TABLE III. Effect of Cholic and Dehydrocholic Acids on Rate of Oxidation of Sodium Acetate-1-C^{14}.

Exp.	Group	Total $C^{14}O_2$, counts/min.	Significance
A	Control	$156.5 \times 10^5 \pm 8.8 \times 10^5$	$P = .65$
	Cholic acid treated (.5%)	$159.7 \times 10^5 \pm 9.8 \times 10^5$	
B	Control	$129.4 \times 10^5 \pm 11.35 \times 10^5$	$P = .10$
	Dehydrocholic acid (.5%)	$146.0 \times 10^5 \pm 12.92 \times 10^5$	

maintained normal tissue cholesterol level. Whether or not the drop in synthetic rate is a primary effect of cholic acid can not be decided from these data. There was a very small but significant increase in liver cholesterol level, and it is well known that accumulated cholesterol will retard the rate of cholesterol synthesis.

The hypercholesterolemia resulting from simultaneous feeding of cholesterol and bile acids, can readily be explained by our results. The data in Table II show that cholic acid, and to a lesser extent dehydrocholic acid, reduced rate of mobilization of serum and liver cholesterol. Pihl has shown that dietary bile acids have little effect on rate of cholesterol absorption at the 0.5% level. Therefore, simultaneous feeding of cholesterol and bile acids must result in cholesterol accumulation.

In agreement with previous studies(1,2) cholic and dehydrocholic acids have similar but quantitatively different effects.

Summary. 1) A 3-week period of feeding a diet containing 0.5% cholic acid did not alter serum and adrenal total cholesterol levels. However, a slight but significant increase in liver total cholesterol was observed. Dietary dehydrocholic acid had no effect on serum, liver or adrenal total cholesterol levels. 2) Cholic acid increased serum bile acid concentration, while dehydrocholic acid had no effect. 3) Dietary cholic acid reduced rates of synthesis and mobilization of cholesterol in both liver and adrenal. Dehydrocholic acid produced similar results but to a lesser degree. 4) Accumulation and mobilization of serum cholesterol were retarded by dietary cholic acid, and slightly by dehydrocholic acid.

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Effects of Gradual Complete Occlusion of Hepatic Veins in Dogs. (24221)

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The basic physiology of portal hypertension and ascites associated with portal cirrhosis is not satisfactorily explained. Proposed experimental methods for producing portal cirrhosis have failed to reproduce a clinical picture of portal hypertension(1-4). Madden *et al.*(5) working with corrosion specimens of the liver postulated that the primary factor in formation of ascites is an obstruction of the outflow tract of the liver, namely, the hepatic veins. This hypothesis appeared to us to be worthy of further experimental verification. After preliminary work on the anatomy of hepatic veins in dogs, we devised a relatively simple procedure for occlusion of these vessels.

Materials and methods. Adult mongrel dogs ranging in weight from 12.5 to 20.0 kg

were anaesthetized with sodium pentobarbital (30 mg/kg body weight) intravenously and the anterior abdominal walls were prepared by the usual sterile methods.

The abdomen was opened through a mid line incision. The portal vein and inferior vena cava were identified and venous pressures in the vessels taken by introduction of a thin walled 15-gauge needle into the lumen of the vessel through an area of vein wall enclosed by a purse string suture of 4-0 vascular silk. Prior to withdrawing the needle from the portal vein 20 cc of 70% Diodrast (Iodopyracet-Winthrop) was injected and a roentgenogram taken. The needle was then withdrawn and the puncture closed by the purse string suture.

A segment of the inferior vena cava cephalad to the renal veins was mobilized for a distance of 3 to 4 cm. Blalock vascular clamps were placed at upper and lower ends of this segment of vein. A piece of thin-walled, wide bore polythene cannula was then selected. A suture of No. 4-0 vascular silk was placed on the caudal end of the cannula to act subsequently as its anchor suture. Several small, silver, neurosurgical clips were placed on both ends of the cannula to facilitate radiological localization of the cannula when it was in place. The Blalock clamps were closed and an incision 1.5 cm long was made into the anterior wall of this isolated segment of the vena cava. The bevelled end of the cannula was introduced into the phlebotomy incision while an assistant released the cephalad Blalock clamp so that the cannula was fully inserted into the lumen of the vena cava (Fig. 1). The anchor suture of the cannula which had the needle still attached was brought out through the vein wall at the caudal end of the incision. The suture was then utilized to close the incision in the wall of the vena cava. A running stitch was employed for this purpose. In earlier cases we had not anchored the cannula in this fashion with the result that it was rapidly carried to the right atrium of the heart and led to the death of the animals. A neurosurgical type suction was found to be the best method for achieving visualization of the wound during closure of the opening in the vena cava. In each operation we selected the largest calibre of cannula which could be conveniently inserted into the vena cava. The abdomen was closed in layers without drainage.

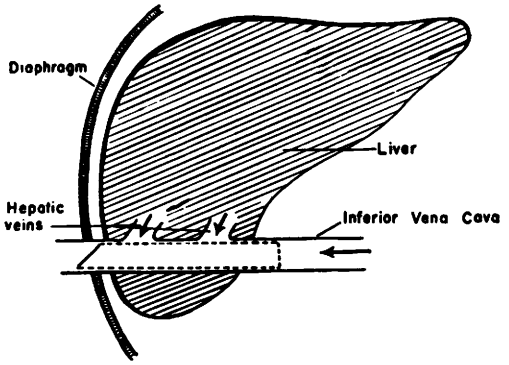

FIG. 1. Lateral projection of liver and inferior vena cava. Dotted lines illustrate position of plastic cannula. Wall of the cannula is in apposition to ostia of hepatic veins.

The following laboratory tests were done on each animal: (a) serum proteins with A/G ratio and electrophoretic fractionation; (b) serum sodium, potassium and chloride and (c) bromsulfalein dye retention(6). These studies were done preoperatively and at 2-week intervals following operation.

When ascites became clinically evident the animals were reoperated. Direct pressure readings were again taken from the inferior vena cava and portal vein. In a certain number of cases the portal venogram was repeated. When the animals were sacrificed necropsy specimens of liver, spleen, kidney and inferior vena cava in the region of the hepatic veins were taken.

Several dogs demonstrated at necropsy a complete obstruction of the vena cava associated with blockage of the hepatic veins. The possible role of the vena caval obstruction in production of the ascites and portal changes was, therefore, investigated and a control experiment was devised. Four dogs were selected and a short cannula of the same material was used. It was placed in the vena cava just cephalad to the renal veins, but well caudad to point of entry of the hepatic veins into the vena cava. The same biochemical studies were made as in the main experiment.

Results. Four animals survived the opera-

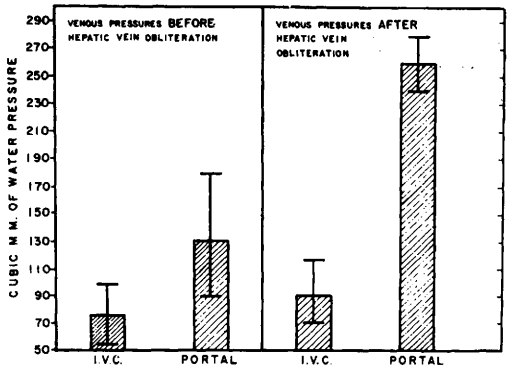

FIG. 2. Pressure (means and ranges for 10 dogs) in inferior vena cava and portal veins before and after obliteration of hepatic veins.

tion but died within a few days and before developing evidence of ascites.

Ten dogs developed clinically demonstrable ascites within 6 to 8 weeks of operation. In these the abdomen became markedly distended and tortuous venous collateral channels became prominent in the abdominal wall. When the ascites reached full clinical proportions, the animals developed a pitting oedema over the hind legs. Amount of ascitic fluid present varied with size of the animal, but ranged from 3500 to 5500 cc.

The pressures in the inferior vena cava and in the portal vein taken at the time of the original operation in this group averaged 75.3 mm and 130.5 mm of water respectively. When the animals were reoperated after establishment of ascites the pressures in these vessels averaged 90.5 mm and 260 mm of water respectively (Fig. 2). It was interesting to note that in this group the portal-systemic collateral venous channels were markedly dilated.

In each of the 10 animals the peritoneal cavity was filled with a clear yellow fluid of high specific gravity which had a protein pattern very similar to that of the plasma of the animal. The portion of the vena cava which contained the plastic cannula was thickened and examination of its intima showed that the ostia of the hepatic veins had been obliterated by organized thrombi in the lumen of each vein (Fig. 3). Various stages of thrombus formation and organization could be recognized in serial sections of the hepatic veins (Fig. 4). Sections of the liver taken at necropsy revealed marked congestion in the central region of the liver lobules. Fibrosis of the liver substance was not a prominent fea-

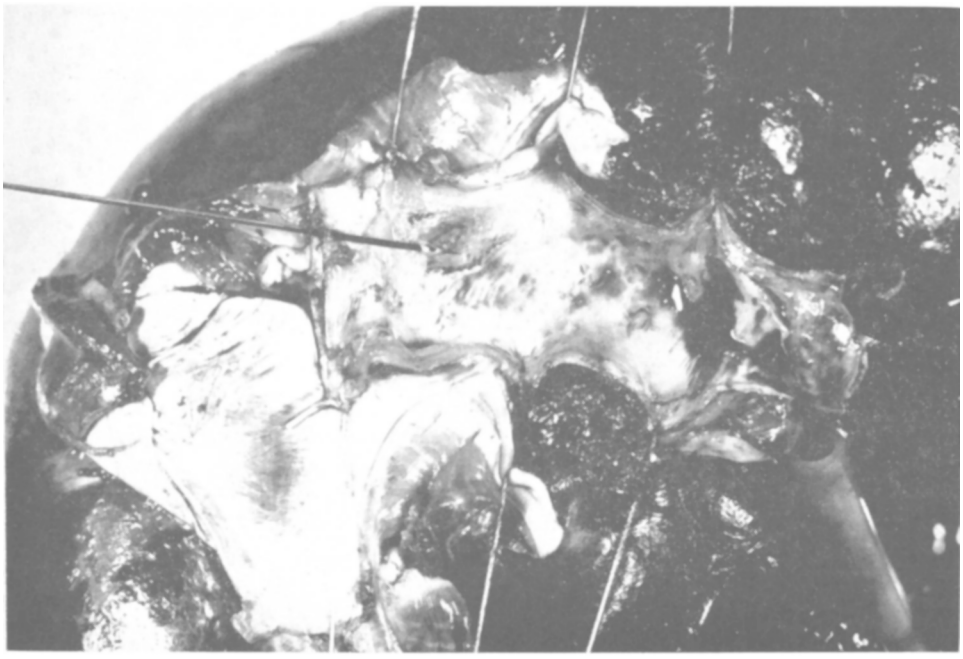

FIG. 3. Inferior vena cava has been opened in region of hepatic vein ostia. Scarred area at tip of pointer marks position of an obliterated hepatic vein ostium.

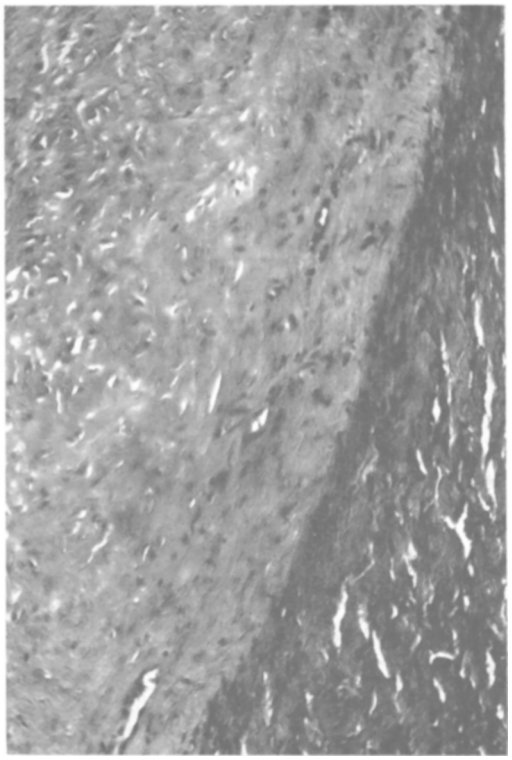

FIG. 4. Thrombus organization in lumen of an hepatic vein. The darker tissue represents the original wall of hepatic vein, the lighter tissue the organized thrombus.

ture in any of our animals. Sections of the spleen and kidneys revealed moderate congestion.

Four control dogs remained healthy for a 6-month period following operation. There was no evidence of clinical ascites or portal hypertension and their biochemical tests remained normal. When sacrificed the cannula was patent in 2 of the animals and completely thrombosed in the other 2, indicating that in these 2 the factor of vena caval obstruction had been reproduced. In none of these animals was there evidence of occlusion of the hepatic veins. This would indicate that the pathology resulting in the original series was due to occlusion of the hepatic veins and not to occlusion of the inferior vena cava.

The animals showed an overall decrease in total serum protein with a reversal of the albumin-globulin ratio and an abnormal electrophoretic pattern: significant decrease of albumin and rise of alpha$_2$ and gamma globulins. The bromsulfalein dye retention(6) increased from 10% to 70% as the ascites progressed. Serum sodium, potassium and chloride showed little fluctuation and remained essentially normal throughout the procedure.

Discussion. Presented data show that marked ascites and a degree of portal hypertension are produced in all animals in which this procedure is correctly employed. It is necessary to stress the importance of accurately placing the cannula so that fibrosis of the ostia of all the hepatic veins is produced. Failure to obliterate even one large hepatic vein may permit enough venous outflow from the liver to prevent formation of ascites and portal hypertension. We feel the control experiment described demonstrates that the important factor in production of portal hypertension and ascites is the occlusion of the hepatic outflow tract and that the inferior vena caval obstruction which occurs in some of the animals is not an important factor. This procedure is relatively simple technically and produces uniform results. It provides a source of clinical and experimental material by which we may assess the relative merits of the types of therapy currently prescribed for these conditions.

Summary. A new method for producing gradual, complete occlusion of the hepatic veins is described. Associated with this is the successful production of ascites and a degree of portal hypertension.

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