MEDICAL GRAND ROUNDS

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UNIVERSITY OF TEXAS, SOUTHWESTERN MEDICAL SCHOOL AT DALLAS

HEPATIC ENCEPHALOPATHY

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OUTLINE

I. INTRODUCTION

Hepatic encephalopathy (HE) is a derangement of brain function probably caused by failure of a diseased liver to remove certain endogenous toxins from the blood. This impaired clearance of toxins is due partly to hepatocellular disease and partly to natural and surgical shunts which allow blood to bypass the liver. In patients with fulminant hepatic failure, encephalopathy or "hepatic coma" is usually a preterminal complication. Although certain features such as agitated delirium and seizures are largely confined to the HE which accompanies acute hepatic failure, the episodic encephalopathy of patients with chronic liver disease is probably another form of the same basic syndrome. Generally, HE is entirely reversible if liver function improves and/or effective therapy is given. This suggests that the brain disorder results from metabolic derangements rather than structural injury. Certain irreversible neurologic disorders do occur more often in patients with long-standing liver disease, however, and may follow repeated episodes of HE. These include a chronic organic brain syndrome, transverse myelitis and "non-Wilsonian hepatolenticular degeneration". Whether these permanent neurologic disorders are caused by the same factors producing HE is uncertain. Hepatic-or portal-systemic encephalopathy has been the subject of several extensive reviews over the past decade.(1-6). The present discussion will concern only the more firmly established information from the older literature and, beyond that, will emphasize more recent data regarding pathogenesis, provocative factors and treatment of hepatic encephalopathy.

II. CLINICAL FEATURES OF HEPATIC ENCEPHALOPATHY

Table I describes the clinical stages of HE. The characteristic *mental changes* are indicated. This description applies to both acute and chronic HE.

Table I
Stages of Hepatic Encephalopathy

Stage	Mental State	Asterixis	EEG
I	Euphoria, occasionally depression. Fluctuating, mild confusion. Slurred speech Slow mentation and affect. Untidy. Reversed sleep rhythum	Slight	Usually Normal
II	Accentuation of Stage I Drowsiness. Inappropriate behavior.	Definite	Abnormal
III	Sleeping most of the time, but rousable. Incoherent speech. Marked confusion.	(Present)	Abnormal
IV	Not rousable. May or may not respond to noxious stimuli	-	Abnormal

Modified from Trey C, Davidson CS: Prog Liver Dis 3:282, 1970

NUMBER CONNECTION TEST I

PATIENT'S NAME_____

DATE_____ TIME TO COMPLETE_____ SECONDS

TESTER'S INITIALS_____ PT. CHART NO._____

PATIENT'S SIGNATURE _____

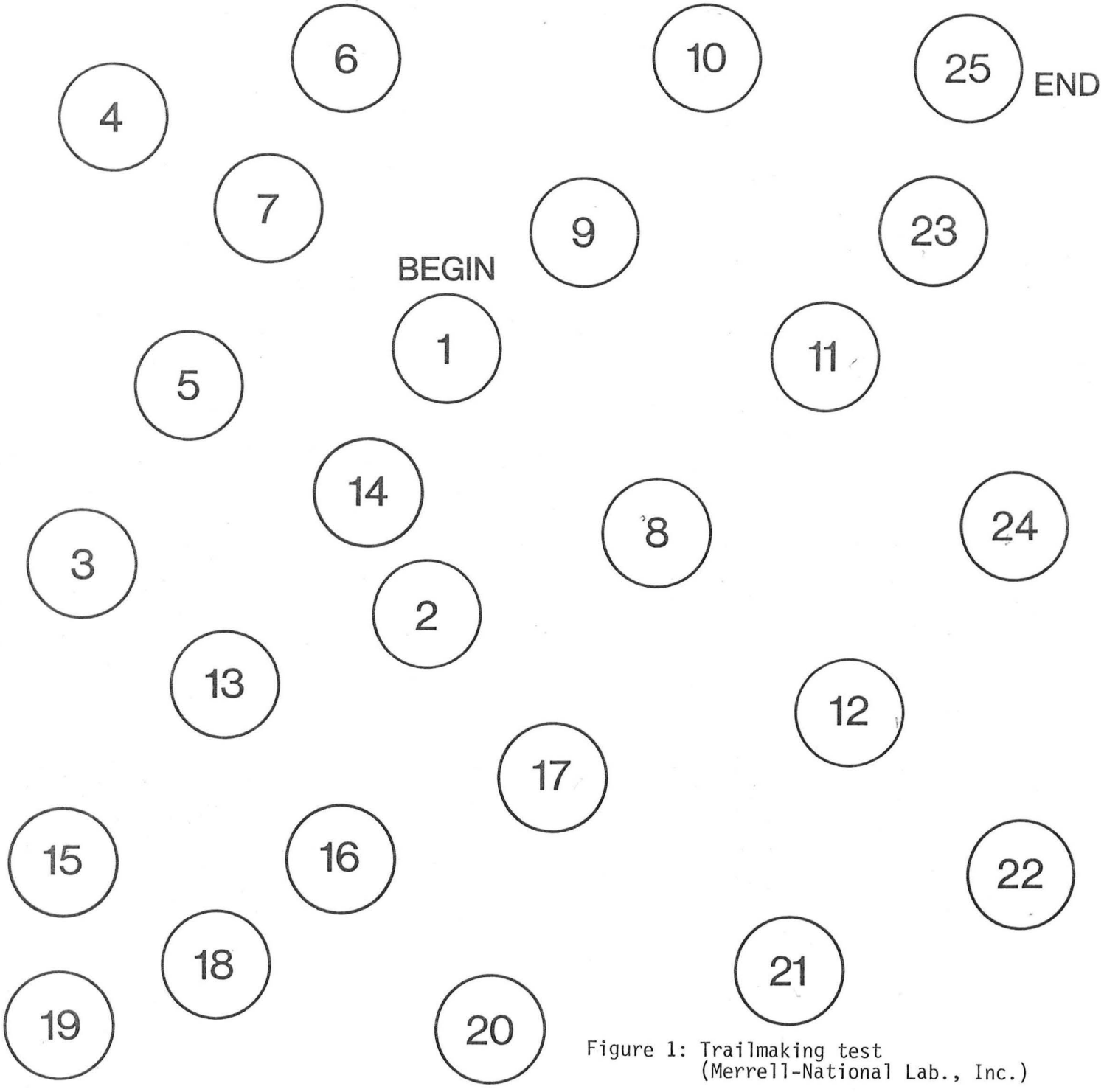

Figure 1: Trailmaking test
(Merrell-National Lab., Inc.)

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It is important to recognize that certain patients with chronic liver disease, especially those with portal-systemic shunts, may be judged "normal" by the criteria described in Table I, and yet, with more refined psychometric testing, are shown to be marginally encephalopathic (7). One of the best indicators of such minimal brain dysfunction may be the trailmaking test (Reitan test), in which the patient is timed as he draws lines connecting a sequence of numbers (Figure 1). Mistakes are pointed out and the time taken to correct them is included in the overall time score. The normal range of completion times has been defined by studies of normal persons (8). The trailmaking test is more sensitive than electroencephalography for detection of minimal HE (7)(Figure 2).

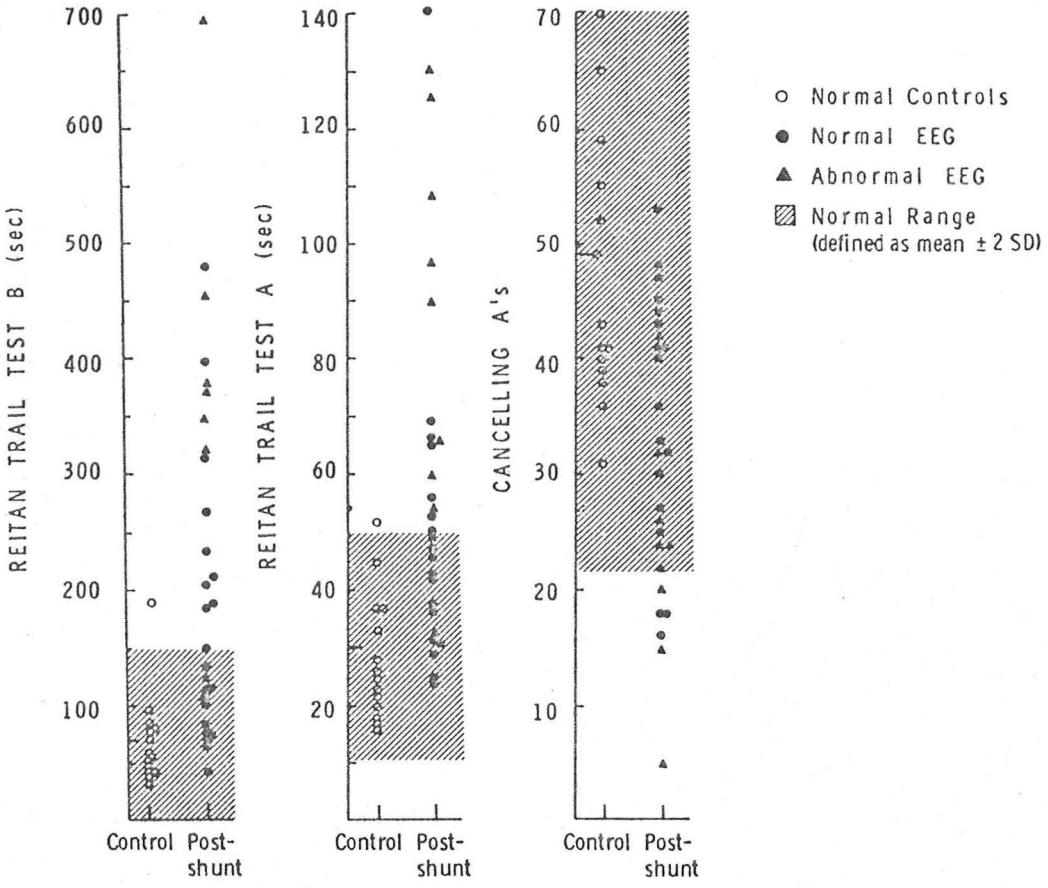

FIG. 2. Comparison of the performance of control and postshunt patients on the Reitan Trail B, Trail A, and Cancelling A's tests. *Shaded area* represents the mean ± 2 SD of the control group. Postshunt patients are separated by *symbols* denoting normal and abnormal EEG's as indicated. Trail B and Trail A scores were abnormally prolonged in 60 and 53% of patients, respectively, and 29% of postshunt patients performed significantly worse than controls on the Cancelling A's test.

Asterixis, the inability to sustain a voluntary posture, is a characteristic and relatively early physical sign of HE. This sign is non-specific, however, and is associated with the metabolic encephalopathies accompanying uremia, hypercapnia, hypokalemia, and hypoglycemia (2).

Other *neurologic features* include abnormal deep-tendon reflexes (hyperactive in early stages and depressed in comatose patients) and positive Babinski responses which are sometimes unilateral.

The *sleep rhythm* may be disordered so that the patient tends to sleep during the day and remain awake at night.

Fetor hepaticus, a fairly characteristic odor of the breath variously described as resembling the smell of old wine, acetone, freshly mowed grass, etc. is one of the more specific signs of HE. This odor, which may also be present in the urine and which disappears after administration of neomycin, is probably due to dimethylsulfide, a metabolite of methionine produced in the GI tract by bacterial action (9).

Hypothermia may develop.

III. LABORATORY TESTS

Only a few tests in addition to liver function studies are of value in distinguishing HE from other types of encephalopathy.

The *serum ammonia* determination was used extensively for many years to aid in the diagnosis of HE. Ammonia is generally regarded as the primary cerebrotoxin responsible for the development of HE, and there is a fairly close correlation between serum ammonia levels and the degree of encephalopathy. Since resting skeletal muscle removes 10 to 30% of ammonia from perfusing blood, arterial ammonia determinations are preferable to venous. Ideally, the blood sample should be placed in ice and taken directly to the laboratory for prompt testing. Discrepancies between the serum ammonia level and the clinical state are sufficiently frequent to diminish the diagnostic value of the test (Figure 3). For this reason, serum ammonia determination has been used less often in recent years, and a number of clinicians have essentially abandoned the test.

Cerebrospinal fluid glutamine appears to be a more specific indicator of HE, but may also give false-positive, or -negative results (10). Most laboratories are not set up to perform glutamine determinations routinely.

It has been suggested that CSF *alpha ketoglutaramate*, the deaminated derivative of glutamine, is a more specific test for HE than glutamine itself, but this awaits confirmation (10).

ELECTROENCEPHALOGRAPHY

With increasing depth of HE, the EEG pattern passes from the normal waking alpha rhythm (8-13c/s) to the slower theta rhythm (4-7c/s) and finally to the very slow, high voltage delta rhythm (0-3c/s). These changes are bilaterally symmetrical and are most prominent in the frontal leads, progressing towards the occipital leads as coma deepens (Figure 4).

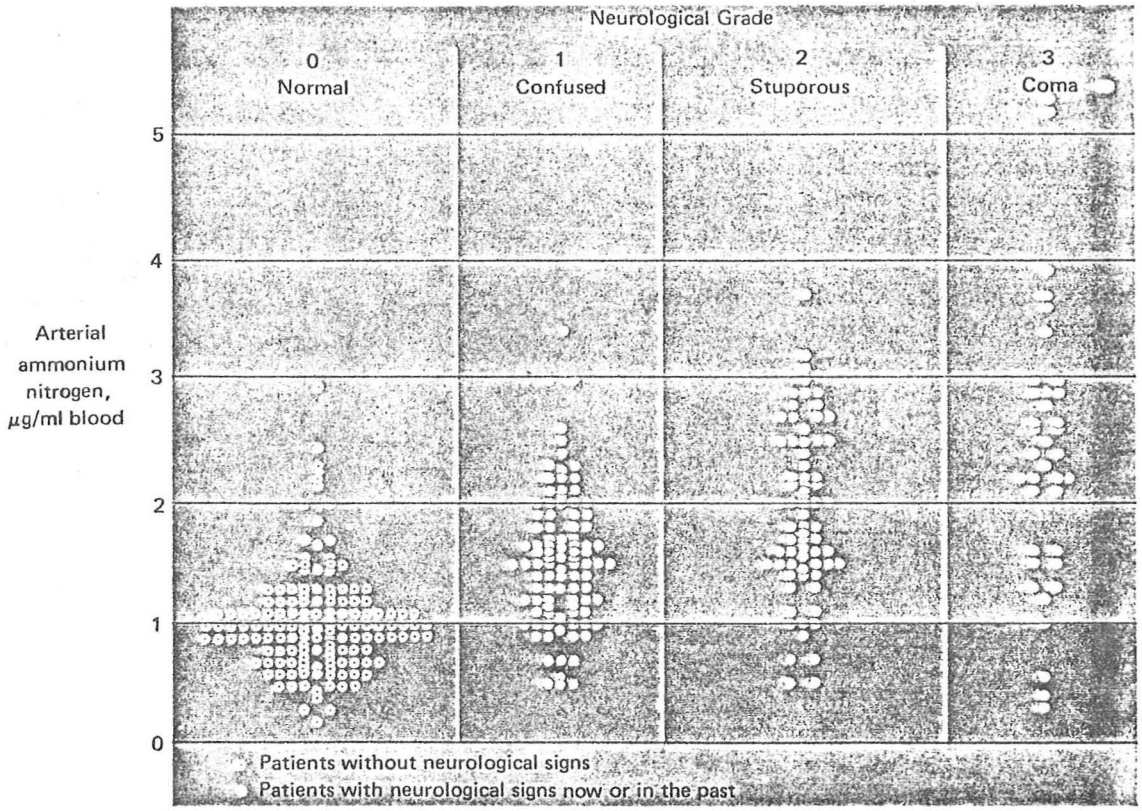

Figure 3: Blood ammonia level in patients with liver disease and various grades of hepatic coma. (Sherlock S).

Essentially the same pattern may be seen in patients with encephalopathy due to uremia, hypercapnia and hypoglycemia. Several years ago it was suggested that "triphasic waves" were highly characteristic or even pathognomonic for HE, but these waves are now regarded as relatively non-specific (11).

EEG is sometimes more sensitive than clinical evaluation in detecting early HE. Improvement in the EEG pattern may lag a few days behind clinical improvement in the patient who is recovering from HE.

Considering the expense and time demand of EEG, its incomplete specificity and the fact that the simple and inexpensive Reitan trail-making test may be an even more sensitive indicator of early encephalopathy (7), there is little justification for routinely performing this procedure in HE patients.

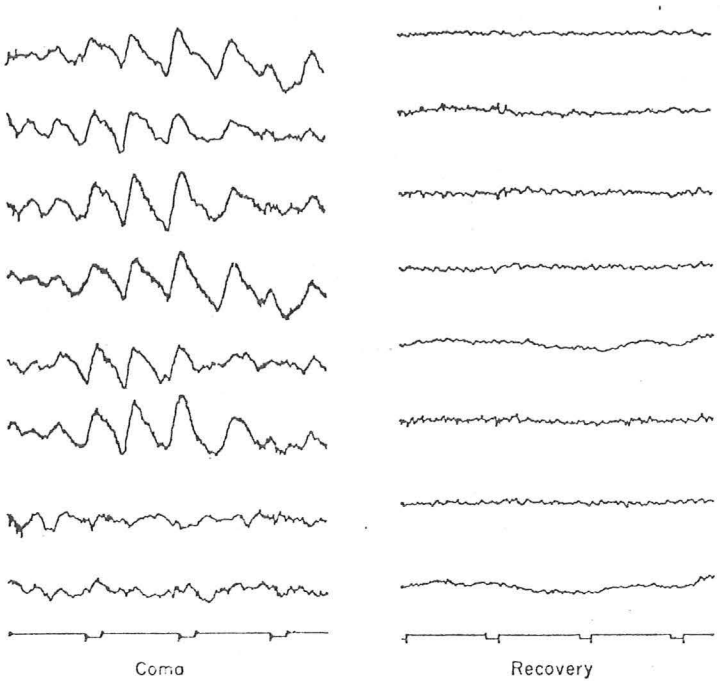

Figure 4: EEG of a patient in hepatic coma (left) showing bilaterally synchonous, high-voltage slow (delta) waves, most prominent in the anterior leads (upper tracings). After recovery two days later, the normal alpha rhythm is seen (right). (S. Sherlock)

IV. CEREBRAL DYSFUNCTION IN HE

The specific derangement(s) of brain function underlying the clinical syndrome of HE remains unknown. Presumably the cerebrotoxins of hepatic failure might impair function in one or more of three different areas--nerve cell and/or glial metabolism, nerve cell membrane activity, or synaptic transmission.

The study of cerebral metabolism in experimental animals with HE has been extremely difficult. A number of careful animal studies in mice, rats, dogs and pigs acutely intoxicated with ammonia are of uncertain significance because of doubts about the validity of such preparations as models of human HE. Further problems concern the effects of sedative drugs used in some of these studies, the rapid decay of unstable metabolites prior to freezing, the paucity of data reflecting the turnover rates of metabolites, and perhaps most troublesome, the problem of "compartmentation", i.e. the possibility of overlooking the effect of a cerebrotoxin on a particular substrate or enzyme in minute, focal areas of the brain when measuring such factors in a homogenate of brain tissue.

Cerebral blood flow, oxygen consumption, and to a lesser extent, glucose uptake, are reduced in human subjects during HE. These are believed to be secondary changes, and oxygen administration is not beneficial to these patients (3).

Several years ago, Bessman proposed that ammonia, by forcing the conversion of alpha-ketoglutarate to glutamic acid and subsequently to glutamine (Figure 5) in brain cells, syphoned substrate from the Krebs cycle thereby "crippling" its function (12). No convincing experimental evidence in support of this concept has been forthcoming and it has been considered improbable on theoretical grounds.

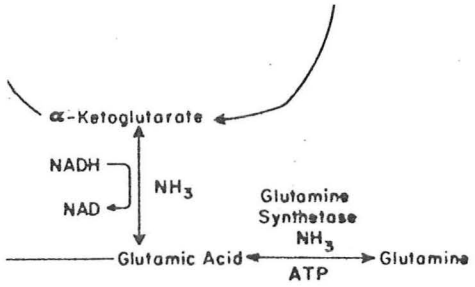

Figure 5: Pathway of ammonia-induced depletion of tricarboxylic cycle substrate (α-ketoglutarate), proposed by Bessman as the mechanism of hepatic encephalopathy.

Similarly, proposals by several authors of a number of other sites where ammonia and other toxins might impair cerebral metabolism (summarized in reference 1) remain unsubstantiated.

V. PATHOGENESIS OF HEPATIC ENCEPHALOPATHY

HE is generally regarded as a functional disorder because of its potential for prompt and complete reversal, and because only minimal anatomic changes are found in the brains of many patients dying in hepatic coma. In some cases, particularly in patients dying of fulminant hepatic failure, cerebral edema may be present, and resultant uncal or tonsilar herniation may be the immediate cause of death (13). Such brain swelling is lacking in other cases, however, and it is apparently not an essential factor in the development of HE. Microscopically, the most consistent change has been enlargement and proliferation of protoplasmic astrocytes (Alzheimer Type II).

A. PUTATIVE CEREBROTOXINS

1. AMMONIA

For many years ammonia has been the prime candidate as the cerebral toxin responsible hepatic encephalopathy. Supporting

evidence includes the following. First, blood ammonia is elevated in most encephalopathic patients, roughly in proportion to the stage of encephalopathy. Second, in patients with chronic liver disease, HE can be precipitated by administration of ammonium compounds or ammonia-loaded cation-exchange resins (14). Third, a number of precipitating factors of HE such as gastrointestinal hemorrhage, hypokalemia, constipation and infection cause hyperammonenia which may be the final common pathway by which they all act. Finally, several effective modes of therapy result in reduced blood ammonia levels.

The principle source of ammonia is the gastrointestinal tract, in which it is produced by bacterial breakdown of nitrogenous compounds including dietary protein, blood and urea which diffuses into the GI tract from the serum. Other, undefined, factors in addition to bacterial degradation may be involved in GI ammonia production. Nance, et al. found that infusion of blood into the stomach of germ-free Eck-fistula (porto-caval shunt) dogs led to the same degree of blood ammonia increase as was seen in conventional Eck-fistula dogs (15).

Under conditions of hypokalemia and of metabolic acidosis the kidneys may release considerable quantities of ammonia into the circulation (16,17). This is particularly true of patients with renal tubular acidosis associated with advanced liver disease in whom the relative acidity of the blood as compared to the urine favors the movement of ammonia into the circulation.

Although resting skeletal muscle removes ammonia from the blood, so that the ammonia level of venous blood from the lower extremity may be 20-30 percent lower than the arterial level, exercising muscle produces large amounts of ammonia and may contribute to hyperammonemia in an agitated patient.

Normally the liver clears about 80% of ammonia from the perfusing blood, disposing of it by synthesis of glutamine and urea. Hyperammonemia developes in patients with advanced liver disease particularly if there are spontaneous or surgical-portal-systemic shuntsallowing blood to bypass the liver.

Although there can be little doubt that ammonia plays an important role in the pathogenesis of HE, and despite the generally good correlation between serum ammonia levels and the degree of HE, a disturbing number of patients develop indisputable hepatic coma despite near normal ammonia levels while other patients without encephalopathy have elevated levels (18). A reasonable explanation for these observations is discussed below (synergistic effect of combined cerebrotoxins).

2. MERCAPTANS

Several years ago methionine was used as a lipotropic factor for treatment of patients with chronic liver disease, but was

later shown to worsen encephalopathy (19). Plasma methionine concentrations are greatly elevated in patients with both acute and chronic hepatic failure (20). Bacterial degradation of methionine in the GI tract results in production of small sulfur-containing compounds including methanethiol (CH3-SH), ethanethiol (CH3-CH2-SH) and dimethylsulfide (CH3-S-CH3). The plasma levels of these compounds are raised in the presence of liver disease and, as noted above, the latter is believed to be the cause of hepatic fetor.

These compounds cause coma when administered to rats, methanethiol being by far the most toxic member of the group (21). The mechanism of this toxicity is unexplained.

3. SHORT-CHAIN FATTY ACIDS

As is the case with ammonia and the mercaptans, short chain fatty acids (SCFAs) (C4-C8) are elevated in the serum and CSF of cirrhotic patients and are highest in those who are encephalopathic. They cause coma when administered to experimental animals (22) but in at least one study of cirrhotic patients, administration of C6 to C10 fatty acids failed to produce changes in mental state, EEG, or arterial ammonia concentration (23).

The major fraction of serum octanoate is derived from beta oxidation of long-chain fatty acids while most of the remainder is synthesized de novo, little if any being of direct dietary origin (24).

It has been suggested that the toxicity of SCFAs may actually relate to their displacement of tryptophan from its plasma albumin binding sites, allowing increased amounts of this amino acid to enter the brain (25). The possible cerebrotoxicity of tryptophan is discussed below.

4. AMINO ACIDS

Characteristic patterns of serum amino acid abnormalities have been demonstrated repeatedly in patients and experimental animals with HE (26). In fulminant hepatic failure, all amino acids are increased with the exception of the branched chain amino acid (BCAAs), leucine, isoleucine and valine, which are normal (Figure 6 lower panel). In chronic liver disease, particularly in the presence of HE, serum levels of phenylalanine, tyrosine, methionine, aspartate and glutamate are elevated while the BCAAs are below normal concentrations (Figure 6, upper panel). In the latter case, amino acid elevations are attributed to their reduced uptake by the diseased liver. By contrast, the BCAAs are metabolized mainly in skeletal muscle, where their uptake may be accelerated by the effect of the high plasma insulin concentrations in these patients (27).

Correction of plasma amino acid abnormalities in Eck-fistula dogs leads to reversal of encephalopathy and prolongation of survival (28). Similarly, improvement of HE in patients with chronic

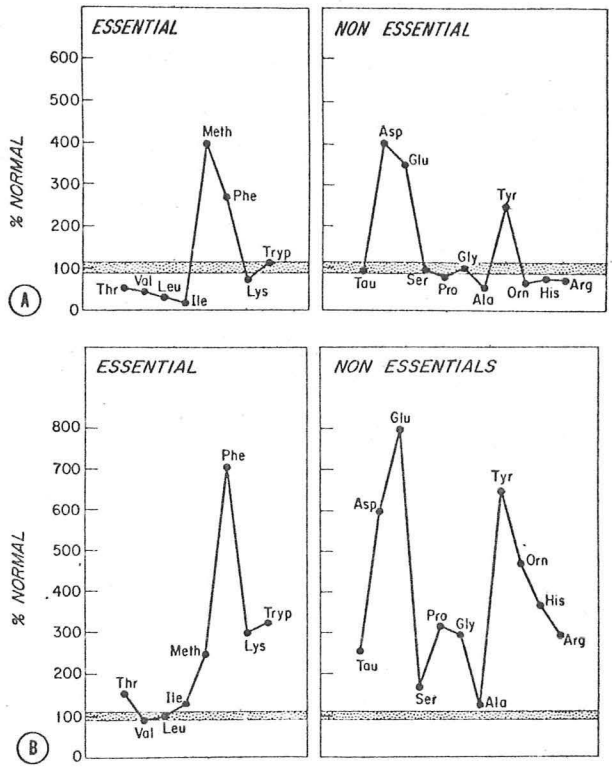

Fig. 6 Amino acid patterns in Group 1 *(A)*, patients with cirrhosis, and Group 2 *(B)*, patients with viral hepatitis. The patterns are somewhat different. The patients with cirrhosis show increased phenylalanine and tyrosine, aspartate and glutamate, as well as methionine, whereas threonine and the branched chain amino acids are decreased. In the patients with viral hepatitis all amino acids, with the exception of the branched chain amino acids, are elevated.

liver disease after normalization of the plasma amino acid pattern was reported (26). These findings suggest that plasma amino acid imbalance may play a role in the etiology of HE.

The mechanism of the amino acid effect is unknown. There is no indication that cerebral BCAA deficiency is a factor. Since the neutral amino acids share a common carrier system at the blood-brain barrier, a deficiency of branched-chain (neutral) amino acids is believed to allow increased transport of other neutral amino acids including the potentially toxic aromatic AAs, into the brain.

In recent years, Fischer and associates have published a number of papers concerning his *false neurochemical transmitter theory of the pathogenesis of HE*. In its present form, this two-component theory may be stated as follows:

As a result of the plasma amino acid imbalance described above, excessive quantities of phenylalanine and tyrosine (neutral, aromatic amino acid; AAAs) enter the brain. Within the cerebral neurons, the

relatively excessive phenylalanine competes with tyrosine for binding to tyrosine hydroxylase, the rate-limiting enzyme in the norepinephrine synthetic pathway. As a result CNS norepinephrine synthesis is reduced. Norepinephrine is believed to be an important neurotransmitter in brain stem "alerting" centers. In addition, the tyrosine which accumulates because of the tyrosine hydroxylase block is diverted to an alternative pathway, decarboxylation to tyramine (Figure 7). Tyramine is further metabolized to octopamine and other beta hydroxylated-phenylethanolamines. These false neurochemical transmitter (FNT) compounds share certain structural features with the normal neurotransmitters, dopamine and norephinephrine. These properties result in the FNT being stored, together with the normal transmitters in synaptosomes, partly displacing these normal transmitters, and being released when the nerve ending is depolarized. Octopamine and related compounds are regarded as *false transmitters*, however, because their potency at the post-synaptic receptors is far

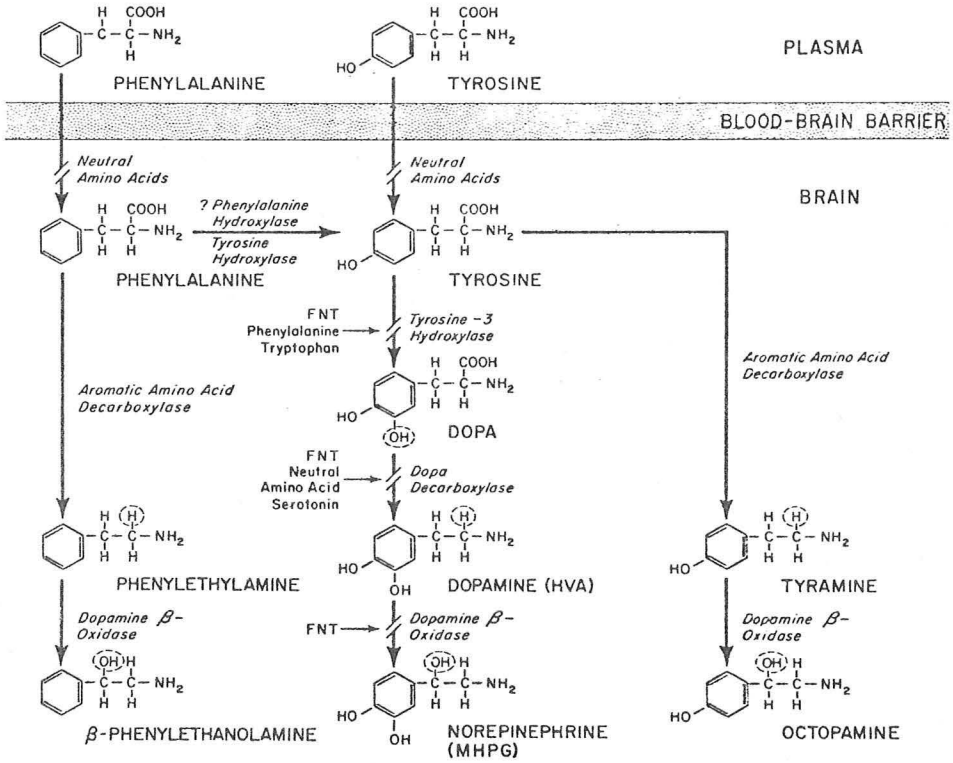

FIG. 7 Synthetic scheme of catecholamines in brain. Although tyrosine is normally the principal precursor for catecholamines, phenylalanine that is hydroxylated to tyrosine may similarly serve as a precursor for catecholamine synthesis. When tyrosine accumulates, it may be preferentially decarboxylated to tyramine and then to octopamine. Potential or actual synthetic blocks are shown by slashes at the various enzymatic points. HVA (Homovanillic acid) is shown in parentheses next to dopamine as it represents a metabolite. MHPG (3-methoxy-4-hydroxy-phenylglycol) is a metabolite of norepinephrine that may be detected in the spinal fluid.

lower then that of the normal transmitters. Consequently, according to the FNT hypothesis, synaptic transmission is impaired in patients with HE by insufficient release of dopamine and norepinephrine at the nerve endings due to the combined effects of reduced catecholamine synthesis and normal transmitter displacement by the FNT_s.

Several observations lend support to the FNT theory. As noted above, correction of the plasma amino acid imbalance is sometimes followed by improvement of encephalopathy in patients and experimental animals. Increased cerebral concentrations of octopamine and reduced concentrations of norepinephrine have been found in the brains of experimental animals with HE. HE in animals and patients can be rapidly, though only temporarily, reversed by administration of L-DOPA, a dopamine/norepinephrine precursor which enters the catecholamine synthetic pathway beyond the inhibited tyrosine hydroxylase step.

As attractive as the FNT hypothesis has been, it may have received a crippling if not lethal, blow when it was observed that infusion of octopamine directly into the cerebral lateral ventricles of normal rats, in concentrations producing brain octopamine levels 20,000 - fold greater than normal, and causing up to a 90% reduction of brain dopamine and norepinephrine concentrations, changes far more extreme than noted in encephalopathic animals, were not accompanied by any detectable changes in the animals alertness or activity (29).

It is possible that the beneficial effects of L-DOPA in HE are the results of a relatively non-specific "alerting" affect of the drug which overrides the sedative affect of the cerebrotoxins causing HE.

Tryptophan is the precursor of serotonin, a putative CNS neurotransmitter believed involved in the neurophysiology of sleep (30). Total serum tryptophan levels are normal or only moderately increased in patients and animals with HE. Tryptophan is unique, however, in that it is largely bound to albumin in serum and only the unbound fraction is available for transport into brain (25). Patients with chronic liver disease, especially those who are encephalopathic, characteristically have elevated plasma levels of free fatty acid (FFAs), which compete with tryptophan for albumin binding. The increased levels of free plasma tryptophan are believed to be the main reason for the increased levels of tryptophan, serotonin, and 5-HIAA (serotonin metabolite) found in brain and CSF in encephalopathic subjects. Additionally, it has been suggested that the increased circulating insulin levels in patients with severe liver disease directly stimulate tryptophan transport into brain (31). These two mechanisms for increased movement of tryptophan into brain are believed to be more important than the effect of reduced BCAA competition for the neutral amino acid carrier sites (32).

Quantitatively, *aspartate and glutamate* are said to be among the most important CNS neurotransmitters (33). In recent studies of rats

made encephalopathic by ammonium acetate administration several weeks after porto-caval shunting, Hindfelt et al. demonstrated an acute depression of aspartate and glutamate in brain tissue at the onset of encephalopathy (34). In these detailed studies, they demonstrated that these intracerebral amino acid deficiencies apparently were secondary to an ammonia-induced block in the conversion of pyruvate to citrate.

B. CEREBRAL ENERGY METABOLISM

It has long been suspected that, whatever their basic mechanisms of CNS toxicity, ammonia and other hepatic failure toxins might act by impairing the generation of brain ATP and phosphocreatine. Schenker demonstrated a selective depletion of ATP in the brain stem of ammonia-intoxicated rats (35). However, in the studies of Hindfelt et al. noted above, those authors found that although brain ATP fell significantly in ammonia-intoxicated rats, the onset of encephalopathy clearly preceded the reduction of ATP, and they concluded that the later was a secondary phenomenon (34). Of course, the possibility always remains that HE results from ATP depletion in a very small but functionally critical region of the brain and that this deficiency is undetectable when measuring ATP in the homogenate of a much larger volume of brain tissue. This is another example of the eternal "compartmentation" dilemma.

C. SYNERGISTIC EFFECTS OF COMBINATIONS OF CEREBROTOXINS

Despite abundant evidence for a role of ammonia in the causation of HE, in a number of patients serum ammonia levels fail to correlate with the presence and degree of encephalopathy (Figure 3). Similarly, considerably higher concentrations of cerebrotoxins (ammonia, mercaptans, short-chain fatty acids) than are present in encephalopathic patients are required to produce coma in experimental animals. Zieve offered a possible explanation for these discrepancies in a series of studies of the effects of various combinations of the three types of toxins in large groups of rats (36,37). After determining the dose of each toxin which produced coma in 50% of animals (CD^{50}), he showed that addition of a second toxin, at a dose which alone failed to cause coma in any animal, reduced the CD^{50} of the first toxin markedly. This phenomonen is illustrated for ammonia and methanethiol (MT) in Figure 8 and for ammonia and octanoate (a SCFA) in Figure 9. Finally, he was consistently able to induce coma in normal rats by administration of the three toxins together in doses which raised the plasma concentrations of each only to the levels found in rats whose encephalopathy was produced "naturally" by ischemic liver injury.

Schenker has proposed that some patients with chronic liver disease and porto-systemic shunting, while their mental status may be normal, are chronically closer to the threshold of encephalopathy than are normal persons. This "sensitized brain" concept may, in

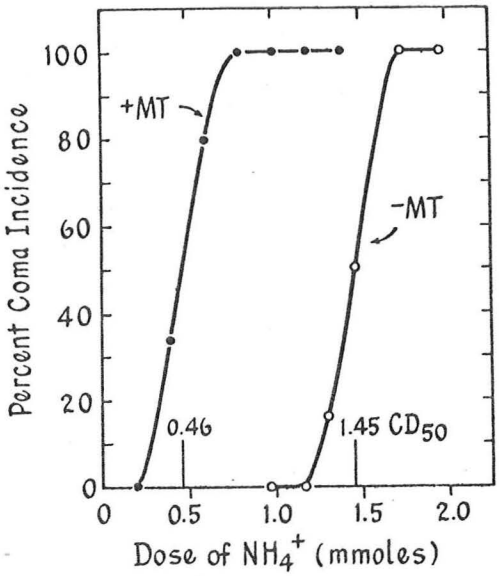

Fig. 8 Dose-response curves for the production of coma by NH_4^+ in the presence and absence of a subcoma dose (0.12 per cent) of methanethiol (MT). Ammonium chloride was the ammonium salt used here and in Fig. 6.

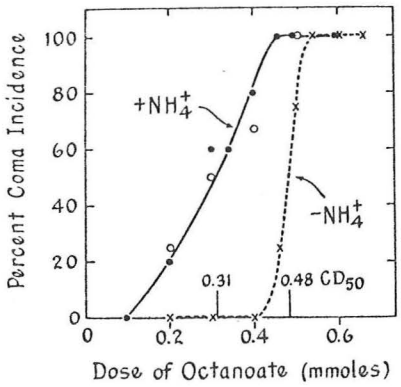

FIG. 9 Dose response curves for the production of coma by fatty acid (octanoate) in the presence and absence of NH_4^+. Ammonium acetate (●) or ammonium chloride (○), 1.0 mmol, was used. ×, sodium octanoate alone.

part, explain why apparently comparable patients may vary considerably in their propensity to develop HE in response to a given degree of stress. Presumably, this relates to different long-term "baseline" plasma concentrations of the cerebrotoxins which, even in combination, are present at sub-coma-producing levels. The prolonged use of neomycin or lactulose in patients with frequent episodes of HE may reduce the baseline levels of toxins, making the patient more resistant to the inevitable periodic stresses.

VI. PRECIPATATING FACTORS

A. Dietary Protein

Bacterial degradation of ingested protein in GI tract is a major source of serum ammonia. In addition, certain amino acids, notably threnonine, serine, glycine, glutamine, and histadine give rise to ammonia after absorption from the gut or when given intravenously. This is believed to be the result of their prompt deamination and deamidation (38).

Hepatic encephalopathy has developed in cirrhotic patients in response to parenteral hyperalimentation with amino acid solutions. It has been suggested that this is more closely related to an aggravation of the abnormal plasma amino acid pattern in such patients, (discussed above), than to the ammoniagenic effect of the infused amino acids (39,6).

B. Gastrointestinal Hemorrhage

Large amounts of ammonia are produced by the degradation of blood protein in the GI tract. With severe bleeding, hypotension leading to diminished cerebral and hepatic perfusion may compound the encephalopathic effect of the cerebrotoxins. Ammonia is generated in stored banked blood and hyperammonemia may be worsened by large-volume blood transfusions. Gastrointestinal hemorrhage is one of the most common precipatating causes of HE.

C. Constipation

Constipation increases total quantity of ammonia absorbed from the fecal mass.

D. Azotemia

Urea diffuses into the GI tract from the circulation and is degraded by gut bacteria to ammonia, which is reabsorbed. In azotemic patients this effect is magnified. In addition, the ill-defined "uremic toxins" may have an additive effect with the hepatic toxins in producing cerebral dysfunction.

E. Drugs

Sedatives and analgesic drugs, particularly opiates, appear to have additive (or greater) effects with the endogenous cerebrotoxins in producing HE. While every effort should be made to avoid these agents, if sedation of an agitated patient with HE is essential (a rather uncommon situation), oxazepam (Serax) in carefully titrated doses (p.o. or via nasogastric tube) may be the drug of choice. This benzodiazepine, unlike diazepam and others of this group, is

converted to pharmacologically inactive metabolites and so may present less risk of cumulative toxicity (40) *Diuretics* tend to provoke HE mainly by means of producing hypokalemia (see below). Pre-renal azotemia precipatated by overly aggressive diuresis may lead to increased GI ammonia production from breakdown of urea. HE has been produced, apparently by the latter mechanism in the absence of hypokalemia, by use of large doses of spironolactone (41). Acetazoleamide (Diamox) apparently provokes HE by increasing intracellular CO_2 tension in brain cells, since a similar worsening of encephalopathy was observed in patients breathing a 5% CO_2-in-air mixture in an attempt to treat the respiratory alkylosis commonly accompanying HE (42).

F. Hypokalemia

Patients with chronic liver disease tend to become hypokalemic for a variety of reasons including poor potassium intake, vomiting, secondary aldosteronism, purging and diuresis.

In the presence of hypokalemia, renal ammonia production is greatly increased (16). Hypokalemia, especially in the setting of metabolic alkylosis is believed to promote increased movement of ammonia into brain cells by the mechanism illustrated in Figure 10. With loss of potassium from the brain cells, hydrogen ions (and sodium) move into the cells in its place, and as a result, the "downward" pH gradient into the cells becomes steeper. The extracellular alkylosis tends to shift plasma ammonia (pK 9.1) from the ionized NH_4+ form to the more lipid-soluble and diffusible NH_3 form. Once in the cell, NH_3 is converted back to NH_4 in the presence of the low pH, and is thereby trapped intracellularly.

VII. THERAPY OF HEPATIC ENCEPHALOPATHY

A. Standard Treatment

The basic and obvious management of HE involves attempts to reverse the precipatating factors discussed above, i.e., correction of GI bleeding, constipation, fecal impaction, azotemia, and hypokalemia, discontinuation of offending drugs and reduction of dietary protein intake.

1. Dietary Protein

At the outset of therapy, unless encephalopathy is mild, all protein is removed from the diet. When recovery is well under way, protein is reintroduced in increments of 10 to 20 grams per day, every two to three days, up to a maximum of about 60 grams per day. There does not appear to be any additional benefit from a higher protein diet in such patients, and the risk of recurrent HE is simply increased.

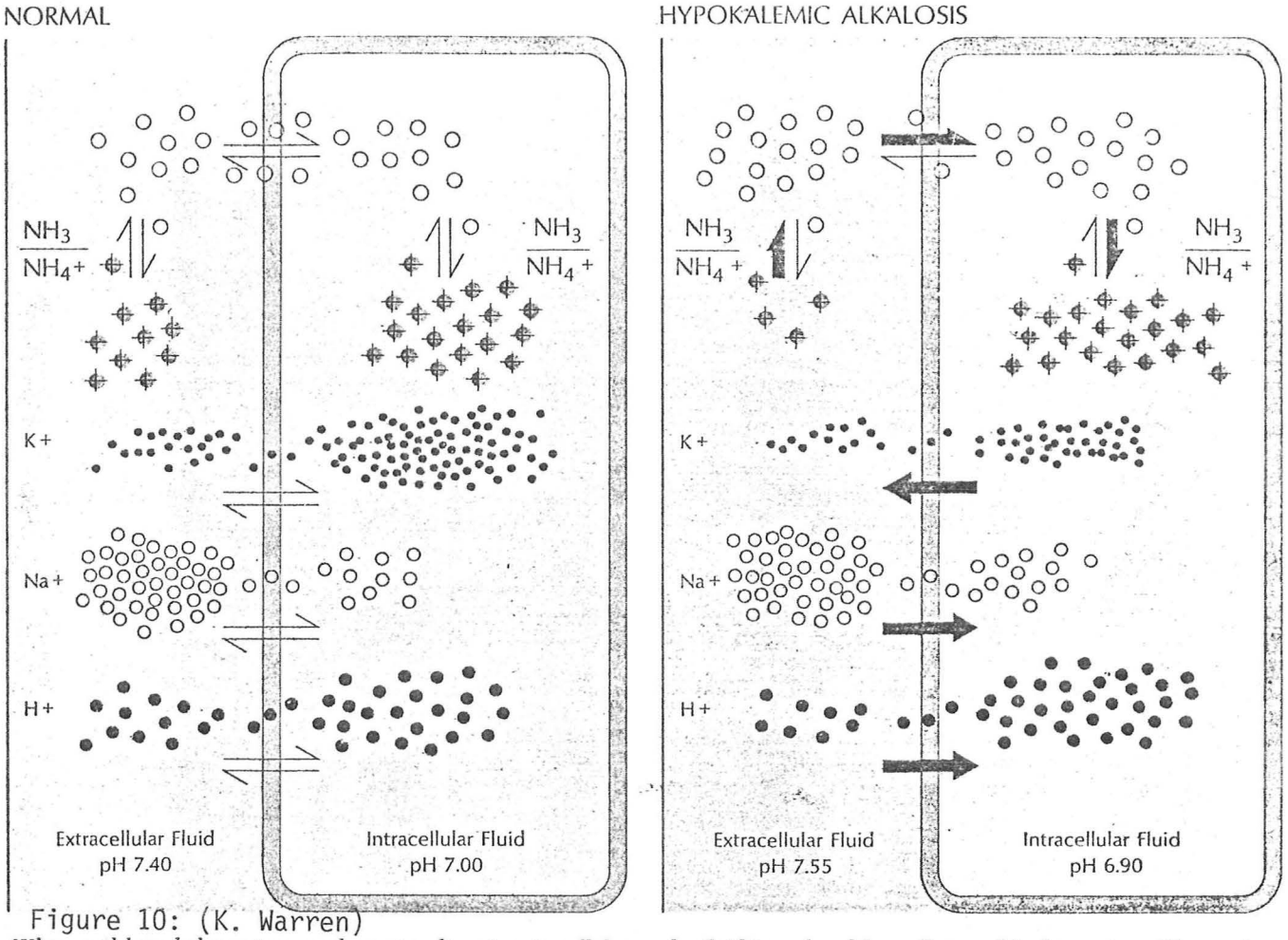

Figure 10: (K. Warren)

When acid-base balance is normal, most sodium is extracellular and most potassium and hydrogen is intracellular. "Ammonia" exists as an equilibrium between gaseous ammonia (NH_3), which can cross the cell wall, and ammonium ion (NH_4^+), which cannot (left). In potassium depletion, potassium lost from the intracellular fluid is replaced by sodium and hydrogen ions. The resulting change in pH gradient favors formation of gaseous ammonia in the extracellular fluid, which is attracted to the acid medium of the intracellular fluid. The result is ultimately to increase the concentration of ammonium ion within the cell (schematic at right).

It has been demonstrated that both patients (43) and dogs (39) with porto-caval shunts tolerate milk and cheese protein better than meat protein in comparable amounts. In the dog study (39), the animals tolerated fish meal somewhat better than meat but not as well as milk. The tendency of the different forms of proteins to cause HE does not correlate well with their contents of the more "ammoniagenic" amino acid discussed above (38,39), but it may be significant that meat contains relatively greater amounts of aromatic amino acids than fish or milk, and milk contains more branched-chain amino acid then either fish or meat. Also it is conceivable that lactase-deficient subjects may benefit from a lactulose-like effect of lactose in the milk diet. The milk diet was noted to produce diarrhea in some dogs (39).

2. Neomycin

Neomycin is an essentially nonabsorbable antibiotic whose beneficial effect in treatment of HE is believed to relate to suppression of urea-splitting gut bacteria. Treatment is usually begun with 8 grams per day, p.o., and this is reduced to a maintenance dose of 2 to 4 grams per day. For the occassional patient requiring long-term neomycin therapy, it may be advisable to perform audiometric studies periodically to minitor for ototoxicity of the drug.

It is important to recognize that 0.6 to 3.0 percent of neomycin actually is absorbed into the circulation. The absorbed drug is excreted into the urine, but in the presence of renal insufficiency, neomycin may accumulate in the circulation and its nephrotoxic effect may aggravate the renal failure (44). Because of the frequency of functional renal failure ("hepatorenal syndrome") in patients hospitalized with HE, and because of the frequent need to treat such patients with other nephrotoxic agents, notably gentamycin, it would seem preferable to begin therapy of HE with lactulose instead of neomycin in severely ill patients.

3. Lactulose

Lactulose is a synthetic disaccharide 1,4-beta-galactosidofructose which is not hydrolyzed by small intestinal disaccharidases. The unabsorbed sugar is carried to the colon where it has two important effects, first, it serves as a simple osmotic cathartic and second, due to partial degradation to acidic metabolites (lactate, acetate) it causes a reduction of fecal pH. Although some benefits of lactulose probably derive from the laxative effect, therapeutic efficacy is more closely related to acidification of the stool. Although it was originally proposed that lactulose might favor the overgrowth of lactobacilli in the colon which, in turn, would suppress the growth of urea-splitting proteolytic bacteria, no consistent changes in stool flora have been noted with lactulose therapy. It was then believed that the principle lactulose effect was the trapping of newly generated ammonia in the fecal mass, and indeed, even a possible "sump" effect whereby ammonia was withdrawn from blood stream into the acidified colon. That this cannot be the complete explanation for the beneficial action of lactulose was indicated by Agostini's studies in which he was unable to document the increased ammonia content of excreted feces which one would expect from the "ammonia-trapping" hypothesis (45), despite repeated documentation of reduced plasma ammonia levels in lactulose treated patients. The obvious question "where does the ammonia go?" may be answered by the *in vitro* studies of Vince et.al.(46). These authors separated the effects of low fecal pH (which caused reduced ammonia production, apparently by way of a general reduction of bacterial

metabolism), from an additional, specific effect of lactulose by which fecal ammonia concentration was actually reduced. The latter affect was attributed to the role of lactulose as a bacterial substrate in either increasing bacterial assimilation of ammonia or reducing deamination of nitrogenous compounds.

The usual initial dose of lactulose is 30 ml p.o., t.i.d. Thereafter the dose should be adjusted so that the patient has two to three soft stools per day. Sixty ml may be given as a first dose for its cathartic effect.

Lactulose may also be used as a retention enema by installation of a mixture of 240 ml (one 8 oz bottle) of lactulose and 600 ml of tap water, carefully administered through a foley catheter with an inflated 30 ml balloon. The catheter is clamped for 20-30 minutes and then removed to release the enema. The procedure may be repeated every 12 hours as necessary. There is unconfirmed evidence that lactulose by enema is more rapidly effective than when given orally (47).

The side-effects of oral lactulose are relatively minor and include flatulence (which may improve after a few days), occasional intestinal cramping, and diarrhea. Post-gastrectomy patients may suffer "dumping" symptoms, requiring a reduction or further fractionation of the dose.

As might be expected, encephalopathic lactase-efficient patients have benefited from treatment with oral lactose (48).

Some treatment failures have occurred in patients who do not develop diarrhea on an ordinarily cathartic dose of lactulose. Conn noted an increase in the blood glucose of such a patient after lactulose ingestion and postulated that bacteria in abnormal numbers in the upper small bowel may have degraded the lactulose to absorbable sugars so that none reached the colon (49). Lactulose has generally been as effective as neomycin for treating HE (50). One might suspect that neomycin would cancel the effect of lactulose if the two agents were used concurrently, by suppressing lactulose - metabolizing organisms. In support of this supposition, an increase in stool pH of patients given neomycin while on lactulose therapy has been observed (49).

A significant number of post-portocaval shunt patients who lack the usual clinical indicators of encephalopathy, may, in fact, have minimal HE detectable only by use of refined psychological tests (7). The demonstration that this encephalopathy may be reversed by short term lactulose treatment, may suggest that many shunted patients should be taking this drug chronically.

B. DISCONTINUED FORMS OF THERAPY

Several different measures, all directed at reductions of serum ammonia levels by one means or another, have been abandoned as ineffective or impractical. These include the administration of arginine, glutamate, ornithine alpha-ketoglutarate and acetohydroxamic acid, an inhibitor of ureases in the GI tract. Colectomy and colon by-pass procedures were associated with an unacceptable high operative mortality rate and were only of temporary benefit since eventually heavy bacterial colonization of the small bowel developed and ammonia production rose toward its previous levels.

C. EXPERIMENTAL METHODS OF TREATMENT

1. L-DOPA and Bromocriptine

Rapid but transient reversal of HE has been reported in several patients with fulminant hepatic failure and in others with chronic liver disease who were treated with L-DOPA by mouth. The advisability of its use in acute hepatic coma is uncertain, particularly in view of its transient effectiveness. The drug tends to cause gastritis and, conceivably, could promote development of GI hemorrhage which is already a major risk in patients with fulminant hepatitis (50). The drug has also been administered by enema with beneficial effect.

In a study of six patients with chronic HE, prolonged use of L-DOPA produced improvement in three patients, but because of drug-related GI distress, only one of the three patients was able to tolerate this treatment for more than a few months (51). In hope of avoiding those side effects, the same group treated an additional patient with bromocriptine, a dopamine agonist, with impressive control of his encephalopathy over a long period of time and without significant side effects (52). It appears that this drug may not be effective in all patients with HE, however (53).

2. Keto-Acid Therapy

Maddrey, Walser, and associates reported that the keto-acid analogues of 5 essential amino acids (valine, leucine, isoleucine, methionine and phenylalanine), administered orally or parenterally to 11 patients with chronic liver disease, resulted in the clinical improvement of 8 as judged by the clinical status and by psychological testing (54). Use of the analogs of methionine and phenylalanine in such patients seems irrational, however, since serum levels of these amino acids are already increased, and since each has been associated with worsening of HE, as discussed above. These studies suggest that the keto-analogs of essential amino acids are converted to the corresponding amino acids, probably with glutamine serving as the primary nitrogen donor. Use of the keto-acids allows administration of a "protein

equivalent" for the patients nutritional benefit, but without the need to increase nitrogen intake.

3. Hemodialysis

Hemodialysis has been employed several times over the past two decades as attempted treatment of life-threatening fulminant hepatitis, with consistently disappointing results (55). In the past few years there have been several reports of the use of a polyacrylonitrile dialysis membrane whose larger diameter pores permit clearance of molecules up to 15,000 daltons in size, as compared with an upper limit of 1000 daltons for a standard cuprophan membrane. In both experimental animals (pigs with ischemic liver injury) and in patients with fulminant hepatitis, encephalopathy improved with polyacrylonitrile membrane dialysis to a significantly greater degree then occurs with standard dialysis (56,57). It is presumed that removal of cerebrotoxic "middle molecules" (MW 1000 - 15,000) was responsible for this improvement.

The principle objective of this treatment of patients with fulminant hepatitis is, of course, improved survival, rather than simply the reversal of hepatitic encephalopathy. Unfortunately, an effect on survival does not yet appear to have been accomplished (55).

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