Bleeding Esophageal Varices

A Study of the Cause of the Associated "Hepatic Coma" *

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IT HAS LONG BEEN a clinical aphorism that patients with hepatic disease do not tolerate hemorrhage well. Presumably this has been based on the common observation that bleeding esophageal varices is one of the recognized factors in precipitating "hepatic coma."

The exact mechanism of the series of events which so commonly attend bleeding from esophageal varices has never been well clarified, although the role of the liver in shock has been the subject of great interest and extensive investigations for many years. The problem is too complex and controversial to review in detail in this report. Obviously a decrease in effective blood flow to the liver may result in varying degrees of temporary hepatocellular dysfunction and long-standing anoxia may result in cellular death in the liver as elsewhere. However, studies on the effect of experimentally produced massive hemorrhage on hepatic function in normal dogs showed that a definite but only relatively slight impairment of hepatic function was produced by massive acute hemorrhage.[13] Frank [7] has studied in some detail the various effects of shock on the liver and concluded that "the development of overt hepatic insufficiency as a consequence of shock and its persistence as the cause of death after recovery from shock must be a rare clinical experience." It would seem therefore unlikely that permanent hepatocellular damage alone would account for the frequency of the occurrence of "hepatic coma" in patients with bleeding esophageal varices.

The problems attendant upon bleeding esophageal varices are in the process of review at this hospital.[1] One aspect of these data is particularly pertinent to the problems which have been studied in this paper. During one ten-year period there were 118 patients who had portal hypertension and who entered the Massachusetts General Hospital with massive gastro-intestinal bleeding: the total number of episodes was 179. In this group there were 68 deaths and it is of interest to evaluate, if possible, the cause of death. In only 18 of the patients who died could the death be directly attributable to exsanguination. Twelve patients died of causes not related directly to hepatic function. The particular fact which is relevant to the studies reported herein is that 38 patients died in coma without having demonstrated at anytime a severe degree of shock or evidence of uncontrollable and exsanguinating hemorrhage. This again points out the fact that blood loss alone does not account for the high mortality in this disease and that it seems very unlikely that permanent hepato-

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TABLE I. *Normal Dogs. The effects of blood in the gastro intestinal tract*

Amount of Blood (divided doses at hourly intervals)	NH_3-N Levels (γ %)					B.U.N. Levels (mg. %)					Comment
	Initial	Peak	Time Hours	Final	Time Hours	Initial	Peak	Time Hours	Final	Time Hours	
500 ml. (2 doses)	45	100	2	65	3.5	9.5	39	5	39	5	Normal dog
500 ml. (2 doses)	60	160	3	65	10	9	40.7	6	21	13	Normal dog
500 ml. (2 doses)	55	90	7	70	9	9.8	33.8	7	19.2	13	Normal dog (see Fig. 1).

cellular damage could account for these deaths in so-called "hepatic coma."

This leads to consideration of another factor involved in portal hypertension which has been assuming increasing prominence in recent years. This is the role which absorbed substances from the gastro-intestinal tract, circumventing the liver through spontaneously developed portal systemic shunts, may play in the development of the syndrome of so-called "hepatic coma." The phenomenon of absorption of nitrogenous materials from the gastro-intestinal tract in the presence of gastro-intestinal hemorrhage which was described in 1934 by Sanguinetti,[21] has been studied extensively by Harkins and his associates.[2, 3, 11, 12] These investigators defined and studied the entity of so-called "alimentary azotemia" which is now a well-recognized accompaniment of massive gastro-intestinal bleeding from any source. In a normal individual this absorptive phenomenon results in an innocuous azotemia but in a patient who has a portal-bed block and has developed spontaneous portal-systemic shunts around the liver, the absorption of nitrogenous materials from the gastro-intestinal tract may have serious consequences. The syndrome of intolerance to nitrogenous materials introduced into the gastro-intestinal tract of a patient with cirrhosis of the liver has been described by Davidson and his colleagues [9, 17] in this country and by Stahl and his associates [20, 22] in France. Studies from this laboratory have described this phenomenon in a patient with a surgically constructed Eck fistula in the presence of a normal liver and have related the ensuing central nervous system symptoms to toxic levels of ammonia in the peripheral blood.[14] Similar studies carried out on dogs with Eck fistulas have demonstrated that "meat intoxication" in the Eck fistula dog which was initially described by Pavlov [10] in 1883 is in fact ammonia intoxication.[18] Subsequent studies from this hospital have shown that ammonia intoxication is far from a rare clinical entity and may occur in patients with either surgically constructed portal-systemic shunts or in patients in whom a portal-bed block has led to the development of spontaneous portal systemic collaterals.[19, 15, 16] In a number of these patients the precipitating factor in the development of ammonia intoxication has been the sudden massive hemorrhage from esophageal varices so commonly seen in patients with portal-bed block.

It is the purpose of this communication to report a series of experimental and clinical studies designed to clarify the role of massive gastro-intestinal hemorrhage in precipitating so-called "hepatic coma."

PART I—EXPERIMENTAL

Methods: Ten experiments were carried out on five healthy adult mongrel dogs in whom Eck fistulas had been constructed from one to 20 months prior to the experiments.

Normal adult mongrel dogs on which three experiments were done were used as controls.

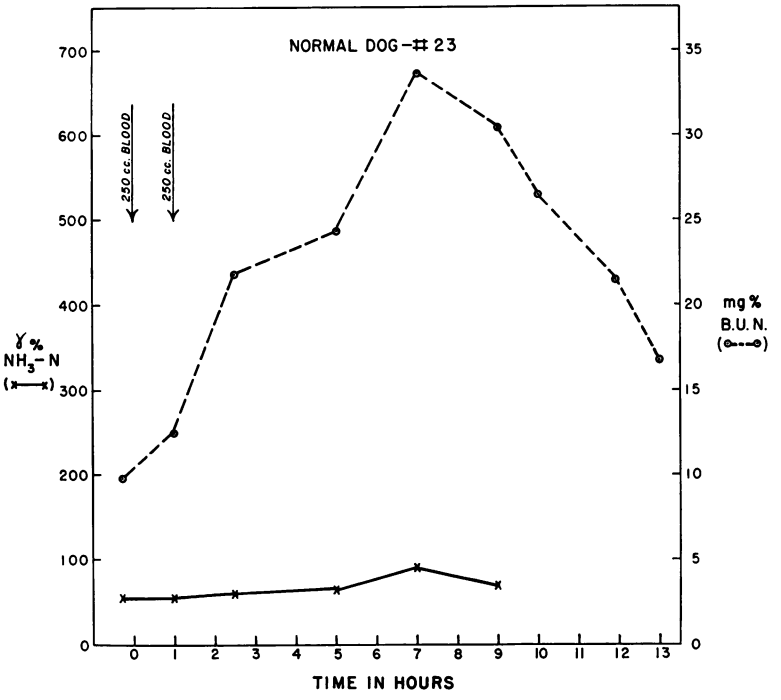

FIG. 1. Normal dog. The biochemical effects of blood in the gastro-intestinal tract.

Normal animals were given the standard meat feedings of the animal farm. The dogs with Eck fistulas were fed on a diet of milk and meal which had been regulated over the past three years in such a way that "meat intoxication" would not develop. In all but one instance, the dogs were fasted for 24 hours prior to the experiment.

The blood which was introduced into the gastro-intestinal tracts of the animals was drawn from lots which had been discarded for any one of a number of reasons by the blood bank of the Massachusetts General Hospital. The blood was introduced into the gastro-intestinal tract by an inlying gastric tube.

During experiments on these animals blood ammonia levels and blood urea nitrogen levels were determined at hourly intervals until both had returned to near the initial values or, in one case, until the experiment was concluded by the death of the animal.

Both the ammonia and blood urea concentrations were determined on peripheral venous blood. The ammonia determinations were done by a previously reported modification [14] of the microdiffusion technic described by Conway [5] and the blood urea nitrogen by a similar technic also described by Conway [4] in which the blood is mixed with urease prior to diffusion.

Results: Results of these experiments are shown in Tables I and II and in Figures 1 to 4.

In the normal dog there was a sharp rise in the blood urea nitrogen following the introduction of blood into the gastro-intestinal tract (Table I), (Fig. 1); these results were quite consistent with the studies done by Harkins and his associates in their investigations on the syndrome of alimentary azotemia.[2, 3, 11, 12] In these animals however there was no appreciable change in the blood ammonia levels during the course of the experiments.

The Eck fistula animal showed a distinctly different response following the in-

TABLE II. *Eck Fistula Dogs. The effects of blood in the gastro intestinal tract*

Dog No.	Experiment No.	Amount of Blood (divided doses at hourly intervals)	NH_3-N Levels (γ %)					B.U.N. Levels (mg. %)					Comment
			Initial	Peak	Time Hours	Final	Time Hours	Initial	Peak	Time Hours	Final	Time Hours	
19	3	500 ml. (3 doses)	130	675	3.5	190	9						Neurological symptoms (ataxia, lethargy) occurred in 6 hours and lasted 3 hours.
19	2	500 ml. (2 doses)	150	515	2	245	8						No symptoms.
19	1	250 ml. (1 dose)	180	600	2	225	8.5	5.5	13.3	2	10.7	8.5	No symptoms.
19	4	200 ml. (1 dose)	150	550	3	380	5.5	7	11.5	3	10.5	5.5	Experiment designed to demonstrate the effect of L-glutamic acid on NH_3 levels. (See Fig. 4.)
20	1	500 ml. packed red cells (2 doses)	165	867	2	260	9	5.4	17.9	3.5	11	9	Transient lethargy.
20	2	200 ml. (1 dose)	260	675	2	390	8	8.7	21.5	4	17.1	8	No symptoms. fasting.
21	1	500 ml. (2 doses)	100	515	3.5	150	5.5	7.4	29	5.5	29	5.5	No symptoms.
21	2	2700 ml. (8 doses)	85	298	2	240	9.5	9.2	29	6	21.3	9.5	No symptoms. Vomited after each dose of blood.
22	1	500 ml. (2 doses)	110	615	6	120	11.5	5.3	23	6	12.4	13	No symptoms. (See Fig. 2.)
29	1	3350 ml. (9 doses)	140	1190	31	1190	31	7	42.5	31	42.5	31	Dog died in coma. (See Fig. 3.)

troduction of blood into the gastro-intestinal tract. There was a consistent and distinct rise in the blood urea nitrogen although this was considerably less than in the normal animals; again this reproduces the results described by Harkins *et al.*[12] The significant part of these experiments was demonstrated in the blood ammonia levels in the Eck fistula dogs which, in contrast to the normal animals, showed elevations to a range between 400 and 900 micrograms per cent, depending to some extent on the amount of blood which had been introduced (Table II), (Fig. 2). In the initial experiments these elevations, while striking, were not high enough or sustained enough to induce the central nervous system symptoms which had been produced by forced-feeding of meat in studying the syndrome of "meat intoxication." Therefore it was decided to increase the amount of blood in order to ascertain if a syndrome similar to "meat intoxication" could be produced. In dog number 19 a total amount of blood of 500 ml. was given via the gastric tube in three doses; this was sufficient to produce a level of 675 micrograms per cent of ammonia nitrogen and was accompanied by the typical symptoms of "meat intoxication" which in this case consisted of ataxia, amaurosis and lethargy which lasted about three hours. In dog 21 the amount of blood given was pushed to a total of 2700 ml. given in eight divided doses; this experiment was unsatisfactory, however, inasmuch as the dog vomited after each attempt to introduce blood and never developed central nervous system symptoms and never reached an ammonia level higher than 298 micrograms per cent. In Dog No. 29 however, a total of 3,350 ml. of blood was given in ten doses over a period of 32 hours. The results of this experiment are shown in detail in Figure 3 and demonstrate quite clearly that not only can severe central nervous system symptoms be induced by the introduction of blood into the gastro-intestinal tract but that death can

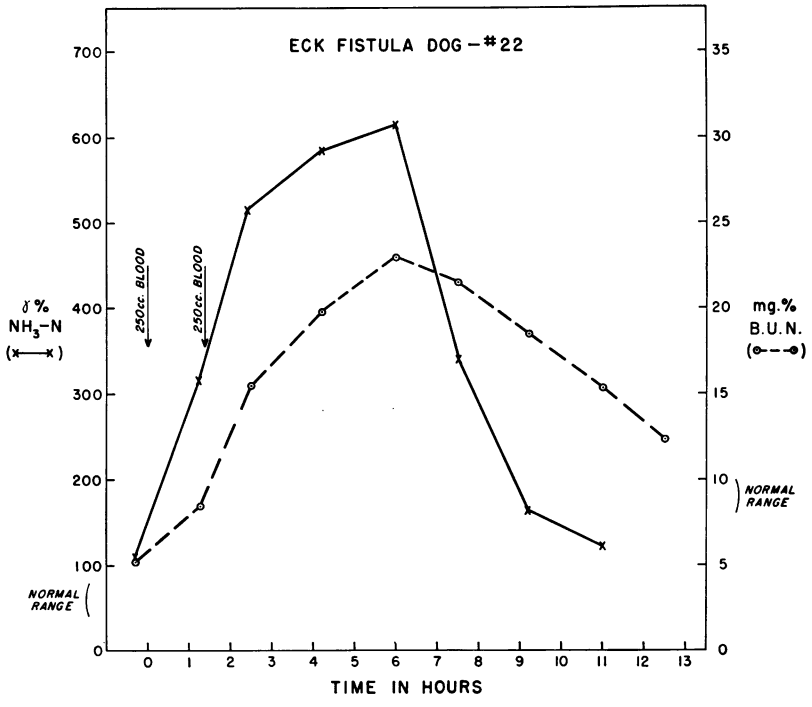

FIG. 2. Eck fistula dog. The biochemical effects of blood in the gastro-intestinal tract.

eventuate from this type of nitrogenous pool in the presence of an Eck fistula. At the time of death the blood ammonia level had reached almost 1,200 micrograms per cent. This experiment was carried to its ultimate conclusion because it was felt important to demonstrate that not only neurological symptoms and coma but actual death could result from nothing more than the introduction of blood into the gastro-intestinal tract in an animal who is in otherwise good condition except for the presence of a previously constructed Eck fistula. In the fourth experiment on Dog No. 19, 5 Gm. of sodium glutamate were given paenterally during the phase of absorption of blood when the blood ammonia level was rising. There was a sharp fall in the blood ammonia level followed by a rise again when the parenteral glutamate was discontinued (Fig. 4).

The implications of these experiments will be discussed in connection with the results of clinical studies on patients with bleeding esophageal varices.

PART II—CLINICAL

Methods: Studies were carried out on 18 patients who entered the Massachusetts General Hospital during the years 1953, 1954 and 1955 with severe bleeding from esophageal varices and varying degrees of disturbance in the function of the central nervous system. This group does not represent the total experience over this period of time nor was there any common denominator for selection. Obviously in a random study such as this there is no rationale for attempting a controlled series so that the present study consists solely of observations of certain clinical and biochemical changes which occur in patients with bleeding esophageal varices and attendant central nervous system symptoms.

In those 18 patients who had bleeding esophageal varices and concomitant central

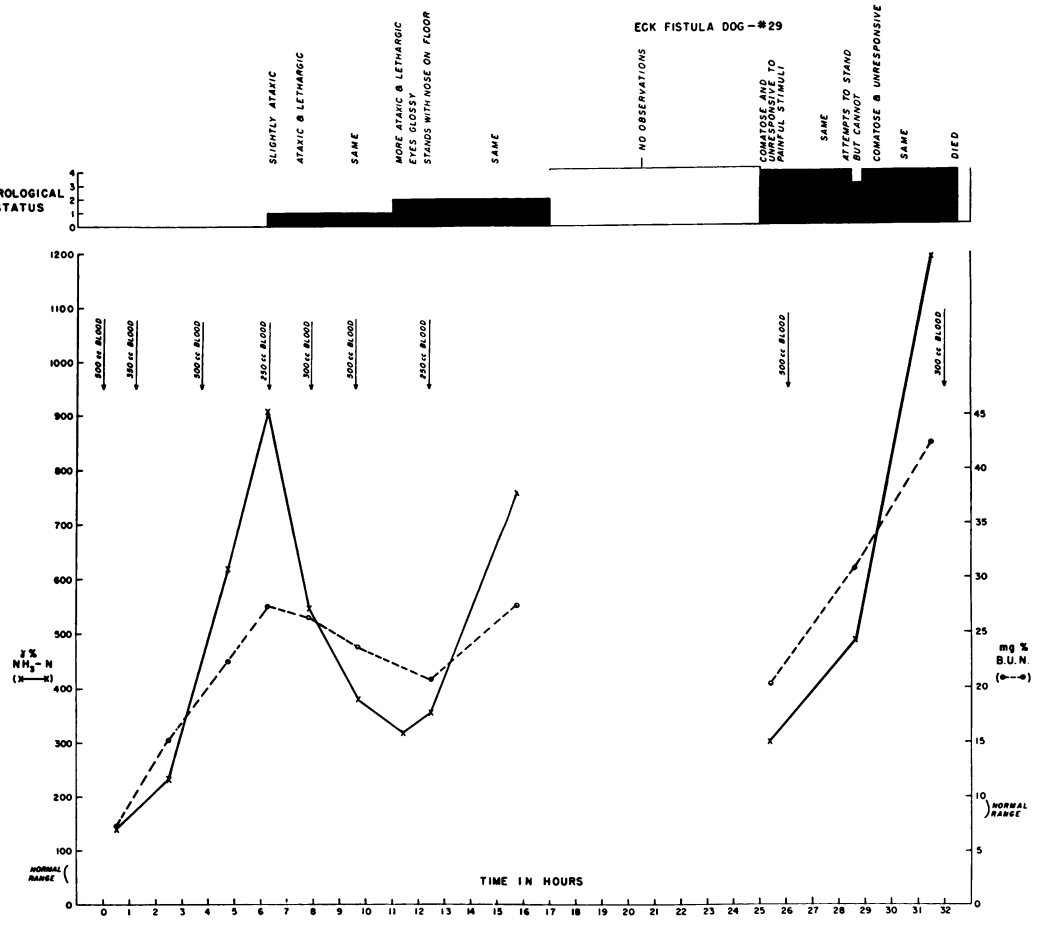

FIG. 3. Eck fistula dog. The effect of large amounts of blood in the gastro-intestinal tract in inducing ammonia intoxication, coma and death.

nervous system symptoms the degree of neurological abnormality was graded according to a previously described system [14] in which one represents mild confusion and disorientation, two and three represent increasing degrees of abnormality, up to category four which comprises deep coma.

Determinations of blood ammonia levels in peripheral venous blood were done by a previously reported modification [14] of the microdiffusion technic described by Conway.[5]

Results: A tabulated summary of the significant clinical and biochemical observations in these 18 patients is given in Table III. This table represents a summation of the entire study and will have to be broken down further in order to point out the significance of the observations.

In Figure 5 a diagrammatic correlation is made between the highest level of blood ammonia nitrogen observed in each individual patient and the degree of neurological abnormality observed clinically. Also in this figure the survivors and deaths have been represented and in addition, the patients who died have been described as dying either from "hepatic coma" or from some other cause. Further explanation of this distinction is in order. When a patient is classified as dying from "hepatic coma" it is meant that there was no other demonstrable cause of death beyond the deep coma attendant upon the bleeding from

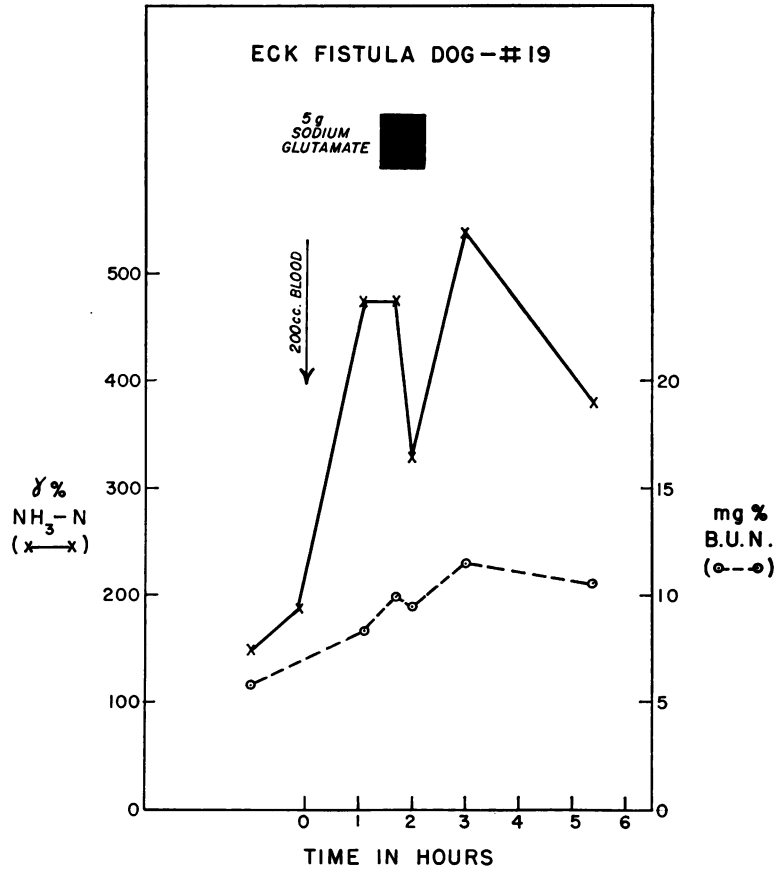

FIG. 4. Eck fistula dog. The effect of L-glutamic acid on the biochemical changes induced by blood in the gastro-intestinal tract.

esophageal varices. If there is any other obvious cause of death such as exsanguination from uncontrollable hemorrhage or some postoperative complication the patient was classified as dying from a cause other than "hepatic coma." In the group of 12 patients who died following or during the hemorrhage from esophageal varices four died with no cause of death other than "hepatic coma." Three patients died because of uncontrollable exsanguinating hemorrhage. Three patients died as the result of complications attributable to operations designed to control the massive gastro-intestinal bleeding. In the remaining two patients who died, autopsy showed that mesenteric thrombosis was the actual direct cause of death.

In Figure 5 it is interesting to note the very good correlation between the degree of central nervous systems observed in these patients and the blood ammonia level. It is also significant that all four patients who died of "hepatic coma" had ammonia levels of well over 300 micrograms per cent. It is probably also of significance that all the patients who had levels of over 300 micrograms per cent and were classified as category four in the degree of central nervous system symptoms died during their hospital admission. While the authors have classified "hepatic coma" as the cause of death in only four of the patients in this particular block, nonetheless a careful study of Table III will show that the syndrome of "hepatic coma" was undoubtedly a con-

TABLE III. *A Detailed Summary of the 18 Patients Included in the Clinical Section of This Report*

Case No.	Patient	Unit No.	Diagnosis	Highest NH_3 Level γ %	Operation	L-glutamic Acid	Outcome	Comment
1	I. K. (1953)	811106	Alcoholic cirrhosis	331			Died in coma	No evidence of "shock" prior to death. (Fig. 6.)
2	H. P. (1953)	817385	Alcoholic cirrhosis	214	Ligation of esophageal varices		Recovered	Stupor improved rapidly after bleeding was controlled and NH_3 level returned to normal. (Fig. 7.)
3	S. T. (1953)	828879	Alcoholic cirrhosis	518		75 Gm. in 48 hours	Died in coma	Bleeding controlled by Sengstaken tube. NH_3 level fell rapidly following glutamate infusions but patient never recovered from the deep coma. (Fig. 8.)
4	L. D. (1953)	808056	Alcoholic cirrhosis	485			Recovered	Entered in coma but not in shock. Recovered slowly when bleeding was controlled by balloon tamponade. (Fig. 9.)
5	H. O'M. (1954)	836803	Alcoholic cirrhosis	318	1. Ligation of esophageal varices 2. "Tanner" operation	50 Gm. in 36 hours	Died	Temporary improvement but became hypotensive, febrile and died. Autopsy—mesenteric thrombosis and infarction.
6	M. L. (1953)	118741	Polycythemia vera and portal hypertension	250	Ligation of esophageal varices (6 months prior to death)	25 Gm. in 24 hours	Died	Lapsed into coma shortly after a recurrent hematemesis. Actual cause of death was mesenteric thrombosis.
7	N. F. (1953)	752426	Alcoholic cirrhosis	412	Ligation of esophageal varices		Recovered (Died later)	Entered in coma. After control of bleeding, neurologic symptoms disappeared. Died later of unrelated cause.
8	W. M. (1954)	672743	Alcoholic cirrhosis	240	Ligation of esophageal varices	150 Gm. in 5 days	Recovered (Died later)	In deep stupor following bleeding from varices. Recovered following ligation but died later with empyema and overwhelming sepsis.

TABLE III. *Continued*

Case No.	Patient	Unit No.	Diagnosis	Highest NH_3 Level γ%	Operation	L-glutamic Acid	Outcome	Comment
9	C. M. (1954)	774789	Alcoholic cirrhosis	300		25 Gm. started	Died	Went into coma following bleeding from varices. Vomited, aspirated and died during attempt at balloon tamponade.
10	J. L. (1953)	825343	Alcoholic cirrhosis	478		75 Gm. in 3 days	Died	Temporary improvement after each glutamate infusion but died in coma.
11	M. M. (1953)	823575	Alcoholic cirrhosis	252	Ligation of esophageal varices	75 Gm. in 3 days	Recovered (Died later)	Recovered from coma but died later of other causes. (Fig. 10.)
12	M. McG. (1954)	741652	Alcoholic cirrhosis	225		100 Gm. in 4 days	Recovered	In deep stupor following bleeding from varices. Recovered when bleeding was controlled and glutamate therapy given.
13	H. J. (1954)	857528	Alcoholic cirrhosis	216			Recovered	Mildly confused after transient hemorrhage.
14	C. G. (1954)	845239	Alcoholic cirrhosis	124	Ligation of esophageal varices		Recovered	Drowsiness and mild confusion improved rapidly postoperatively.
15	N. S. (1954)	180376	Alcoholic cirrhosis	251	Sigmoid resection	50 Gm. in 48 hours	Recovered	In stupor following operation for bleeding sigmoidal varices but improved rapidly during glutamate therapy.
16	C. O. (1953)	795439	Alcoholic cirrhosis	158	Ligation of esophageal varices		Died	Mild neurologic symptoms disappeared following operation but patient died later of severe bronchopneumonia and pulmonary edema.
17	E. B.	768591	Alcoholic cirrhosis	773		75 Gm. in 48 hours	Died of exsanguinating hemorrhage	Patient brought in with bleeding esophageal varices and lapsed into deep coma. Bleeding controlled by balloon tamponade and NH_3 level fell after glutamic acid therapy. Patient improved steadily for days and then died suddenly of exsanguinating hemorrhage. (Fig. 11.)
18	J. F.	336787	Portal cirrhosis	451	Transthoracic ligation of esophageal varices		Died in coma	Bleeding could not be controlled by balloon tamponade so operation was done despite comatose state.

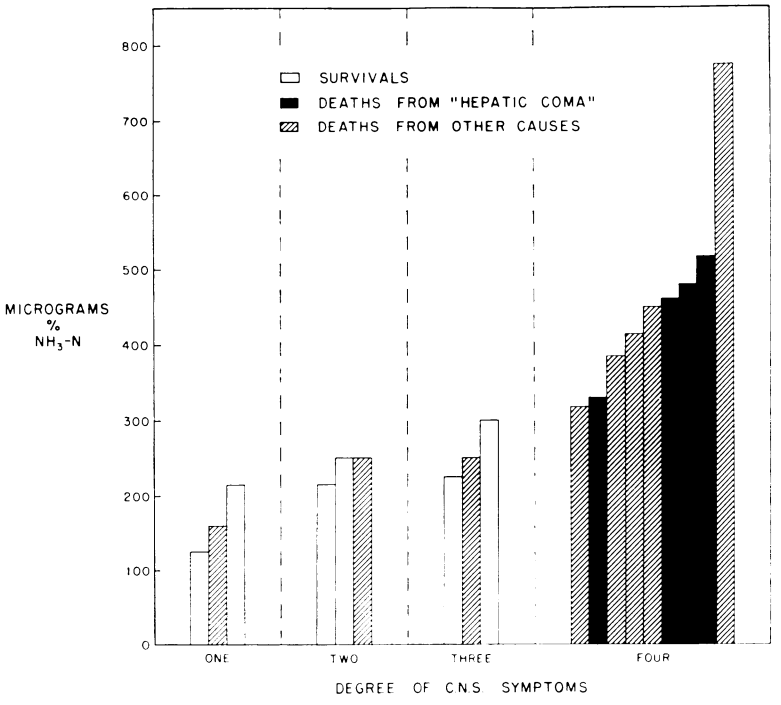

FIG. 5. Diagrammatic correlation of ammonia levels, central nervous system symptoms and mortality in 18 patients with bleeding esophageal varices.

tributing cause in many of the other deaths. The six patients who survived out of the 18 studied, all demonstrated less severe degrees of central nervous system abnormality and all of them had maximum ammonia levels under 300 micrograms.

Perhaps the implications of this particular study can be best demonstrated by the following abbreviated case histories and accompanying diagrammatic figures of their hospital course, neurologic abnormalities, and associated biochemical changes.

CASE REPORTS

Case 1. (Admitted on September 23, 1953 and died on October 10, 1953.) The patient (I. K.—Unit No. 811106) was a 47-year-old male with known cirrhosis of the liver who entered the hospital because of hematemesis. Balloon tamponade was instituted and the bleeding was controlled, but the patient became increasingly drowsy and lapsed into deep coma. The tube was deflated after 48 hours and there appeared to be some slight improvement, but further hemorrhage occurred and despite control of the bleeding with balloon tamponade the patient again lapsed into deep coma. The blood ammonia level reached 331 gamma per cent and the patient died (Fig. 6). Autopsy revealed severe portal cirrhosis, esophageal varices with ulceration and hemorrhage and multiple pulmonary emboli.

Comment: It is interesting that at no time did this patient show evidence of exsanguinating hemorrhage but he nonetheless lapsed into deep coma and died despite the fact that the hemorrhage was adequately controlled.

Case 2. (Admitted on July 6, 1953 and discharged on July 28, 1953.) The patient (H. P.—Unit No. 817385) entered the hospital because of hematemesis and melena in the 24 hours prior to admission. Fifteen years before admission the diagnosis of cirrhosis of the liver had been established. On the day following admission transthoracic ligation of esophageal varices was carried out because gastro-intestinal bleeding continued. Just prior to operation his mental status was described as impaired and following operation he lapsed into a deep stupor with an elevation of the ammonia level to 214 micrograms per cent. With no further treatment beyond control of hemorrhage, the ammonia level fell rapidly to normal and the patient concomitantly recovered from the

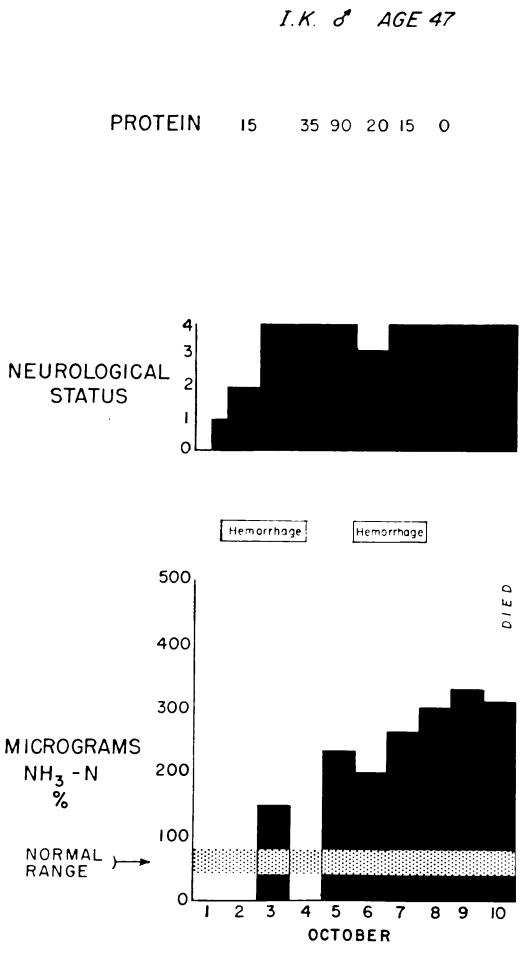

FIG. 6. Alcoholic cirrhosis with bleeding esophageal varices. (Case #1—I. K.)

stupor and was discharged after an uneventful convalescence (Fig. 7).

Comment: This case represents mild ammonia intoxication which spontaneously cleared when bleeding was controlled.

Case 3. (Admitted on October 25, 1953 and died on October 27, 1953.) The patient (S. T.—Unit No. 828879) was a 47-year-old female with known alcoholic cirrhosis. In the evening before admission she vomited a "pint of blood" and in the morning her husband noticed that she was drowsy and arranged for hospital admission. In the succeeding 6 hours she became increasingly drowsy, then maniacal, and finally lapsed into deep coma. On admission the ammonia was 518 micrograms per cent. Bleeding was easily controlled by means of balloon tamponade, but despite this, patient remained in deep coma until death which occurred about 48 hours after admission (Fig. 8).

Comment: It is interesting to note that the use of L-glutamic acid as a sodium salt was associated with a rapid fall in ammonia levels. The fact that there was no clinical improvement and that death ensued very shortly after admission suggests that this syndrome of ammonia intoxication may be irreversible despite control of the peripheral blood levels.

Case 4. (Admitted on April 16, 1953, and discharged on May 2, 1953. The patient (L. D.—Unit No. 808056) was a 42-year-old male who was known to be a chronic alcoholic. Twenty-four hours prior to admission he passed a stool containing gross blood and had been found in coma by a relative 6 hours before admission. On admission to the hospital he was unresponsive to all but extremely painful stimuli. There was evidence of continued slow bleeding which was controlled by balloon tamponade. Ammonia level of admission was 485 gamma per cent. Very shortly after the bleeding was controlled and the ammonia level returned almost to normal levels and this was attended by a slower but steady improvement in his mental status. When he was able to take oral feedings, a high protein intake was instituted but ammonia level rose again and was attended by a deterioration of his mental status. When protein feedings were withdrawn and then re-instituted on a restricted level of 50 Gm. daily, his mental status returned to normal and he was discharged after an uneventful convalescence (Fig. 9).

Comment: This case illustrates the fact that any nitrogenous pool in the gastro-intestinal tract whether it is blood or a high protein intake may induce the syndrome of ammonia intoxication.

Case 11. (Admitted on September 7, 1953 and died on September 19, 1953). The patient (M. M.—Unit No. 823575) was a 52-year-old female who had recovered uneventfully from an attack of infectious hepatitis 2 years prior to admission. One year thereafter she had a transient episode of gastro-intestinal bleeding when she vomited blood and passed tarry stools but did not seek medical aid. Two days before admission she vomited a large amount of blood and balloon tamponade was instituted at an outside hospital. She was then transferred to the Massachusetts General Hospital at which time she was in a stuporous state responding only to painful stimuli. Blood ammonia level on entry was 252 micrograms per cent. Treatment with parenteral sodium glutamate was started and the ammonia level fell rapidly to near normal. The patient's mental status improved over the following four days and the gastric and esophageal balloons were deflated. Further hemorrhage occurred so immediate transthoracic ligation of esophageal varices was carried out. The patient died subsequently of

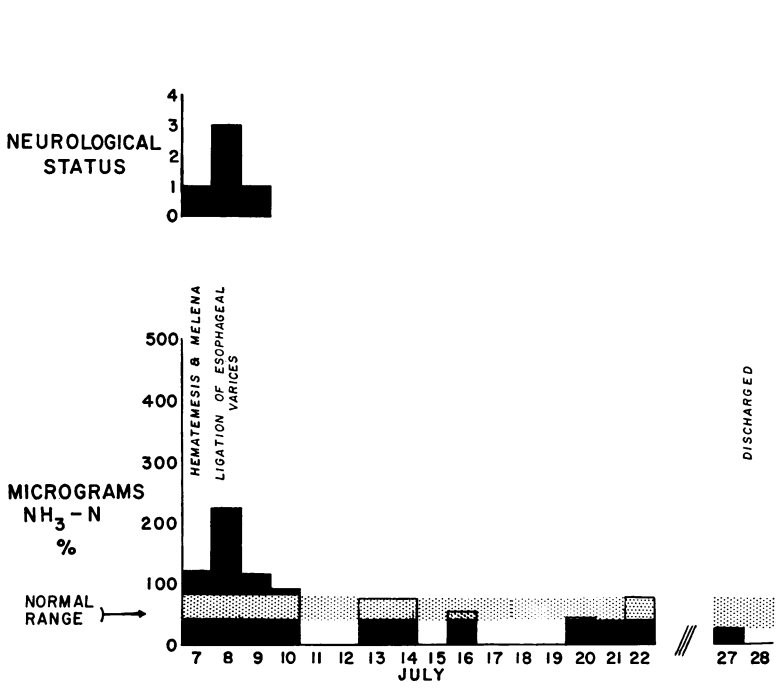

FIG. 7. Alcoholic cirrhosis with bleeding esophageal varices. (Case #2—H. P.)

a postoperative complication unrelated to the present problem (Fig. 10).

Comment: This is another example of ammonia intoxication which occurred after gastro-intestinal bleeding from esophageal varices and which improved rapidly when the bleeding was controlled. It also was interesting to note that because of the early surgical attack on the second episode of gastro-intestinal hemorrhage there was no appreciable elevation of blood ammonia and no severe deterioration in mental status.

Case 17. (Admitted on March 18, 1954 and died on March 25, 1954.) The patient (E. B.—Unit No. 768591) was a 73-year-old female who entered because of hematemesis. There was no history of alcoholism but hepatosplenomegaly and the typical clinical and laboratory findings of cirrhosis were discovered. Because of continued bleeding, balloon tamponade was instituted but the patient lapsed rapidly into deep coma. Ammonia level was recorded at 654 micrograms per cent and treatment with sodium glutamate was started. With 24 hours the ammonia levels had fallen dramatically and from this point on there was continued slow but steady improvement in her mental status so that she became increasingly responsive although she never returned to normal. Esophageal and gastric balloons were deflated and tube feedings started. On the eighth hospital day however the patient had a sudden massive exsanguinating upper gastro-intestinal hemorrhage and expired within an hour.

Comment: It was interesting that all the attending physicians felt that this woman was in terminal coma but that steady improvement occurred when bleeding was controlled and ammonia levels had returned to near normal levels, perhaps influenced by the treatment with sodium glutamate. Death occurred rapidly after the second hemorrhage and on this occasion was attributed to exsanguination.

DISCUSSION

In the clinical and experimental studies reported, evidence has been presented which indicates that, in the presence of spontaneous or surgically constructed portal-systemic shunts, the introduction of blood into the gastro-intestinal tract is accompanied by striking elevations in the level of peripheral blood ammonia. If the elevations in blood ammonia are sufficiently high, central nervous system symptoms ap-

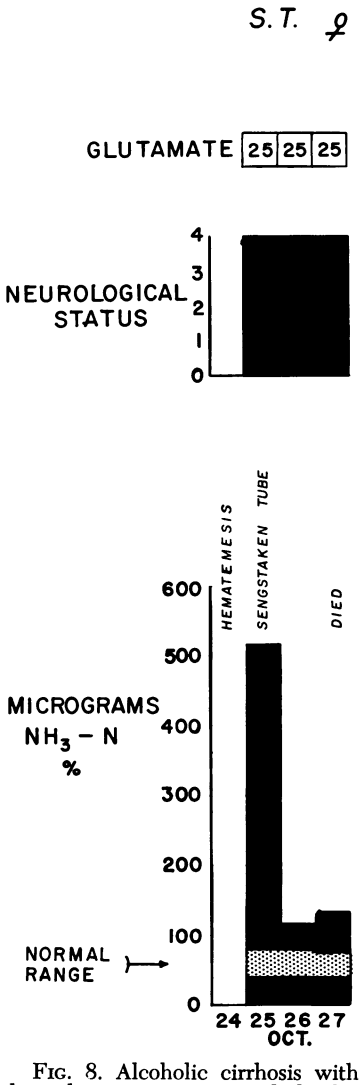

FIG. 8. Alcoholic cirrhosis with bleeding esophageal varices. Coma and death ensued despite treatment with sodium glutamate. (Case #3—S. T.)

pear which range from mild confusion and disorientation to deep coma. Frequently the symptoms are reversible but the clinical syndrome may terminate fatally.

In the animal experiments it is particularly significant that the hyperammoniaemia did not parallel the "alimentary azotemia." The normal animals demonstrated the expected rise in blood urea nitrogen but blood ammonia levels remained normal. In the Eck fistula dogs however, there was a much less significant rise in blood urea nitrogen but a consistent and striking hyperammoniaemia. As in the studies on the etiology of "meat intoxication" in the Eck fistula dog which were previously reported from this laboratory, central nervous system symptoms may appear if the level of blood ammonia is sufficiently high. It is particularly significant that a dog with an Eck fistula of long standing who is in excellent general health may die solely from the effects of blood introduced into the gastro-intestinal tract.

The clinical studies in this report are not as clear-cut as the animal experiments for a number of reasons: (1) The biochemical abnormalities were of necessity observations carried out during the course of an acute and variable disease process rather than during planned experimental procedures. (2) The degree of portal-systemic shunting in the patients was quite variable. (3) There was a variable degree of hepatocellular damage which introduced the multiple problems associated with disordered metabolism in the liver. (4) Hemorrhage from esophageal varices invariably causes some decrease in the effective circulating blood volume which obviously was not consistent throughout the 18 patients studied.

Despite all these variables, however, all the patients studied showed striking elevations in the peripheral blood ammonia and the degree of elevation correlated reasonably well with the severity of the central nervous system symptoms.*

The rationale of these observations is fairly clear. Both in the dog and in man it has been shown that the portal vein consistently contains a large amount of ammonia nitrogen which fluctuates with the amount of nitrogenous material taken into the gastro-intestinal tract.[8, 15] From the evi-

* This biochemical abnormality and the attendant clinical syndrome is by no means demonstrable in all patients with bleeding esophageal varices because of the number of factors described which are involved in the pathogenesis.

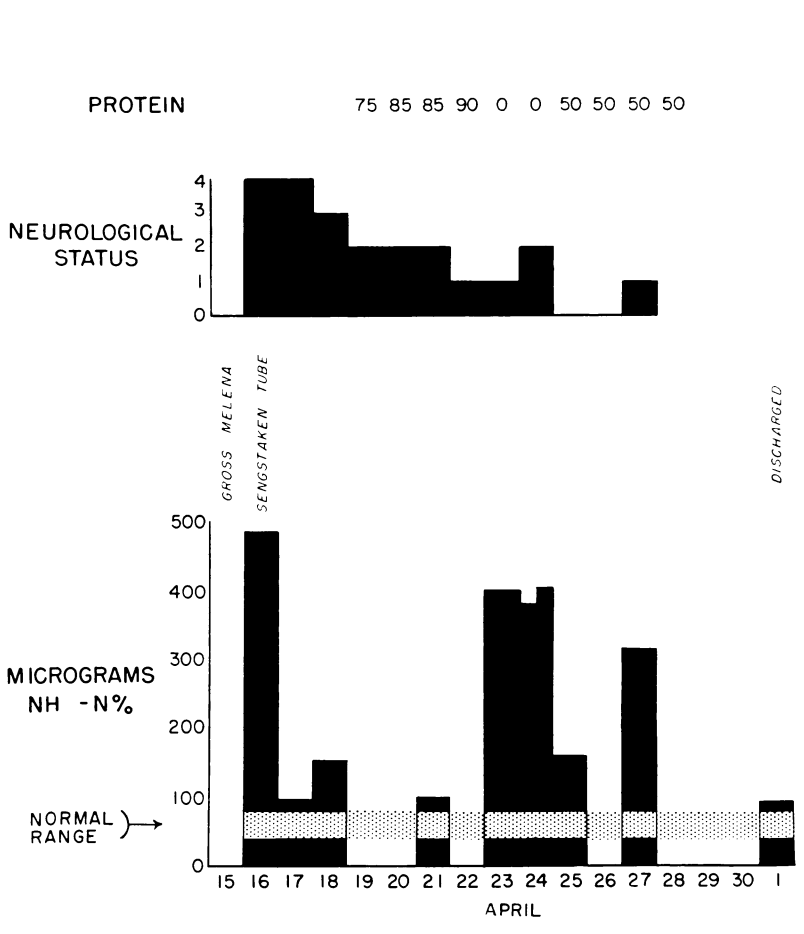

FIG. 9. Alcoholic cirrhosis with bleeding esophageal varices. The relationship of hemorrhage or protein intake with ammonia levels and central nervous system symptoms. (Case #4—L. D.)

dence available it would appear that this ammonia nitrogen is derived from the action of amino acid oxidase and urease on ingested protein and other nitrogenous substances; these enzymes are apparently derived from the intestinal micro-organisms.[6] Normally, this ammonia is synthesized to urea in the liver which thus forms a protective barrier against the accumulation of toxic levels of ammonia in the systemic circulation. In the presence of spontaneous or surgically constructed portal-systemic shunts, however, channels exist whereby this ammonia derived from enzymatic breakdown of nitrogenous material can bypass the liver and cause abnormal elevations of ammonia nitrogen in the peripheral blood. The fact that there is a lesser degree in elevation of blood urea nitrogen in the Eck fistula dog than in the normal animal would suggest that this shunting of portal blood around the liver interferes with the normal rate of urea synthesis.

It is apparent from these observations that the introduction of blood into the gastro-intestinal tract in the presence of portal-systemic shunts may cause both hyperammoniaemia and central nervous system symptoms. These studies alone do not establish a cause and effect relationship but

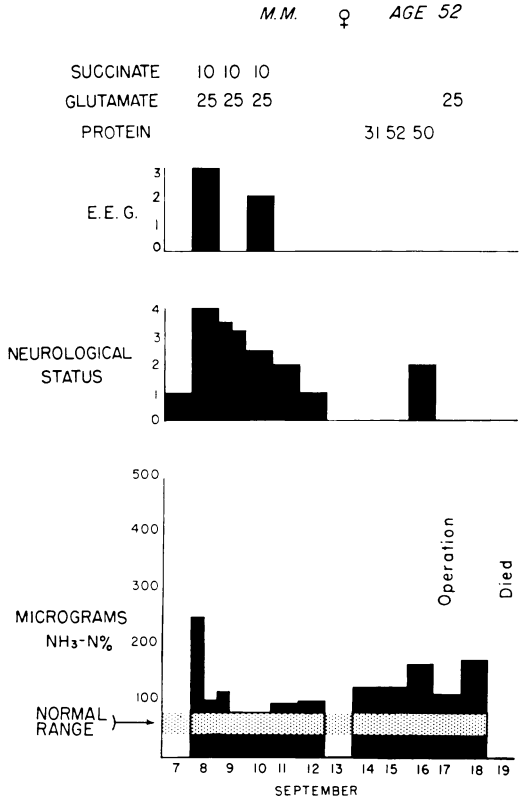

FIG. 10. Alcoholic cirrhosis with bleeding esophageal varices. Recovery from coma after control of hemorrhage and treatment with sodium glutamate. (Case #11—M. M.)

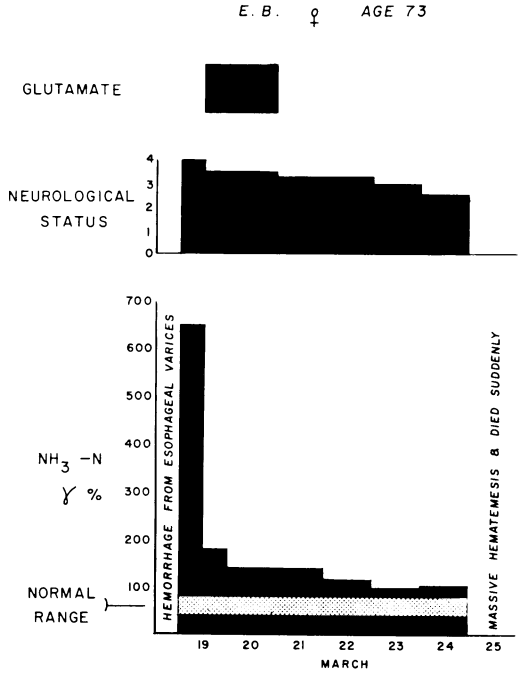

FIG. 11. Post-necrotic cirrhosis with bleeding esophageal varices. Subsequent to control of hemorrhage and treatment with sodium glutamate, ammonia level fill and recovery from coma began. A sudden massive recurrent hemorrhage was almost immediately fatal. (Case #17—E. B.)

previous studies in animals and in man [14, 15, 16, 18, 19] have demonstrated the fact that ammonia intoxication does exist. The analogy seems clear enough to warrant the assumption that this particular metabolic abnormality may well be a serious threat to patients with bleeding esophageal varices and, under these circumstances, is probably the cause of most of the episodes of so-called "hepatic coma."

It should be made clear that the authors do not feel that ammonia intoxication is the only or even the predominant feature of all cases of "hepatic coma." It is apparent that the "coma" associated with terminal hepatic decompensation is a much more complicated metabolic problem than the reversible syndrome dependent on the absorption of nitrogenous material from the gastro-intestinal tract in the presence of portal-systemic shunts.

In this report, no attempt has been made to discuss at any length the use of L-glutamic acid. This amino-acid will bring about a reduction in abnormally elevated levels of blood ammonia and is a valuable adjunct in the treatment of ammonia intoxication or, if one prefers to be less specific, in the treatment of exogenous hepatic encephalopathy. The clinical and biochemical effects of L-glutamic acid in the treatment of "hepatic coma" have been discussed in a previous publication [16] and need not be repeated here.

These studies and observations form the background for a suggested program in the management of bleeding esophageal varices: (1) *Control of hemorrhage.* Even though there is no apparent threat of exsanguination, it is imperative to prevent the accumulation of a nitrogenous pool in

the gastro-intestinal tract. This may be accomplished initially by balloon tamponade and when stabilization has been achieved by transfusions, by direct transthoracic ligation of the varices. (2) *Elimination* of the source of absorbed ammonia. By catharsis and enemas most of the blood can be removed. (3) *Antibiotics.* By depressing the bacterial count in the gastro-intestinal tract, the sources of urease and amino-acid oxidase can be controlled. (4) *L-glutamic acid* has proved to be a valuable adjunct to therapy, and may be given orally or parenterally in the glutamate form as individual circumstances demand.

Since the completion of these studies, an excellent report on portal hypertension has appeared in which Welch and his associates [23] have reached similar conclusions on the clinical management of bleeding esophageal varices.

SUMMARY AND CONCLUSIONS

1. A clinical and experimental study is reported relating to some biochemical abnormalities associated with the introduction of blood into the gastro-intestinal tract in the presence of spontaneous or surgically constructed portal-systemic shunts.

2. Central nervous system symptoms have accompanied these biochemical abnormalities and it is suggested that the syndrome of "hepatic coma" so commonly seen in patients with bleeding esophageal varices is, in fact, due to ammonia intoxication.

3. Based on these observations, a program for the management of bleeding esophageal varices has been outlined.

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DISCUSSION.—DR. C. STUART WELCH, Albany, New York: Again Dr. McDermott is to be congratulated for the excellent work he has done in this field of the investigation of ammonia metabolism in patients with liver disease.

I would like to show, in two slides, some of our experiments along the same line and some of our experiences with clinical cases.

(Slide) This shows that in Eck fistula dogs we have found the same rise in blood ammonia when blood has been fed to these animals. This rise does not occur in milk and mash fed dogs as indicated by the low values for blood ammonia.

(Slide) Here we have some figures on patients. We have now studied some 36 patients who have had gastro-intestinal bleeding with severe liver disease. The point I would like to make, corroborating Dr. McDermott's work, is that the high mortality in patients bleeding from varices occurs in the patients who have an elevated blood ammonia.

As you can see, only five of 20 survived when the ammonia was elevated, in contrast to ten survivals out of 16 when there was no elevation of blood ammonia. So, the coma which ensues and the ammonia intoxication are very significant in the causation of death.

Another important point is shown here. Nine patients died with continuing hemorrhage and coma. Therefore, it is very important that the bleeding be stopped.

The last point is that no patients in our series died in coma after hemorrhage was stopped, showing again the extremely important significance of bleeding and continued bleeding and blood in the intestinal tract.

DR. CHAMP LYONS, Birmingham, Alabama: It is a great privilege to acknowledge the very real help Dr. McDermott has been to Dr. Tom Patton and myself in similar studies. We are in complete accord with his conclusions.

I arise to ask one question. We have been concerned about the role of bacterial production of urease in the gastro-intestinal tract as a contributing factor to the ammonemia. We have been unable to demonstrate the presence of such bacterial enzymes, but the intestinal tract does have a great deal of intracellular urease. The question of antibiotic therapy in these patients hinges a good deal, I think, upon whether or not such enzymes have been demonstrated.

DR. BEN EISEMAN, Denver, Colorado: Our clinical experience has been very similar to that reported by Dr. McDermott. Of 57 patients in hepatic coma in our current series, 12 have had massive gastro-intestinal hemorrhage at the onset of their coma. In all of these cases the blood ammonia levels were elevated, and in 10 patients we feel that the ammonia load resulting from absorption of blood within the intestinal tract probably precipitated coma.

In our experience cases of hepatic coma precipitated by exogenously administered ammonia salts usually have a good prognosis; however, this has not been our experience in patients thrown into hepatic coma following massive gastro-intestinal bleeding. Indeed, as a group their prognosis is among the worst and although the administration of sodium glutamate to these people will temporarily lower the blood ammonia levels following its discontinuance we have found little change. For this reason our practice is to employ a slow infusion over a 24 hour period.

We have recently completed experimental studies on the effect of hemorrhage on ammonia metabolism—that is extra corporeal hemorrhage not bleeding into the intestinal tract. Following bleeding the portal blood ammonia concentration is markedly elevated, but simultaneous portal blood flow measurements indicate that this is merely a reflection of decreased blood flow and that there is no increased endogenous production of ammonia