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NEUROLOGICAL DISORDERS ASSOCIATED WITH HEPATIC DISEASES*
RICHARD R. KNOWLES, M.D.**

INTRODUCTION

The recent application of biochemical methods to the investigation of neurological diseases holds forth the promise of clarifying the pathogenesis of many of the diseases of the central nervous system which previously had been non-specifically described as toxic or degenerative in nature. The most productive investigations in this sphere have been those performed on hepatolenticular degeneration and on hepatic coma. Below is presented a brief review of the results of these investigations and the current feelings regarding the biochemical defects and pathogenesis of these entities.

HEPATOLENTICULAR DEGENERATION

Wilson's disease is a familial disease with signs and symptoms secondary to pathological changes in the central nervous system (especially the basal ganglia), the liver and the cornea. Pathologically, the gross nervous system changes consist of varying degrees of atrophy of the cerebrum and the corpus striatum, especially the lenticular nuclei. These changes may be so severe that actual cavitation occurs in the basal ganglia and even in the cerebral cortex. Microscopically, there is a wide-spread loss of neurons with a diffuse increase in glial cells, especially the astrocytic series which undergoes a rather prominent hyperplasia. These changes are most pronounced in the cerebral cortex and in the basal ganglia, and are remarkably similar to those seen in manganese poisoning. The protoplasmic astrocytosis is identical to that seen in patients dying with hepatic coma. The liver shows the characteristic changes of the postnecrotic type of cirrhosis with many small nodules which vary considerably in size and are separated by wide fibrous tissue trabeculae. The cornea shows fine yellow granules in Descemet's membrane. The selective involvement of the basal ganglia is felt to be the result of the highly vascular nature of this area and hence its susceptibility to respiratory enzyme inhibitors. A similar selectivity is seen also in carbon monoxide, cyanide, manganese and carbon disulfide poisoning, all of which are well known inhibitors of respiratory enzymes.

Clinically the usual course is characterized by onset during adolescence, although it has been noted as early as the age of four and as late as the age of forty-five. The disease is slightly more common in males and there is much suggestive evidence that it is inherited as a recessive trait. Usually the signs of liver disease are not prominent, although in a few cases they have appeared early — even before neurological disease has become apparent. The liver function tests, however, and liver biopsy are always abnormal. The neurological picture is as varied as one might expect from the pathology, but basal ganglia signs are almost invariably the most prominent, although on rare occasions cerebellar and cortical symptoms—intellectual deterioration and loss of emotional control — are the most prominent. The tremor varies both in nature and degree; it may be intentional in type, a classic Parkinson tremor, or, more characteristically, the flapping tremor which is seen in impending hepatic coma. The tremor is most commonly maximum in the distal portions of the extremities and consists of rhythmic

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**Resident, Department of Medicine.
flexion-extension movements.

PATHOGENESIS

The first clue as to the biochemical lesion in hepatolenticular degeneration came in 1930, when Horowitz demonstrated an increased copper concentration in the brain and liver of patients with this disease. The next significant developments occurred some 18 years later when Denny-Brown found a persistent amino-aciduria and increased urinary copper in several patients with this disease.

Elaboration of these studies of copper metabolism have yielded some highly interesting and relatively specific deviations from normal in patients who suffer from this disease. The normal serum copper level is a highly constant one, varying less than 5 per cent from the normal of approximately 110 micrograms per cent, while in patients with Wilson’s disease the serum copper varies from 20 to 80 micrograms per cent. The normal urine contains from 0 to 25 micrograms of copper per day, while in patients with hepatolenticular degeneration the urinary copper content averages from 100 to 1,000 micrograms per day; that is, some 4 to 25 times more copper than normal. Various tissues have been analyzed for copper level and it has been found that the level in patients with this disease is ten times greater than normal in brain, liver and Descemet’s membrane. Renal tissue also contains an increased copper concentration. Balance studies have shown that there is a definitely increased absorption of copper from the gastrointestinal tract in patients with Wilson’s disease. The mechanisms controlling gastrointestinal absorption of copper have not been worked out, but it is probably dependent upon, and inversely proportional to the serum copper level. The serum transport of copper is felt to be highly, if not exclusively, dependent upon a specific plasma protein called ceruloplasmin. Ninety per cent of serum copper is bound to this protein. In Wilson’s disease ceruloplasmin is at a low level.

In normal patients there is a relatively constant urinary output of small amounts of the amino-acids taurine, aspartic acid, isoleucine, histidine and arginine, but in patients with hepatolenticular degeneration there are persistently increased amounts of these amino-acids, plus proline, citrulline and a group of dicarboxylic peptides which are never found in normal urines. The urinary pattern is not a constant one, but rather varies from day to day, depending upon the amount and type of protein ingested and other as yet unknown factors. Significantly, there is no correlation between the degree of amino-aciduria and the severity of the hepatic disease, nor is there any elevation in the blood alpha amino-nitrogen level. The copper spillage rather appears to be related to a specific defect in renal tubular absorption, perhaps secondary to tubular injury (in the form of respiratory enzyme inhibition) produced by the elevated tubular copper level.

Copper is a powerful inhibitor of oxidative enzymes even in highly dilute solution. Lipman found that a copper concentration of 0.636 milligrams per cent inhibited glycolysis by muscle tissue. In a patient with Wilson’s disease Glazebrook found that the copper concentration in the basal ganglia was of the order of 1.28 milligrams per cent, i.e., twice the concentration necessary to produce an histotoxic anoxia and tissue necrosis.

There is then a highly distinctive biochemical picture in Wilson’s disease, characterized by a low serum copper, increased tissue copper, increased urinary copper, and amino-aciduria. This urinary picture is found only in Wilson’s disease and in the nephrotic
syndrome—a disease which is also associated with renal tubular injury.

It has been suggested that the basic defect in hepatolenticular degeneration is an inability to synthesize ceruloplasmin, as a result of which the serum is saturated with copper at a low concentration. This low concentration is responsible in some unknown manner for increased gastro-intestinal absorption of copper which is then deposited in increased amounts in the brain, liver and kidney, producing the pathologic and pathophysiologic picture of the disease by virtue of the toxic effect of the increased tissue concentration of this ion.

TREATMENT

If this pathogenetic formulation is accepted, any definitive therapeutic measures should be directed at lowering the tissue copper level or, more basically, increasing the serum ceruloplasmin. Many workers have made attempts to do this by the administration of BAL which binds copper as

\[ \text{HO} - \text{CH}_2 - \text{HCS} - \text{Cu} \]

by use of chelating agents such as versene, by the use of potassium sulfide to bind the ingested copper as copper sulfide, and by the use of high protein diets in an attempt to increase the urinary loss of copper, thus producing a negative copper balance. Crystalline ceruloplasmin is available for experimental purposes, but has not been adequately evaluated.

The results of such therapeutic measures have been difficult to evaluate with some patients showing remarkable improvement as manifested by a decrease in the Kayser-Fleischer ring, decreased tremor and rigidity. The improvement has lasted from several weeks to a year. Other patients, however, have shown little or no improvement. Considering the pathological changes in the disease, these findings are perhaps as would be expected. The true value of these therapeutic measures will become apparent only when many minimal cases have been treated, and even then it will be exceedingly difficult to evaluate the results because of the chronic and variable course of the disease. One early case has been treated by the use of the above measures for approximately four years and has shown no progression during this period.  

HEPATIC ENCEPHALOPATHY

A second particularly fruitful field of research involving the relationship between hepatic and neurological disease has been the investigation of the etiology of hepatic coma. Historically, the study extends back for 60 years to 1893, when Pavlov described a syndrome in dogs which he called “meat intoxication.” He was able to repeatedly induce a state of confusion and coma in dogs with Eck fistulas by feeding them meat. This remained an isolated observation and no further work was reported in this field until 1932, when Van Caulaert showed that the ingestion of ammonium chloride by cirrhotics produced the picture of hepatic encephalopathy. In 1934 Krauss related these two observations by demonstrating that the syndrome of meat intoxication described by Pavlov was associated with an elevated blood ammonium. He postulated that the basic defect was an inability of cirrhotics to utilize ammonium in the synthesis of urea. However, in 1936 Kirk showed that cirrhotics had no disturbance in urea synthesis and he suggested that ammonium and/or meat intoxication was the result of direct absorption of nitrogenous substances into the peripheral circulation by virtue of the circulatory shunt
around the liver in the Eck fistula animal or in the cirrhotic. For some strange reason, little further work was done until 1952, when Davidson using three patients with Laennec’s cirrhosis, was able to consistently induce encephalopathy by feeding them nitrogenous substances. Extending this work in 1954 McDermott put one patient who had a portacaval shunt on a virtual merry-go-round, inducing eight episodes of stupor by feeding the patient protein, urea, ammonium chloride and ammonium resins. In this one patient he found a consistent correlation between the clinical state and the blood ammonium level, but in his other patients he found only a suggestively positive correlation with many individual exceptions. Neurologically the patient showed confusion, clouding of consciousness, grasping and sucking reflexes, the flapping tremor that was described in connection with Wilson’s disease, and finally coma. The electroencephalographic changes consisted primarily of bilateral synchronous slow waves from the frontal areas.

The failure of many individual cases to show a positive correlation between the venous ammonium level and the clinical picture remained a mystery until late 1955, when Bessman studied the arterial ammonium concentration in a group of patients with hepatic disease. In this group of patients the arterial level was often definitely elevated while the venous level would be normal or only slightly elevated, and in one patient who was in hepatic coma, there was a definite correlation between the arterial ammonium concentration and the clinical state although the patient maintained an essentially normal venous concentration of ammonium throughout. He also showed that muscle utilizes approximately 40 per cent of the ammonium reaching it while brain tissue utilizes only 20 per cent. Since the muscle mass is far greater than the brain cell mass and since muscle utilizes twice as much ammonium, the mixed peripheral venous ammonium concentration may well be normal while cerebral venous and arterial concentrations are moderately elevated.

**PATHOGENESIS**

Muscle tissue and brain are thought to utilize ammonium by the same biochemical pathway—the Krebs cycle.
When the arterial ammonium concentration is increased, the side reaction (A) is increased with a resultant decrease in the alpha ketoglutaric acid concentration and consequent slowing of the cycle. Replacement of any of the intermediates should restore the cycle. As can be seen from the diagram, there are several potential methods by which the essential intermediates might be replaced. Brain cells, however, are impermeable to amino acids with one important exception—glutamic acid. Thus there can be no direct replacement of any of the reactants in Krebs cycle. The reaction pyruvate plus carbon dioxide to oxaloacetate can occur only in the liver and cardiac muscle because of the absence of necessary enzymes elsewhere. Thus this reaction is also not available to brain cells. Oxidative deamination of aspartic acid to oxaloacetate could theoretically occur but does not actually do so, again because of the impermeability of the brain cells to amino acids. Muscle tissue, on the other hand, can utilize all of these methods. The brain is thus extremely limited in its ability to replenish the constituents of the Krebs cycle.

Krebs in 1935 made an important and fundamental observation when he showed that in the presence of adequate amounts of glucose, brain slices can synthesize glutamine from glutamic acid and ammonium, and that this reaction occurs in a preferential fashion. This observation provides the rationale for the utilization of glutamic acid in the treatment of ammonium intoxication since, as is apparent from the diagram, glutamic serves to prevent the side reaction (A) from occurring and thus protects the Krebs cycle.

Considerable amounts of ingested nitrogenous substances are broken down in the gastrointestinal tract to yield free ammonium which is then absorbed. In a normal person this absorbed ammonium is metabolized in the liver while in patients with hepatic disease, this protective mechanism is lacking either as a result of specific liver cell failure and/or the result of collateral circulation. Sherlock attempted to define the role of impaired liver function and of collateral circulation in the production of the picture of hepatic encephalopathy. In a group of patients with viral hepatitis, the hepatic vein blood increased more after the ingestion of ammonium chloride than did the peripheral blood, suggesting that ammonium passed directly through the liver without undergoing any metabolic transformation. On the other hand, a group of advanced cirrhotics with extensive collateral circulation showed the reverse situation, that is, the peripheral blood ammonium concentration increased considerably more than did the hepatic vein concentration, suggesting that both functional impairment and circulatory shunts are important in the production of hepatic coma; the relative importance of each varying with the underlying hepatic pathology.

An interesting but as yet unexplained observation is that patients with Banti’s syndrome, who have marked collateral circulation around their livers, allegedly do not show cerebral symptoms. I have not, however, been able to find any report of blood ammonium levels in such patients.

TREATMENT

Numerous papers have appeared since Walshe’s original report of the successful treatment of four out of five episodes of hepatic coma in three patients in 1953. The results have been conflicting, and often directly contradictory, but much of the confusion may be cleared by the adoption of the classification suggested by Eiseman and McDermott who have proposed that the patients be divided into three groups accord-
ing to the mode of onset of the encephalopathy. They typify the patients as spontaneous, induced and chronic examples of encephalopathy. In the spontaneous group they include those patients who, without obvious precipitating factors, pass rapidly into hepatic encephalopathy with a rapid progression of symptoms. In the induced group they include those patients who have fallen into coma as the result of some usually obvious precipitation factor such as hemorrhage, large ingestion of protein, or ingestion of ammonium. In the chronic group they include those patients who show long standing evidences of encephalopathy without definite progression of the symptoms and without any obvious precipitating factors. In McDermott’s series of 28 patients treated with L glutamic acid the results were as follows: (11)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Fall In NH₄</th>
<th>Improved Clinically</th>
<th>Normal Clinically</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Spontaneous</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>II Induced</td>
<td>14</td>
<td>13</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>III Chronic</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

Out of the 28 cases studied, 24 showed a fall in ammonium concentration after the administration of glutamic acid, and nine of those with induced encephalopathy showed improvement clinically with five returning to a normal status. In the chronic group, seven of the eight improved clinically and six were felt to return to normal status. As can be seen, the results in the spontaneous group are poor.

The conclusions which they reached are that ammonium intoxication is a specific form of exogenous encephalopathy which is reversible within limits by glutamic acid, but that in the spontaneous, and probably in the chronic cases, there are other as yet unknown, but undoubtedly complex, chemical changes which do not respond to glutamic acid administration. Their conclusions and their classification probably best summarize the whole problem of therapy at the present time.

**SUMMARY**

Although the therapeutic benefits derived from these investigations are not as dramatic as might be desired, the results do give us some idea of the success to be expected from the continued application of biochemical methods to the study of neurological diseases which are presently of an obscure etiology.

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Hepatic Encephalopathy


