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THE ROLE OF AMMONIA INTOXICATION IN HEPATIC COMA*

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HISTORICAL BACKGROUND

THE present interest in the relationship between ammonia metabolism and hepatic coma can be traced back to Nikolai Eck[1] who first demonstrated the feasibility of diverting the portal blood in a dog to the systemic circulation by constructing a fistula between the portal vein and the inferior vena cava; this fistula has since come to bear his name and it is common usage to use this term in reference to any surgically constructed shunt between the portal and systemic circulations. These original experiments of Eck which were carried out in 1877 were important primarily because they stimulated work in Pavlov's laboratory on the physiological effects of such a shunt. In 1893 Hahn and associates[2] observed a syndrome of neurological abnormalities in these dogs and on empirical grounds related it to a high intake of meat. Since that time this syndrome has come to be known as "meat intoxication".

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Over the ensuing years, considerable work was done in an attempt to clarify the etiology of this bizarre syndrome; the intoxication was variously ascribed to many substances of bacterial or chemical origin but in none of these studies was there any definitive proof of the etiological agent.

Shortly after these observations on the occurrence of meat intoxication in the Eck fistula dog, interest arose in the metabolism of ammonia stimulated by the work of Folin and Denis.[3] Nash and Benedict[4] showed that the kidneys, instead of excreting ammonia from the total body pool contributed to its formation and demonstrated that bilateral nephrectomy caused a rise in all the nitrogenous constituents of the blood except ammonia which remained normal until death. Prompted by these previous studies, Burchi,[5] in 1927, suggested that disturbances in ammonia metabolism might account for some of the symptoms of "hepatic coma". With the increasing knowledge of the mechanisms of urea synthesis in the liver, Van Caulaert and associates,[6, 7] Kirk[8] and Gaustad[9] all described central nervous system symptoms in patients with liver disease which, they suggested, might be attributable to ammonia by-passing the liver through portal-systemic shunts.

Because of the lack of a satisfactory technique for measurement of blood ammonia, no further progress was made in this field until Conway[10] published his studies on microdiffusion analysis and offered a satisfactory method of measuring peripheral blood ammonia.

Again, however, there was a considerable lag period before this basic technique was adopted for use in clinical medicine. In 1952 Stahl and his colleagues[11, 12] in France and workers in the Thorndike Memorial Laboratories in Boston,[13, 14] demonstrated that symptoms resembling hepatic coma could be induced in patients with cirrhosis of the liver by the administration of nitrogenous material by mouth. In 1953 studies from this laboratory were completed on a patient who had a resection of the portal vein for cancer of the pancreas with an end-to-side anastomosis constructed between the superior mesenteric vein and the inferior vena cava; this patient developed a series of reversible disturbances of central nervous system function which were found to be associated with the ingestion of protein or other nitrogenous substances, were associated with a striking rise in the peripheral blood ammonia and which could be controlled by limiting the nitrogenous intake and by the administration of antibiotics by mouth.[15]

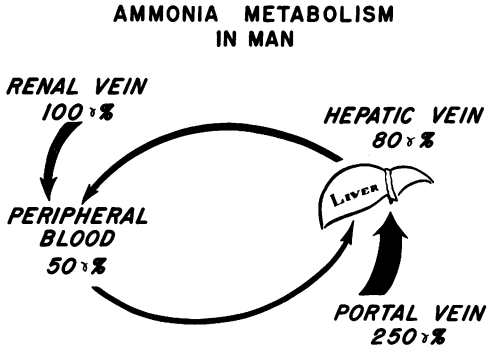

Figure 1*—A simplified diagram of ammonia metabolism in man. Published in *Annals of Surgery,* Oct. 1954 (ref. 18).

* Figures 1-4, inclusive, reprinted by permission.

Since that time there has been an increasing number of studies on this phenomenon of central nervous system symptoms associated with disease of the liver or portal circulation and, while the intricacies of ammonia metabolism in man are far from clarified, there would appear to be a very distinct relationship between the phenomenon of absorbed ammonia from the intestinal tract by-passing the liver and the occurrence of central nervous system symptoms.

The Effect of Gastrointestinal Hemorrhage in the Presence of Portal Hypertension

Figure 1 is a simplified diagram of ammonia metabolism in man based on information obtained in this hospital over the past few years. This demonstrates how spontaneously developed or surgically constructed portal-systemic shunts may lead to hyperammoniemia. It should be stressed at this time that existence of an elevated blood ammonia level is, in the main, an index of collateral circulation around the liver and not specifically a test of liver function. It is probable that an advanced degree of liver damage could so impair the normal mechanisms of urea synthesis that ammonia would accumulate and rise to abnormal levels in the blood; from observations to date however, this would appear to be a more unusual event than the hyperammoniemia associated with extensive portal systemic collaterals and an excessive nitrogen load in the intestinal tract.

This brings us to a consideration of the effect of blood in the gastro-

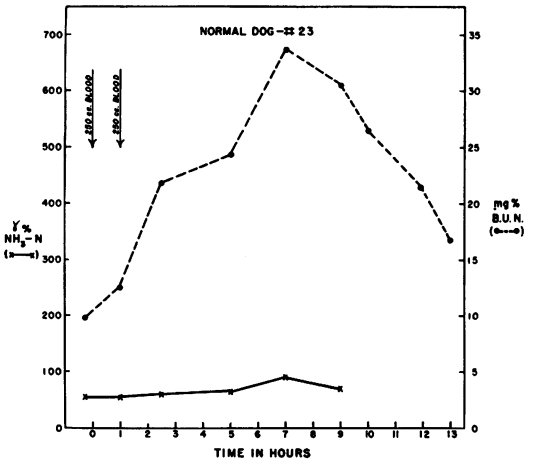

Figure 2—Effect of blood in the gastrointestinal tract of a normal dog. Published in *Annals of Surgery*, Sept. 1956 (ref. 17).

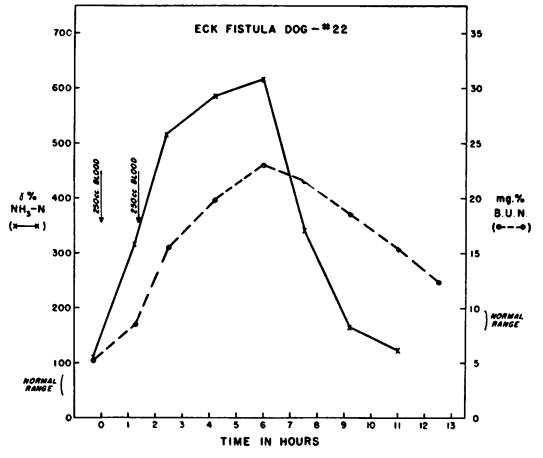

Figure 3—Effect of blood in the gastrointestinal tract of a dog with an Eck fistula. Published in *Annals of Surgery*, Sept. 1956 (ref. 17).

intestinal tract in the normal dog and in the dog with a surgically constructed Eck fistula. In Figure 2 we see the effect of the administration of blood to a dog via an inlying gastric tube. There is a distinct rise in the blood urea nitrogen, a syndrome which has been referred to as "alimentary azotemia" but the blood ammonia levels stay within the

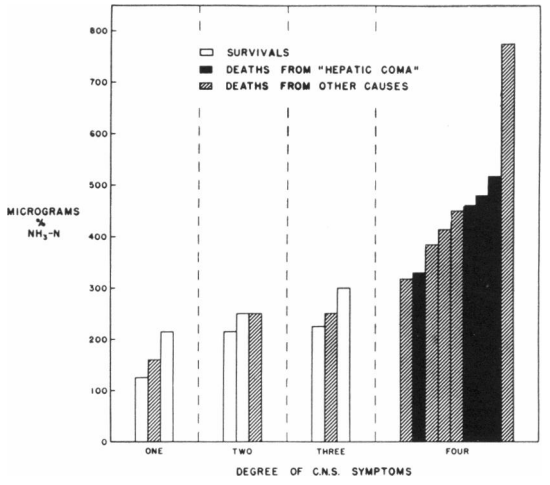

Figure 4—Effect of hemorrhage from esophageal varices on ammonia levels and clinical status. Published in *Annals of Surgery,* Sept. 1956 (ref. 17).

normal range. In the dog with an Eck fistula however, Figure 3, a striking hyperammoniemia develops and symptoms can be induced which resemble the symptoms of meat intoxication in the Eck fistula dog, a phenomenon which studies in this laboratory[16] have suggested was due to ammonia intoxication.

This experimental study bears such a striking resemblance to the situation which exists in a patient who enters the hospital with bleeding esophageal varices that a comparison is inevitable. Obviously, the existence of esophageal varices presupposes some type of portal bed block and the development of collateral circulation between an obstructed portal outflow and the systemic circulation. With these facts in mind, a series of patients with bleeding esophageal varices were studied with particular emphasis on disorders of ammonia metabolism.[17] In Figure 4 we see the correlation between blood ammonia levels in patients with acutely bleeding esophageal varices and the degree of disorder of the central nervous system. It should be stressed at this point that these symptoms are not related to "shock" or to any consistent degree of derangement of liver function. In other words this is primarily an absorptive phenomenon. If this phenomenon of "ammonia intoxication" exists as a clinical entity, where and how does this hyperammoniemia exert its untoward effect? It has been suggested[18, 19] that ammonia may

combine with alpha keto-glutarate and thus interrupt the citric acid cycle; in turn this would effectively interrupt the normal pathways of aerobic glycolysis on which the central nervous system depends so much for its normal metabolic activity. Proof of this hypothesis is extremely difficult to obtain and much of the evidence in favor of this thesis depends upon indirect evidence. We know that "hepatic coma" is almost invariably associated with elevations of the blood pyruvate and lactate,[20] that glutamine[21] is elevated in the cerebrospinal fluid and that cerebral oxygenation is decreased in patients with hepatic coma.[22] Weil-Malherbe[23] has reviewed the evidence which pointed towards an important role of L-glutamic acid in the maintenance of normal central nervous system physiology because of its ammonia binding capacity. With this in mind and because of the known importance of glutamic acid in carbohydrate metabolism, Walshe[24] suggested the use of glutamic acid in the treatment of "hepatic coma" and reported good results in five episodes occurring in three patients. The value of glutamic acid as a clinical tool has been the subject of controversy in the subsequent years; it is apparent that glutamic acid is no panacea in the treatment of this severe metabolic derangement nor should it be expected that the administration of one amino acid could effectively restore all patients with multiple gross derangements of metabolism to a normal status. Nonetheless, it is apparent that glutamic acid does have an ammonia binding capacity in man,[25, 26] and that it undoubtedly is a useful adjunct in the treatment of patients with "ammonia intoxication".

Another amino acid has more recently come to prominence in relation to this metabolic derangement. Greenstein and associates[27] reported that administration of arginine protected rats from ammonia intoxication induced by the administration of large amounts of other amino acids. These experimental observations were tested clinically by Najarian and Harper[28] and have since been utilized in other centers[29, 30]. Again, it would appear that arginine has a very definite effect on hyperammoniemia and probably contributes to the correction of at least one of the abnormalities associated with "hepatic coma". Again, however, it should not be expected that this will prove to be a universal panacea nor should it be expected that any one administered substance could effectively reverse all the derangements associated with abnormalities of the liver and portal circulation.

Conclusion

At the present time we cannot give a single answer to the complex biochemical changes associated with the clinical syndrome of "hepatic coma". In its simplest manifestation this syndrome appears in a patient with a well compensated or normal liver who has spontaneously developed or surgically constructed shunts between the portal and systemic circulations, and has a nitrogenous load introduced into the gastrointestinal tract. This particular set of circumstances probably represents ammonia intoxication since it is not dependent on severe liver damage and the syndrome should be reversible. We can at least outline a logical course of therapy based on the information that is available.

This plan of therapy can be summarized as follows:

1. Withdraw "nitrogen" or in the case with a patient with bleeding esophageal varices, make an early and vigorous effort to control the bleeding.
2. Immediate use of cathartics and enemas to eliminate the pool of nitrogenous material in the gastrointestinal tract.
3. Oral administration of broad-spectrum antibiotics in order to eliminate as much as possible the bacterial flora of the intestinal tract which are the source of the enzymes which form ammonia from ingested "nitrogen".
4. Parenteral administration of glutamic acid because of its known ammonia binding capacity.
5. The administration of arginine because of its apparent effect in lowering the blood ammonia and increasing the blood urea nitrogen.

As stated above it would appear that there is a specific syndrome of ammonia intoxication with a consistent biochemical and clinical pattern. This however, refers primarily to the syndrome which we have described as "exogenous hepatic coma". In the patients with "spontaneous hepatic coma" in whom no specific precipitating nitrogenous factor can be incriminated and in whom there is extensive liver damage, the pattern of the disordered ammonia metabolism as reflected in the peripheral venous blood is far from consistent and is not related in degree to the depth of the "coma". This inconsistency has been recognized by many investigators and a number of possible explanations have been offered. Studies on arterial venous differences in ammonia levels, and on the cerebral and peripheral uptake in release of ammonia[31, 32] have

been extremely interesting and contributed to our understanding of the puzzling patterns which occur in the presence of decompensating liver function. A recent very intriguing concept has been offered by Jacquez and by Lawrence and their associates[33, 34] working in Randall's laboratory. These investigators have pointed out the importance of acid-base balance and have utilized the concept of pNH_3 in the transport of ammonia across the cell membrane. We do not as yet know exactly what we are measuring when we refer to the total "ammonia" content of blood as either measured by Conway[10] or Seligson[35] techniques. We are faced with the difficulties of interpreting what is going on in the cell from measurements of circulating blood; we do not understand the factors controlling the transport of ammonia across the cell membrane; we have no satisfactory tools as yet for measuring the normal intracellular mechanisms of protection against abnormal concentrations of ammonia nor have we anything but indirect evidence to point out how ammonia can be toxic to the cell.

Perhaps it might be well to close at this point with a quotation from Thurber's "Fables For Our Times",—"it is better to know some of the questions than all of the answers".

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