Reversal of Hepatic Venous Circulation in Dogs *

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IN THE PAST new knowledge of the anatomy, function, and circulatory hemodynamics of the liver has been developed by studying the effects of surgically altering the normal vascular relationships of this organ. Occlusion of the portal vein,[1] resection of the hepatic artery,[2] end-to-side and side-to-side portacaval shunts,[3] portacaval transposition,[4] partial occlusion of the hepatic veins,[5, 6] and arterialization of the portal blood [7] have each, in its own way, contributed substantially to understanding better hepatic function in man and experimental animals.

In 1952 one of us (C. G. C.) postulated that if the hepatic venous circulation could be reversed, new information concerning the liver might be acquired. Unknown to us at that time a similar assumption had been made in 1942 by Didier [8] who, at the suggestion of Hallion, performed experiments in dogs whereby the portal blood flow alone through the liver was reversed. Didier, however, was unable to keep his animals alive for prolonged periods of time; one died during the first night after operation, the other the next morning (Fig. 1).

This report is concerned with the development of an operation in the dog by which all caval blood caudad to the diaphragm traverses the liver in reverse. Although the majority of our animals died within 24 hours of operation, an appreciable number survived two to three months and one lived five months.

Methods of Reversing Hepatic Venous Blood Flow

1. Vena Caval-Iliac Homograft

Initially we conceived that hepatic venous blood flow could be reversed by occluding the vena cava just cephalad to the entrance of the hepatic veins and decompressing the portal vein into the vena cava above its point of occlusion. We believed a "Y" homograft consisting of the vena cava and iliacs of a donor dog ideally suited to such an experiment. The proposed experimental conditions were fulfilled by inserting the two arms of such a graft between the divided portal vein and suturing the proximal end of the graft to the host's inferior thoracic vena cava. Upon visual and tactile assurance that this shunt was functioning satisfactorily, the vena cava just above the diaphragm was suddenly and completely occluded by a stout ligature. We were gratified that caval blood of the host apparently traversed the liver in reverse, left the liver through the portal vein, joined splanchnic blood at the junction of the iliacs with the divided portal vein and entered the vena cava above the diaphragm through the caval graft. How

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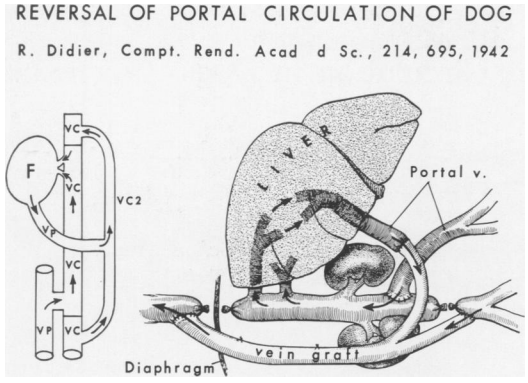

FIG. 1. Reversal of portal circulation of dogs. On the left is reproduced Didier's original diagram of his reversal of portal circulation in two dogs. On the right this diagram has been expanded pictorially to correspond with the remaining illustrations of this article. One of Didier's animals lived a few hours after operation; the other died the next morning.

normal hepatic arterial blood flow accommodated to this new direction of sinusoidal venous flow is still a matter of conjecture. Our initial operation is represented diagrammatically in Figure 2. Six dogs survived uneventfully until their abdominal wounds were closed. This so tightly compressed the caval segment of the graft between the swollen liver and the inferior thoracic cage that huge amounts of blood were impounded within the splanchnic venous bed. Systemic arterial blood pressure fell rapidly to zero and our animals died. The cause of death seemed obvious—shock due to loss of effective circulating blood volume.

2. Glass "Y" Cannula

Discouraged by our animals' inability to survive closure of their abdominal wounds, we devised glass cannulae roughly conforming in size and shape to the vena cava and iliac veins. Their inner surfaces were coated with silicon. These could be inserted rapidly into the inferior thoracic vena cava and the divided ends of the host's portal vein. Once again the hepatic venous circulation was reversed successfully after the vena cava was occluded just above the entrance of the hepatic veins. Such a preparation is represented diagrammatically in Figure 3. This time the abdominal and thoracic wounds could not be closed without disastrously kinking the portal vein and inferior thoracic cava at points of attachment to the cannula. These animals also died of shock—this time due to excessive blood in the liver and splanchnic bed.

3. Crimped Teflon Tube

When crimped woven teflon tubes were developed,[9] a prosthesis appropriately combining flexibility and rigidity became available to us for these experiments. Rather than relying upon a "Y" prosthesis we simplified the procedure by inserting an appropriate prosthesis of this material between the side of the portal vein and the side of the vena cava just above the diaphragm. When blood seemed to flow readily through this shunt, the vena cava was occluded at the diaphragm. This revised operation is shown diagrammatically in Figure 4.

By this method the hepatic venous circulation has been reversed in 43 dogs

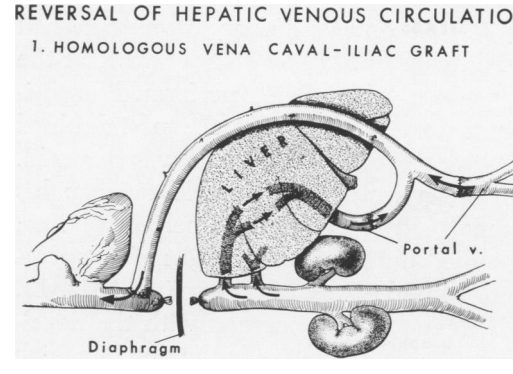

FIG. 2. Reversal of hepatic venous circulation of dogs. Method 1. Here an homologous graft is depicted decompressing the divided portal vein into the inferior thoracic vena cava after this vessel has been ligated and divided at the diaphragm. This preparation functioned nicely but the graft was occluded by compression between the liver and lower thorax when the abdominal wound was closed.

weighing between 12 and 43 kilograms. The junction of the portal and superior mesenteric veins was approached through a combined right thoraco-abdominal incision and the inferior thoracic vena cava through the bed of the 7th rib. One end of a crimped woven teflon tube 9.5 mm. in diameter was sutured to the anterior surface of the portal vein at the junction of this vessel with the superior mesenteric vein. This tube was then passed from abdominal to right thoracic cavity through a small rent in the anterior leaf of the right hemi-diaphragm. In the chest the other end of this tube was sutured, again in the end-to-side position, to the inferior thoracic vena cava. Both anastomoses were performed with the aid of clamps which only partially occluded the portal vein and vena cava. Immediately on releasing these clamps a slow infusion of 300 ml. of saline containing 50 mg. of heparin was started in a branch of the superior mesenteric vein. This did not seriously depress the animal's peripheral clotting mechanism but successfully avoided immediate clotting in the prosthesis. As soon as this variation of portacaval shunt appeared to be functioning nicely, the vena cava at the diaphragm was doubly ligated and divided between ligatures. Thus all caval blood caudad to the diaphragm entered the liver through the hepatic veins, presumably mixed with hepatic arterial blood at sinusoidal level and escaped from the liver through the portal vein. At the junction of the portal and superior mesenteric veins with the prosthesis hepatic blood mixed with splanchnic venous drainage traversed the prosthesis and reentered the general circulation through the inferior thoracic vena cava.

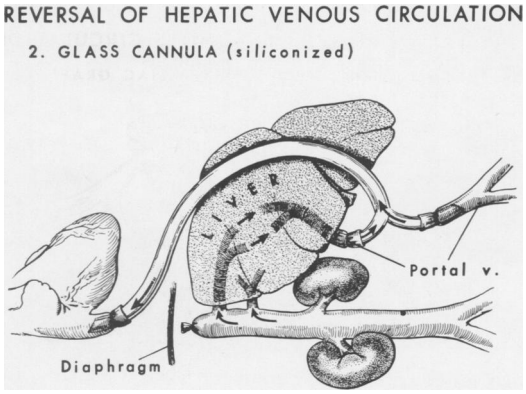

FIG. 3. Reversal of hepatic venous circulation of dogs. Method 2. Here an appropriately fashioned glass cannula is depicted decompressing the divided portal vein into the inferior thoracic vena cava after ligation and division of this vessel at the diaphragm. This functions splendidly until closure of the abdominal wound is attempted. Then occlusive kinking occurs at the sites of venous insertion of the ends of the cannula.

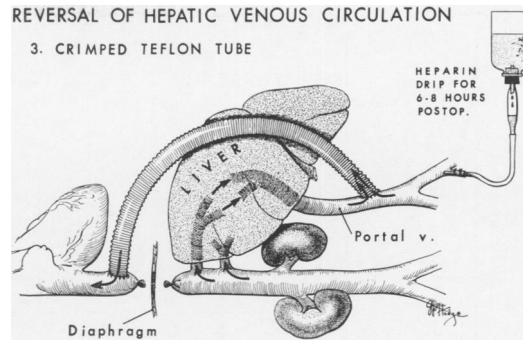

FIG. 4. Reversal of hepatic venous circulation in dogs. Method 3. Here an appropriate shunt has been secured by a crimped teflon tube. This procedure, a simplification of methods 1 and 2, has been followed by survival up to five months.

In the majority of animals the liver became turgid, dark red in color, and its edges blunted as soon as the vena cava was occluded. For some obscure reason the livers of a few dogs remained normal in appearance during hepatic venous reversal.

Mortality of Hepatic Venous Reversal

The hepatic circulation was reversed successfully in 43 dogs (see Method 3, above and Fig. 4). Thirty of these died within 24 hours and constitute our early mortality; 13 survived from four to 22 weeks and comprise a group of animals surviving two to five months (Fig. 5).

a) *Early Mortality.* Fortunately the second and third dogs in this series survived

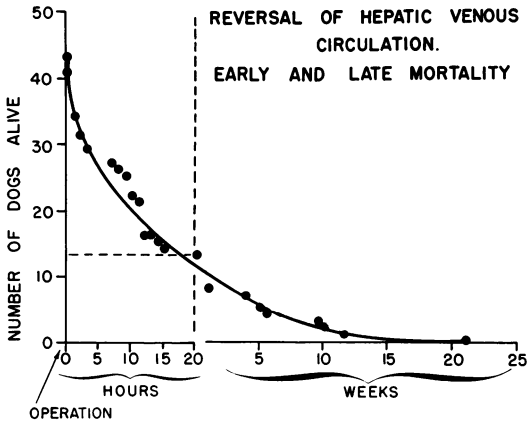

FIG. 5. Graphic representation of the period of survival following reversal of hepatic venous circulation. Thirteen animals survived the immediate postoperative period and comprise the late mortality group.

uneventfully. At four weeks their shunts were visualized roentgenographically by injecting diodrast into their inferior vena cavae. Study of these films clearly demonstrated the contrast media entering the liver through the hepatic veins and leaving through the prosthesis. One of these films together with an explanatory diagram is reproduced in Figure 6. Had it not been for these two successful experiments, we would probably have abandoned our efforts to reverse the hepatic venous circulation. With two exceptions our next ten animals died within 15 hours of operation. The cause of death so soon after operation has been, we believe, due to irreversible shock secondary to impounding of blood within the liver. Beginning at the time of occlusion of the vena cava the systemic arterial blood pressure fell relentlessly in spite of supportive transfusions and hydrocortisone (Fig. 7). During the period of survival peripheral venous blood pH [10] and total plasma CO_2 [10] fell while alpha ketoacids [10] and ammonia [11] rose (Fig. 8).* These observations together with the steady decline in blood pressure support our belief that shock secondary to loss of effective circulating blood volume was the cause of death

* After plotting the blood pH and plasma bicarbonate on a pH-bicarbonate diagram with PCO_2 isobars, it is readily apparent that accompanying the development of metabolic acidosis an important component of respiratory acidosis appears.

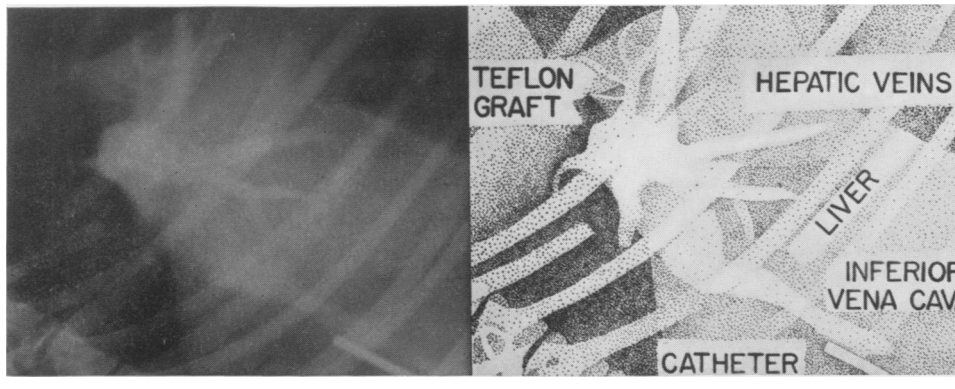

FIG. 6. Roentgen hepatography. On the left is an unretouched photograph of a roentgenogram obtained four weeks after successful reversal of the hepatic venous circulation of dog #58-112. This is representative of other similar studies. A catheter has been introduced into the inferior vena cava through which 20 cc. of 70 per cent diodrast was injected rapidly. During injection of the last few milliliters this film was obtained. It visualized nicely the contrast medium entering the liver through the hepatic veins. Only the major hepatic veins are visualized although the hepatic shadow assumes a ground glass appearance. Apparently the diodrast is so diluted by hepatic arterial blood that branches of the portal vein are not visualized. In the upper left hand segment of this film the diodrast appears in the prosthesis in sufficient quantity to once more become evident on this film.

The diagram on the right represents our interpretation of the venous shadows in this film.

early after reversal of the hepatic circulation.

The 30 animals in this group were examined shortly after death. In only one was the prosthesis completely occluded by antemortum thrombus. In another the portal anastomosis was occluded by an ill placed suture. In both of these animals marked congestion of the splanchnic venous bed was evident. In the remaining 28 animals the prosthesis was patent but in each one the liver was hugely engorged with blood. Save for this striking hepatic congestion, other abnormalities were not detected. These observations strengthen our belief that early death following reversal of the hepatic venous circulation has been due to impounding of blood within the liver. Why this occurs in some animals but not in others continues to perplex us.

Three efforts were made to avoid this immediate postoperative catastrophe. 1) Four dogs were given 50 mg. of cortisone acetate

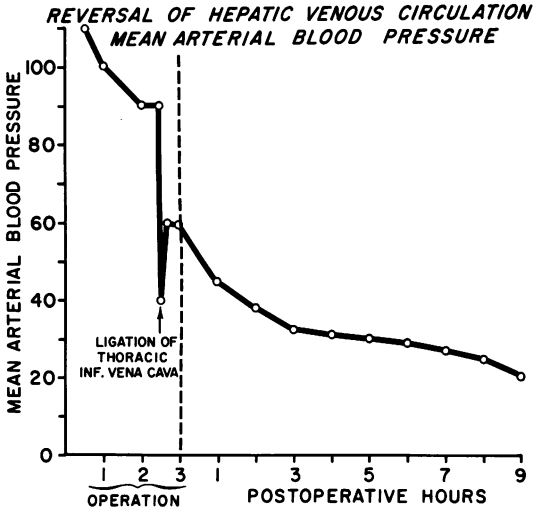

FIG. 7. Fall in arterial blood pressure in animals succumbing within 10 or so hours after reversal of hepatic venous circulation. This graph is a composite of the mean arterial blood pressure of 10 animals who died within 10 hours after reversal of hepatic venous circulation. The evidence of shock presented here togther with that presented in Figure 8 has convinced us that these animals have all died in shock secondary to impounding of blood in their livers.

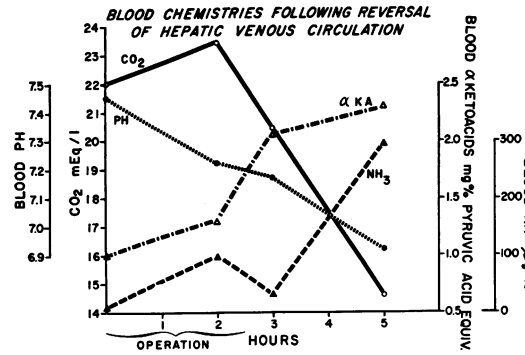

FIG. 8. Venous blood pH, venous blood ammonia, plasma CO_2, and plasma alpha ketoacids expressed as pyruvic acid equivalents among animals who died following reversal of hepatic venous circulation. Progressively during and after reversal plasma CO_2 and blood pH fell while alpha ketoacids and ammonia rose. These changes are commonly associated with hemorrhagic shock.[10, 11]

intramuscularly for three days prior to operation. During operation an infusion of 50 mg. of hydrocortisone was administered. Two animals died within six hours. The two animals that survived (31 and 93 days respectively) were given 50 mg. of intramuscular cortisone acetate daily for four days after operation. 2) The vena cava was constricted 50 per cent as a first stage operation in six animals. Here two survived five and 30 days respectively but four died in the immediate postoperative period. 3) Papaverine 30 mg. was given as an intravenous infusion to several animals hoping to relax intrahepatic smooth muscle and thereby to promote reversed intrahepatic blood flow. This too was without effect upon the mortality for all of these animals died.

b) Survivors and Late Mortality. Five animals died during the first week after operation. Death in two appeared to be due to extensive empyema but in the other three the cause of death was not evident. The prostheses were patent in all five. Eight animals survived 26 to 150 days. During this period serum bilirubin, blood ammonia, hematocrit, and transaminase were without striking abnormality. Serum albumin levels,

TABLE 1. *Observations on Eight Animals Surviving Reversal of Hepatic Venous Circulation*

Dog # and Period of Survival (Days)	Body Wt. Loss (%)	Change in Liver Wt.* (%)	Ascitic Fluid Vol. (ml.)	Comment	Blood Chemistries Following Operation**					
					Weeks After Oper.	T.P. (Gms./100 ml.)	A/G	NH_3 (mcg./100 ml.)	Hct. (%)	B.S.P.***
#58-112	48	−56.5	900	Prosthesis patent.	1	5.8	2.4/3.4			0.100
150 Days				Portal pressure 18 cm.	1.5	5.5	2.9/2.6	93	53	
				normal saline at 43 days	2	5.7	3.0/2.7	222	42	
					5	5.6	2.6/3.0	75	41	
					7	5.2	2.8/2.3	235	38	0.073
#58-135	21.4	157.0	5000	Prosthesis occluded	1	5.0	2.5/2.5	98	48	
93 Days					3	4.6	2.2/2.4	29	45	0.084
					8	4.4	2.7/1.7	64	23	0.083
#58-138	26.6	40.6	3000	Prosthesis occluded	1	5.0	2.5/2.5	145	49	
68 Days					3	4.7	2.5/2.2	50	49	0.082
					4	4.2	2.1/2.1	43	37	0.094
#58-162	23.7	32.8	2000	Prosthesis patent	2	4.9	2.0/2.9	40	34	0.100
64 Days					4	5.1	2.6/2.5	40	38	0.079
					5	4.9	2.9/2.0	42	39	0.082
#58-203	24.8	− 0.7	1600	Constriction of vena cava preoperatively. Prosthesis occluded						
31 Days										
#58-121	15.8	59.7	300	Empyema. Prosthesis	2	5.2	2.8/2.4	171	28	
31 Days				patent	3	5.7	2.4/3.3	280	43	
#58-100	13.5	−25.7	500	Aspiration during anes-	1	6.4	3.1/3.3	191		0.088
49 Days				thesia. Portal pressure	1.5	6.0	3.1/2.9	134	49	
				20 cm. normal saline at	2.5	6.8	2.9/3.9	149	38	0.078
				49 days. Prosthesis patent	5	7.1	2.7/4.4	117	42	
#58-170	17.3	12.4	2000	Empyema. Prosthesis occluded						
26 Days										

* Expressed as % change from estimated preoperative hepatic weight.

** Apologies are offered for not having preoperative values in these animals. Due to our inability to predict survivals preoperative values, although obtained in nearly all other animals, were capriciously omitted in this particular group.

*** Expressed as excretion rate constant at 5 minutes.

however, tended to fall in most of these dogs. Abdominal ascites in varying amounts was present in all long term survivors. Four ultimately died of occlusion of their prostheses by thrombus; the prosthesis, however, was patent in four at the time of death. All lost weight steadily; all ate poorly; all presented the clinical picture, including terminal coma, of animals succumbing to the effects of an Eck fistula. A variety of pertinent observations upon these animals has been summarized in Table 1.

Discussion

In this experience with reversal of the hepatic venous circulation in dogs we have been disappointed at the early high mortality of 70 per cent and our inability to secure long term survivors in appreciable numbers. We had hoped, of course, to establish a colony of animals in whom to study the effects of hepatic venous reversal upon regeneration of the liver and alterations in metabolism. We believe it would be important to determine whether such a preparation with its copious hepatic blood flow could survive resection of its hepatic artery. With additional experience we believe all these objectives can be achieved in time.

In the interim a number of additional observations upon these animals merit comment. In nine of the 13 animals surviving the immediate postoperative period, the teflon prosthesis was patent. Thrombosis occurred four times and in each the prosthesis had been in place three weeks or longer. Thus in 50 per cent of those animals

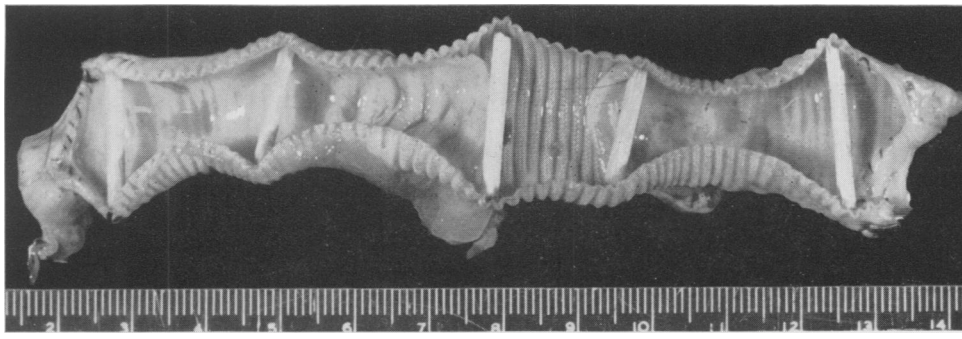

FIG. 9. Unretouched photograph of a teflon tube which successfully decompressed the portal circulation of dog #58-112 into the inferior thoracic vena cava for a period of 150 days. This is lined with a smooth glistening membrane which upon microscopic examination proved to be neointima composed of flattened dense collagenous connective tissue. The separation in the mid portion of the neointima occurred during preparation of the specimen for photography.

surviving longer than three weeks, the teflon tube was patent. Throughout the entire length of those remaining open, a smooth grey glistening lining was obvious (Fig. 9). Microscopic examination proved this to be neointima consisting of flattened dense collagenous connective tissue. Where occlusion had occurred the line of anastomosis was free of thrombus. The point of thrombosis was about a centimeter inside the suture line. The mid portion of the tube had been compressed but not occluded by the enlarged liver. In animals with occluded prosthesis the collateral circulation was striking. Dilatation of the azygous system was particularly prominent. Esophageal varices, however, had not formed. Two hundred to five thousand milliliters of ascitic fluid distended the peritoneal cavities of each animal. The volume was greatest in those animals in which the prosthesis was occluded. Nevertheless a patent shunt did not preclude ascites. Occlusion of the tube, of course, constituted total ligation of the supradiaphragmatic portion of the inferior vena cava. Survival of these animals depended upon collateral circulation for decompression of the venous system below the diaphragm. Analysis of ascites obtained by paracentesis and serum drawn simultaneously appears in Table 2. Although only two animals were investigated in this manner the total protein and albumin globulin ratio are quite similar to the values found in dogs following partial constriction of the thoracic inferior vena cava and maintained on a high protein and high sodium chloride diet.[6] Our animals have been maintained on a standard laboratory diet consisting of dog meal and canned horse meat.

Microscopic examination of sections of the liver reviewed at postmortem examination and at exploratory celiotomy revealed: 1) dilatation of the subcapsular lymphatics, 2) congestion of the hepatic veins, 3) small

TABLE 2. *Analysis of Sodium, Albumin, and Globulin in Serum and Ascites*

	Serum			Ascites		
Dog #	Sodium (mEq./L.)	Albumin (Gm./100 ml.)	Globulin (Gm./100 ml.)	Sodium (mEq./L.)	Albumin (Gm./100 ml.)	Globulin (Gm./100 ml.)
58–135	146	2.0	4.0	147	1.4	1.4
58–138	143	2.2	2.4	143	1.5	1.3

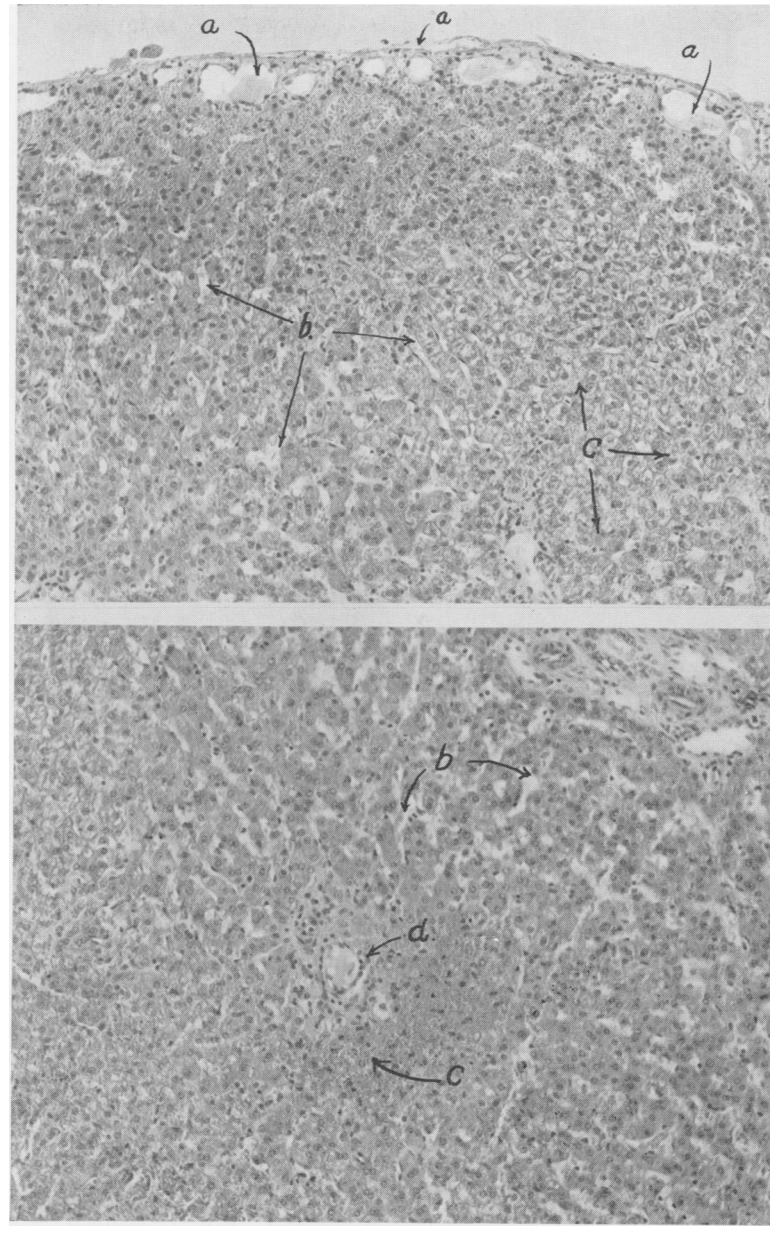

FIG. 10. Representative microphotographs of liver after reversal of hepatic venous circulation in dog #58-112 at 42 days afttr procedure. *A* (upper). Section through the surface of the liver. Here the most striking feature is marked distention of the subcapsular lymphatics (a). In addition the sinusoids are distended with blood (b) and there is minimal evidence of pericentral degeneration of hepatic cells (c). *B* (lower). Section from deep within the liver. Here the most prominent feature is distention of the central veins (d), degeneration of adjacent hepatic cells and sinusoidal distention with blood of (b).

areas of necrosis in the central portion of the hepatic lobule and 4) sinusoidal congestion (Fig. 10, A and B). These changes are similar in all respects to those described by Bolton following constriction of the supradiaphragmatic inferior vena cava in cats.[5] Where the prosthesis was occluded congestion of the hepatic veins and sinusoids was prominent and in many instances areas of hemorrhage into the hepatic parenchyma was demonstrated.

These animals have reflected many of the clinical features common to dogs with Eck fistulae. During the pre-terminal period all were anorexic and debilitated. Semicoma intervened just prior to death. In all instances weight loss was noted even in the presence of large volumes of ascitic fluid.

Hypoalbuminemia and periodic hyperammonemia, phenomena well known in the Eck fistula dog, were also present in our animals shortly prior to death.

Certain features present in these animals are not, however, commonly seen in dogs with Eck fistulae. Abdominal ascites was a consistent finding. This, of course, is not encountered in animals with end-to-side portacaval shunts. Comparison was made of the hepatic weight at the time of postmortem examination and an estimated preoperative hepatic weight. This latter figure was based on the known ratio of hepatic weight to body weight in a group of normal dogs. With two notable exceptions the weight of the liver increased in animals surviving more than three weeks following operation (Fig. 9). This is in contrast to the Eck fistula preparation in which a decrease in weight of the liver has been found.[12]

Conclusions

1. Dogs may survive as long as five months after complete reversal of hepatic circulation.

2. A high postoperative mortality is presumed due to shock secondary to impounding of blood within the liver.

3. Late deaths appear due to a combination of an Eck fistula effect and hepatic ascites.

4. Crimped teflon prostheses have remained patent in low pressure venous systems for as long as five months.

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Discussion

DR. HAROLD LAUFMAN: I think we would all agree that it would be most feasible to have a preparation to reproduce the pathologic condition of esophageal varices as we see it in the human being. Consequently for the past five years we have been studying the natural history of portal hypertension in the macacus Rhesus monkey.

This is rather easily produced by superimposing two procedures that other people have used separately for other purposes. If a partially occluding band is placed around the inferior vena cava