

against a major role for the ovary in control of the 5α enzyme level. The more marked effects of hypophysectomy are difficult to interpret, especially as several trophic hormones were able in some degree to restore the levels of activity toward normal.

Summary. 1. The rate of Δ^4 reduction of 11-deoxycortisol was 3-4 fold greater in female than in male rat liver whole homogenates. The same sex difference was found in microsomal fractions containing the Δ^4 - 5α -hydrogenase. 2. Evidence was found for only one Δ^4 -hydrogenase (5α -microsomal) in female rat liver in contrast to the male liver which contains the soluble Δ^4 - 5β -hydrogenase as well. 3. Ovariectomy of adult female rats

did not produce any marked change in enzyme titer. Hypophysectomy resulted in a sharp drop which could be reversed in part by ACTH, growth hormone or pregnant mare's serum. 4. Rapid increases in the titer of Δ^4 - 5α -hydrogenase in the liver of the female rat occurred prior to the known stages of sexual maturation.

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Reversal of Hepatic Venous Circulation in Dogs.* (24431)

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(Introduced by J. M. Hayman, Jr.)

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Much has been learned over the years about the function of liver in animals by surgically altering its normal vasculature. Ligation of the hepatic artery(1), Eck fistula(2), transposition of portal vein and vena cava(3), and partial occlusion of the hepatic outflow tracts (4) have all contributed to a better understanding of the complexities of hepatic function. Several years ago one of us (CGC) conceived that additional information about function and hemodynamics of the liver might be gained were it possible to study for prolonged periods animals whose hepatic venous circulation had been reversed. This report describes experiments in dogs as a result of which all caval blood caudad to the diaphragm enters the liver through the hepatic veins and leaves, together with the hepatic arterial blood, by way of the portal vein. Dogs with this type of reversal of hepatic blood flow have now survived up to 57 days in apparent good health. Didier(5) demonstrated in dogs that the flow of portal blood alone could be re-

versed for a few hours. He did his experiments at the suggestion of M. Hallion, but did not, as far as we have been able to determine, secure prolonged survival among his animals. Didier's experiments were not known to us when we started our investigations of reversal of hepatic venous circulation.

Materials and methods. Healthy mongrel dogs weighing 12 to 44 kg were anesthetized with intravenous pentobarbital sodium, 60 mg/2.2 kg of body weight. Animals were maintained during open thoracotomy by intermittent positive pressure endotracheal insufflation. A crimped teflon[†] vascular prosthesis, 1 cm internal diameter and varying in length with size of dog from 11 to 15 cm, was used to maintain free flow of blood from the side of the superior mesenteric vein to the side of thoracic inferior vena cava. After completion of end to side anastomoses, 50 mg of heparin in 500 ml of isotonic saline solution was administered slowly over 3 hours into a convenient vein in the jejunal mesentery. When the vascular prosthesis between superior mes-

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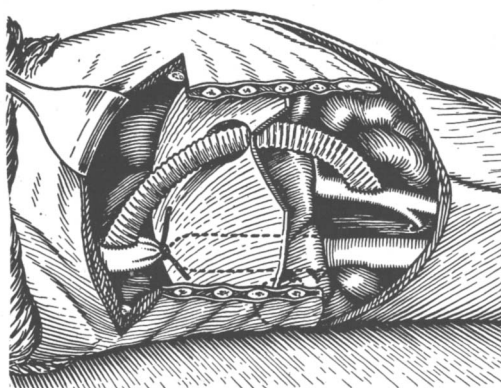


FIG. 1. Diagrammatic representation of reversal of hepatic venous circulation in the dog, right upper abdomen, right lower thorax and right diaphragm are exposed. Free blood flow from superior mesenteric vein to inferior thoracic vena cava is provided by crimped teflon vascular prosthesis sutured in end-to-side positions. The vena cava has been securely ligated with heavy braided silk just above diaphragm. All caval blood, to and including diaphragmatic veins, enters liver through the hepatic veins and leaves the organ through the portal vein. It is joined at sinusoidal level by the hepatic arterial blood and at about site of superior mesenteric anastomosis by splanchnic venous drainage. Preparations of this type are now surviving 2 mo after operation in apparent good health.

enteric vein and inferior thoracic vena cava appeared to be functioning nicely, the vena cava was securely ligated, and in many dogs divided, just cephalad to diaphragm (Fig. 1). The abdominal and thoracic wounds were then closed in layers. During operation unmatched citrated whole dogs' blood was administered when necessary. On the day following operation and thereafter the animals were allowed free access to water and a standard laboratory diet consisting of dog meal and canned horse meat. Seven and 30 days following operation cinefluoroscopic and venographic studies were performed upon 3 survivors. In each instance 20 ml of 70% Diodrast solution was injected into the inferior vena cava just below entrance of the renal veins. The opaque mass could be followed radiographically to the sinusoidal level within the liver. Here, free mixing with hepatic arterial blood precluded visualization of portal venous radicals. The hepatic shadow could be, however, identified. As caval and hepatic arterial blood left the liver, its Diodrast content was further diluted by mixing at site of portal anastomosis with splanchnic portal blood. Nevertheless, visualization of the

vascular prosthesis was obtained. A representative caval venogram and hepatogram is reproduced in Fig. 2, together with an explanatory diagram. Microscopic sections were made of small segments of liver removed from some animals on 4th, 5th, 42nd, and 50th days after operation. The only microscopic features of these livers, distinguishing them from

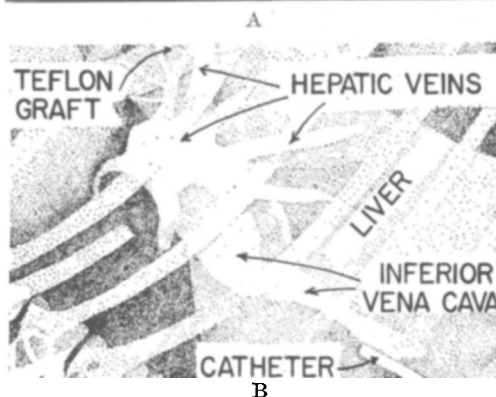


FIG. 2A and 2B. Caval-hepatic venogram, following reversal of hepatic venous circulation.

FIG. 2A. Unretouched cavalgram and hepatic venogram obtained by inj. 20 ml of 70% Diodrast into vena cava of dog just caudad to entrance of renal veins. The contrast medium can clearly be seen in the vena cava, in hepatic veins, in liver and faintly in teflon vascular prosthesis.

FIG. 2B. Tracing of roentgenogram (A) appropriately labeled.

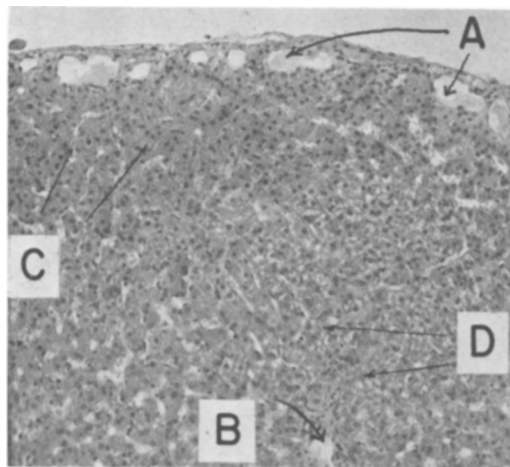


FIG. 3. Microscopic sections obtained from dog whose hepatic venous circulation had been reversed for 47 days. A = dilated subcapsular lymphatics; B = dilated central veins; C = sinusoidal congestion; D = central necrosis.

normal, are: (1) dilated subcapsular lymphatics; (2) dilated central veins; (3) sinusoidal congestion; and (4) small areas of central necrosis of hepatic cells. Representative microscopic section is reproduced in Fig. 3. Total protein, serum albumin, serum globulin, serum bilirubin, blood ammonia, bromsulfalein excretion, and serum glutamic oxaloacetic transaminase were measured at intervals after operation in the peripheral blood of surviving animals. The only consistent abnormality was a persistently elevated blood ammonia in most animals.

Results. Hepatic venous circulation has been reversed in 19 dogs. Seven have survived 4, 5, 17, 23, 27, 47, and 57 days after operation. One healthy survivor died during an exploratory celiotomy performed 47 days after operation. The cause of death was clearly pulmonary aspiration of gastric contents. The remaining 12 animals died within 6 to 18 hours of operation. In 8 the teflon prosthesis and both anastomoses were patent; in 4 these were partially compromised by thrombi. The cause of this high postoperative mortality has been obscure. At one time we thought it might relate to inactivation of cortical adrenal steroids by their immediate passage through the liver(6). Cortisone acetate administered before and after operation failed, however, to alter our rate of survival.

The abdominal cavities of 2 animals were explored at 42 and 47 days respectively. Each contained several hundred ml of ascitic fluid. The liver in each was enlarged, tense, and dark red in color with areas of blue mottling. The portal pressures were 18 and 20 cm of saline. The peritoneal cavities of 2 animals which died at 4 and 5 days contained 700 to 800 ml of ascitic fluid. The composition of the fluid in these 4 animals was essentially the same as that produced in dogs by partial constriction of the thoracic inferior vena cava with a metal band.

Dogs surviving this operation from 17 to 57 days have all lost up to 30% of preoperative body weight. In this respect they resemble animals with end to side portacaval shunts (Eck fistulae). Whether they will exhibit further nutritional deterioration, "meat intoxication" and death, characteristic of animals with an Eck fistula, is currently under investigation(7).

Conclusions. 1. Dogs survive for prolonged periods, at least 57 days, following reversal of their hepatic venous circulation. 2. Crimped teflon vascular prostheses remain patent in these low pressure venous systems and function satisfactorily enough to achieve objectives of this experiment. 3. This experimental preparation is presented as one potentially capable of contributing materially to studies of hepatic function and intrahepatic and extrahepatic vascular hemodynamics.

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