub J, Rosenberg IH: Folate transport in isolated brush-border membrane vesicles from rat intestine. J Biol Chem 256:4489–4493, 1981
6. Rosenberg IH: Digestion and absorption of dietary folate. Fed Proc 43:2428–2429, 1984
7. Horne DW, Briggs WT, Wagner C: Transport of 5-methyltetrahydrofolic and folic acid in freshly isolated hepatocytes. J Biol Chem 253:3529–3535, 1978
8. Steinberg SE: Mechanisms of folate homeostasis. Am J Physiol 246:G319–G324, 1984
9. Hillman RS, McGuffin R, Campbell C: Alcohol interference with the folate enterohepatic cycle. Trans Assoc Am Physicians 90:145–156, 1977
10. Zamierowski MM, Wagner C: Identification of folate binding proteins in rat liver. J Biol Chem 252:933–938, 1977
11. Suzuki N, Wagner C: Purification and characterization of a folate binding protein from rat liver cytosol. Arch Biochem Biophys 199:236–248,1980
12. Wittwer AJ, Wagner C: Identification of the folate-binding proteins of rat liver mitochondria as dimethylglycine dehydrogenase and sarcosine dehydrogenase. J Biol Chem 256:4109–4115, 1981
13. Sullivan LW, Herbert V: Suppression of hematopoiesis by ethanol. J Clin Invest 43:2048–2061, 1964
14. Eichner ER, Pierce HI, Hillman RS: Folate balance in dietary-induced megaloblastic anemia. N Engl J Med 284:933–938, 1971
15. Eichner ER, Hillman RS: Effect of alcohol of serum folate level. J Clin Invest 52:584–591, 1973
16. Hillman RS, Steinberg SE: The effects of alcohol on folate metabolism. Annu Rev Med 33:345–354, 1982
17. Strum WS: Characteristics of the transport of pteroylglutamate and amethopterin in rat jejunum. J Pharmacol Exp Ther 216:329–333, 1981
18. Halsted CH, Robles E, Mezey E: Decreased jejunal uptake of labeled folic acid (^{3}H-PGA) in alcoholic patients: roles of alcohol and nutrition. N Engl J Med 285:701–706, 1971
19. Romero JJ, Tamura T, Halsted CH: Intestinal absorption of [^{3}H] folic acid in the chronic alcoholic monkey. Gastroenterology 80:99–102, 1981
20. Halsted CH, Robles E, Mezey E: Intestinal malabsorption in folate-deficient alcoholics. Gastroenterology 64:526–532, 1973
21. Russell RM, Dhar GJ, Dutta SK, Rosenberg IH: Influence of intraluminal pH on folate absorption: studies in control subjects and in patients with pancreatic insufficiency. J Lab Clin Med 93:428–436, 1979
22. Horne DW, Briggs WT, Wagner C: Studies on the transport mechanism of 5-methyltetrahydrofolic acid in freshly isolated hepatocytes: effect of ethanol. Arch Biochem Biophys 196:557–565, 1979

23. Steinberg SE, Campbell CL, Hillman RS: The effect of alcohol on hepatic secretion of methylfolate ($CH_3H_4PteGlu_1$) into bile. Biochem Pharmacol 30:96–98, 1981

24. Steinberg SE, Campbell CL, Hillman RS: Effect of alcohol on tumor folate supply. Biochem Pharmacol 31:1461–1463, 1982

25. Brown JP, Davidson GE, Scott JM, Weir DG: Effect of diphenylhydantoin and ethanol feeding on the synthesis of rat liver folates from exogenous pteroylglutamate [^{3}H]. Biochem Biopharmacol 22:3287–3289, 1973

26. Weir DG, McGing PG, Scott JM: Folate metabolism, the enterohepatic circulation and alcohol. Biochem Pharmacol 34:1–7, 1985

27. Tamura T, Romero JJ, Watson JE, Gong EJ, Halsted CH: Hepatic folate metabolism in the chronic alcoholic monkey. J Lab Clin Med 97:654–661, 1981

28. Tamura T, Halsted CH: Folate turnover in chronically alcoholic monkeys. J Lab Clin Med 101:623–628, 1983

29. Cherrick GR, Baker H, Frank O, Leevy CM: Observations on hepatic avidity for folate in Laennec's cirrhosis. J Lab Clin Med 66:446–451, 1965

30. Tamura T, Stokstad ELR: Increased folate excretion in acute hepatitis. Am J Clin Nutr 30:1378–1379, 1977

30a. McMartin KE: Increased urinary folate excretion and decreased plasma folate levels in the rat after acute ethanol treatment. Alcohol Clin Exp Res 8:172–178, 1984

31. Lumeng L, Li TK: Vitamin B_6 metabolism in chronic alcohol abuse. J Clin Invest 53:693–704, 1974

32. Ludwig S, Kaplowitz N: Effect of pyridoxine deficiency on serum and liver transaminases in experimental liver injury in the rat. Gastroenterology 79:545–549, 1980

33. Matloff DS, Selinger MJ, Kaplan MM: Hepatic transaminase activity in alcoholic liver disease. Gastroenterology 78:1389–1392, 1980

34. Stone WJ, Warnock LG, Wagner C: Vitamin B_6 deficiency in uremia. Am J Clin Nutr 28:950–957, 1975

35. Middleton HM III: Uptake of pyridoxine hydrochloride by the rat jejunal mucosa in vitro. J Nutr 107:126–131, 1977

36. Middleton HM III: In vivo absorption and phosphorylation of pyridoxine Hcl in rat jejunum. Gastroenterology 76:43–49, 1979

37. Yoshida S, Hayashi K, Kawasaki T: Pyridoxine transport in brush border membrane vesicles of guinea pig jejunum. J Nutr Sci Vitaminol (Tokyo) 27:311–317, 1981

38. Middleton HM III: Characterization of pyridoxal 5'-phosphate disappearance from in vivo perfused segments of rat jejunum. J Nutr 112:269–275, 1982

39. Hamm MV, Mehanso H, Henderson LM: Transport and metabolism of pyridoxamine and pyridoxamine phosphate in the small intestine of the rat. J Nutr 109:1552–1559, 1979

40. Mehanso H, Hamm MV, Henderson LM: Transport and metabolism of pyridoxal and pyridoxal phosphate in the small intestine of the rat. J Nutr 109:1542–1551, 1979

41. Middleton HM III: Intestinal hydrolysis of pyridoxal 5'-phosphate in vitro and in vivo in rats. Effect of protein binding and pH. Gastroenterology 91:343–350, 1986

42. Middleton HM III, Mills LR, Singh M: Effect of ethanol on the uptake of pyridoxine. HCl in the rat jejunum. Am J Clin Nutr 39:54–61, 1984

43. Mitchell D, Wagner C, Stone WJ, Wilkinson GR, Schenker S: Abnormal regulation of plasma pyridoxal 5'-phosphate in patients with liver disease. Gastroenterology 71:1043–1049, 1976

44. Labadarios D, Rossouw JE, McConnell JB, Davis M, Williams R: Vitamin B_6 deficiency in chronic liver disease—evidence for increased degradation of pyridoxal 5'-phosphate. Gut 18:23–27, 1977

45. Lumeng L, Schenker S, Li TK, Brashear RE, Compton MC: Clearance and metabolism of plasma pyridoxal 5'-phosphate in the dog. J Lab Clin Med. 103:59–69, 1984

46. Parker TH, Marshall JP, Roberts RK, Wang S, Schiff ER, Wilkinson GR, Schenker S: Effect of acute alcohol ingestion on plasma pyridoxal 5'-phosphate. Am J Clin Nutr 32:1246–1252, 1979

47. Lumeng L: Effect of ethanol on vitamin B_6 metabolism. Alcohol and Nutrition. NIAAA Research Monograph 2, United States Dept. of Health, Education and Welfare, Rockville, MD, 1979, pp 251–266

48. Li TK, Lumeng L, Vietch RL: Regulation of pyridoxal 5'-phosphate metabolism in liver. Biochem Biophys Res Commun 61:677–684, 1974

49. Vietch RL, Lumeng L, Li TK: Vitamin B_6 metabolism in chronic alcohol abuse. J Clin Invest 55:1026–1032, 1975

50. Lumeng L, Li TK: Characterization of the pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate hydrolase activity in rat liver. J Biol Chem 250:8126–8131, 1975

51. Sorrell MF, Baker H, Barak AJ, Frank D: Release by ethanol of vitamins into rat liver perfusates. Am J Clin Nutr 27:743–745, 1974

52. Hoyumpa AM, Middleton HM, Wilson FA, Schenker S: Thiamine transport across the rat intestine. I. normal characteristics. Gastroenterology 68:1218–1227, 1975

53. Hoyumpa AM, Strickland R, Sheehan JJ, Yarborough G, Nichols S: Dual system of intestinal thiamine transport in humans. J Lab Clin Med 99:701–708, 1982

54. Rindi G: Thiamin absorption by small intestine. Acta Vitaminol Enzymol 6:47–55, 1984

55. Hayashi K, Yoshida S, Kawasaki T: Thiamine transport in the brush border membrane vesicles of the guinea pig jejunum. Biochim Biophys Acta 641:106–113, 1981

56. Tomasulo PA, Kater RM, Iber FL: Impairment of thiamine absorption in alcoholism. Am J Clin Nutr 21:1340–1344, 1968

57. Thomson AD, Baker H, Leevy CM: Patterns of ^{35}S-thiamine hydrochloride absorption in the malnourished alcoholic patient. J Lab Clin Med 76:34–45, 1970

58. Balaghi M, Neal RA: Effect of chronic ethanol administration on thiamin metabolism in the rat. J Nutr 107:2144–2152, 1977

59. Hoyumpa AM, Breen KJ, Schenker S, Wilson FA. Thiamine transport across the rat intestine. II. Effect of ethanol. J Lab Clin Med 86:803–816, 1975

60. Hoyumpa AM, Nichols S, Wilson FA, Schenker S: Effect of ethanol on intestinal (Na, K)-ATPase and intestinal thiamine transport in rats. J Lab Clin Med 90:1086–1095, 1977

61. Hoyumpa AM, Nichols S, Henderson GI, Schenker S: Intestinal thiamin transport: Effect of chronic ethanol administration in rats. Am J Clin Nutr 31:938–945, 1978

62. Breen KJ, Buttigieg R, Iossifidis S, Lourensz C, Wood B: Jejunal uptake of thiamin hydrochloride in man: influence of alcoholism and alcohol. Am J Clin Nutr 42:121–126, 1985

63. Camilo ME, Morgan MY, Sherlock S: Erythrocyte transketolase activity in alcoholic liver disease. Scand J Gastroenterol 16:273–276, 1981

64. Gray JP, Hoyumpa AM, Dunn GD, Wilson FA, Swift LL: Effect of ethanol on fluidity of enterocyte membranes. INSERM 95:469–476, 1980

65. Gray JP, Henderson GI, Dunn GD, Swift LL, Wilson FA, Hoyumpa AM: Effect of ethanol on viscosity and lipid composition of enterocyte membranes. Alcohol Clin Exp Res 5:151, 1981

66. Frank O, Luisada-Oper A, Sorrell MF, Thomson AD, Baker H: Vitamin deficits in severe alcohol fatty liver of man calculated from multiple reference points. Exp Mol Pathol 15:191–197, 1971

67. Lumeng L, Edmondson JW, Schenker S, Li TK: Transport and metabolism of thiamin in isolated rat hepatocytes. J Biol Chem 254:7265–7268, 1979

68. Chen C-P: Active transport of thiamine by freshly isolated rat hepatocytes. J Nutr Sci Vitaminol (Tokyo) 24:351–361, 1978

69. Shaw S, Gorkin BD, Lieber CS: Effects of chronic alcohol feeding on thiamin status: biochemical and neurological correlates. Am J Clin Nutr 34:856–860, 1981

70. Frank O, Baker H: Vitamin profile in rats fed stock or liquid ethanol diets. Am J Clin Nutr 33:221–226, 1980

71. Blass JP, Gibson GE: Abnormality of a thiamin-requiring enzyme

in patients with Wernicke-Korsakoff syndrome. N Engl J Med 297:1367–1370, 1977

72. Nixon PF, Kaczmarck MJ, Tate J, Kerr RA, Price J: An erythrocyte transketolase isoenzyme pattern associated with the Wernicke-Korsakoff syndrome. Eur J Clin Invest 14:278–281, 1984

73. Van Thiel DH, Gavaler J, Lester R: Ethanol inhibits vitamin A metabolism in the testes: possible mechanisms for sterility in alcoholics. Science 186:941–942, 1974

74. McClain CJ, Van Thiel DH, Parker S, Badzin LK, Gilbert H: Alterations in zinc, vitamin A, and retinol binding protein in chronic alcoholics: A possible mechanism for night blindness and hypogonadism. Alcohol Clin Exp Res 3:135–141, 1979

75. Russell RM: Vitamin A and zinc metabolism in alcoholism. Am J Clin Nutr 33:2741–2749, 1980

76. Leo MA, Lieber CS: Hepatic vitamin A depletion in alcoholic liver injury. N Engl J Med 307:597–601, 1982

77. Sato M, Lieber CS: Hepatic vitamin A depletion after chronic ethanol consumption in baboons and rats. J Nutr 111:2015–2023,1981

78. Sato M, Lieber CS: Changes in vitamin A status after acute ethanol administration. J Nutr 112:1188–1196, 1982

79. Leo MA, Sato M, Lieber CS: Effect of hepatic vitamin A depletion on the liver in humans and rats. Gastroenterology 84:562–572, 1983

80. Lieber CS, Leo MA: Interactions of ethanol with vitamin A. Alcohol Clin Exp Res 7:15–21, 1983

81. Leo MA, Lowe N, Lieber CS: Decreased hepatic vitamin A after drug administration in men and rats. Am J Clin Nutr 40:1131–1136, 1984

82. Thomson AD, Frank O, Baker H, Leevy CM: Thiamine propyl disulfide: absorption and utilization. Ann Intern Med 74:529–534, 1971

83. Russell RM, Morrison SA, Smith FR, Oak EV, Carney EA: Vitamin A reversal of abnormal dark adaptation in cirrhosis. Ann Intern Med 88:622–626, 1978

84. Farris W, Erdman J: Protracted hypervitaminosis A following long term low level intake. JAMA 247:1317–1318, 1982

85. Leo MA, Lieber CS: Hepatic fibrosis after long-term administration of ethanol and moderate vitamin A supplementation in the rat. Hepatology 3:1–11, 1983

86. Weber FL, Mitchell GE, Powell DE, Reiser BJ, Banwell JG: Reversible hepatoxicity associated with hepatic vitamin A accumulation in a protein-deficient patient. Gastroenterology 82:118–123, 1982

ERRATUM

In the article "Alcohol Use by Adolescents in Disrupted Families," written by Burnside et al. which appeared on pages 275–278 in the May/June 1986 issue (vol 10, no 3) there is a correction to Table 1. It should have been set as follows:

Table 1. Categories of Alcohol Use Based on Reported Frequency of Consumption and Quantity Consumed on Each Occasion

No. of alcoholic drinks per occasion	No. of occasions of alcohol use in past month				
	0	1 or 2	3 to 5	6 to 20	More than 20
0	A. Nonusers	A'. Use last month, but nonuse for quantity			
Less than 1	B. Any volume but not last month	C. Infrequent—low volume		E. Infrequent—high volume	
1 or 2			D. Frequent—low volume		F. Frequent—high volume
3 to 5					
At least 6					

Note: students in category A' consisted of 6.5% of the sample and were omitted from data analyses.