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Hepatic and Wernicke's encephalopathies: current concepts of pathogenesis[1-3]

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The aim of this brief review is to assess the current state of knowledge of the pathogenesis of hepatic and Wernicke's encephalopathy. The common theme of these two disorders is that they both occur most frequently in the setting of alcoholism and that they are potentially fully and rapidly reversible with appropriate treatment implying a metabolic (i.e., neurochemical/neurophysiological) encephalopathy, as contrasted to one characterized by fixed structural lesions (i.e., cerebrovascular insult). However, the differences are profound in that hepatic encephalopathy is due to liver disease and/or shunting of portal blood around the liver with resultant altered metabolism of nitrogenous substances, while Wernicke's encephalopathy is due to a deficiency of thiamin.[4]

Hepatic encephalopathy

Hepatic encephalopathy comprises a spectrum of disease (1) including *1*) delirium, convulsions, and decerebrate rigidity which may develop explosively without obvious precipitating cause in the setting of acute fulminant liver failure due to viral or toxic liver injury, *2*) portalsystemic encephalopathy (PSE), a more common and more indolent alteration in the level of consciousness, often induced by some precipitating event (i.e., gastrointestinal hemorrhage, infection, constipation) and developing in the course of cirrhosis, and *3*) hepatocerebral degeneration or spastic paraparesis characterized respectively by neurological changes resembling Wilson's disease and long tract motor changes and hyperreflexia similar to those seen with a spinal cord lesion. Bridging the spectrum of hepatic encephalopathy are certain common clinical features. These consist of *1*) an abnormal (depressed) mental state with impaired consciousness, decreased intellectual performance (often picked up only by subtle psychomotor testing (2–4)) and altered personality, *2*) an abnormal neuromuscular state characterized often by the presence of a metabolic flap (asterixis) and fluctuating neurological findings, *3*) the presence of liver disease and usually portalsystemic shunting, and *4*) characteristic but nonspecific laboratory findings of increased blood ammonia (an inconstant observation), high cerebrospinal fluid glutamine and an electroencephalogram consisting of a slow, high amplitude wave pattern. Ultimately the diagnosis of hepatic encephalopathy is a clinical one and is based on history and physical examination, exclusion of other causes of deranged mental status, buttressed (but not always) by the above mentioned laboratory data and sometimes ultimately confirmed by a trial of therapy for this disorder.

Before proceeding to a discussion of the pathogenesis of hepatic encephalopathy, it is worth considering the general concept of the anatomic basis of consciousness and the mechanisms which regulate it (5). Although the precise cerebral areas that modulate consciousness are still uncertain, it is presently postulated that the reticular activating system is involved in the "on and off" aspect of

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[4] A few patients with clinical Wernicke-Korsakoff syndrome may eventually prove to have another etiology, suggesting that this may be a biochemically heterogeneous disorder. Blass, J. P. and G. E. Gibson. Genetic factors in Wernicke-Korsakoff syndrome. Alcoholism. Clin. Exptl. Res. 3: 126, 1979.

awareness while the cortex modifies its content (6). Undoubtedly other areas of the brain also have an important input. Regardless of specific area(s) involved, three general mechanisms have been implicated over the years in the maintenance and disorders of consciousness. They are altered brain energy metabolism, a disturbance of the neuronal membranes and deranged neurotransmitter balance (1). These mechanisms are clearly not mutually exclusive and presumably exert their effects on cerebral function by altering orderly transmission of nervous impulses. It is likely that hepatic encephalopathy also ensues as a result of one or more of these derangements.

It is useful to consider hepatic encephalopathy as a multifactorial problem. The relative importance of these factors will vary with the type of encephalopathy. For instance in PSE it appears that coma ensues as a result of an interaction of three types of cerebral insults. First, some of these patients exhibit increased sensitivity to various metabolic changes induced spontaneously or as a result of therapeutic interventions. Typical examples of such increased cerebral susceptibility are the development of coma in previously overtly alert cirrhotics following sepsis or the use of sedatives/tranquilizers which are tolerated relatively well by noncirrhotic individuals. The factors that may account for such increased sensitivity to sedatives and other insults in cirrhotic patients are depicted in **Figure 1.** Second, various toxins may accumulate in patients with cirrhosis to induce coma. These toxins (**Table 1**) may contribute to a different degree and by diverse mechanisms (Table 1) to the induction of coma in individual patients. Finally, numerous physiological derangements, i.e., azotemia, hypokalemic alkalosis, etc., may summate with the toxins in a susceptible patient to precipitate encephalopathy. Lastly the possible contribution of some protective substance(s) usually synthesized by a normal liver has not been excluded. These interactions are considered in greater detail in recent reviews (1, 5). While these considerations may apply to cirrhotics with PSE, in patients with fulminant liver failure it is likely that massive accumulation of toxin(s) and/or failure to provide protective substances play a predominant role. Cerebral edema is an important factor in this type of hepatic encephalopathy and this may to some extent set it apart pathogenetically from the other types of hepatic coma (1). The place of hepatocerebral dysfunction in the spectrum of hepatic encephalopathy is still unclear but it resembles more advanced PSE (1).

Of the various toxins that have been incriminated in the causation of hepatic encephalopathy (Table 1), excess ammonia and altered amino acid balance seem to be the leading candidates and will be considered in detail. In the case of ammonia several mechanisms for the toxicity have been described. First, ammonia may exert a direct effect on neuronal cell membranes. For example, ammonia inhibits the Na^+, K^+-activated ATPase activity by competing with K^+ (7) and it has been reported to inhibit an outwardly directed chloride pump which normally maintains a proper neuronal transmembrane chloride gradient (8). In vitro ammonia (in concentrations achieved in rats with ammonia-induced encephalopathy) decreases the frequency of spontaneous action potentials in guinea pig cerebellar slices. This may be initiated by increased anaerobic glycolysis, accumulation of lactate and a fall in tissue pH which in turn alters the transfer of electrolytes and eventually of water across the membrane (9). Second, ammonia may decrease the concentration of excitatory amino acid neurotransmitters (glutamate, aspartate) in brain (10). For glutamate this may be due to enhanced detoxication of ammonia to glutamine in a critically located glial compartment in the brain (1, 11). For aspartate it may be due to enhanced concerted transamination of pyruvate with aspartate to yield alanine and oxalacetate. Changes of aspartate and glutamate in brain of rats given ammonia have been reported. Even though the decrements have been small, such measurements do not assess possible alterations in cellular or regional brain pools wherein the changes and their effects may be greater (1, 5). (As was mentioned earlier, ammonia metabolism in brain is compartmented and one such an important pool appears to be confined to astroglial cells (12).)[5] Third, ammonia may alter the malate/aspartate shuttle of reduced

[5] Recent studies have also shown ammonium chloride (2 to 5 mM) inhibits the KCl-evoked release of endogenous glutamate from hippocampal slices of rats. Hamberger, A., B. Hedquist and B. Nystrom. Ammonium ion inhibition of evoked release of endogenous glutamate from hippocampal slices. J. Neurochem. 33: 1295, 1979.

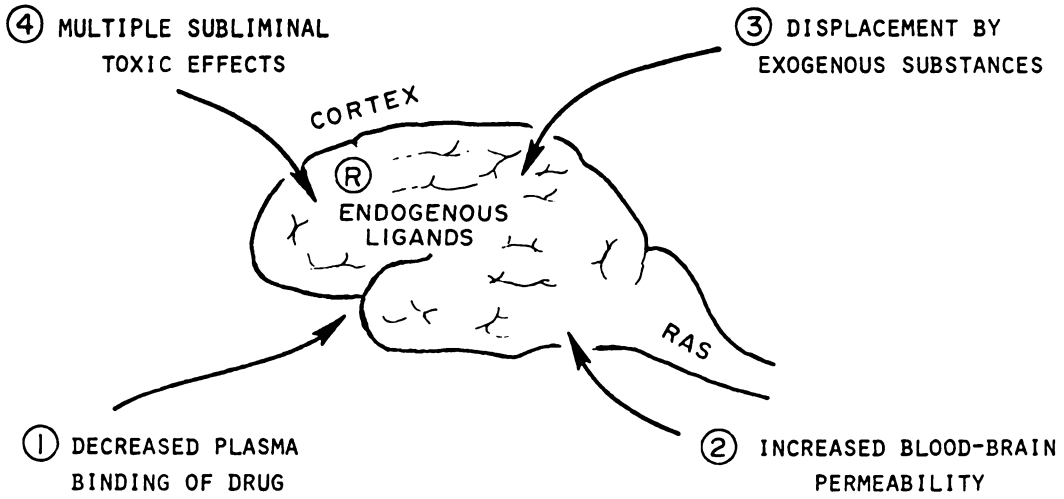

FIG. 1. Increased cerebral sensitivity to sedatives in patients with cirrhosis. This schematic representation shows the two presumed cerebral sites which modulate consciousness, the reticular activating system (RAS) and the cortex. Increased sensitivity to sedatives may be due to *1*) decreased plasma binding of the drugs due to lower serum proteins resulting in more rapid access of the sedative to cerebral receptor sites, *2*) possible increase in blood-brain permeability (21), *3*) possible displacement of endogenous, consciousness-mediating ligands from their receptor sites (R) by exogenous toxins—possibly certain amino acids—or increased cerebral receptor sensitivity, and *4*) accumulation of multiple subliminal toxic effects, with sedatives as additive insults to the brain.

equivalents between the cytoplasm and mitochondria, altering the cytoplasmic/mitochondrial NADH/NAD ratio. A decrease of the mitochondrial NADH/NAD ratio has been calculated for the brain of rats intoxicated with ammonia (10). Although the calculation was indirect and its basis has been questioned (13), such a fall in mitochondrial NADH could result in impairment of the electron transport chain and energy synthesis. Indeed decreased energy stores in brain of rats intoxicated with ammonia have been reported (especially in the brainstem) but this was felt to be a secondary phenomenon and not the initiator of the coma (13). Recent studies in our group, however, have assessed sequentially the adenosine triphosphate (ATP) and phosphocreatine (PCr) stores in microregions of mouse brain wherein the areas corresponding to the reticular activating system in the brainstem could be analyzed. Even prior to overt coma induced acutely by ammonia there was a substantial and statistically significant fall in ATP and PCr in the reticular activating system area but not in the posterior colliculi (as a control) of the same animals (D. W. McCandless, unpublished data). Thus, changes in energy stores in special regions of the brain may accompany early ammonia intoxication even though it is uncertain if these are causative or merely associated phenomena. It appears, therefore, that ammonia may have a direct neuronal effect, may alter cerebral neurotransmitters[6] and may change regional brain energy stores (1, 5). The precise mechanism(s) responsible for induction of coma, however, are still unknown.

As regards the weak (false) neurotransmitter concept of the causation of PSE, the hypothesis is that a fall in the branched chain/aromatic amino acid ratio alters cerebral norepinephrine and dopamine stores and thus alters true neurotransmission in brain. These concepts have been extensively reviewed elsewhere (1, 5, 14, 15). The proposed mechanistic aspects of this concept are as follows: *1*) increased plasma phenylalanine competes for transport of tyrosine across the blood brain barrier (14, 16) and increased brain phenylalanine serves as a competitive substrate for tyrosine decarboxylase (17). The net effect is

[6] It has been suggested recently that increased efflux of glutamine from the brain may enhance the entry of neutral amino acids into the brain, thus possibly linking cerebral ammonia metabolism with the false neurotransmitter hypothesis (James, J. H., C. Cangiano, P. Cardelli-Cangiano and J. E. Fischer. Glutamine links hyperammonemia and neurotransmitter derangements in portal systemic shunting. Gastroenterology 78: 1308, 1980).

TABLE 1
Putative toxins and their mechanism(s) of action[a]

Toxins	Mechanism(s) of action
Ammonia[b]	A. Direct effects on neuronal membrane B. Decreased amino acid neurotransmitters C. Alteration of malate/aspartate shuttle and cytoplasmic/mitochondrial NADH/NAD ratio with disturbance in energy metabolism
Various amino acids	A. Derange normal neurotransmitter status of brain B. Generate ammonia C. Generate mercaptans
Mercaptans	A. ? derangement of neuronal membrane activity via interference with Na-K-stimulated ATPase activity B. Impairment of ammonia detoxication
Fatty acids	A. Impairment of ammonia detoxication B. Direct effects on neuronal/synaptic membranes C. ? compete for intravascular binding of putative toxins
Other[c]	

[a] Modified with permission from Hoyumpa, A. M., P. V. Desmond, G. R. Avant, R. K. Roberts and S. Schenker. Clinical conference: Hepatic encephalopathy. Gastroenterology 76: 184, 1979. [b] May especially affect glial function. [c] An inhibitor of γ-aminobutyric acid binding to neural membranes has recently been found in sera of rabbits with galactosamine-induced acute encephalopathy (Schafer, D. F., J. G. Waggoner and E. A. Jones. Sera from rabbits in acute hepatic coma inhibit the binding of [^{3}H]γ-aminobutyric acid to neural membranes. Gastroenterology 78: 1320, 1980).

decreased conversion of tyrosine to dopamine and norepinephrine in brain. *2*) Cerebral tyrosine not converted normally to dopamine and norepinephrine may be decarboxylated to tyramine and then to the weak neurotransmitter octopamine (14). *3*) Increased passage of tryptophan into brain (due to decreased competition for this transport by lower branched chain amino acids) generates serotonin, a putative inhibitory neurotransmitter (5). The evidence for and against the false neurotransmitter concept of PSE has been extensively discussed in recent reviews (1, 5, 15) and is briefly summarized in **Table 2.** Suffice it to say that this exciting concept remains unproven. It is uncertain if the changes in amino acids and neurotransmitter status are causal or merely associated events. It is conceivable that some critical balance of neurotransmitters in specialized brain areas may be important. Further research in this area is clearly indicated.

The roles of mercaptans and of fatty acids in the induction or perpetuation of hepatic encephalopathy are still uncertain. Their presumed mechanism(s) of action are listed in Table 1. It is likely that they (especially the fatty acids) act not as primary toxins but rather synergize with other cerebral insults at the level of the brain (18) or by inhibiting the detoxification of ammonia (19) or each other (20).

One may sum up this brief consideration of the pathogenesis of hepatic encephalopathy as follows: *1*) The pathogenesis is multifactorial and represents a summation of various insults, possibly acting differently, on the brain. All types of encephalopathy may not have the same pathogenesis. Some factors may act on the brain in a synergistic manner (i.e., mercaptans, fatty acids and ammonia). *2*) The precise manner in which coma is induced (i.e., effects on neuronal membrane, neurotransmitter status, energy stores) is still uncertain. *3*) The brain is a very heterogeneous organ and the metabolism of key toxins (i.e., ammonia) is compartmented. Detailed microregional studies, probably in different cell populations, will be needed to unravel this problem. This will require sophisticated neurochemical/neurophysiological techniques and better animal models of various types of human hepatic encephalopathy.

Wernicke's encephalopathy

Wernicke's encephalopathy is a cerebral disorder caused by thiamine deficiency and characterized by a disorder of consciousness, ophthalmoplegia, and ataxia. The disorder of consciousness varies from mild confusion to coma. The ocular disturbances often begin as nystagmus but may progress to complete sixth nerve palsy. Not all patients with this disorder manifest the full syndrome. At times inapparent thiamin deficiency may be converted to fullblown Wernicke's encephalopathy by the administration of glucose without added

TABLE 2
Evidence in favor and against the false neurotransmitter hypothesis of hepatic encephalopathy[a]

A. In favor:
1. Weak (false) neurotransmitters accumulate in serum and urine of patients with PSE, correlating roughly with its clinical grade.
2. False neurotransmitters accumulate in brain of rats with experimentally induced hepatic coma.
3. The concentration of norepinephrine is decreased in brain of rats with coma induced by hepatic devascularization.
4. Treatment of rats with portacaval shunts with antibiotics decreases cerebral weak neurotransmitter concentrations.
5. Branched chain/aromatic amino acid ratio falls in plasma of most patients with PSE, coma may be induced in dogs infused with large quantities of phenylalanine and tryptophan together, branched-chain amino acid infusions may reverse this effect in dogs and possibly in patients with PSE.
6. Anecdotal reports of beneficial effect of *l*-dopa (precursor of brain norepinephrine) in patients with PSE.
7. Reported beneficial effect of bromocriptine (dopamine receptor agonist) in patients with hepatocerebral type of PSE.

B. Against:
1. Massive amounts of weak neurotransmitter, octopamine, administered into the brain failed to induce coma in rats.
2. Dramatic decreases (to 10–15% of normal) in whole brain norepinephrine and dopamine in rats given octopamine or 6-OH dopamine failed to alter consciousness.
3. Controlled trials of *l*-dopa failed to show therapeutic benefit in patients with PSE.
4. No alteration in regional brain norepinephrine or dopamine in patients with PSE.

[a] Modified with permission from Schenker, S., P. V. Dsmond, K. V. Speeg, Jr., and A. M. Hoyumpa, Jr. The cryptic nature of bromocriptine therapy in portalsystemic encephalopathy. Gastroenterology 78: 1094, 1980.

thiamin. While the mechanism of this phenomenon is not fully worked out, it would appear that the metabolism of carbohydrate utilizes thiamin (**Fig. 2**) and this may precipitate overt Wernicke's encephalopathy in an asymptomatic but thiamin deficient person. Sometimes Wernicke's encephalopathy may be accompanied by peripheral neuropathy characterized by a glove-stocking combined motor-sensory deficit or may merge into Korsakoff's psychosis with cognitive defects, impaired time perception, loss of memory for recent events and classically confabulation. The latter two clinical syndromes are usually attributed primarily to thiamin deficiency but chronic alcoholism may also play a role. This overview of pathogenesis will refer exclusively to Wernicke's encephalopathy.

The key concepts relevant to the pathogenesis of Wernicke's encephalopathy are listed in **Table 3** (22). They consist of metabolic, neurophysiological, genetic, and combined derangement hypotheses. Historically, metabolic derangements were incriminated in the pathogenesis of this syndrome. Three cerebral enzymes are dependent on thiamin pyrophosphate as coenzyme: transketolase (EC2.2.1.1), pyruvate decarboxylase (EC4.1.1.1), and α-ketoglutarate decarboxylase (EC1.2.4.2). One hypothesis held that a depression of transketolase, an important component of the pentose phosphate cycle, may inhibit the generation of NADPH via the pentose phosphate cycle and this in turn could decrease the synthesis of lipid for cerebral myelination (Fig. 2). However, while transketolase activity does fall briskly in brain with thaimin deficiency, there is much evidence against this hypothesis. Thus, *1*) there is good evidence that the pentose phosphate cycle in brain is not impaired in thiamin deficiency (23), *2*) neurological signs of thiamin deficiency reverse with thiamin administration with only a slight increase in brain transketolase activity (24), and *3*) this neurological recovery is faster than the turnover of various brain myelin components (25). Thus there is not much evidence at present that the depression of brain transketolase initiates the encephalopathy. The second hypothesis suggested that an impairment of pyruvate decarboxylase activity due to thiamin deficiency could interfere with cerebral energy metabolism via the tricarboxylic acid cycle (Fig. 2) (22). Indeed in most studies pyruvate decarboxylase activity in brain decreases with thiamin deficiency, the pyruvate level rises and following administration of

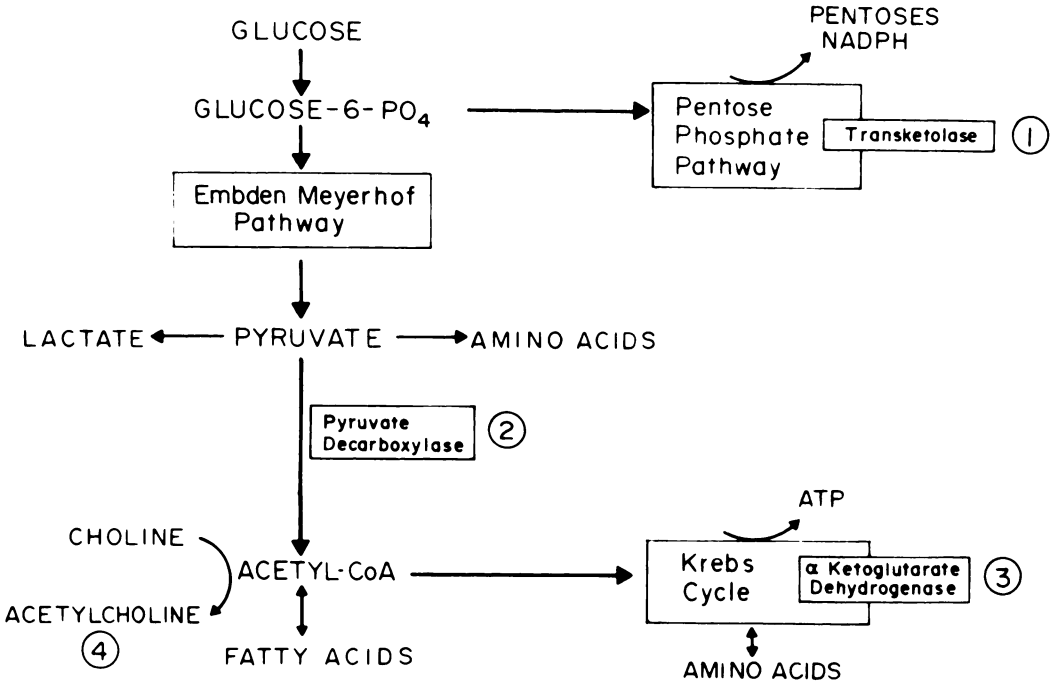

FIG. 2. Sites of impaired enzyme activity in Thiamin deficiency. The *numbers* indicate the biochemical sites wherein thiamin deficiency may interfere with metabolism. These relate to *1*) transketolase, an important enzyme in the pentose phosphate pathway, *2*) pyruvate decarboxylase, *3*) α-ketoglutarate dehydrogenase, and *4*) the synthesis of acetylcholine. (Modified with permission from Henderson, G. and S. Schenker. Cerebral metabolic abnormalities in thiamin deficiency. In: Alcohol and Abnormal Protein Biosynthesis: Biochemical and Clinical, edited by M. A. Rothschild, M. Oratz and S. S. Schreiber. New York: Pergamon Press Inc., 1975, p. 449.)

TABLE 3
Wernicke's encephalopathy: pathogenetic possibilities

A. Metabolic disturbance	1. Impairment of pentose phosphate pathway (transketolase depression)
	2. Impaired energy (ATP) synthesis (pyruvate decarboxylase depression)
	3. Impaired acetylcholine synthesis
B. Neurophysiological disturbance	1. Neuronal membrane effect (thiamin triphosphate)
	2. Impairment of cerebral serotonergic system
C. Genetic abnormality	1. Altered kinetic property of transketolase (high Km enzyme)

thiamin both rapidly revert toward normal. However, high energy phosphate levels and their turnover in various parts of the brain of thiamin-deficient animals have been shown to be normal (24, 26). Thus, unless the defect in cerebral energy metabolism is confined to some critical site, this concept is at present untenable. Another variant of the pyruvate decarboxylase depression hypothesis focuses on impaired acetylcholine (ACh) synthesis. This theory stipulates that decreased acetylCoA formation may ensue in thiamin deficiency and may result in a decrease in the generation of the neurotransmitter ACh. The data concerning brain ACh concentrations in thiamin deficiency have been somewhat variable but the most recent studies (27) have shown normal levels in various regions of the brain with a small decrease in ACh turnover. It is difficult to interpret these data in terms of physiologic significance but the observations that a major fall in brain ACh induced

by hemicholinium-3 did not alter consciousness in rats (28) rather argues that the small changes in ACh turnover in thiamine deficiency do not explain the neurological signs observed.

Since the coenzyme (metabolic) functions of thiamin do not readily account for Wernicke's encephalopathy, neurophysiological effects were proposed. It was suggested that thiamin triphosphate may be essential to neuronal membrane integrity and propagation of the neuronal electrical potential. This concept was supported by several studies showing that thiamine triphosphate is localized to nerve membranes and is released with electrical stimulation of nerves (29–31). However, thiamin triphosphate does not fall in brain of rats with severe diet-induced thiamin deficiency (32) and a recent study failed to confirm changes in thiamin triphosphate in brain upon electrical stimulation or depolarization by potassium (33). Recently it has been suggested that there may be an increase in serotonin turnover in thiamin-deficient brain (34) but the physiological significance of this finding is still uncertain.

Finally, it has been suggested by Blass and Gibson (35) that a genetic abnormality in the kinetic properties of transketolase is responsible for the development of Wernicke's encephalopathy in only a small population of chronic alcoholics. The evidence for this consists of *1*) less avid binding of thiamin pyrophosphate by fibroblasts of patients with Wernicke's and *2*) persistence of this abnormality in fibroblasts serially grown in tissue culture containing excess thiamin and no alcohol. According to this concept, Wernicke's is a combination of genetically mediated decreased affinity of transketolase for thiamin plus a decrease in thiamin intake and/or assimilation. This interesting idea requires further validation in a larger number of patients and their relatives as well as suitable controls. Unfortunately it does not resolve the critical question why a decreased transketolase activity causes neurological changes.

It is evident from this discussion that although the metabolic functions of thiamin are well known, a good animal model of human Wernicke's encephalopathy is available and much work in the field has been done, the pathogenesis of this disorder still eludes us.

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