CLINICAL AND EXPERIMENTAL INVESTIGATION OF THE CIRCULATION OF THE LIVER

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by

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OWING TO THE many physiologic activities in which the liver is concerned, none will doubt that it ranks high among the most important organs in the body. Magnificent contributions have been made by a countless number of investigators relating to these activities in sickness and in health. Those of us interested primarily in clinical surgery are greatly in their debt for supplying us with information that has proved to be of inestimable value in diagnosis and therapy. That many challenging questions remain to be answered is evident.

Modifications affecting the afferent vessels of the liver, both arterial and portal, and the efferent venous collecting system cannot but manifest themselves in altered physiologic activity. In an effort to determine whether or not the laboratory worker has supplied the surgeon with material that has clinical application, it seemed appropriate on this occasion to review some of the recent experimental investigations of the circulation of the liver that have been carried out by my colleagues in the Division of Experimental Medicine of the Mayo Foundation. Sincere appreciation is expressed to Drs. Frank C. Mann, Jesse L. Bollman and John H. Grindlay for their assistance in assembling the material and for their generosity in granting permission to include data that have not been published.

Effect of Occlusion of the Arterial Blood Supply to the Normal Liver

Mass ligation of the cystic duct and cystic artery in the performance of cholecystectomy is a procedure that is mentioned only to be condemned. It is fraught with the hazard of disrupting the integrity of the major extrahepatic ducts or the right branch of the hepatic artery or both, owing to the fact that, except in rare instances, it is impossible to demonstrate unequivocally the cystic duct and the cystic artery without meticulous dissection. The surgeon has been taught from the beginning of his training to respect the integrity of the hepatic artery and the dire results of the inadvertent ligation of one of the main branches supplying arterial blood to the parenchyma of the liver have been impressed upon the mind of the young surgeon with such emphasis that an incongruous situation presents itself where practice and teaching place this major vessel in jeopardy. To stress the importance of this point to an audience

such as this may be construed by some as being trite and elementary. The obstinate perseverance in such practices by many reputable surgeons is offered by way of explanation and apology.

Fortunately, because of the surgeon's training in institutions where every effort is made to ascertain the sequence of events leading to a fatal outcome, the opportunity rarely is afforded to observe the results following ligation of the right branch of the hepatic artery. Evidence has accumulated, however, that in many instances of the so-called "liver deaths" the fatal result may be attributed to this cause.

After it had been shown by Markowitz, Rappaport and Scott[1] that most dogs survived that had received penicillin after ligation of the hepatic artery, a study was carried out by my colleagues, with the aid of penicillin, to learn whether, in dogs, ligation of the hepatic artery stopped all flow of arterial blood, either temporarily or permanently, and to observe whether restoration of arterial supply occurred in dogs which might recover after penicillin therapy.

A description of the methods and materials used in this study will be published in detail at a later date. Suffice it to report at this time that the experiments confirmed those recorded by Markowitz, Rappaport and Scott that penicillin prevents early death of some dogs after an effective ligation of the hepatic artery, presumably owing to an inhibition of growth of anaerobic bacteria.

The study did not show, on the other hand, that penicillin would protect the liver from all effects of deprivation of arterial blood. Recovery of the treated dogs (only 50 per cent.) appeared to be related to the development of an adequate number of collateral vessels to the intrahepatic arterial system. All of the dogs to which no penicillin was given died within 24 hours and the livers showed massive necrosis and hæmorrhage. Of the five dogs which died or were moribund in spite of penicillin therapy, no significant amount of radiopaque material could be seen to reach the liver after arterial injection in the case of four dogs, and no material entered a major lobe of the other dog. Arterial injection in three of the five dogs which recovered demonstrated good filling of the intrahepatic system. Instead of entering the liver through the hepatic artery, the injection material reached the intrahepatic arteries mainly by way of vessels coming from the diaphragm which are present normally, but small and inconspicuous, and which had enlarged to many times their normal size. Two dogs were living seven months after operation and it was assumed that a collateral hepatic arterial supply had developed.

To apply the results of experiments on dogs to human patients is a notoriously hazardous procedure. Two practical lessons may be learned from this, however. One is that the administration of adequate quantities of penicillin is definitely beneficial when the liver has been deprived of arterial blood, and it should be administered generously if there is any doubt as to the integrity of the hepatic artery or its right branch. The other relates to the seriousness of major deprivation of arterial blood

to the liver even in the dog, an animal that is notoriously resistant to trauma. There is little experimental or clinical evidence that would suggest that there is any appreciable collateral circulation between the right and left sides of the liver in the human subject. The evidence would seem sufficient to stress the importance of meticulous dissection whilst performing cholecystectomy in order to preserve the integrity of the hepatic artery and to banish any impression that ligation of the right branch of the hepatic artery can be performed with impunity.

Influence of Portal Circulation on Restoration of the Parenchyma of the Liver

To preserve normal hepatic function and to avoid or obliterate any circumstance that would injure the parenchyma of the liver are goals towards which most operations on the biliary tract are directed. In those patients in whom there has been partial or complete occlusion of the extrahepatic bile ducts or in whom a hepatotoxin has been operative, damage to the substance of the liver has occurred to a greater or lesser degree, and restorative forces normally are set in motion. The influence of portal circulation on restoration of the parenchyma of the liver, therefore, is of more than passing interest.

Following removal of approximately 70 per cent. of the dog's liver, without disturbance of the portal (Fig. 1) or arterial blood flow to the portion that remains, the liver is rapidly restored to its original weight in 30 days. Partial hepatectomy, performed after diversion of the caval blood to the portal vein and ligation of the vena cava above the anastomosis (reversed Eck fistula), likewise permits complete restoration of the liver (Fig. 2, *right*). Similar hepatectomy following, or occurring simultaneously with, diversion of the portal blood from the liver (true Eck fistula) is followed by only slight restoration of the liver (Fig. 2, *left*). Ligation of the vena cava and the portal vein above the site of anastomosis in dogs with portacaval shunt (Fig. 3) permits almost normal restoration of the liver after partial hepatectomy.

After placement of slightly constricting cellophane bands on the portal vein or vena cava, fibrosis develops around the band which usually occludes the vein within a few weeks. When the portal vein alone has been occluded in this manner (Fig. 4) only slight, if any, restoration of the hepatic substance will occur after partial hepatectomy. Partial hepatectomy after band occlusion of both the portal vein and the vena cava near the hilus of the liver (Fig. 5) is followed by almost normal restoration of the liver but no gross venous congestion of the liver and no ascites are produced. When the vena cava above the liver and the portal vein are occluded (Fig. 6), regeneration to normal or almost normal extent occurs and congestion of the liver and ascites are produced. The liver apparently regenerates because of the necessity of having a larger vascular bed through which to filter its venous blood supply.

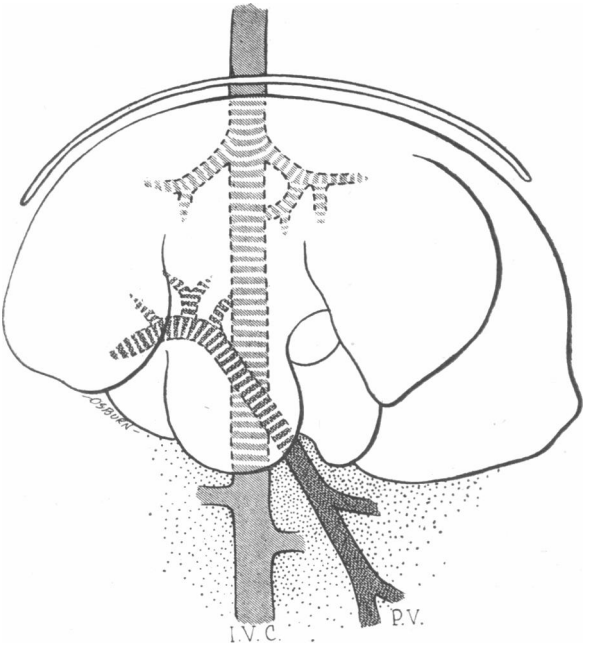

Fig. 1. Schematic representation of the inferior vena cava and the portal vein in the dog when no interference with the flow of blood exists in either structure.

In those animals in which no regeneration had occurred, the only common factor that obtained seemed to be the absence of portal blood. This had been prevented from reaching the liver either by occlusion of the portal vein or by shunting all of the portal blood into the vena cava.

In those animals in which regeneration had occurred, the blood had reached the liver by way of the portal vein, or in those animals in which this source had been denied, congestion of the hepatic veins was obvious or could have been produced. Obvious obstruction to venous drainage occurred when the vena cava had been ligated above the diaphragm. Less obvious obstruction to venous drainage was present in dogs with constriction or ligation of the vena cava below the liver and with ligation of the portal vein or when a similar situation obtained but with porta-caval shunt. An attempt to explain the less obvious obstruction to venous drainage in these last two experimental procedures opens the field to speculation ; the exact mechanism has not as yet been described.

Regeneration of a liver which has suffered acute or chronic injury does occur in varying degrees. One of the criteria that the pathologist insists should be fulfilled before making a diagnosis of cirrhosis is evidence of regeneration. Regeneration in itself may produce mechanical interference to the egress of blood (from the liver) through the hepatic venous

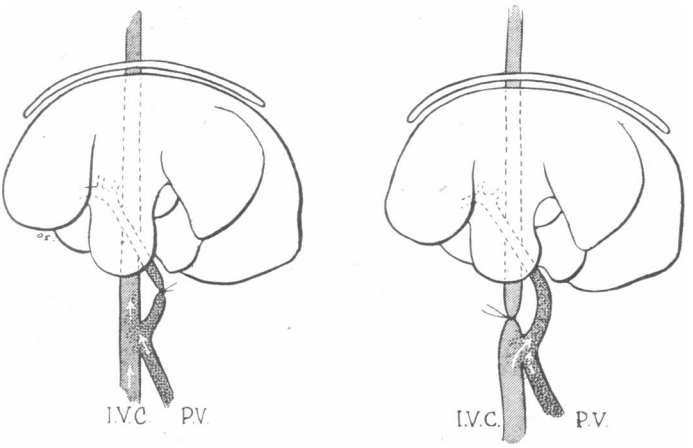

Fig. 2. *Left*—Eck fistula. *Right*—Reversed Eck fistula.

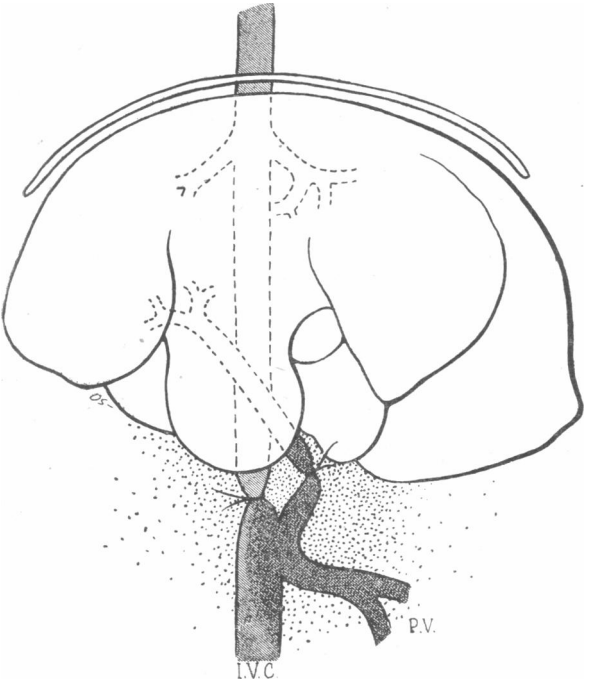

Fig. 3. Occlusion of the portal vein and the inferior vena cava above site of anastomosis in dogs with portacaval shunt.

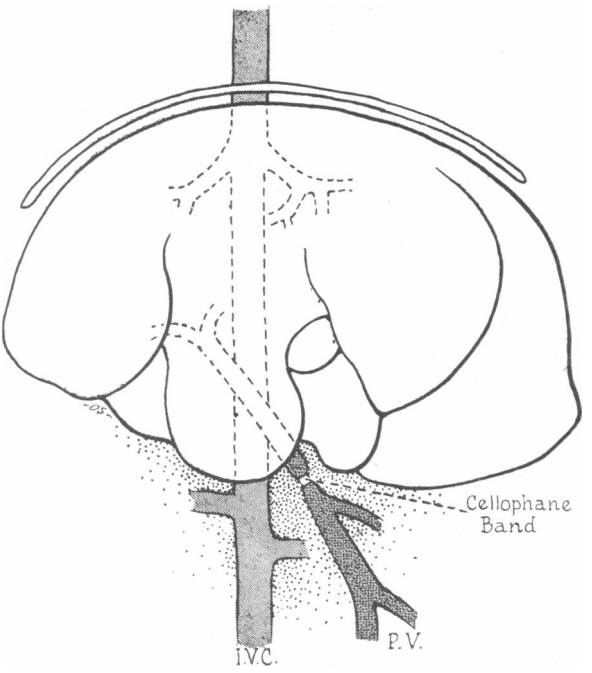

Fig. 4. Occlusion of the portal vein in the dog by the placement of a slightly constricting cellophane band.

collecting system and by so doing may increase hepatic venous congestion. A vicious cycle thereby may be created owing to the stimulus to further regeneration that occurs with hepatic venous congestion. In those patients with hepatic damage and congestive splenomegaly with hæmorrhagic oesophageal varices, the rationale of diverting the flow of portal blood into the inferior vena cava in order to decrease portal hypertension seems reasonable, but, by creating this portacaval shunt in the effort to protect the patient against further hæmorrhagic episodes, it is possible that the liver is being denied venous blood upon which it depends for regeneration. It is to be hoped that experiments such as these may direct the surgeon to a practical method of producing venous engorgement in order to stimulate regeneration of the injured liver without aggravating an abnormal condition that may be associated with acute or chronic hepatic injury.

Formation of Ascites

No single direct cause of ascites exists. In the line of present knowledge, factors requiring consideration in the aetiology of ascites include increased portal venous pressure, depletion of serum albumin, retention of sodium, and a specific antidiuretic activity. To these might be added the rôle of lymph.

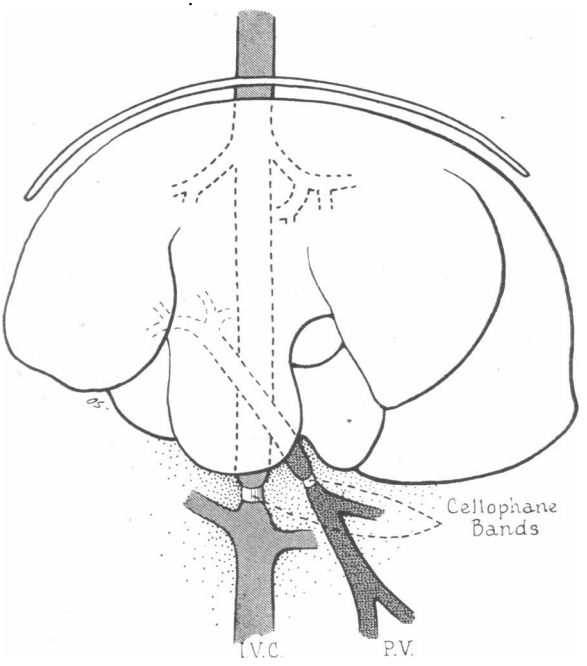

Fig. 5.—Occlusion of the portal vein and the inferior vena cava near the hilus of the liver in the dog by the placement of slightly constricting cellophane bands.

It has been noted that in normal dogs, lymph formed in the liver leaves by way of lymphatics in the hilar area, passes through one or more lymph nodes at the caudal end of the foramen of Winslow and empties into the cisterna chyli. If more lymph is formed in the liver than can be removed in the manner described, some lymph evidently will extravasate from the greatly distended, thin-walled hilar or capsular lymphatics and accumulate within the peritoneal cavity.

Excessive production of lymph may be expected to occur when there is interference with venous drainage of the liver such as in certain instances of cirrhosis or when there is obstruction of the vena cava above the liver. It is important to note that impedance of hepatic venous drainage presumably leads to increased filtration pressure and transudation of ascitic fluid and not portal obstruction *per se*. It is not inconceivable that the absence of any obstructive process to the venous drainage from the liver may explain the lack of ascitic fluid in severe states of cirrhosis, and that the inability of the venous blood adequately to leave the liver may account for the ascites when only mild or moderate degrees of cirrhosis are present. Impedance of venous drainage from the liver by a tumour with associated ascites has been observed clinically when the liver in other respects has been essentially normal. In patients in whom it may have been

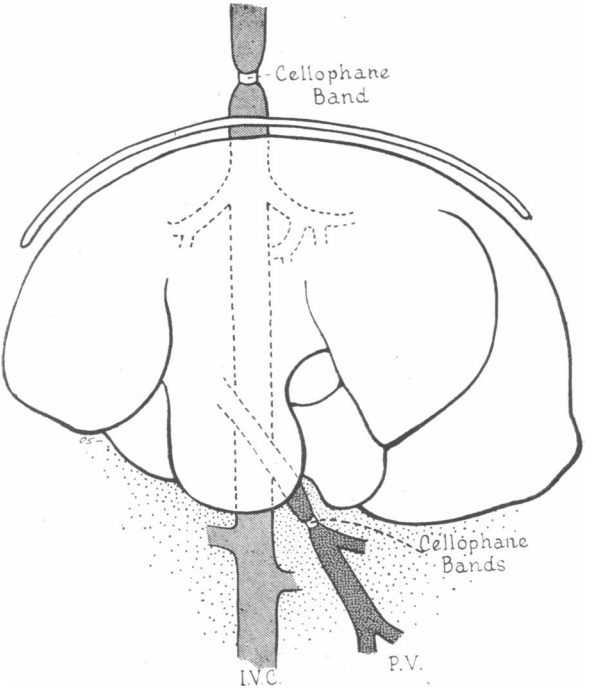

Fig. 6. Occlusion of the portal vein and the inferior vena cava above the liver in the dog by placement of slightly constricting cellophane bands.

assumed that intrahepatic obstruction to the portal blood has resulted in the formation of an ascitic fluid, careful inspection in the region of the hilus of the liver will reveal marked enlargement of the lymphatic vessels.

Accumulated experimental evidence suggests that ascitic fluid is predominantly hepatic in origin and is the result of the obstruction of the venous outflow from the liver rather than a transudation from portal visceral surfaces or from intestinal lymphatics with associated portal obstruction.

In one group of experiments, two-stage ligation of the portal vein, gradual occlusion or severe constriction of the portal vein by a cellophane band, and obstruction of both the portal vein at the hilus of the liver and the vena cava below the liver, failed to produce ascites, in spite of the fact that in these animals there developed as severe states of " portal hypertension " as in those with obstruction of venous drainage of the liver.

In the second group of experiments studies made in the presence of obstruction to venous drainage disclosed the lymphatics of the liver to be increased many times in number, size, and in tortuosity while the intestinal lymphatics were observed to be normal. The flow of

nepatic lymph was increased as much as 30 times normal when venous congestion was present, but under the same conditions no increase in the flow of intestinal lymph could be observed. Comparison of ascitic fluid, lymph from the liver, and lymph from the portal bed has shown that ascitic fluid of hepatic disease is clear while intestinal lymph is more or less opaque, that ascitic fluid has the faint yellow colour of lymph from the liver, and that lymph from the liver resembles ascitic fluid in chemical composition.

It is interesting to apply this conception of the formation of ascites to such clinical entities as some types of myocardial failure, constrictive pericarditis, intrathoracic tumour (with compression of the inferior vena cava), and thrombosis of the hepatic veins (Chiari's syndrome), as the underlying mechanism of all will produce venous congestive swelling of the liver. It is not possible to account, in this manner, for the presence of ascites when multiple peritoneal implants of metastatic carcinoma have occurred in the presence of an apparently normal hepatic circulation nor in the case of certain solid ovarian tumours (Meigs' syndrome). That irritation of any serosal surface will result in the transudation of fluid is common knowledge, but whether this phenomenon takes place in the pleural space, the pericardial sac or in the abdominal cavity, the sequence of events as stated represents cause and effect rather than a complete and satisfactory explanation of the mechanism by which the free fluid is produced.

Determination of Portal Pressure in Human Subjects

Abundant data have accumulated relating to studies of the pressure in the portal system of experimental animals in normal and abnormal conditions. Although much information has been obtained from observations of the portal pressure in human subjects when disease has been present, only meagre and isolated reports have been available of studies in the normal human subject. As a result, differences of opinion have been expressed relating to what constitutes normal portal pressure in man. That a normal base line of portal pressure must be established before it is possible to determine whether or not hypertension exists is fundamental to the surgical approach to the problem, whenever elevation of pressure in the portal system is suspected. We are now concerned with studies pertaining to portal pressure in patients in whom it is not possible to demonstrate evidence of hepatic disease or abnormalities of the extrahepatic portal circulation. It is not the purpose of this portion of the presentation to report the results of these observations as the work has not been completed. The method, however, by which determinations of portal pressure are accomplished may be of some interest.

Through the collaboration of Dr. Earl Wood and Dr. E. H. Lambert in the Section on Physiology of the Mayo Foundation a strain-gauge manometer has been adapted for physiologic use; this was constructed by Mr. Richard Jones in the Section on Engineering of the Mayo Clinic.

This ingenious instrument has been devised for the accurate measurement of intravenous pressures. The instrument consists of two parts (Fig. 7). In one is contained a pressurized wash bottle, the strain-gauge element, a dry-cell battery and a range selector. In the other is contained the galvanometer which, as the name implies, detects and measures the intensity and direction of an electric current. For use in the operating room both parts of the apparatus are secured to a small portable table in order that the instrument may be moved easily with the minimum of jolting.

Before use, the section of plastic tubing that is attached to the manometer is rinsed with benzalkonium chloride U.S.P. (zephiran chloride), which is flushed out of the system with normal saline solution from the pressurized wash bottle, making sure that there are no air bubbles trapped within either of these two elements. The galvanometer gauge is then calibrated with various known pressures by holding the tip of the glass connection at 0, 5, 10, 15, 20, 30 and 40 cm. above the level of the strain-gauge manometer, and a graph is constructed in which the calibration pressures are plotted as the ordinate and the reading of the galvanometer gauge as the abscissa. This will produce a straight line if the points on the graph are connected.

The surgeon then procures a long sterile plastic tube, one end of which contains an adapter of glass tubing; this end is passed to the person who is operating the instrument. This end is connected to the tubing from the manometer and the system is again flushed with saline solution in order to fill completely the tubing and eliminate air bubbles. At the surgeon's end of the tubing is an adapter to which a 19-gauge needle is attached for performing the venipuncture.

In order to establish a consistent base line, the surgeon first places the tip of the adapter on a level with the anterior surface of the body of the vertebra, just below the attachment of the transverse mesocolon, which is approximately the level of the right auricle, and a reading from the

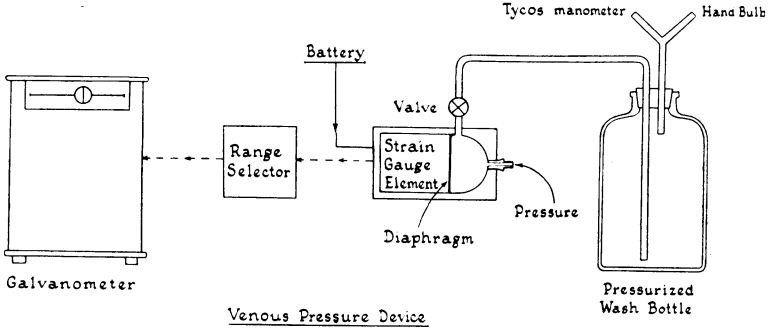

Fig. 7. Schematic representation of a strain-gauge manometer that has been adopted for physiologic use.

galvanometer is recorded. The tubing is flushed once more and the needle is placed within an easily accessible vein, usually the right gastro-epiploic. A few drops of saline solution are forced through the needle to make sure that the venipuncture is accurate and a new galvanometer gauge reading is obtained within a few seconds.

In order that the final reading on the galvanometer gauge may be translated into pressure measured in cubic centimeters of water, the base-line reading from the level of the vertebra and the final reading are plotted on the calibration line that has been constructed. The difference between these two as measured along the ordinate has been shown to be the pressure within the vein. The operator of the instrument records the systolic blood pressure coincident with the reading of the galvanometer gauge. Since the manometer is calibrated before the operation begins, an assistant can leave the operating table to record the readings and change gown and gloves to resume the operation within four minutes.

It may be argued that the pressure within a tributary of the portal vein, such as the right gastro-epiploic, will not represent the pressure within the portal vein itself. For practical purposes we feel that this method is accurate if great care is exercised to make sure that the bevel of the needle point is not resting against the wall of the vein and that no angulation of the vein has occurred. For obvious reasons we do not feel that time should be consumed to expose the portal vein nor that on general principles is it fair to the patient to traumatize even slightly this vital structure. The right gastro-epiploic vein has been chosen because it is readily accessible, is usually of sufficiently large calibre to permit satisfactory venipuncture, and can be ligated with impunity if slight pressure on the vein, after the needle has been removed, fails to control extravasation of blood.

It is to be regretted that, owing to unavoidable delay in constructing the venous pressure device, the final figures on portal pressure in a sufficiently large series of patients are not available at this time. We expect to continue this portion of the study until determinations have been made in at least 100 " normal " individuals and then to study the effects on portal pressure that may be produced by an intriguing number of factors. Thus far it has been possible to make satisfactory determinations of portal venous pressure in 21 " normal " individuals. As a preliminary report, it may be of interest to mention that there is evidently a great variation of intraportal pressure when no evidence of hepatic disease is present or when the extrahepatic portal system is apparently normal. Sixty-two per cent. of the determinations were found to be within the range of 16 and 21, while the lowest reading was calculated to be 13·6 and the highest was 23·5 cc. of water.

It is apparent that great caution must be exercised when contemplating an extensive surgical procedure for hæmorrhagic oesophageal varices, owing to the futility of performing any type of portacaval shunt when a normal pressure obtains in the portal vessel to be used in the

anastomosis. Oesophageal varices may be present in the absence of any occluding process to the egress of venous blood from lower portions of the oesophagus and cardia of the stomach except in the coronary vein. In such circumstances it is interesting to speculate as to the rôle played by the azygos system. In attempting to solve the problem presented by the patient who has experienced a hæmorrhage from oesophageal varices, it should be realized that the anatomic relationship of the coronary and splenic veins has been found to be inconsistent. The coronary vein may not empty into the splenic vein but may empty directly into the portal vein or even into the superior mesenteric vein. Although, in most instances, evidence of hypertension in a portion or all of the portal system will be evident when oesophageal varicose veins are present, this need not necessarily be so and the explanation of the phenomena that are encountered may remain obscure.

Summary and Comment

Several phases of clinical and experimental investigation of the circulation of the liver that have presently interested my colleagues and myself in the Mayo Clinic and Mayo Foundation have been presented briefly in four categories: the effect of occlusion of the arterial blood supply to the normal liver, the influence of portal circulation on restoration of the parenchyma of the liver, the rôle of lymph in the formation of ascites, and the determination of portal venous pressure in human subjects. No attempt has been made to include or evaluate the numerous magnificent contributions to this intriguing subject that have been made in Britain and abroad. Prof. H. P. Himsworth, Prof. J. McMichael, Sir Archibald McIndoe, and many others in England have done much fundamental work concerning the importance of circulatory factors of the liver in the pathogenesis of hepatic lesions.

It would appear that circulatory factors play a large part in determining not only the course but the actual appearance of many hepatic lesions. It is well known that differences in circulation to the different parts of the liver account for the irregular distribution of certain types of necrosis within the organ as a whole. Disturbance of blood supply by fibrosis or even swelling of the parenchymal cells may so interfere with intralobular circulation that damage is produced. Thus, it may be that many abnormal conditions of the liver are due not to the direct and specific action of a pathogenic agent which may initiate the illness but to secondary phenomena consequent upon a derangement of the intrahepatic circulation.

That the clinical surgeon will profit by familiarity with the work of experimental investigators is acknowledged but only infrequently is it realized that the reverse obtains. Close collaboration between the clinical surgeon and the laboratory worker is essential if the goal of improved service to the patient is to be achieved.

REFERENCE

[1] MARKOWITZ, J., RAPPAPORT, A. and SCOTT, A. C. (1949). Function of the Hepatic Artery in the Dog. *Am. J. Digest. Dis.* **16**, 344-348.