Absence of Recurrent Ammonia Intoxication Following Right Hemicolectomy with Anastomosis of the Superior Mesenteric Vein to the Inferior Vena Cava *

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THE OCCURRENCE of hepatic coma in patients with cirrhosis after massive bleeding from esophageal varices and on occasion following portacaval shunt is widely known. During the past six years four cases have been reported in which a patient without pre-existing liver disease or portal hypertension has been subjected to resection of the portal vein with portacaval anastomosis in order to remove an otherwise inoperable carcinoma of the head of the pancreas. [7, 10, 11] After this procedure each of these patients developed periodic episodes of stupor resembling hepatic coma. These attacks usually followed the ingestion of a high protein diet and could be experimentally induced by feeding the patient an ammonium salt or ammonia releasing compounds. In one case studied extensively by McDermott,[10] episodes of confusion and coma correlated well with elevations in the blood ammonia concentration and this clinical syndrome is now attributed to ammonia intoxication. This complication is encountered less commonly following portacaval shunt for portal hypertension presumably because long-standing obstruction to portal blood flow favors the development of an extensive hepatopedal collateral circulation permitting portal blood to reach the liver. Because of the potentially serious nature of ammonia intoxication, it has often been deemed inadvisable to carry out a portacaval anastomosis in the absence of portal hypertension even though such anastomosis might permit more extensive removal of a neoplasm.

The purpose of this report is to describe the interesting aspects of a patient in whom anastomosis of the superior mesenteric vein to the inferior vena cava was performed in conjunction with right hemicolectomy for carcinoma of the transverse colon. Since this operation the patient has remained free of recurrent episodes of hepatic coma while consuming a diet containing normal amounts of protein. Studies of her blood ammonia concentrations following oral administration of ammonium salts and urea were carried out, and an explanation for the absence of ammonia intoxication in this case is presented.

Case Report

M. M. (PBBH No. C 1325), a 66-year-old widow, entered the Peter Bent Brigham Hospital on March 17, 1960, with anemia and occult blood in her stool. Barium enema revealed a constricting neoplasm of the transverse colon near the hepatic flexure. She gave no history of melena, constipation or weight loss. In 1953, she had a hysterectomy, an appendectomy and shortly afterward, a right below-knee amputation for a malignant mesenchymoma of the ankle. She had received radiation to her right inguinal region fol-

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lowing this amputation. Her mother died of carcinoma of the breast.

Physical examination revealed a somewhat obese white woman with a right below-knee amputation. Her pulse was 106 and blood pressure 150/68. Except for a strongly positive test for occult blood in her stool, her examination was otherwise not remarkable. Her admission hematocrit was 25 per cent. Preoperative liver function tests were limited to a serum alkaline phosphatase of 4.0 Bodansky units per hundred ml. and a prothrombin time of 91 per cent of normal. She was transfused with packed red blood cells and was given oral neomycin and sulfasuxidine prior to operation.

On March 22, 1960, an exploratory laparotomy was performed. A small carcinoma was found in the transverse colon near the hepatic flexure. There were several hard, enlarged lymph nodes about the origin of the middle colic artery. The liver appeared grossly normal and free of tumor. A right hemicolectomy was performed. Considerable difficulty was encountered in attempting to secure an adequate margin proximal to the tumor-bearing lymph nodes and the superior mesenteric vein was divided where it was adherent to the mass. The small bowel was observed during completion of the colectomy, and most of the ileum became suffused and covered with petechiae. Re-anastomosis of the divided superior mesenteric vein was technically impracticable, therefore, the end of the superior mesenteric vein was joined to the side of the inferior vena cava establishing a porta-caval shunt. Although not specifically noted, the inferior mesenteric vein was presumed to enter the splenic vein. An ileo-transverse colostomy was completed after the shunt was opened. She was observed closely in the postoperative period for signs of ammonia intoxication, and on the second day an electroencephalogram was interpreted as diffusely abnormal and consistent with a metabolic encephalopathy. The following day the patient was noted to be drowsy although completely oriented and a metabolic flap was demonstrated. The blood ammonia concentration at that time was 297 micrograms per cent. Oral neomycin was started and the flap disappeared within the next 24 hours. The subsequent clinical course is summarized in Figure 1. The sixth day she was given a 45-Gm. protein diet and started on sulfasuxidine. Neomycin was stopped. She showed no further signs of ammonia intoxication in spite of somewhat elevated blood ammonia levels on two occasions. Liver function tests were not greatly altered (Table 1). Sulfasuxidine was discontinued

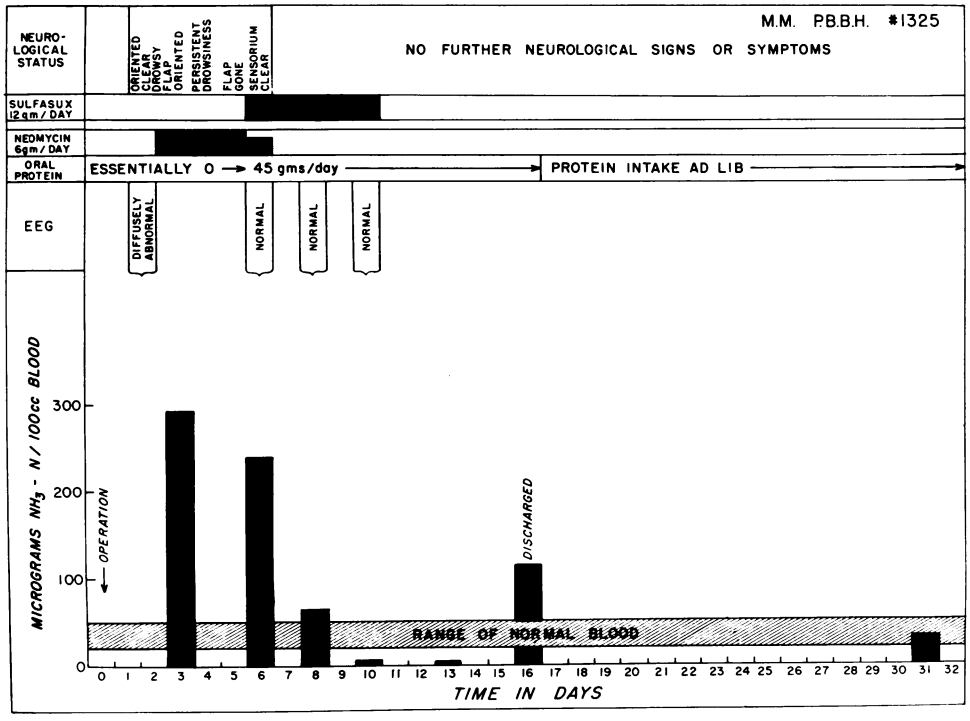

FIG. 1. Diagrammatic representation of the patient's clinical course, correlating neurological status, electroencephalographic changes, and medication with blood ammonia concentrations.

TABLE 1. *Postoperative Chemistries Relative to Liver Function*

Date	Bilirubin mg.%	Cephalin Flocculation	Thymol Turbidity	Alkaline Phosphatase (Bodansky U.)	Prothrombin Time % of Normal	Total Protein Gm.%	Serum Albumin Gm.%	Bromsulfalein % Retention	Lactic Dehydrogenase (Wacker U.)
3-28-60		0	.42	9.6	82			23	
4-4-60	1.03	0	1.16	13.9		6.0	4.1		120
4-7-60			.71	9.2				23	
6-30-60	0.91			9.3		6.3	4.2		
7-20-60					59				58

and she was discharged on the sixteenth postoperative day. Immediately following discharge, she resumed her regular diet without protein restriction and reported no untoward effects. Blood ammonia levels were normal or slightly elevated on several occasions but no flap nor disorientation was observed. A barium enema on May 3, 1960, showed a normal functioning ileo-transverse colostomy.

On June 22, 1960, exactly three months after her right colectomy, she was re-admitted to the hospital with fever and what appeared to be an abdominal wall abscess. After this was drained, however, barium enema demonstrated a fistula from the site of the previous anastomosis into the abscess cavity. A few days later, wide drainage of a large intra-abdominal abscess was instituted. No evidence of recurrent carcinoma was found. Because of a persistent fistula seen on a repeat barium enema examination, a new ileo-transverse colostomy was created on July 29, 1960. The abscess and the previous anastomotic line were completely defunctioned. The liver, the area of the previous suture line, and the retroperitoneal tissues were all free of any gross tumor. On July 7, 1960, her blood ammonia concentration was 36 micrograms per cent after five hours of fasting. She was receiving oral neomycin for her preoperative bowel preparation at that time. She was discharged from the hospital on August 12, 1960, without medication and on a diet unrestricted in proteins.

Methods

In this study, ammonia determinations were done by the microdiffusion technic of Conway[3] as modified by McDermott.[10] Ammonia levels are expressed in micrograms per cent of ammonia nitrogen. The normal values on peripheral blood obtained by this laboratory* are from 20 to 50 micrograms per cent.

Results

In seeking an explanation for this patient's freedom from episodic stupor, it was decided to study the effect on her sensorium of ingesting an ammonium salt. An ammonium tolerance test was performed on May 25, 1960, the results of which are illustrated in Figure 2. There was a rapid rise in blood ammonia after the ingestion of 4 Gm. of ammonium chloride. The patient became slightly drowsy during the test but roused easily and conversed intelligently. At no time was there any metabolic flap or disorientation noted. At the end of four hours her blood ammonia returned to near her fasting level. The test indicated that her shunt was open and functioning.

Since the most important source of blood ammonia is probably absorption of ammonia which is formed by bacterial action in the intestinal tract,[4, 11] a urea tolerance test was performed on June 7, 1960. The results are illustrated in Figure 3. Her fasting level of blood ammonia was normal and never rose above normal levels during the period of the test. These results suggest that little if any conversion of urea to ammonia occurred in her small intestine.

* Clinical Chemistry Laboratory, Children's Medical Center, Boston.

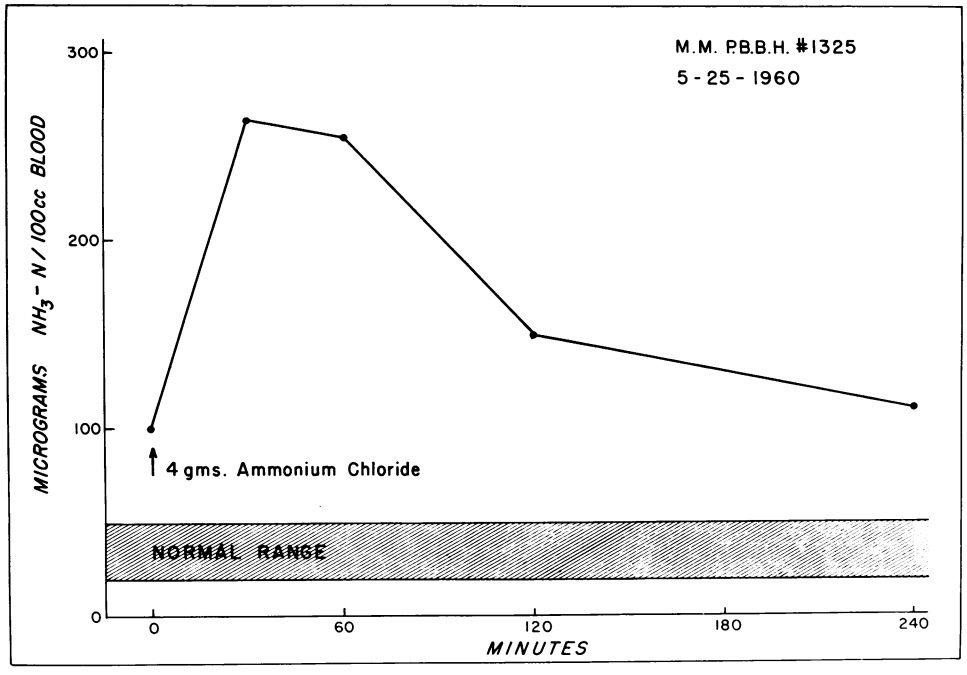

FIGURE 2. Ammonium tolerance curve.

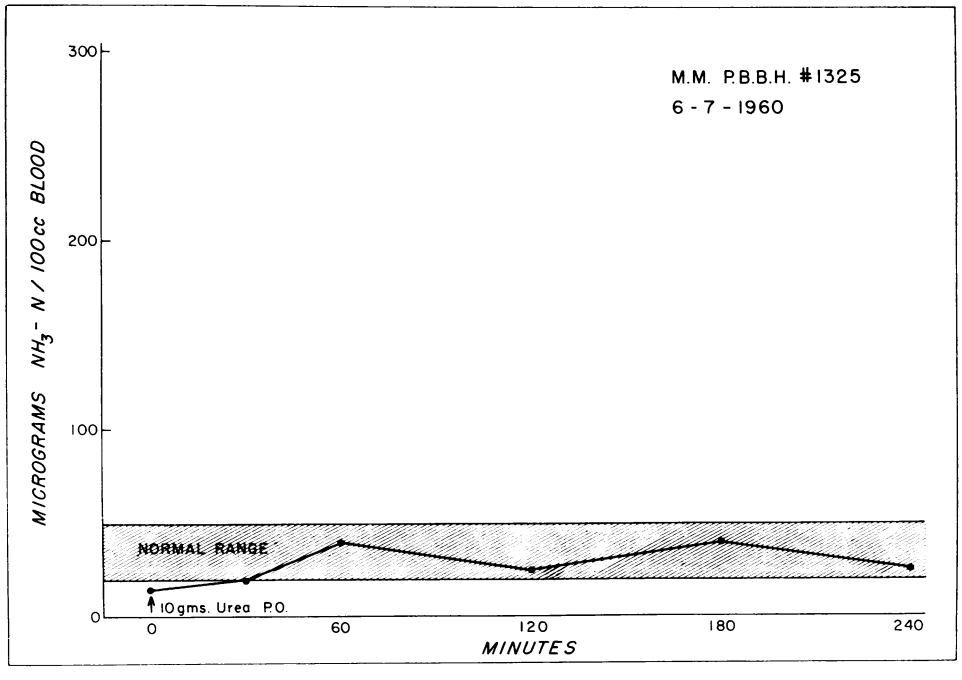

FIGURE 3. Urea tolerance curve.

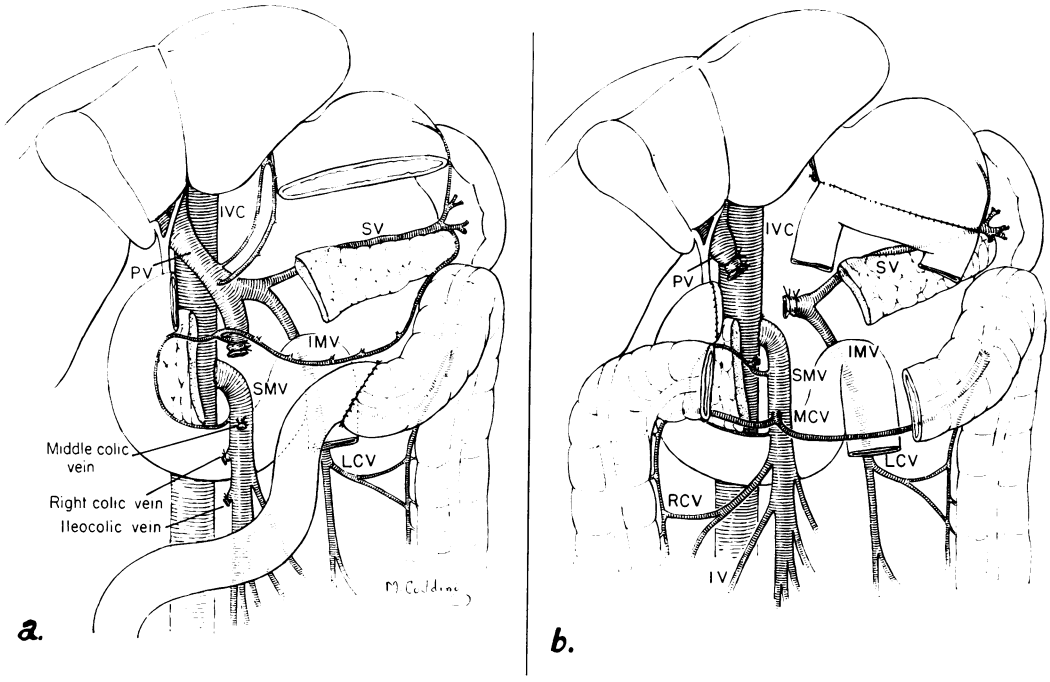

FIG. 4a. Diagram illustrating the anastomosis of the superior mesenteric vein to the inferior vena cava in this patient. b. Diagram illustrating the portacaval anastomosis after resection of the portal vein. Note the persistence of the right and middle colic veins, and the interruption of the splenic vein.

Discussion

To our knowledge this case is unique. There have been previously reported cases of portacaval shunts in humans with normal liver function in order to obtain adequate block resections for carcinoma of the head of the pancreas. In all of these instances, the entire portal bed flow was shunted (Fig. 4b). The normal anatomy of the portal circulation is illustrated in Figure 5 for comparison. Three of these patients demonstrated severe neurologic symptoms and one, electroencephalographic changes which appeared to be the result of altered ammonia metabolism. A fourth patient was maintained on neomycin and sodium glutamate and showed no gross evidence of ammonia intoxication.[7, 10, 11] In each of these cases of both McDermott and Hubbard, the diversion of portal flow was a one-stage procedure. Childs has described four patients with two-stage resections of the portal vein, performed because overwhelming intraoperative hemorrhage was noted to follow direct resection of the portal vein in a patient without portal hypertension.[2] None of these patients appeared to exhibit ammonia intoxication. A possible explanation is that the onset of portal hypertension induced hepato-pedal collaterals to develop during the time between the ligation of the portal vein and its subsequent resection.

In the case reported here, only the venous drainage from the small intestine was diverted from the portal into the systemic circulation. The right colon, a source of considerable ammonia formation,[4] was removed. The ammonia produced in the left colon is transported to the liver directly via the inferior mesenteric and the splenic veins and is converted to urea (Fig. 4a).

It has been shown in mice,[4] cats[5] and dogs[6, 13] that the small intestine contributes relatively little ammonia to the portal blood. This would explain the normal and near normal fasting blood ammonia concentrations in this patient. However, ingested ammonium salts are rapidly absorbed in the small intestine and produce an immediate elevation of blood ammonia. The immediate postoperative elevation of blood ammonia and symptoms of ammonia intoxication might have been the result of absorption of ammonia released by bacterial enzymatic action on the contents of the distal small bowel. Postoperative ileus with stasis of intestinal contents as well as enzymatic action from colonic bacteria refluxed into the distal ileum through the ileo-transverse colostomy may have released ammonia within the small intestine until normal motility was restored. Further support for this hypothesis is found in a recent report on the successful treatment of recurrent hepatic coma by colectomy and ileo-rectal anastomosis.[1]

This patient, therefore, has two complementary factors which tend to decrease the likelihood of her developing ammonia intoxication. The first is the absence of the right colon—possibly the principal source of ammonia production in the gut. The second is the probable maintenance of the normal venous pathway of the inferior mesenteric vein. Thus, any ammonia production in the remaining colon is effectively detoxified by the liver in the usual manner.

It is our opinion that the elevated serum alkaline phosphatase and the abnormal bromsulfalein retention does not necessarily reflect hepatocellular damage but rather a faulty clearance of these substances due to the altered portal circulation. It is known that alkaline phosphatase is produced by the small intestine and that this enzyme is normally cleared by the liver.[8, 12] Emptying of this source of enzyme directly into the systemic blood could

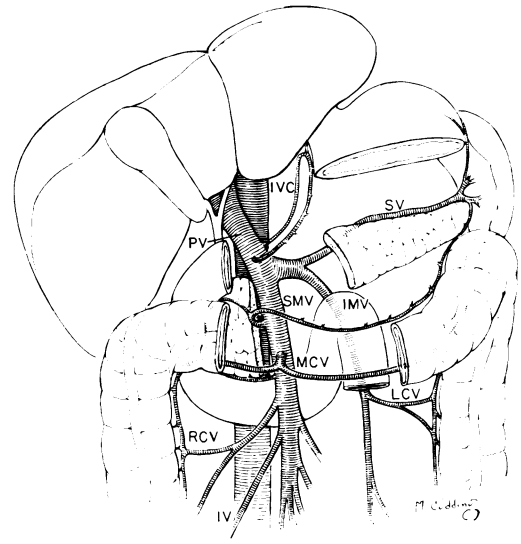

FIG. 5. Diagram of the normal portal vascular tree.

account for the small persistent elevation noted after surgery. Similarly, bromsulfalein is excreted in bile and is reabsorbed in appreciable quantities by the small intestine.[9] In this patient the reabsorbed bromsulfalein is shunted away from the liver and causes a prolonged retention. We have not observed hypoalbuminemia reported by other investigators.[7, 11, 14]

The unusual opportunity to study this patient with a concomitant partial portacaval shunt and right hemicolectomy has helped to provide physiologic explanations for clinical observations in other patients with portal hypertension. It also lends support to the theoretical concept that anastomosis of the superior mesenteric vein to the inferior vena cava in conjunction with a right hemicolectomy can be performed without danger of ammonia intoxication. This procedure may be useful in facilitating the removal of otherwise inoperable infiltrative tumor in the region of the superior mesenteric vessels.

Summary

1. A superior mesenteric vein to inferior vena cava anastomosis has been performed

in conjunction with a right hemicolectomy in a human with normal hepatic function. The physiologic significance of this unique type of shunt has been considered in the light of our present knowledge of portal circulation.

2. The patient developed transient signs of ammonia intoxication immediately after operation. These cleared rapidly and never recurred. At the present time she is neither on a restricted protein diet nor any program of bowel sterilization.

3. Urea and ammonium tolerance tests were performed, and their results are discussed in relation to ammonia metabolism in this patient.

4. It is proposed that anastomosis of the superior mesenteric vein to the inferior vena cava combined with a right hemicolectomy might be employed in similar cases without danger of ammonia intoxication.

Acknowledgment

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Addendum

This patient was last seen in August 1961, and she had no evidence of recurrent disease. She was free of symptoms of ammonia intoxication.

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