Influence of Stomal Size of Portacaval Shunts on Peripheral Blood Ammonia Levels *

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ALTHOUGH the causes of hepatic coma are obscure, considerable evidence suggests that the encephalopathy associated with portal-systemic venous anastomoses in both animals and man is related to the shunting directly into the systemic circulation of large quantities of ammonia absorbed from the intestines. Of the various nervous disorders included in the term *hepatic coma,* support for an etiologic role of ammonia intoxication is perhaps greatest in those disturbances which occur in the presence of portal-systemic shunts.[12] While the frequency of central nervous system symptoms following shunt operations has not been accurately established, the reported experience indicates that the incidence is sufficiently high to seriously compromise the beneficial effects of these operations in the therapy of portal hypertension.[6, 9, 13]

In normal subjects, be they humans or dogs, ammonia absorbed from the gastrointestinal tract is carried directly to the liver where it is detoxified rapidly, mainly by transformation to urea by a highly efficient and durable enzyme system.[2] In subjects with portal-systemic shunts, much of the ammonia which is absorbed into the portal system bypasses the liver and enters directly into the systemic circulation where it is capable of reaching toxic concentrations before recirculation and hepatic degradation occur. In the presence of an intact urea-forming mechanism in the liver, the ammonia level in the peripheral blood is determined by a number of factors, among which are the quantity and rate of intestinal ammonia absorption, the rate at which ammonia is shunted from the portal into the systemic circulation, the rate of tissue uptake of ammonia, and the rate at which systemic ammonia is returned to the liver for detoxification. The second of these factors, i.e., the rate of ammonia shunting, presumably is related to the blood flow rate through the portal-systemic shunt which in turn may be influenced by the size of the shunt.

The present investigation was undertaken to evaluate the influence of the stomal size of portacaval shunts on the concentration of ammonia in the peripheral blood. To this end, 112 experiments were performed in which the systemic levels of blood ammonia were monitored following the administration of standard ammonium loads to 32 dogs with end-to-side portacaval anastomoses of various sizes and to 22 normal control dogs.

Materials and Methods

Portacaval Shunts. End-to-side portacaval anastomoses were created in 32 healthy adult male and female mongrel dogs varying in weight from 16 to 30 kilo-

* Submitted for publication October 12, 1962.

** Markle Scholar in Medical Science.

Aided by United States Public Health Service Grant A-3048 and the John and Mary R. Markle Foundation.

grams. The operations were performed with sterile technic under intravenous sodium pentobarbital anesthesia administered in a dose of 30 mg./kg. body weight. A right thoraco-abdominal incision was used, extending through the tenth intercostal space, across the costal cartilages, and onto the abdominal wall as a right rectus incision. A side-to-side anastomosis between the portal vein and inferior vena cava was constructed, following which the hepatic limb of the portal vein was occluded with two heavy silk ligatures, thereby converting the anastomosis to an end-to-side shunt (Fig. 1).

The size of each shunt was planned by careful measurement with calipers and delineation with marking sutures of the segments of portal vein and vena cava to be excised for the anastomosis. Segments of the lateral wall of the portal vein and anteromedial wall of the vena cava measuring 0.5 cm. in thickness and from 0.5 to 3.5 cm. in length were excised. It was planned to divide the animals into two groups, one with large shunts greater than 2.0 cm. in largest diameter, and the other with small shunts less than 1.5 cm. in largest diameter.

All animals were sacrificed upon completion of the ammonia studies and the patency and internal dimensions of the anastomosis were determined *in situ*. All shunts were found to be patent. The internal size at autopsy was almost invariably larger than was predicted on the basis of the external measurements made at the time of operation. The largest internal diameter of the shunt, which in all was the length, was used as the index of shunt size. Based on this measurement at autopsy, the shunt dogs were divided into two groups of 16 animals each, one with *large* shunts and the other with *small* shunts. In the large shunt group the anastomoses varied in length from 2.0 to 4.2 cm., and in the small shunt group the anastomoses varied in length from 0.35 to 1.8 cm. (Fig. 2).

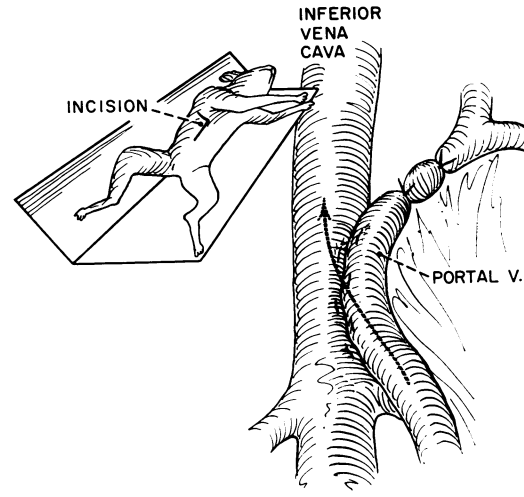

FIG. 1. Technic of end-to-side portacaval shunt. A side-to-side anastomosis was constructed, following which the hepatic limb of the portal vein was occluded with heavy ligatures, thereby converting the anastomosis to an end-to-side shunt.

Pressures in the portal vein and abdominal inferior vena cava were determined by needle puncture during the operation, before and after construction of the portacaval shunt. A spinal manometer filled with a heparin-saline solution was employed and the level of the vein in which pressure was being measured was used as the reference point.

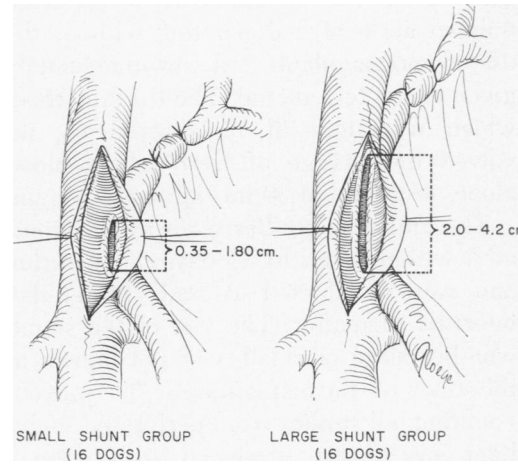

FIG. 2. The two groups of shunt dogs, based on measurement at autopsy of largest internal diameter of shunt.

TABLE 1. *Mean Peak Blood Ammonia Levels Following Ammonium Loading* in Dogs with Large and Small Portacaval Shunts*

	Large Shunts (16 dogs)		Small Shunts (16 dogs)
Ammonium citrate (0.5 Gm./Kg.)			
No. experiments	31		27
Mean peak blood NH_3-N (mcG.%)	1,648		1,095
P value		0.00005	
Blood (30 ml./Kg.) plus urease (4 u./ml.)			
No. experiments	8		9
Mean peak blood NH_3-N (mcG.%)	1,336		991
P value		0.02	
Blood (30 ml./Kg.)			
No. experiments	7		8
Mean peak blood NH_3-N (mcG.%)	688		538
P value		0.17	

* All agents were instilled in the stomach by gavage.

Methods of Inducing Ammoniemia. Three standardized methods were used to induce peripheral ammoniemia in 112 separate experiments. The first method, which was employed in 80 studies, involved the intragastric instillation by gavage of ammonium citrate in a dose of 0.5 Gm./kg. body weight. The second method, which was used in 17 experiments, consisted of the intragastric instillation of fresh whole blood in a dose of 30 ml./kg. body weight, followed immediately by gavage of urease * in a dose of 4 Sumner units/ml. of blood. The blood was obtained from the cannulated aorta of a donor dog without the use of anticoagulants and was immediately given to the test animal. The third method, which was used in 15 experiments, involved the gavage of fresh whole blood alone, in a dose of 30 ml./kg. body weight.

The ammonia studies were usually initiated within seven to 14 days of operation and were conducted at four- to ten-day intervals thereafter. The size of the shunt, whether large or small, was not known at the time of the experiments. To prevent vomiting, all studies were performed under light anaesthesia, produced with intravenous sodium pentobarbital in a dose of 10 mg./kg. body weight.

Blood Ammonia Analysis. With all three methods of inducing ammoniemia, venous blood for ammonia analysis was obtained in heparinized ** syringes by puncture of the femoral vein. Samples were collected just prior to administration of the test substance and hourly thereafter for six hours. The blood samples were rapidly frozen within five minutes of shedding by a technic described previously [15] and were analyzed within two hours.

A modification of the microdiffusion and titration method of Conway [1] was used for measuring blood ammonia nitrogen. One ml. of blood was added to 1.0 ml. of 40 per cent saturated potassium carbonate in the outer well of a standard Conway dish and the liberated ammonia was collected in 0.1 ml. of 0.01 N. or 0.05 N. sulfuric acid in the center well of the dish. Diffusion was enhanced by placing the dishes on an Eberbach-Kahn shaker rotating at 120 r.p.m. A ten-minute diffusion period was employed. The contents of the center well were titrated, using a mixture of methyl red and bromocresol green as the indicator, with

* Urease Type II Powder manufactured by Sigma Chemical Co., St. Louis, Mo.

** Heparin manufactured by Maurry Biological Co., Los Angeles, Calif. was used in all studies.

standard sodium hydroxide delivered from a Rehberg burette, which allowed calculation of the amount of ammonia bound to acid. Since only approximately 40 per cent of the ammonia content of the blood specimen diffused during the short ten minute diffusion period, a factor was introduced to calculate the total ammonia concentration in the blood. Because of the short diffusion period, no correction was believed necessary for *nonspecific* liberation of ammonia due to the action of alkali on blood. All samples were analyzed in triplicate.

Results

In Table 1 are shown the mean peak blood ammonia levels obtained in the two groups of Eck-fistula dogs by the three methods of inducing ammoniemia. All three technics of ammonium loading resulted in higher peak blood ammonia concentrations in the animals with large portacaval shunts than in those with small portacaval anastomoses. The larger the ammonium load introduced into the gastro-intestinal tract, the greater were the differences in peak blood ammonia levels between the two groups. Thus, in the experiments with enteral ammonium citrate, which consistently resulted in very marked elevations of peripheral blood ammonia, the dogs with large portacaval shunts developed peak blood ammonia levels which averaged 553 mcG. per cent greater than the concentrations obtained in the dogs with small shunts. This difference was statistically significant with a P value of 0.00005. The differences in peak ammonia levels in the two groups were less striking, although statistically significant ($P = 0.02$), in the studies with blood plus urease and they were not significant when blood alone was used. With the latter method it was difficult to demonstrate large differences in the magnitude of ammoniemia because of the relatively low peak blood ammonia levels which occurred in both groups.

The mean hourly blood ammonia concentrations resulting from the three technics of ammonium loading are given in Table 2 and the curves corresponding to these values in the two groups of Eck-fistula animals and a third group of normal control dogs are compared in Figures 3, 4, and 5. It is of interest that in all studies the mean control levels of blood ammonia in the animals with large shunts were higher than those in the dogs with small

TABLE 2. *Mean Hourly Blood Ammonia Levels Following Ammonium Loading* in Dogs with Large and Small Portacaval Shunts*

	Mean Blood Ammonia-Nitrogen—mcG.%						
	Control	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.	6 Hr.
Ammonium citrate (0.5 Gm./Kg.)							
Large shunt group	204	1,191	1,385	1,270	1,031	755	596
Small shunt group	190	761	831	746	654	515	321
22 normal dogs	72	123	138	119	92	75	64
Blood (30 ml./Kg.) plus urease (4 u./ml.)							
Large shunt group	240	988	1,219	1,128	917	882	835
Small shunt group	227	574	775	737	875	701	645
Blood (30 ml./Kg.)							
Large shunt group	261	457	543	479	504	455	510
Small shunt group	241	358	398	400	454	495	450

* All agents were instilled in the stomach by gavage.

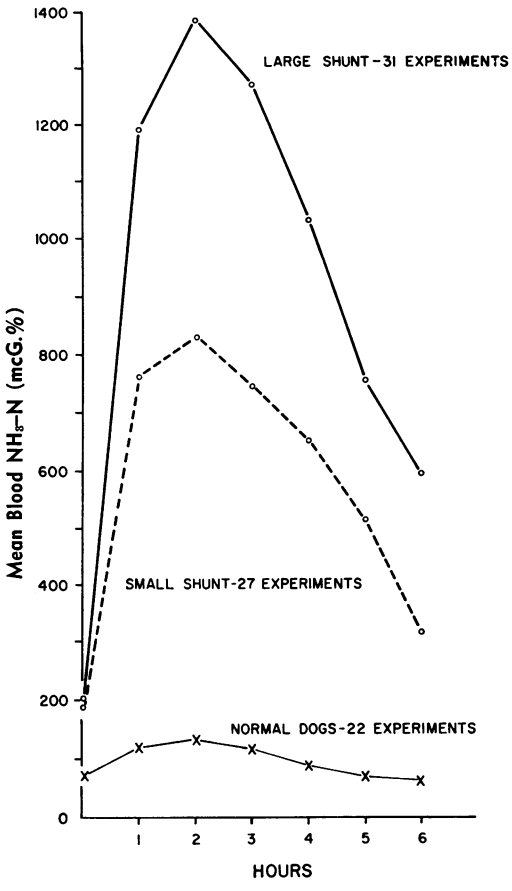

FIG. 3. Mean hourly blood ammonia levels following enteral ammonium citrate (0.5 Gm./Kg.) in dogs with large and small portacaval shunts.

shunts. With the enteral ammonium citrate load (Fig. 3), the blood ammonia curve in the large shunt group ascended to a much higher level than in the dogs with small shunts, and remained elevated for a longer period of time. When the experiments were concluded at the end of six hours, the mean blood ammonia concentration in the animals with large shunts was still three times higher than the control level. Similar differences in the curves from the two groups of dogs were found with the enteral blood plus urease load (Fig. 4). With the blood load alone (Fig. 5), the rise in blood ammonia was relatively small in both groups; although a higher level was reached in the large shunt group, the differences in the two curves were not significant.

Pressure measurements obtained at operation after completion of the anastomosis revealed, in the large shunt group, a mean portal vein pressure of 90.9, a mean vena cava pressure of 89.6, and a mean pressure gradient across the shunt of 3.0 mm. saline. Only one animal with a large anastomosis had a pressure gradient across the shunt as high as 10 mm. and this dog developed the smallest rise in blood ammonia of any in the group. In the small shunt group, mean pressures in the portal vein and vena cava were 104 and 73, re-

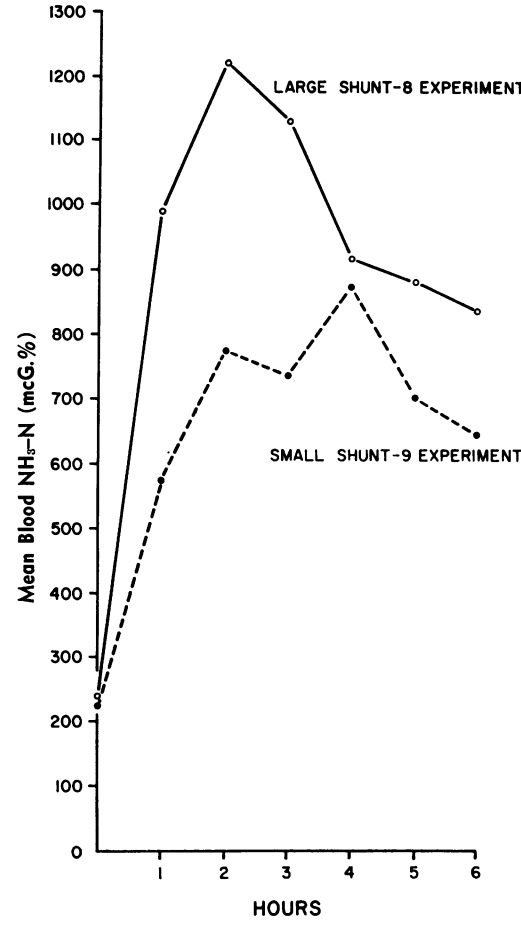

FIG. 4. Mean hourly blood ammonia levels following enteral blood (30 ml./Kg.) plus urease (4 u./ml.) in dogs with large and small portacaval shunts.

spectively, and the mean gradient across the shunt was 31 mm. saline. Only two dogs with small shunts had a pressure gradient less than 10 mm. and one of these developed the highest blood ammonia levels in the group, which reached a peak level twice as high as the group mean level. Although all animals in the small shunt group had a definite reduction in portal pressure following construction of the portacaval shunt, and all had post-shunt portal pressures within the normal range, the significant pressure gradient across the shunt indicates that complete portal decompression was not achieved.

In Table 3 the mean peak blood ammonia concentrations in the animals whose pressure gradients across the shunt were 0 to 8.0 mm. saline are compared with those whose pressure gradients exceeded 10 mm. With three exceptions, the dogs with little or no measurable gradient were in the large shunt group and those with a gradient of 10 mm. or more were in the small shunt group. The dogs with a pressure gradient of 8.0 mm. or less developed higher mean peak blood ammonia levels with all three methods of inducing ammoniemia. The differences in peak concentrations were statistically significant with both the enteral ammonium citrate load and the enteral blood plus urease load.

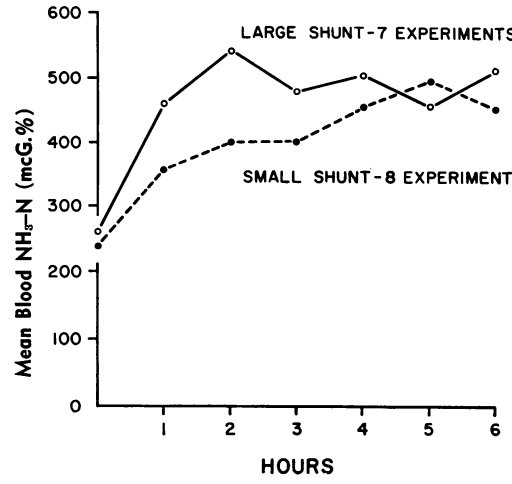

FIG. 5. Mean hourly blood ammonia levels following enteral blood (30 ml./Kg.) in dogs with large and small portacaval shunts.

Discussion

In 1893, Hahn, Massen, Nencki, and Pavlov [5] described in dogs with Eck fistulas a syndrome of central nervous system symptoms which followed the ingestion of meat and subsequently became known as *meat intoxication.* Although the St. Petersburg workers found elevated levels of blood

TABLE 3. *Relationship of Pressure Gradient Across the Portacaval Shunt to Mean Peak Blood Ammonia Level*

	Pressure Gradient—mm. saline		
	0–8		10 or greater
Ammonium citrate (0.5 Gm./Kg.)			
No. experiments	32		26
Mean peak blood NH_3-N (mcG.%)	1,546		1,020
P value		0.00004	
Blood (30 ml./Kg.) plus urease (4 u./ml.)			
No. experiments	8		9
Mean peak blood NH_3-N (mcG.%)	1,330		996
P value		0.03	
Blood (30 ml./Kg.)			
No. experiments	7		8
Mean peak blood NH_3-N (mcG.%)	637		551
P value		0.45	

ammonia in their animals, and considered the possibility that ammonia was responsible for the symptoms, it remained for Monguio and Krause,[14] in 1934, to relate the central nervous system disturbance in the Eck-fistula dog to increased concentrations of ammonia in the blood. In 1954, McDermott and Adams [11] described a similar syndrome in a patient with a portacaval shunt and demonstrated a direct relationship between spontaneous and induced episodes of stupor and elevated blood ammonia levels. Since then, several authors have reported elevations of blood ammonia in patients who had disturbances of consciousness following portal-systemic venous anastomoses.[3, 7, 8, 10, 16, 19, 20]

A number of workers recently have pointed out the lack of correlation between the systemic blood ammonia concentrations and the onset and course of many nervous disorders associated with chronic liver disease and commonly termed *hepatic coma*.[3, 13, 18] However, in patients with portal-systemic shunts, in whom nervous symptoms often are precipitated by ingestion of protein or gastro-intestinal bleeding, substantial evidence has been accumulated to lend weight to the proposal that ammoniemia is responsible for the encephalopathy.[3, 7, 8, 10, 11, 16, 19, 20] To distinguish this form of hepatic coma, presumably due to ammonia intoxication, from the nervous disorders associated with hepatic cell failure, and not clearly related to increased blood ammonia, the term *exogenous hepatic coma* has been proposed.[12] It is to this clinical form of hepatic encephalopathy in man that the results of experimental studies in the Eck-fistula dog, such as the present investigation, may be applicable.

It is not possible to determine accurately the incidence of neurologic symptoms following portal systemic shunts since in reporting the results of large series of these operations, many authors have focussed their attention on the rates of survival and recurrence of bleeding. Nevertheless, some data have appeared which indicate that post-shunt encephalopathy is a disturbingly frequent problem. Hallenbeck and Shocket [6] reported that six of 40 patients (15%) who survived shunt operations developed neurologic sequelae and cited a personal communication from Child, who estimated a similar incidence in his large series of shunts. It is perhaps significant that the incidence of encephalopathy was 26 per cent in the 23 patients with direct portacaval shunts, 22 of which were of the end-to-side type, while none of the 17 patients with splenorenal shunts developed central nervous system symptoms. One explanation for this may be found in the pressure data which show that the mean reduction in portal pressure in the splenorenal shunt group was only 6.0 cm. (as compared to 20 cm. in the portacaval shunt group) and the mean post-shunt pressure was 30 cm., which indicates that a relatively small quantity of portal blood was being carried across the splenorenal shunts into the systemic circulation.

Sedgwick and Hume [17] reported that only two of 37 patients with portal systemic shunts developed central nervous system symptoms, an incidence of 5.0 per cent, which is lower than that found by most other authors. It may be significant that two-thirds of their patients had splenorenal shunts.

Linton, Ellis, and Geary [9] reported that 30 of 169 cirrhotic patients (18%) developed neurologic symptoms in the immediate postoperative period following portal-systemic shunts and of 137 of these patients who were followed for significant periods of time, 41 (30%) developed late neurologic sequelae such as pre-coma and coma. It is of interest that the incidence of immediate symptoms in the patients with splenorenal shunts was 14 per cent as compared to 28 per cent in those with direct portacaval shunts, and the incidence of late pre-coma or coma was 17 per cent in the splenorenal shunt group as compared

to 68 per cent in the direct portacaval shunt group. Almost all of the direct portacaval anastomoses were of the end-to-side type. Again, the difference in the frequency of nervous disorders between the splenorenal and direct portacaval anastomoses may have been a reflection of differences in shunt size and blood flow rate.

McDermott, Palazzi, Nardi, and Mondet [13] in a study which included some of the patients of Linton and Ellis reported that 33 (18%) of 176 patients with portal-systemic shunts who were followed for more than one year developed encephalopathy. In 15 (8.5%) the disorders of consciousness were severe and recurrent. The incidence of neurologic symptoms among the patients with splenorenal shunts (19%) was similar to that in the patients with direct portacaval anastomoses (17%). The report does not state how many of the direct portacaval shunts were of the end-to-side or side-to-side type.

The results of the present investigation show that the stomal size of end-to-side portacaval shunts was one factor which determined the concentration of ammonia in the peripheral circulation. The dogs with large portacaval shunts maintained consistently higher levels of blood ammonia from day to day than did those with small shunts and developed greater elevations of blood ammonia following the enteral administration of standard ammonium loads. The differences in the magnitude of ammoniemia between the two groups of animals increased as the enteral load of ammonium was increased.

It would seem reasonable to assume that the rate of intestinal absorption of ammonia was similar in the two groups of dogs. If this was the case, then the influence of shunt size on the peripheral blood ammonia presumably was a reflection of the effect of different rates of blood flow across the shunts which in turn reflected different rates at which ammonia was spilled abruptly into the systemic circulation. Substantiation of this presumption is provided by the results of pressure measurements across the shunt which showed a consistently inverse relationship between pressure gradient on the one hand and the stomal size and blood ammonia levels on the other.

Application of the hydraulic formula described by the Gorlins [4] for calculation of the area of cardiac valves and circulatory shunts provides further support for the hypothesis that peripheral ammoniemia was related to portacaval shunt size and, in turn, to blood flow. This formula as it applies to the present studies may be stated in general terms as follows:

$$\text{Flow Rate} = \text{Orifice Area} \times \text{Constant} \sqrt{\text{Pressure Gradient}}$$

The dimensions of each shunt orifice were determined at autopsy and the pressure gradient across the shunt was measured at operation; therefore, it was possible to make approximate calculations of blood flow rates through the shunts in the two groups of dogs. These calculations generally showed higher flow rates in the animals with large shunts. Since, in a portacaval shunt, as the orifice area of the stoma decreases, the pressure gradient across the shunt increases, these two factors have an opposing influence on the flow rate calculated from the formula. However, in using the actual measurements in the formula, the the present study in the Eck-fistula dog influence of orifice area was greater than that of the square root of pressure gradient, so that as shunt size decreased, flow rate also decreased even though pressure gradient increased.

In performing the direct end-to-side portacaval anastomosis, it has become accepted practice to create the largest possible anastomotic stoma in order to assure maximal portal decompression and thereby prevent esophageal varix bleeding. The results of the present study in the Eck fistula dog with a normal liver may not apply directly

to the usual clinical circumstance in which a portacaval shunt is performed in man in the face of a diseased liver, portal hypertension, and multiple spontaneous portal-systemic collateral connections. If they are applicable, the results suggest that the price for creating the largest possible shunt may be an increased incidence of post-shunt encephalopathy. While in terms of survival, paying this price may well be justifiable, it is possible that, by creating a smaller shunt or employing a different type of shunt with a lower blood flow rate, portal decompression adequate to prevent bleeding may be achieved without imposing so frequent a hazard of nervous dysfunction.

Summary and Conclusions

Reported experience indicates that nervous disorders occur with disturbing frequency following portal-systemic venous shunts in man. Substantial evidence suggests that the encephalopathy is due, at least in part, to ammonia intoxication resulting from the shunting directly into the systemic circulation of large quantities of ammonia laden portal blood. To determine the influence of the stomal size of portacaval anastomoses, and in turn of the blood flow rate through the anastomoses, on the concentration of ammonia in the peripheral blood, induced ammoniemia was studied in two groups of 16 dogs each, one of which had large end-to-side portacaval shunts measuring at autopsy 2.0 to 4.2 cm. in greatest diameter, and the other of which had small end-to-side portacaval shunts measuring 0.35 to 1.8 cm. in greatest diameter. A third group of 22 normal dogs served as controls. Ammoniemia was induced in 112 experiments by three standardized methods which consisted of the administration by gavage of ammonium citrate (0.5 Gm./kg.), gavage of fresh whole blood (30 ml./kg.) plus urease (4 u./ml.), and gavage of fresh whole blood (30 ml./kg.) alone. All three technics of ammonium loading resulted in higher mean peak blood ammonia levels in the dogs with large shunts than in those with small shunts and the differences were statistically significant with both the enteral ammonium citrate method and the enteral blood plus urease method. Furthermore, in the animals with large shunts, markedly elevated blood ammonia concentrations persisted for longer periods of time. Measurements of the pressure gradients across the shunts at operation revealed a mean gradient of 31 mm. saline in the small shunt group as compared to only 3.0 mm. in the large shunt group. A consistent inverse relationship was demonstrated between the height of the blood ammonia level and the magnitude of the pressure gradient across the portacaval anastomosis. Application of the Gorlins' hydraulic formula to these studies provided support for the presumption that the magnitude of ammoniemia was directly related to the blood flow rate through the shunt. It is concluded that the stomal size of end-to-side portacaval shunts, and in turn the rate of blood flow through the shunts, have a definite influence on the concentration of ammonia in the peripheral blood of the dog. Application of these results to man are speculative, but they suggest the possibility of a relationship between shunt size and post-shunt encephalopathy.

Acknowledgment

The authors gratefully acknowledge the technical assistance of Mrs. Sigrid Coulbourn and Mr. Bennie Hillman.

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