# Experimental Portal Hypertension *

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THE INABILITY to solve the riddle of portal hypertension stems largely from not being able to produce the disease experimentally in animals. The purpose of this present communication is to evaluate some of these experimental efforts and see if they explain the course of the disease in man. A multiplicity of experimental methods suggests that none are completely satisfactory. To these are added our own experiences of producing cirrhosis by injecting silicon dioxide into the portal venous system.

## METHOD

Any discussion of this condition must include a definition of the term portal hypertension. Formerly,[4, 21] all portal venous pressures above 20 cm. of water were considered hypertensive. It soon became evident that this pressure was in no way abnormal. The average portal pressures recorded in normal patients is 20 cm. with the lowest reading in the neighborhood of 14 cm. and the highest 26 cm. Thus, pressures below 30 cm. would seem to be in the normal range; pressures of 40 to 50 cm. are certainly hypertensive with those in the intermediate 30 to 40 cm.-range debatably hypertensive.[21]

Eight mongrel dogs were used, each weighing between 25 and 35 pounds. At intervals varying from three weeks to three months each animal was anesthetized and the abnormal cavity opened. A convenient loop of small intestine or omentum was brought loosely into the wound so that one of its larger veins could be easily canalized with a 19-gauge needle. The portal pressure was then taken using an ordinary calibrated glass standpipe filled with saline. The solution was allowed to fall until it reached a level dictated by the portal pressure. This reading was corrected to the level of the anterior surface of the upper lumbar vertebral bodies. Care was taken so that the loop of mesentary or omentum lay completely limp in the wound as any traction or binding on the wound margin caused a false elevation of the pressure. A good valid reading was obtained when there was a slight fluctuation of the water column caused by the animal's respiration.

After the portal venous pressure was taken a suspension of silicon dioxide was injected into the radical of the portal vein. This was done by means of an Asepto syringe connected to the needle by a rubber tube. The silicon used was obtained through the courtesy of Dr. L. W. Spolyar of the Indiana State Board of Health. The quartz flour was 99.4 per cent $SiO_2$. Its particles varied in size from 1 to 50 $\mu$ and by volume about half were under 3 $\mu$. From one and one-half to two grams of this material were suspended in 30 cc. of saline for injection. The number of such doses varied in different animals and none was given if gross necrosis was present in the liver. Likewise no further silicon was given after the onset of actual hepatic scarring.

This method had the distinct disadvantage of requiring a formal operation at each time a pressure reading was taken or quartz flour injected. It did, however, seem important to present a running log of portal pres-

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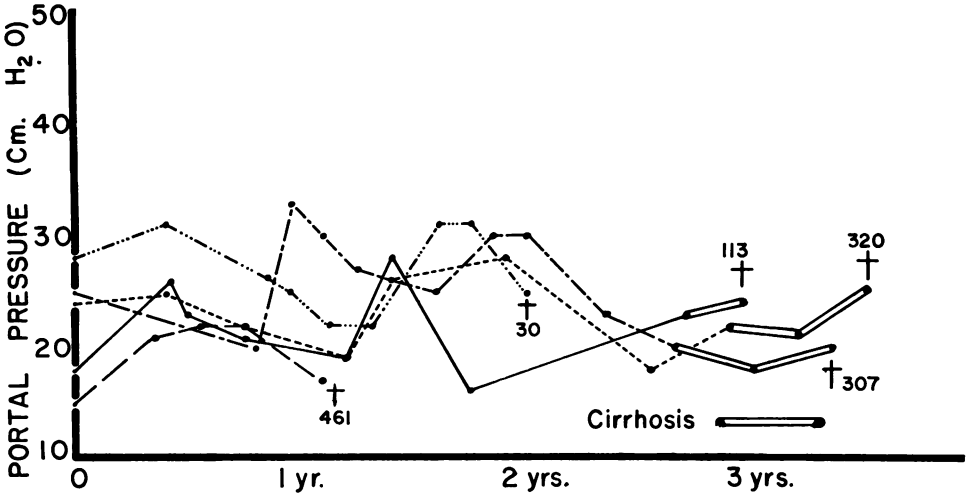


FIG. 1. Graphic representation of portal pressures in five dogs injected with silicon dioxide over a period of three years. Two animals died apparently with liver failure during the first two years. This was true also of dog 113. Dogs 307 and 320 were killed to terminate the experiment. The silicon caused varying degrees of liver necrosis which after two and a half years was replaced by scar and diffuse cirrhosis. It will be noted that though the consecutive pressures were not uniform, none can be considered hypertensive.

sures from beginning of liver necrosis to liver scar. Three of the dogs were operated upon more than 12 times each and each received more than 14 grams of silicon.

## RESULTS

One of our animals died as a result of a technical operative error and two died from causes associated with trying to keep animals alive over long periods of time in a laboratory. These three need not be included since their deaths were in no way connected with the experiment at hand. The remaining five are discussed and the successive portal pressures are diagrammed in Figure 1.

The silicon dioxide in itself seemed to be rather benign but it caused a necrosis in the liver which at times appeared to be quite toxic. Two of our animals died after four and eight injections over a period of one and two years. Nothing was found on postmortem except moderate degenerative changes in the liver. We feel that these and the death of one of the longer survivals (Dog 113) were due to over enthusiastic medication and that any future trials should be done in a more leisurely fashion.

It is shown in Figure 1 that the portal pressure readings remained almost entirely between 20 and 30 cm. of water. If there can be said to be any tendency toward elevated pressure it will be noted that this occurred during the first year or two of medication when only necrosis was seen in the liver. By the time actual scar had appeared the pressures seemed to be somewhat lower.

As noted (Fig. 1) no actual hypertensive readings were found. We must, therefore, conclude that portal hypertension was not produced by this means. There is but one possibility that these interpretations are incorrect and that is the chance that the pressure might have been elevated at some time other than at the time of study. For instance it might have been elevated between readings in the early part of the experiment or it is possible that it still might become elevated months or so after the termination of the experiment. Both these possibilities seem rather unlikely.

The resulting scar and cirrhosis (Fig. 2) was diffuse but had a tendency to produce rather large plaque-like fields. These scars were always preceded by liver necrosis. A small amount of ascitic fluid was common.

It should be noted that no portal varicosities or unusual vascular dilatations were noted during any of the experiments. No vascular abnormalities were seen at postmortem examinations.

### PREVIOUS EXPERIMENTS

Attempts to reproduce the disease experimentally may be grouped in three main categories:

1) Those aimed at obstructing the flow of portal venous blood before it reaches the liver;

2) Obstruction to the flow in the liver itself by means of experimental cirrhosis;

3) Obstruction of the portal flow after it leaves the liver (hepatic vein).

Representative results of these attempts will be discussed under their separate headings. The field is too broad to list all the contributions and many are omitted merely because they are confirmatory of those cited.

### PORTAL VEIN OBSTRUCTION

The simplest, most obvious and logical method of producing portal hypertension is by portal vein obstruction. In the experimental animal or in man there is nothing more dramatic. When the normal portal vein is occluded there is an immediate and inevitable rise in portal pressure to hypertensive levels (40–50 cm. of water). With release of the vein the pressure falls just as rapidly to the original normal reading. This is very definite and convincing but there is one flaw in this experimental argument. It is an acute experiment and valid only as an acute observation.

It has been shown in animals and assumed also to occur in man, that following occlusion of the normal portal vein there is the expected rise in portal pressure to hypertensive levels which is followed by a gradual return of the pressure to normal over a period of a week or two.[6, 9, 12, 15, 17, 24] The return to normal presumably is caused by the development of collateral venous bypasses between the portal and caval systems. It has been discouraging that none of these attempts have reproduced the chronic form of the condition seen in man.[5, 10] Every altered pressure returns to a balanced normal.

It is well known that the dog will not tolerate acute obliteration of the portal vein. Such a procedure results in death in a short time from blood loss from the obstructed veins of the mesentery. However, the portal system of dogs may be completely obstructed in stages with a final resulting pressure which is quite normal. Complete acute interruption of the portal vein during abdominal resections for cancer in man are now commonplace. While these latter procedures are in no way experimental, they have never resulted in a portal hypertension syndrome. Therefore, there is no evidence that this type of extrahepatic portal obstruction causes a persistent elevation of pressure.

For completeness it is proper to include a discussion of arteriovenous shunts as a possible cause of portal hypertension. These have been demonstrated both intra-hepatic and extra-hepatic and undoubtedly play a part in all portal systems. After all, in a broad sense the hepatic artery forms an arterial shunt into the portal system. This explanation, that the disease is the result of congenital or acquired arteriovenous shunts, leaves much to be desired. It does not explain those elevated portal hypertensions in man which return to normal at a later date. It does not explain absence of cardiac hypertrophy as might be expected with a shunt of similar magnitude elsewhere in the body.

Experimental shunts between arteries and portal system have failed to produce

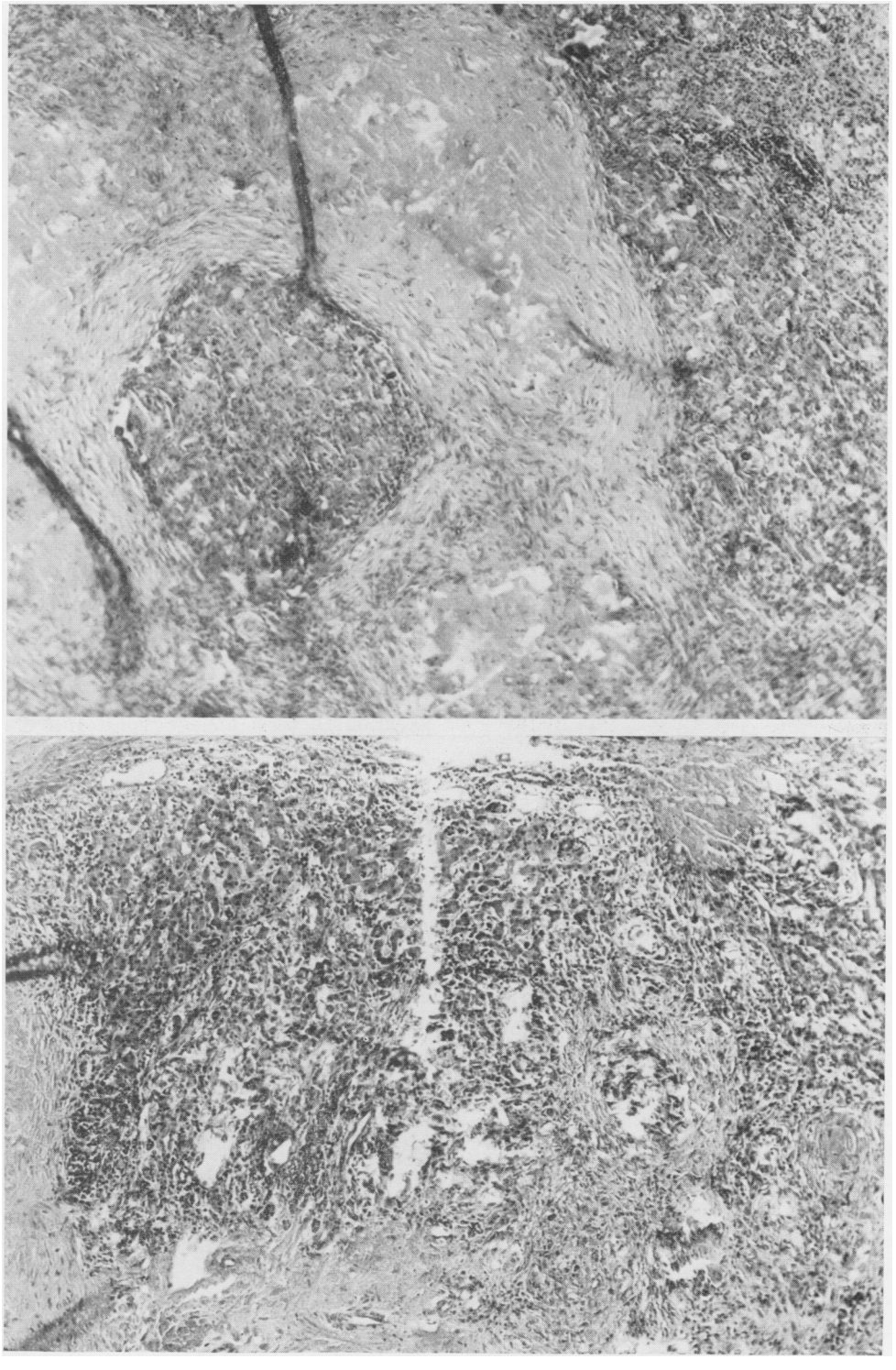

FIG. 2. Representative hepatic scarring after silicon dioxide injection into the portal system.

any significant rise in pressure.[11, 20, 24] Other shunts with the proximal end of the portal vein anastomosed to the aorta and the distal portion anastomosed to the vena cava [18] cannot be considered as simulating the disease in man. Much interesting work has been reported following arterialization of the liver.[7] Much remains to be done but it does not seem to point toward a solution of the disease, portal hypertension.

### HEPATIC OBSTRUCTION, CIRRHOSIS

The production of cirrhosis has long been under experimental scrutiny. Many drugs and toxic substances have been used to produce it.[14] These have run the gamut from protein decomposition and bacterial products to tars and inorganic chemicals. Without listing the various compounds it may be safely stated that any substance which will cause a chronic diffuse hepatitis can result in a diffuse liver scarring indistinguishable from portal cirrhosis.

Recent experiments have largely centered about the use of carbon tetrachloride since this produces a rapid and reliable experimental cirrhosis. Undoubtedly a more nearly physiologic means of producing cirrhosis is by giving diets low in casein (choline or methionine). However, in the problem at hand there seems to be no advantage of this type over that produced more simply with carbon tetrachloride.

During the early analysis of portal hypertension, hepatic cirrhosis was naturally considered to be the obstructive cause of the elevated blood pressure. It seemed only logical to produce an experimental cirrhosis and measure the hypertension which followed. Unexpectedly and quite without explanation the resultant pressures have been within the normal range. An experimental cirrhosis which appeared identical with that seen in man apparently fails to produce the hypertension so frequently seen in the human.

These experiments were mostly single recordings of portal pressures at various times after the initiation of cirrhosis. Baret and Fitts [2] were able to produce portal pressures above 30 cm. of water in three of seven dogs given carbon tetrachloride cirrhosis but two of these three also had ligations of the vena cava above the diaphragm.

It remained for Hoffbauer [12] to obtain consecutive portal pressure readings on the intact postoperative animal having various degrees of liver damage and portal vein constriction. Here again there was no consistent pressure change.

The production of cirrhosis by injection of a silicon dioxide suspension into the portal system of dogs has been considered for many years to be the classical means of producing experimental portal hypertension. This work of Rousselot and Thompson [19] is too often quoted without careful analysis of its real worth. To our knowledge it was not repeated until recently when Volwiler, Grindlay and Bollman [23] again measured portal pressures of dogs made cirrhotic with silicon dioxide. They reported that "a moderate portal hypertension frequently results."

There is no doubt that a diffuse hepatic scarring took place in both instances with a varying degree of ascites. When, however, the actual pressure readings are examined the evidence of portal hypertension is far from convincing. In the original experimental report [19] the highest pressure obtained was 29.5 cm. of water. In the recent work [23] the highest of eight recorded readings was 28 cm. These were maximum readings. By our previously mentioned definition of portal hypertension these are not hypertensive at all—they are quite average and approximate those of the present report.

### HEPATIC VEIN OBSTRUCTION

Interruption of the hepatic vein either by direct ligation or by ligation of the inferior vena cava above the diaphragm has become a standard means of producing ascites in experimental animals. The explanation of ascitic fluid production by this means is still

not fully understood. Electrolytic osmotic changes may be partly responsible for the accumulation of fluid and part may be due to an increased capillary pressure within the abdominal cavity.

We are interested in experimental ascites principally because of the associated increased venous pressure. Strange as it seems, this means of obstructing the return flow of portal blood has produced quite unpredictable results and portal hypertension is by no means a constant result.[1] None of the animals reported in Kershner's [13] experiments reached actual hypertensive levels. Cross [8] produced portacaval shunts on dogs before ligating the hepatic veins and the portal pressure reached 30 cm. of water in only a third of these. His experiments were terminated at two to five weeks and one wonders if the pressure in these would not have returned to normal had observations been carried longer.

This means of producing abdominal ascites and temporary congestion of the portal system has little to do with the disease under consideration. No obstruction of the inferior vena cava or hepatic vein has been demonstrated in man. Admittedly these lesions may be simulated in heart disease or chronic pericarditis but they are not seen in the recognized syndrome of portal hypertension. Therefore, this experimental approach is not very helpful in simulating or studying the disease.

## DISCUSSION

The enigma of portal hypertension is at present complete. It is likely to remain so until an acceptable experimental method of producing it can be found. Also confusing is the fact that the disease itself is quite variable and has no standard pattern. Portal hypertension and hemorrhage may occur with or without liver damage; with or without evidence of portal obstruction; with or without elevated pressure or splenic congestion [16] and lastly the extent of the varicosities are unpredictable. These variations are quite disconcerting and do not lead to a simple analysis. It must be admitted that liver damage is most frequently associated with portal hypertension but may be strangely absent in the Banti's Disease of youngsters.

On first analysis of the problem it seemed so logical that the disease was the result of a simple obstruction to the portal flow. As indicated in this brief review, it is not so simple. The present attempt failed to produce a sustained elevated pressure by means of silicon dioxide cirrhosis. Injection of this material into the portal system resulted in liver necrosis, cirrhosis and ascites but no hypertension. We must finally admit that the clinical disease has not yet been reproduced by mechanical obstruction to portal flow.

It seems strange to draw any distinction between intra and extra-hepatic portal hypertension since no one can produce the extra-hepatic form in man or animal, or the intra-hepatic type in experimental cirrhosis. In making this distinction we are defining that which we know nothing about. Possibly the disease is actually mis-named and the recorded elevated pressure has little to do with esophageal varices or hemorrhage. A peptic erosion into an enlarged vein of normal pressure has been suggested as a possible cause.[3]

At present we have no original experimental approach or thought to suggest. However, while groping about we would like to again point out certain pressure variations [21] which are equally perplexing. As has been noted, the normal average portal pressure in man is 20 cm. of water with the highest normal of 26 cm. Certainly a pressure of 40 to 50 cm. must be considered abnormal—certainly below 30 must be considered normal with the intervening pressures in a very debatable and questionable hypertensive range. There is then no sharp dividing line and as one sees more and more of these borderline cases one wonders at the significance of a 10-cm. increase in

pressure (.74 cm. Hg). Can it be possible that this slight difference in pressure is the cause of this condition? It seems quite doubtful.

As previously indicated [21] there is a pressure differential in the region of the diaphragm which could possibly reach 200 cm. of water. This so far overshadows pressures obtained in so-called portal hypertensives as to make their recordings insignificant. Adding further to our consternation is the realization that the above noted large differential pressures are possible in both normal as well as cirrhotic or abnormal patients.

How completely this clouds the whole picture! All the premises on which this syndrome was built seem doubtful or insecure. Let us reconsider the entire problem and start again.

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