SUDDEN AND COMPLETE OCCLUSION OF THE PORTAL VEIN IN THE *MACACA MULATTA* MONKEY*

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LIMITED AS IT IS by two capillary beds, the portal circulation is unique. Furthermore, it is an invariable characteristic of the venous drainage of the gastro-intestinal tracts of all vertebrates. So striking and unusual has this vascular system appeared that it has been assumed to have some special functional and anatomical significance. For these reasons, teleological as they are, the portal circulation has long interested anatomists, physiologists, and biochemists. More recently, with the discovery that certain defects in the cardiovascular system are amenable to operative correction, surgeons have evidenced increasing interest in the physiology of the portal circulation. Chiefly has attention been paid to lowering portal hypertension by constructing an anastomosis between the portal and systemic venous beds. In addition, interest has been expressed in the possibility of resecting the portal vein if it be found invaded by a malignant tumor.

Our interest in the portal system originated in studying the feasibility of excising the portal vein if invaded by cancer. As the experiments progressed, however, it soon became evident that opportunities were arising to solve some of the problems encountered in normal and abnormal portal physiology and hemodynamics. Shortly we found that our major efforts were being directed toward explaining the etiology of portal hypertension. Although the experiments which we shall report cannot be considered complete we do not apologize for their presentation at this time. Certain aspects have proved so provocative that we feel they must prove of interest to those concerned with this phase of vascular surgery.

It is a common belief among members of the medical profession that sudden and complete occlusion of the portal vein is promptly fatal. Ample evidence can be found that this is the sequence of events in the usual laboratory animals such as the rabbit, cat, and dog. When, however, such information as is available upon this subject in the human being is studied, the evidence clearly indicates that in man the inevitability of death following acute portal obstruction may be doubted.

Credit for the earliest observations on this phenomenon in animals must be given to Oré,[1] to Schiff,[2] and to Claude Bernard.[3] Working in 1856, 1863,

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and 1877 respectively, these men proved that sudden occlusion of the portal vein in rabbits and dogs is promptly followed by death. In explanation of this phenomenon these early experimenters variously offered toxemia, anemia, and liver failure. Within a few years, however, Eck[4] in his classical experiments demonstrated in the dog that death did not follow sudden occlusion of the portal vein if the fistula now bearing his name were constructed between the portal vein and the vena cava. In 1875 Solowieff[5] contributed an additional fact, namely, that the dog could survive total portal occlusion provided its several branches were ligated individually and in stages. The next important observation was that of Neuhof,[6] who in 1913 also demonstrated that this animal survived complete occlusion of the portal vein as long as its lumen was progressively encroached upon at three or four operations spaced a week or so apart. With the exception of a few confusing reports from several continental laboratories, interest in why the cat and the dog die following sudden portal occlusion was not again evinced until 1934 and 1935. At this time Elman and Cole[7] and Boyce[8] reported experiments as a result of which they agreed that loss of effective circulating blood volume was the major cause of death. In addition, Boyce expressed the belief that there was a neurogenic factor involved. In 1945 Brunschwig and Bigelow,[9] patterning their investigations after certain of the earlier experiments, confirmed the fact that the dog tolerated occlusion of the portal vein provided it was performed gradually. In 1947 Schafer and Kozy,[10] in an effort to extend the usefulness of radical pancreatico-duodenectomy, demonstrated in the dog that a portion of the portal vein could be resected if an anastomosis between its distal segment and the inferior vena cava was provided immediately.

From this brief review three conclusions are justified in so far as the common laboratory animals are concerned: first, that they all die more or less promptly following sudden and complete occlusion of the portal vein; second, that the cause of death is shock, primarily due to a sudden diminution of the effective circulating blood volume; and third, that all of these animals survive if provision is made for the escape of blood from the portal to the systemic circulation sufficient in amount to maintain an effective blood volume. This, it has been shown, may be accomplished either directly by an Eck fistula or indirectly by occluding the portal vein in stages. Adequate time must be allowed between operations for the establishment of collaterals.

Upon turning to a consideration of what happens to man following sudden occlusion of the portal vein, it is apparent that any conclusions must be far less definitive. It is quite understandable why surgeons have been reluctant to tamper with the portal vein. In view of the evidence derived from laboratory animals, not only has the portal vein rarely been occluded deliberately, but in addition every effort has customarily been made to avoid damaging this structure. In reviewing this subject in the human being, therefore, it has been necessary to rely for information on such clinical reports as have been published. Accurate evaluation has proved difficult. In nearly all cases in which the portal vein has been ligated the complications of the primary disease or injury have

made any very accurate appraisal of the results of the portal ligation almost impossible. For instance, in 1926 Colp,[11] in an heroic effort to save the lives of patients with suppurative pylephlebitis of appendicular origin, reported three in whom he deliberately ligated the portal vein. Although all three patients lived several days following this procedure, they ultimately died of their primary suppurative disease. Colp did not believe, however, that the cause of death could be assigned directly to ligation of the portal vein. A generous number of comparable experiences could be reviewed, but to no particular end, for Colp,[11] Boyce,[8] and Brunschwig[9] have each published adequate summaries of the reported cases beginning with Gintrac's[12] original article which appeared in 1857. In general, about the only conclusion that is justified at the present time is that man reacts to sudden portal occlusion in a manner quite different from the rabbit, cat, and dog. That he may survive several days or even longer seems obvious, but further than this little can be accepted as proved.

Because it appeared unreasonable to undertake immediately the further study of this problem with man as the experimental animal, and because the experiments reported in the common laboratory animals seemed well substantiated, attention was directed toward one of the primates, the *Macaca mulatta* monkey. This animal was selected for several obvious reasons. In the first place, preliminary investigation revealed that the anatomical relationships of the portal vein, pancreas, and duodenum in this monkey correspond closely to those encountered in the human being. In both, these structures reside in a retroperitoneal position. This, of course, is in direct contrast to the cat and dog, where the pancreas and duodenum occupy an intra-mesenteric position. In the second place, save for one article on hepatectomy (Maddock and Svedberg[13]), no reports could be found indicating that the portal system had been studied in this animal. For convenience in presentation, the various experiments which have been performed to date will be presented and discussed under the following headings:

I. SUDDEN AND COMPLETE OCCLUSION OF THE PORTAL VEIN IN THE MACACA MULATTA MONKEY AND IN TWO PATIENTS WITH INOPERABLE CANCER

Our entire experience with 25 animals in which the portal vein has been suddenly and completely occluded is recorded in detail in Table I. Early in the course of these experiments the portal vein was doubly ligated with silk, while later it was also divided. It is not believed that this difference in experimental technic has materially affected our conclusions. Except where otherwise noted, all of the experiments were performed under open-drop ether. Nineteen of the animals operated upon survived uneventfully, while six died. These six deaths deserve special comment. Three (monkeys No. 28, No. 29, and No. 43) occurred in animals anesthetized with sodium pentobarbital.* Although these deaths may have been due to an advertent overdose

* Veterinary Nembutal Sodium (Pentobarbital Sodium, Abbott), made by Abbott Laboratories; average dose: 0.15 cc. per pound of body weight.

of the drug, it is conceivable that monkeys in which the portal vein has been occluded are less well able to tolerate this barbiturate. This is in accord with Schafer and Kozy's[10] experience with portocaval shunts in the dog. These authors reported abandoning this drug as an anesthetic agent because of a high mortality apparently associated with its use where the portal vein was occluded. Two monkeys (No. 6 and No. 30) received large doses of contrast media in the course of portal venography (vide infra). One was given 30 ml. of Thorotrast while in the other 50 ml. of 70 per cent Diodrast were injected. These, of course, are enormous doses compared upon a basis of body weight with those commonly employed in man. It seems reasonable to believe that the deaths of these two animals should be ascribed to an overdose of these agents rather than to the portal occlusion. One animal (No. 16)

TABLE I.—*Macaca Mulatta Monkey. Summary of 25 Experiments in Which the Portal Vein Has Been Suddenly and Completely Occluded at the Porta Hepatis. Nineteen Animals Survived and Six Died. The Causes of Death Are Discussed in the Text.*

Monkey No.	Vein Occluded		Results
1, 2, 3	Portal	Survived	1 year. Portal circulation reestab.
5	Portal and sup. mes.	Survived	8 mos. Portal circulation reestab.
9, 11	Portal, splenic, and sup. mes.	Survived	1 year. Portal circulation reestab.
17	Portal	Survived	2.5 mos. Portal circ. partially reestab.
18, 19, 21	Portal (Div.)	Survived	7 mos. Portal circulation reestab.
24, 25, 26	Portal (Div.)	Survived	Radical pancreaticoduodenectomy performed
27, 31, 35	Portal (Div.)	Survived	one week after occlusion
37,40, 41	Portal (Div.)	Survived	See Table III
6	Portal and sup. mes.	Died	8 hrs. p. o.? Overdose of Thorotrast
16	Portal	Died	2 days p. o. Dehiscence of abd. wound
28, 29, 43	Portal (Div.)	Died	4 hrs. p. o.? Overdose of sodium pentobarbital
30	Portal (Div.)	Died	1 hr. p. o.? Overdose 70% Diodrast
	Total experiments = 25 { 19 survived, 6 died		

died two days after operation of dehiscence of his abdominal wound and evisceration.

Emboldened by the results obtained in these experiments, we have ligated the portal vein in two patients with inoperable cancer. No untoward sequelae attributable to the portal ligation were detected.

Case 1.—(NYH No. 539941), F.W., age 63. At exploratory celiotomy, this man was found to have a small carcinoma of the lesser curvature of the stomach which had directly invaded the left lobe of the liver. Although the right lobe contained a few small metastatic deposits, it was in no sense replaced by tumor. The portal vein was occluded digitally for an hour and the patient observed for evidence of change in his vital signs. Since none appeared during this period, the portal vein was doubly ligated at the porta hepatis. The patient's recovery from anesthesia was unremarkable and he was discharged from the hospital 23 days after operation. No untoward sequalae attributable to ligation of his portal vein were observed. He died at home two and a half months after his operation. Although autopsy was not obtained, it seemed evident to those observing his terminal illness that death was due to carcinomatosis.

Case 2.—(NYH No. 368488), A.L., age 59. At abdominal exploration this woman was found to have a small cancer in the midportion of the stomach associated with innumerable minute metastatic implants on both peritoneal surfaces. Her portal vein was ligated at the porta hepatis and as in Case 1 no sequelae attributable to her portal occlusion appeared. She died 8 months after operation. Autopsy was obtained, but there was such massive replacement of the upper abdominal viscera with tumor that little could be learned of the effects of her portal ligation. Table II records such postoperative liver function tests as were obtained in these two patients.

No general conclusions concerning portal ligation in man are justified from this meager experience. The most that can be said is that these two patients survived deliberate occlusion of their portal vein without any immediate untoward sequelae which could be detected clinically. Any detailed evaluation of the late effects was quite impossible, for this period was clouded by the progression of their primary gastric cancers. We are well aware, of course, that a measure of criticism may be directed toward these two human experiments. The presence of metastases in the liver may have provided just that amount of intrahepatic block necessary to encourage the formation of sufficient collaterals to permit the survival of these patients. From the appearance of the liver and the veins in the portal bed, however, this possibility is considered unlikely.

II. CIRCULATORY DYNAMICS FOLLOWING PORTAL OCCLUSION IN THE MACACA MULATTA MONKEY

(A) *Effect Upon Systemic Blood Pressure as Measured in the Femoral Artery.* Under open drop ether anesthesia the changes in systemic blood pressure following occlusion of the portal vein were studied. The portal vein was ligated through an upper midline incision and all arterial pressures were taken from the right femoral artery by means of a recording mercury manometer. The results of six such experiments are outlined in Fig. 17. In each instance there was an immediate fall in systemic arterial pressure of about 20 to 30 mm. Hg. Within one to four hours after ligation of the portal vein the arterial pressure had risen to pre-occlusive levels. The results obtained in this type of experiment in the monkey differ dramatically from those reported in the dog. For instance, Elman and Cole[7] proved that in the dog the systemic arterial pressure promptly falls to "shock" levels after occlusion of the portal vein. Here it remains, to be followed within 45 to 70 minutes by death. It is concluded from our experiments that the *Macaca mulatta* monkey can, within one to four hours, return through collateral channels sufficient blood to elevate promptly to normal the slight fall in blood pressure occasioned by sudden portal occlusion.

(B) *The Effect of Sudden Occlusion of the Portal Vein Upon Portal Venous Pressure.* In 15 monkeys measurements of portal venous pressure have been taken before, ten minutes after, and about one week after sudden

TABLE II—(a and b). *Postoperative Liver Function Studies in Two Patients With Inoperable Gastric Cancer in Whom the Portal Vein Was Deliberately Ligated. From a study of These Figures It Can Be Seen That in General, Ligation of the Portal Vein Was Not Followed by Any Changes in the Blood Chemical Values Which Were Obtained.*

(a) Postoperative Blood Chemical Studies and Liver Function Tests Following Sudden Occlusion of the Portal Vein
(Case 1: NYH No. 539941—F.W.—Age 63)

				Prothrombin					Protein										
	Hgb.	RBC	WBC	Undil.	Dil.	St'd.	Urea	Sugar	Total	Alb.	Glob.	Phos.	Ict. Ind.	S. Bilir.	T. Chol. Chol. E.	BSP	Alk. Phos.	T.T.	C.F.
Pre-op.	14.9	4.9	11.0	17.0	32.4	42.7	21	...	7.0	...	...	...	..	0.4	...	...	....	..	..
Ligation portal vein	....	...	....	....	....	....	..	...	...	...	...	...	..	...	194	...	....	..	..
P. O. 1	13.0	...	....	....	....	....	..	...	...	...	...	3.6	..	0.1	...	...	13.1	9	..
P. O. 2	13.0	...	....	17.7	35.7	43.1	..	92	...	...	...	2.3	..	1.0	198	...	10.3	9	9
P. O. 3	12.8	4.2	14.3	13.9	31.2	42.0	..	96	...	...	...	2.6	..	0.2	194	...	12.8	8	11
P. O. 5	....	....	....	15.3	33.9	44.2	..	...	...	...	...	...	..	...	...	...	....	..	..
P. O. 6	....	...	....	15.2	35.2	42.1	..	83	...	...	...	2.9	..	0.7	181	...	14.9	7	13
P. O. 8	....	...	....	17.1	37.5	42.0	..	71	...	...	...	2.4	..	0.5	152	...	15.1	7	..
P. O. 9	....	...	....	18.6	37.3	42.5	..	...	...	...	...	...	..	...	...	...	....	..	..
P. O. 10	....	...	....	16.3	41.5	43.2	..	84	...	...	...	2.9	..	0.5	189	...	19.3	8	11
P. O. 12	....	...	....	....	....	....	..	80	...	...	...	2.5	..	0.5	157	...	15.4	8	12
P. O. 14	....	...	....	....	....	....	..	71	...	...	...	3.2	..	0.5	174	...	23.1	..	14
P. O. 20	....	...	....	....	....	....	..	75	...	...	...	3.2	..	0.1	204	...	29.5	10	15

(b) Postoperative Blood Chemical Studies and Liver Function Tests Following Sudden Occlusion of the Portal Vein
(Case 2: NHY No. 368488—A.L.—Age 59)

				Prothrombin					Protein										
	Hgb.	RBC	WBC	Undil.	Dil.	St'd.	Urea	Sugar	Total	Alb.	Glob.	Phos.	Ict. Ind.	S. Bilir.	T. Chol. Chol. E.	BSP	Alk. Phos.	T.T.	C.F.
Pre-op.	12.6	3.8	6.9	15.2	39.6	40.4	14	...	6.9	5.4	1.5	...	..	...	...	...	....	..	..
Ligation portal vein	....	...	....	....	....	....	13	218*	...	...	...	...	..	...	...	...	....	..	..
P. O. 1	11.1	3.6	....	....	....	....	12	89	6.6	5.0	1.6	3.4	5	...	...	3.4	3.1	1	..
P. O. 2	10.8	3.4	....	14.4	32.9	37.0	9	103	6.7	4.9	1.8	3.5	4	...	...	...	2.4	1	6
P. O. 3	....	....	....	....	....	....	11	104	6.5	4.9	1.6	3.9	4	...	268/195.5	...	2.6	0	6
P. O. 6	....	...	....	....	....	....	..	97	...	...	...	...	..	0.8	...	...	....	1	..
P. O. 10	....	...	....	13.8	35.6	37.5	10	...	5.9	4.2	1.7	...	..	...	...	2.8	3.1	..	6
P. O. 90	11.5	3.9	6.3	....	....	....	..	...	7.0	5.3	1.7	...	..	...	...	1.4	....	2	..
P. O. 150	10.0	3.5	4.9	....	....	....	13	82	6.3	4.5	1.8	...	..	0.3	...	0	....	..	..

* Probably due to a glucose infusion administered during operation.

occlusion of the portal vein.* After determining the normal level of pressure within the portal venous system, the portal vein has been divided between two ligatures of silk. It was found that it required approximately ten minutes for the pressure to reach a stable level. Upon ascertaining the degree of hypertension immediately produced by portal occlusion, the abdominal wounds were closed and the animals permitted to recover. One week after division of the portal vein the abdomens of these monkeys were again opened and the portal pressure measured in a vein as near the one employed initially as possible. In a few animals portal pressures were obtained daily after occlusion and it was interesting to note that a fall toward normal began within 24 hours. Because a daily celiotomy was found to be more than these animals could tolerate equably, most of the late measurements have been taken at the end of about one week.

Figure 18 summarizes the results of some 40 measurements taken on 15 monkeys. Normal values were found to fluctuate from 9 to 18 cm. of saline. No specific explanation could be found to account for this rather wide variation. Ten minutes after portal occlusion the values varied from 24 to 57 cm. of saline. The pressure levels observed at the end of one week were curiously constant. Although there was a marked fall recorded in each animal, there was no instance of complete return to pre-occlusive levels. There always was evident at this time a minor degree of portal hypertension, usually, however, amounting to no more than a centimeter or two of normal saline. No levels of portal hypertension comparable to those seen in human beings suffering from this disease have been obtained. Experiments are currently being performed in an effort to explain this discrepancy.

(C) *Portal Venography Following Sudden and Complete Occlusion of the Portal Vein.* Early in the course of these experiments, efforts were made to follow the changes in portal hemodynamics at autopsy or at an exploratory celiotomy. Postmortem observations were particularly disappointing, for the small collateral veins collapsed and little significant information was obtained. Examination of the vessels in the portal bed at exploratory celiotomy proved only slightly more informative, for its extent was of necessity limited. In a few instances where exploration was performed, two, three, and nine months after portal vein occlusion, there presented a remarkable picture of dilatation

* All of these values have been obtained by inserting a 20-gauge hollow needle into a major vein of the jejunal mesentery approximately 5 cm. beyond the ligament of Treitz. Pressures have been measured by means of a spinal manometer filled with normal saline. The details of this technic are illustrated in Figure 1. The pressure is determined by filling the manometer well above the anticipated level and then permitting the saline to run into the mesenteric vessel. The pressure existing in the portal venous system is accepted to be at that level at which the saline in the manometer and the blood in the mesenteric vein reach equilibrium. In every instance the final value has not been recorded until a fluctuation of a few millimeters was noted in the level of the saline in the manometer. This fluctuation, coincident with respiration, is believed to be an indication that the system is unobstructed and that the readings obtained accurately reflect portal venous pressure.

FIG. 1

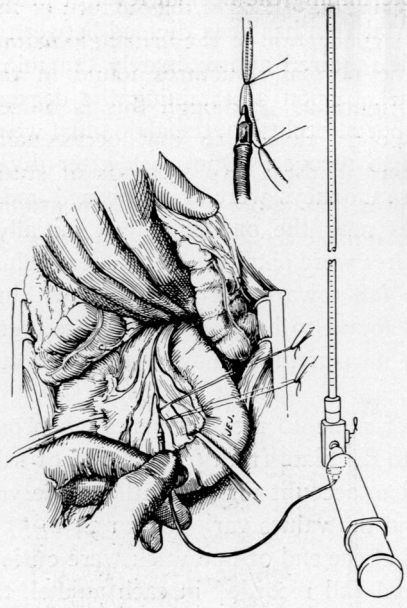
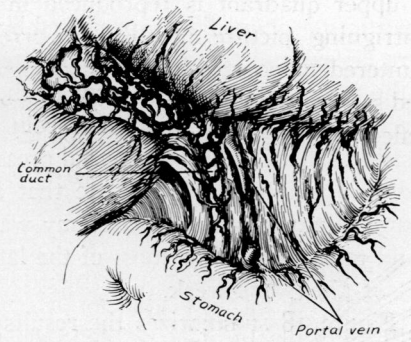


FIG. 2



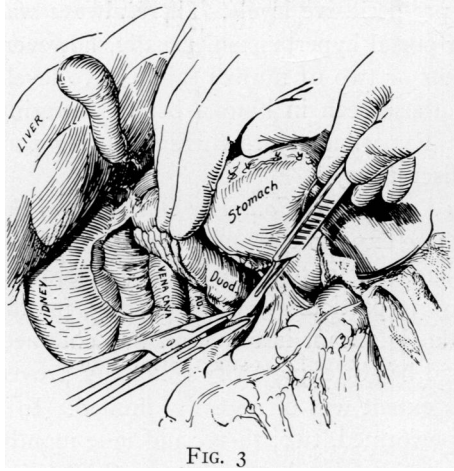


FIG. 3

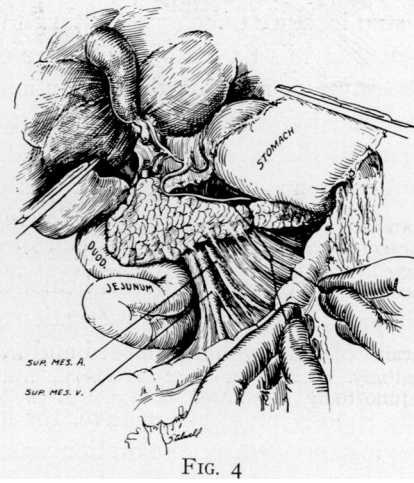


FIG. 4

FIG. 1.—Technic of measuring portal venous pressure in centimeters of saline with a standard spinal manometer.

FIG. 2.—*Macaca Mulatta* Monkey. Artist's conception of the marked venous dilatation developing over the surfaces of the gall bladder and common duct and within the gastrohepatic ligament at about four months after ligation and division of the portal vein. This picture corresponds closely to that described in humans with an extrahepatic portal block.

FIG. 3.—*Macaca Mulatta* Monkey. First step in resection of the pancreas, duodenum, and portal vein. This involves separating the distal third of the stomach from the hepatic flexure of the colon. In addition the lateral peritoneal reflection of the duodenum is completely divided.

FIG. 4.—*Macaca Mulatta* Monkey. Following mobilization of the duodenum and head of the pancreas, the common duct and pancreaticoduodenal artery are divided. The splenic and superior mesenteric arteries are, of course, carefully preserved. At this point the pancreas and splenic veins are divided between ligatures to permit reflection of the entire specimen to the right side of the animal and to expose the portal and superior mesenteric vein.

of the veins in the gastrohepatic ligament and of those on the surface of the common duct and gall bladder. An artist's conception of the hemangiomatous conversion of the superficial veins of the normal structures found in the right upper quadrant is reproduced in Figure 2. Although this is indeed an intriguing picture in that it corresponds closely to that occasionally encountered in portal block in man, neither of these two methods of study proved satisfyingly informative. Recourse was then taken to portal venography as reflected in a roentgen-ray film taken during the course of injecting 35

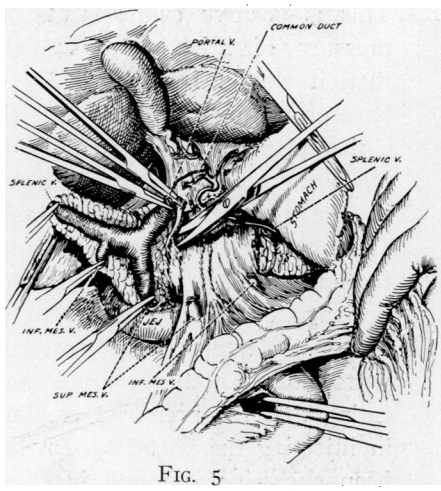


FIG. 5

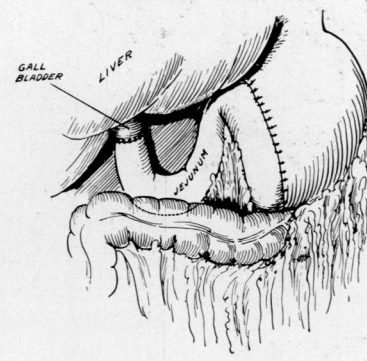


FIG. 6

FIG. 5.—*Macaca Mulatta Monkey.* The entire specimen (head of the pancreas, common duct, duodenum, and the junction of the portal, splenic, and superior mesenteric veins) is reflected to the right side of the animal and its removal completed. The upper few centimeters of jejunum are included in the resection to insure the viability of bowel with which the enteric canal must be reconstructed.

FIG. 6.—*Macaca Mulatta* Monkey. Reconstruction of the enteric canal by means of an end-to-end cholecystojejunostomy and an end-to-side gastrojejunostomy. Both anastomoses are performed in the retrocolic position. Pancreaticojejunostomy is omitted in order to facilitate the procedure.

per cent of 70 per cent Diodrast directly into the portal system. All of the injections were made into a vein in the jejunal mesentery through a small midline incision with the animals under light ether anesthesia. Figures 9 to 11 are representative portal venograms obtained immediately, one, four, and 12 months after sudden and complete occlusion of the portal vein. In Figure 8 is reproduced a normal portal venogram.

The information obtained from examination of 22 portal venograms demonstrates clearly that immediately after ligation portal blood gains access to the systemic circulation primarily through pelvic anastomotic channels, through the hepatopetal vessels, and probably through the other hepatofugal channels conventionally described as being called into play in the human being when the portal vein is blocked. At the end of about two months it is

obvious that the site of occlusion or division of the portal vein is beginning to be by-passed and blood is gaining access to the liver directly. Progressively, the hepatopetal plexus of veins expands so that by the end of a year, and probably earlier, the portal blood traverses the liver normally. With the hepatopetal circulation widely opened the hepatofugal system closes and literally cannot be filled in the course of portal venography. Some criticism can be justly leveled at this method, for no effort has been made to inject the contrast medium at pressures only slightly above those existing in the portal circulation. For instance, in Figure 9 the splenic pedicle is clearly outlined. This is positive evidence that the pressure of injection was higher than it should have been, for we have proved in six experiments that if the splenic vein is ligated following portal occlusion, there is a drop in the portal pressure averaging about 10 cm. of saline. Thus, as in the human being, the splenic venous drainage contributes about 10 per cent to the total value of portal hypertension. Another example indicating that the pressures employed in injecting the portal system have been excessive is found in Figure 13. This portal venogram, obtained after occlusion of the portal vein in monkey No. 30, reflects an injection of 50 ml. of 70 per cent Diodrast within a few seconds. Here are demonstrated innumerable channels which cannot usually be identified, and which undoubtedly indicate injection at an excessively high pressure.

FIG. 7.—Picture of monkey No. 35 five days after resection of the pancreas, the duodenum, and the portal vein.

With some trepidation, portal venography was performed in two human beings (Cases 1 and 2—vide supra) immediately after portal occlusion. These venograms are reproduced in Figures 14 and 15. The close similarity between the films obtained in man and monkey is of interest, and presents further evidence that the portal circulation in these two species is nearly identical. It is understandable that these studies in man could not be repeated at intervals following the occlusion.

III. MICROSCOPIC STUDIES ON BIOPSIES OF THE LIVER OBTAINED SERIALLY AFTER PORTAL OCCLUSION

From 15 monkeys, biopsies of the liver were obtained by exploratory celiotomy at intervals of from one week to one year following portal occlusion.

FIG. 8

FIG. 9

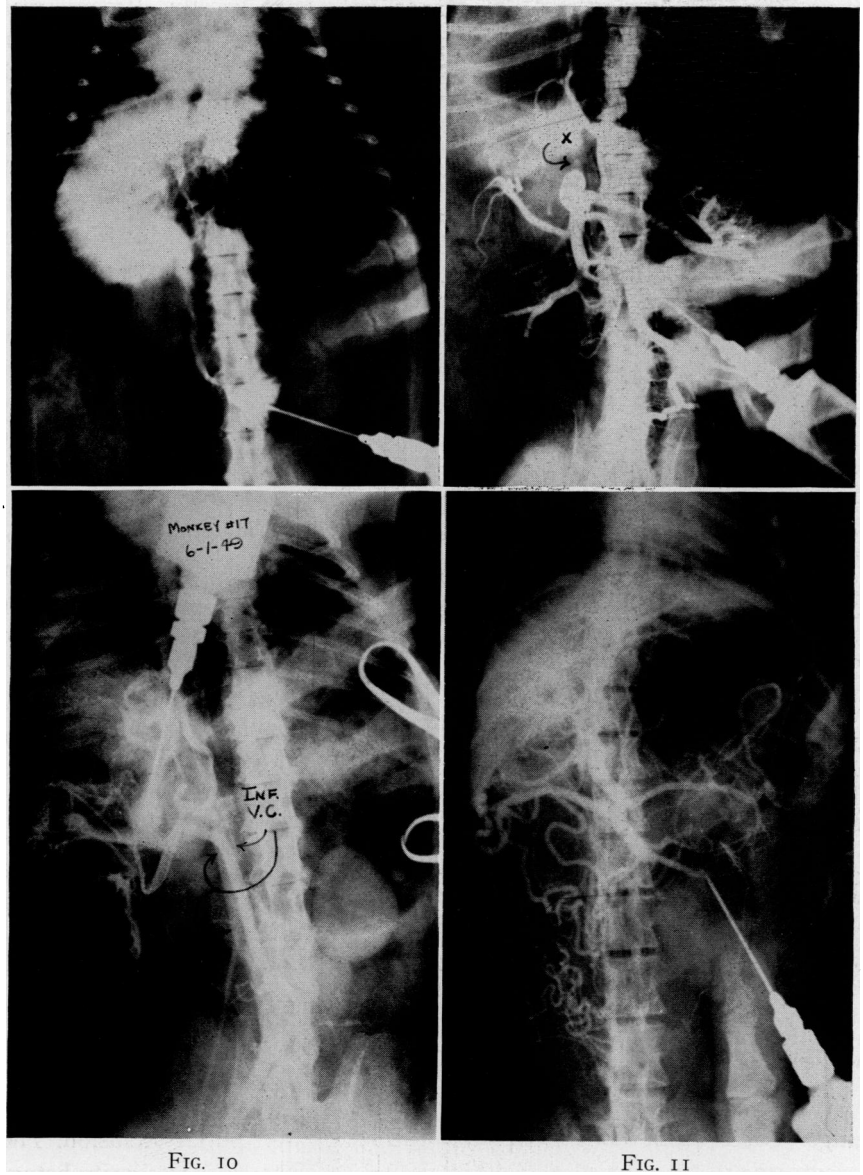


FIG. 10

FIG. 11

FIG. 8.—*Macaca Mulatta* Monkey. Normal portal venogram.

FIG. 9.—*Macaca Mulatta* Monkey. Portal venogram obtained immediately after complete and sudden occlusion of the portal vein. The fact that the splenic pedicle is outlined probably indicates that the contrast medium was injected at an excessively high pressure.

FIG. 10.—*Macaca Mulatta* Monkey. Portal venogram obtained one month after portal occlusion. The majority of the radiopaque dye disappears into the pelvis, returning, however, promptly and in sufficient concentration to outline the inferior vena cava and both iliacs. Already a small amount of dye is gaining access to the liver directly through the hepatopetal system of veins lying in the gastrohepatic ligament.

FIG. 11.—*Macaca Mulatta* Monkey. Portal venogram obtained four months after occlusion.. Here direct filling of the liver is almost complete.

FIG. 12

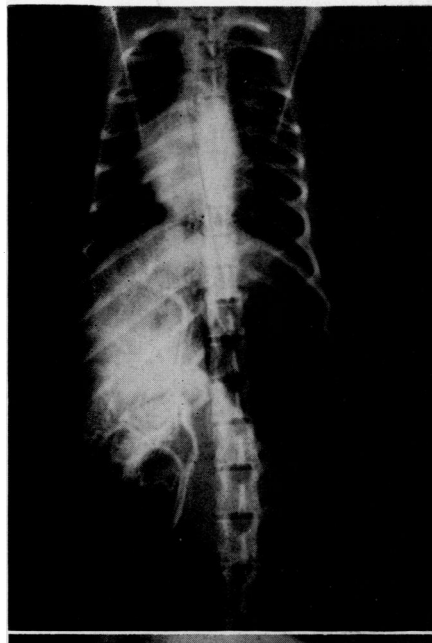
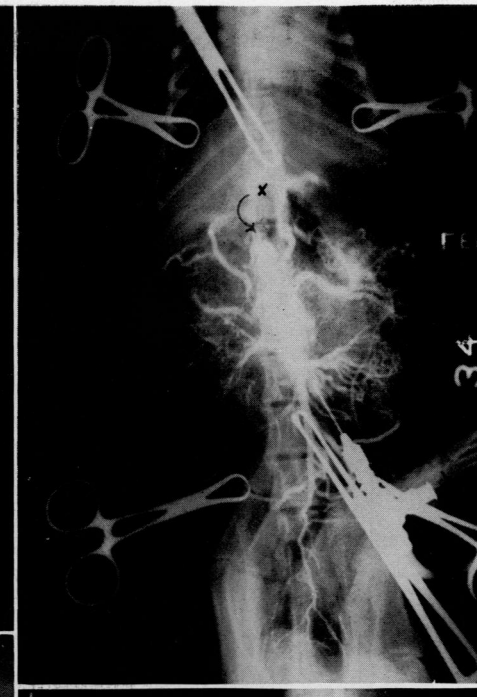
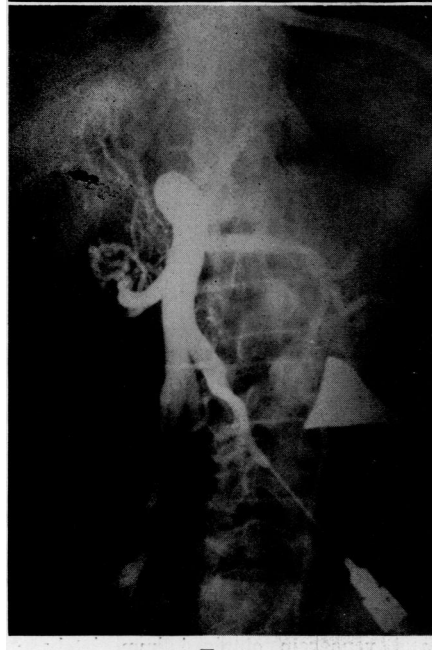


FIG. 13





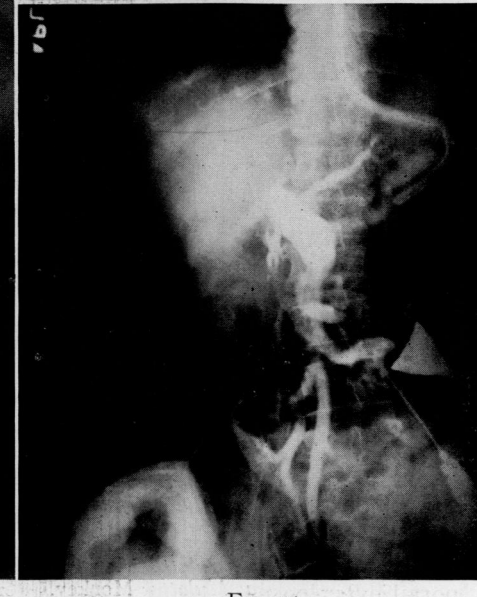


FIG. 14

FIG. 15

FIG. 12.—*Macaca Mulatta* Monkey. Portal venogram at one year. The site of occlusion is now completely by-passed and filling of the liver is direct.

FIG. 13.—*Macaca Mulatta* Monkey. Portal venogram obtained immediately after occlusion of the portal vein. X = point of occlusion. This film was obtained with 50 ml. of 70 per cent Diodrast injected under what is assumed to be excessive pressure. Note extensive filling of even minute radicals.

FIG. 14.—NYH Case 1. Portal venogram obtained immediately after deliberate occlusion of the portal vein.

FIG. 15.—NYH Case 2. Portal venogram obtained immediately after deliberate occlusion of the portal vein.

A total of 24 hepatic biopsies were examined and in no instance could any evidence of morphologic change be identified.

IV. MISCELLANEOUS OBSERVATIONS

As the occasion arose, the livers and spleens of these animals were observed grossly for evidence of change in their appearance. Immediately after ligation of the portal vein the liver apparently shrinks in size ever so slightly while the spleen appears to become engorged. At subsequent abdominal operations, similar observations were made wherever possible, and no gross abnormalities noticed. In no instance has one of these animals developed gross enlargement

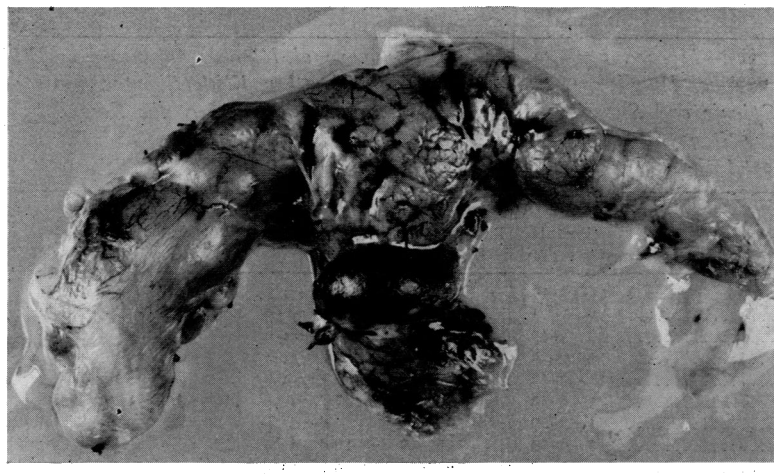


FIG. 16.—*Macaca Mulatta* Monkey. Photograph of specimen removed from monkey No. 40 demonstrating the extent of the portal resection.

of the spleen. Of passing interest is the fact that ascites has never developed. This, of course, is in accord with the recently reported observations of Volwiler, Grindlay, and Bollman[14] and of McKee, Schloerb, Schilling, Tishkoff, and Whipple.[15] These authors report that in the normal dog, ascites does not form unless the hepatic veins are constricted. In a number of our animals, dilated veins have appeared on the anterior abdominal wall about two weeks after ligation of the portal vein. These, persisting for a few weeks and then disappearing, probably reflect a very transient period of minimal portal hypertension.

V. PANCREATICODUODENECTOMY WITH PARTIAL RESECTION OF THE PORTAL, SPLENIC, AND SUPERIOR MESENTERIC VEINS

Having proved that the *Macaca mulatta* monkey could tolerate sudden and complete occlusion of the portal vein, we next attempted to resect the pancreas, duodenum, and portal splenic, and superior mesenteric veins. These

operations followed closely the pattern described for man by Child[16] in 1948 with the exception that no effort was made to perform a pancreaticojejunostomy. This was omitted because it did not seem essential to the experiment. Of seven monkeys in which a one-stage operation has been performed, six died on the table from shock due to blood loss, while for some unexplained reason one animal survived for 24 hours. As soon as the portal and superior mesenteric veins were ligated in these animals bleeding became quite uncontrollable. Although hemostasis had been painstaking, the entire operative field oozed copiously as soon as the portal vein was occluded. Uncontrollable venous bleeding was particularly striking as soon as an effort was made to perform the gastro- and cholecystojejunostomy necessary for

TABLE III.—*Macaca Mulatta Monkey. Summary of Nine Experiments in Which the Pancreas, Duodenum, and Portal Vein, Together With Short Segments of the Splenic and Superior Mesenteric Veins, were Resected at the Second Stage of a Two-Stage Operation. The First Stage Consisted in Ligation and Division of the Portal Vein at the Porta Hepatis.*

Monkey No.	Portal Occlusion	Radical Pancreaticoduodenectomy	Survival Time	Blood Transfusion	Cause of Death
24	11-28-49	12- 6-49	5 hours	0	Shock
25	11- 3-49	11- 9-49	2 days	0	Acute gastric dilatation
26	10-31-49	11- 2-49	5 hours	0	Shock
27	11-10-49	11-16-49	5 hours	0	Shock
31	11-29-49	12- 7-49	6 hours	0	Shock
35	1-16-50	1-24-50	7 days	100 ml.	Peritonitis
37	1-19-50	1-31-50	4 days	80 ml.	Gastric dilatation
40	2- 9-50	2-24-50	16 days	100 ml.	Infection abd. wound
41	2-10-50	2-20-50	4 hours	100 ml.	Shock

reconstruction of the enteric canal. From these seven experiments it was concluded that any operation in the monkey deliberately contemplating pancreaticoduodenectomy and resection of the portal vein in one stage was unsound. Arguing by analogy, any such one-stage operation should not be attempted in man.

Having discovered, as outlined above, that within a week after portal occlusion the portal pressure fell nearly to normal, we turned our attention to a two-stage procedure. At the first stage the portal vein has simply been ligated and divided; at the second stage, performed from five to ten days later, it has been found possible to resect the pancreas and duodenum together with the portal vein. The uncontrollable hemorrhage reported in the one-stage operation was not encountered. Table III outlines our experience with nine two-stage resections. Although five of the nine animals were in severe shock at the end of the operation, they all survived five to six hours. In the remaining four animals the survival time was prolonged from this short period to from two to 16 days by giving these animals 80 or 100 ml. of citrated blood at the close of the procedure. It has been a disappointment, of

course, that we have been unable to secure longer periods of survival, but when the causes of death are studied it seems obvious that our animals have died because of our inability to give them even a small degree of modern postoperative care. All of the postoperative complications so dreaded a decade or two ago have appeared and have, we believe, accounted for these failures. Peritonitis, hypoproteinemia, wound sepsis, and acute gastric dilatation have all been observed. At the present time we are engaged in attempting to persuade our animals to accept chemotherapy, parenteral fluids (including blood transfusion), and gastric aspiration. If this is permitted, we believe we may anticipate a reasonable degree of success in keeping our monkeys alive following this radical surgical procedure. In spite of this high mortality rate it has been demonstrated that if the operation is performed in two

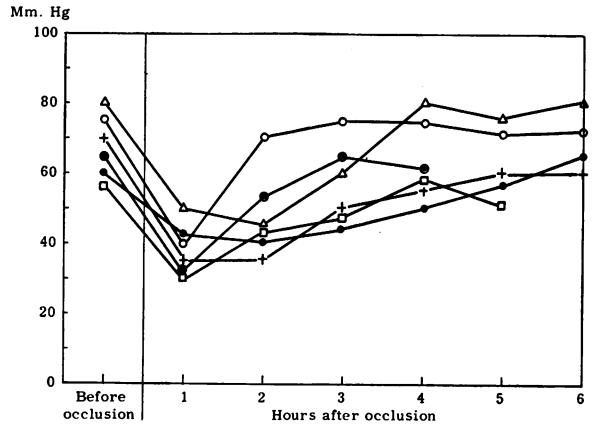


FIG. 17.—*Macaca Mulatta* Monkey. Composite graph of the changes in systemic blood pressure appearing in six monkeys after sudden and complete occlusion of the portal vein. Following a prompt fall of 20 to 30 mm. Hg., the systemic blood pressure rose to normal within one to four hours in all of these animals.

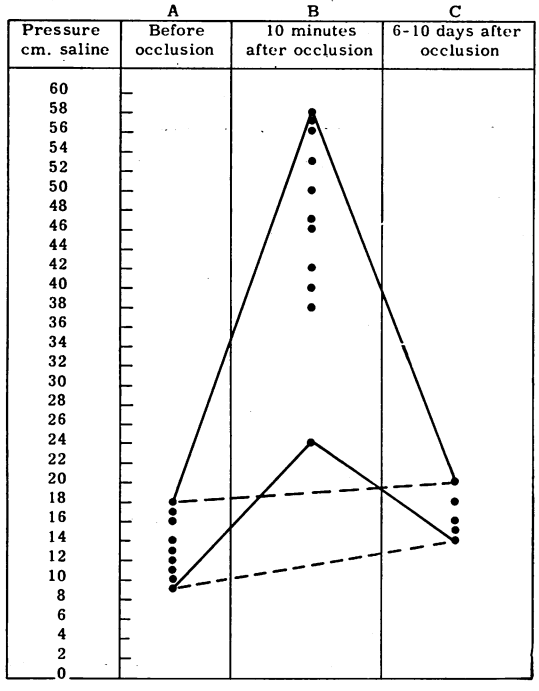
stages the monkey can survive the readjustments in the circulatory dynamics necessary for successful resection of his pancreas, duodenum, and major portal veins. Figures 3, 4, 5, and 6 outline in some detail the type of operation performed at the second stage in these experiments. Figure 16 is a photograph of one of the specimens removed and Figure 7 is a picture of monkey No. 40 five days after operation.

Numerous obvious objections must, of course, be raised if this two-stage operation is proposed for the treatment of patients with pancreaticoduodenal cancers which have invaded the portal, splenic, or superior mesenteric vein. In the first place, it has not been proved that all human beings can tolerate sudden and complete occlusion of the portal vein. In the second place, it can be postulated that if these structures are invaded, the tumor has already progressed beyond the realm of possible cure. And to be sure, the late

results of deliberate portal occlusion in man have not yet been satisfactorily determined.

SUMMARY AND CONCLUSIONS

The purpose of these experiments has been, of course, to attempt to clarify certain unsolved problems in portal physiology. We believe that we have proved that one animal at least, the *Macaca mulatta* monkey, can tolerate sudden division of its portal vein. Aside from its specific interest, this fact is of further significance, for it has served to demonstrate one of the



Monkey No.	A Before occl.	B 10 min. after occl.	C 6-10 days after occl.
24	16	24	17
25	14	57	20
26	13	38	18
27	13	53	18
28	9	56	
29	9	50	
30	18	47	
32	12	40	15
31	9	58	16
33	9	50	
34	17	42	
35	10	57	17
37	11	46	12
40	13	50	14
41	9		14

FIG. 18.—*Macaca Mulatta* Monkey. Changes in portal venous pressure occurring ten minutes and one week after occlusion of the portal vein. Immediately there is a rise of from 20 to 50 cm. of saline. Within a week this has fallen almost to normal.

pitfalls of surgical research, namely, that of applying uncritically to man facts proved true in laboratory animals. Undoubtedly a portion of our belief that man does not tolerate sudden portal occlusion well is derived from the demonstrated fact that the dog succumbs promptly after such a procedure.

One man and one woman have survived deliberate occlusion of the portal vein without detectable untoward sequelae which could be attributed to interruption of the portal blood flow. Before any generalizations are possible for man, however, many more such experiments will have to be performed. Because this opportunity arises but seldom in any one hospital, this is considered a fertile field for general investigation in hospitals throughout the country.

It has been a great temptation to conjecture why our animals have not maintained a degree of portal hypertension comparable to that encountered

in human beings with extrahepatic portal block. Perhaps the monkey is able to open collaterals more widely and more quickly than can man. Perhaps portal hypertension is, as some believe, a manifestation of disease primary in the portal vein and its tributaries. These as well as other possible explanations have proved attractive, but the fact of the matter is that before any conclusions in this regard can be drawn much more work will have to be done. At the present time this too will have to stand as an observation without adequate explanation.

In addition, we believe that we have proved that the monkey can tolerate for a time (at least several days) the circulatory readjustments necessary to permit resection of the portal vein enbloc with the lower stomach, the duodenum, and the pancreas. Whether uneventful survival periods of months or even years can be obtained following such experiments remains to be proved. And it must be proved that these animals can be maintained in good health for long periods of time before any thought is given to the application of the operation to man for the cure of pancreaticoduodenal cancers.

BIBLIOGRAPHY

1 Oré, M.: Comptes Rendus Hebdom. des Séances de l'Académie des Sciences, **42**: 497, 1856.
2 Schiff, M.: Centralbl. f. d. Med. Wissensch., No. 8, 115, 1863.
3 Bernard, C.: Leçons sur le Diabète et la Glycogenèse Animale; viii, 576 pp., Paris, 1877 (J.-B. Baillière & fils).
4 Eck, N.: Voyenno-med. J., S.-Petersb., 130, 2. sect., 1, 1877.
5 Solowieff, A.: Virchow's Arch. f. Path. Anat., **62**: 195, 1875.
6 Neuhof, H.: Surg., Gynec. & Obst., **16**: 481, 1913.
7 Elman, R., and W. H. Cole: Arch. Surg., **28**: 1166, 1934.
8 Boyce, F. F.: The Role of the Liver in Surgery (Chapter X); Springfield, Ill., 1941, Charles C. Thomas.
9 Brunschwig, A., R. Bigelow, and S. Nichols: Surgery, **17**: 781, 1945.
10 Schafer, P. W., and J. S. Kozy: Surgery, **22**: 959, 1947.
11 Colp, R.: Surg., Gynec. & Obst., **43**: 627, 1926.
12 Gintrac, J. M. H.: Schmidt's Jahrb., **93**: 48, 1857. (Journ. de Bord., Janv., Févr., Mars 1856.)
13 Maddock, S., and A. Svedberg: Am. J. Physiol., **121**: 203, 1938.
14 Volwiler, W., J. N. Grindlay, and J. L. Bollman: Gastroenterol., **14**: 40, 1950.
15 McKee, F. W., P. R. Schloerb, J. A. Schilling, G. H. Tishkoff, and G. H. Whipple: J. Exper. Med., **87**: 457, 1948.
16 Child, C. G.: Surgery, **23**: 492, 1948.

DISCUSSION.—DR. ALTON OCHSNER: The question of venous thrombosis has become increasingly more significant, because it is a more prevalent condition than previously.

As you know, in New Orleans we have been interested in venous thrombosis for a number of years, and for a number of years felt that we could do something to prevent the occurrence of this complication.

We have gone over a series of 1002 cases at the Charity Hospital in the last 11 years—1002 cases of phlebothrombosis, thrombophlebitis and/or pulmonary embolism, and I would like to give you some of the results of that study.

[Slide] It is not only the number of cases but the progressive increase in the number of cases which seems to us extremely important. In spite of the measures that we