A STUDY OF CERTAIN ANATOMICAL AND PHYSIOLOGICAL FACTORS CONCERNED IN THE CONTROL OF THE HEPATIC CIRCULATION

THESIS SUBMITTED FOR THE DEGREE OF

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PART I

OBSERVATIONS ON THE ANATOMY OF THE LIVER

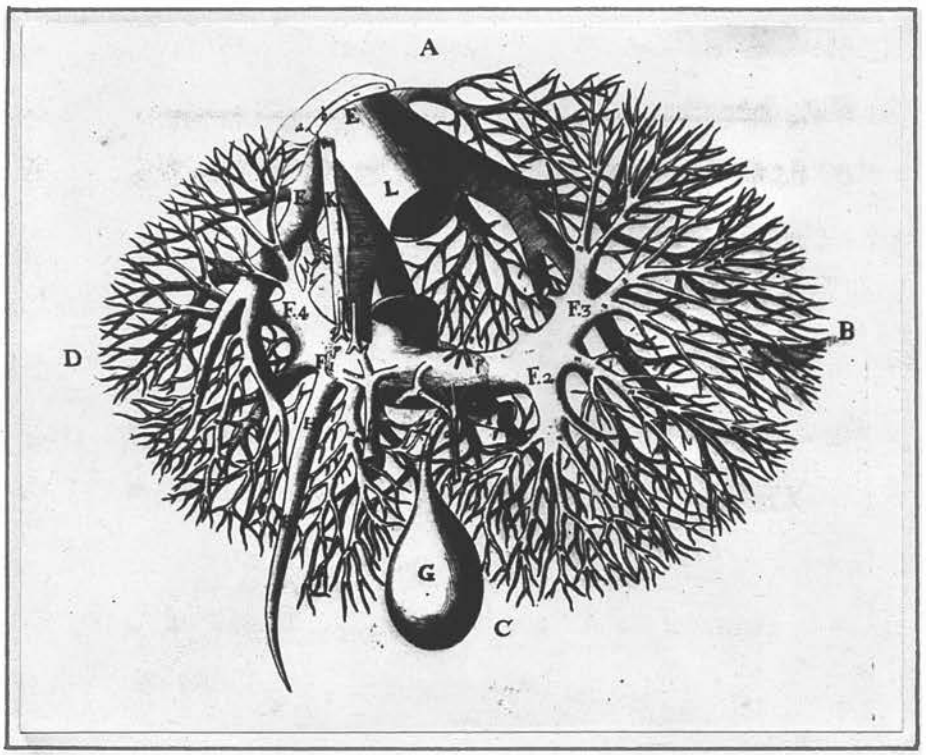

Fig. 1.- The relationships of the portal and hepatic veins within the liver (Glisson, 1654).

OBSERVATIONS ON THE ANATOMY OF THE LIVER

The earliest relic of man's interest in the anatomy of the liver is a small clay model of a sheep's liver cast some five thousand years ago. A systematic description of the gross anatomy of the blood vessels of the liver was not available, however, until 1654 when Francis Glisson published his classical "Anatomica Hepatis", in which the illustrations of the ramifications of the portal and hepatic venous systems bear scrutiny even in the light of modern knowledge (Fig. 1).

More recently, attention has been directed to the study of the fundamental architecture of the liver but it must be admitted that even to-day this aspect of anatomy remains only partially understood. The present study of the micro-anatomy of the liver was undertaken as a prelude to certain physiological experiments on the hepatic circulation. It was felt that the commonly accepted concepts of liver architecture were in some ways unacceptable and that first-hand experience of three-dimensional anatomy was necessary if these difficulties were to be resolved.

Methods

Preparation of Neoprene Casts

Neoprene casts were prepared from 12 human specimens obtained from the post mortem room and the livers obtained from /

from eight recently killed dogs. In each case the hepatic artery and portal vein were cannulated and the organ was perfused with normal saline at room temperature until the fluid issuing from the hepatic veins became free from blood staining. In many experiments the infra-diaphragmatic portion of the inferior vena cava was also cannulated and the supra-diaphragmatic portion ligated so as to permit retrograde injection of the hepatic venous system. The common bile duct was also canmulated to obtain a detailed cast of the biliary tract. During the course of the perfusion, leakage from extra-hepatic vessels was controlled by ligatures.

The neoprene latex solution was injected through the various cannulae from a pressure bottle by means of compressed air, the pressure being controlled by a mercury manometer. Separate colours were reserved for each system: portal vein - blue, hepatic artery - red, hepatic venous system - white and biliary system - yellow. In order to obtain penetration of the medium into the finer hepatic blood vessels, pressures between 300 and 400 mm.Hg were used for injection of the hepatic arterial system and between 100 and 200 mm.Hg for the other systems. Previous workers have used considerably lower injection pressures but their aim was merely to outline the major blood vessels.

When sufficient penetration of the medium had been obtained, evidenced by appearance of colour on the surface of the liver and by cessation of flow in the injection system, /

system, the cannulae were removed after the application of ligatures. The liver was then completely immersed in a solution of commercial hydrochloric acid for a period of four to five days, after which the digested tissue was removed with a fine jet of water and the liver was again immersed in hydrochloric acid for a few more days. Digestion was usually completed within seven days, when any portions of liver still adhering to the cast could be easily dislodged by a stream of water. The completed cast was stored in 10 per cent. formalin.

Methods of Study

The gross anatomy of each cast was examined by the naked eye and then in more detail with the aid of a low powered dissecting microscope. Segments showing features of particular interest were then removed and subjected to more detailed microscopical examination under a standard microscope, using direct floodlighting from a 500 Watt spot light. By this technique, magnifications up to 200 times could be employed to gain a clearly defined three-dimensional picture of the minute vessels of the liver. Coloured photomicrographs which illustrate certain features of the micro-anatomy of the liver were made with a Zeiss Ultrapak camera.

Technique of Intravital Injection of Indian Ink in the Rat and Dog.- The abdomen was opened through a midline incision under ether anaesthesia and the spleen delivered into /

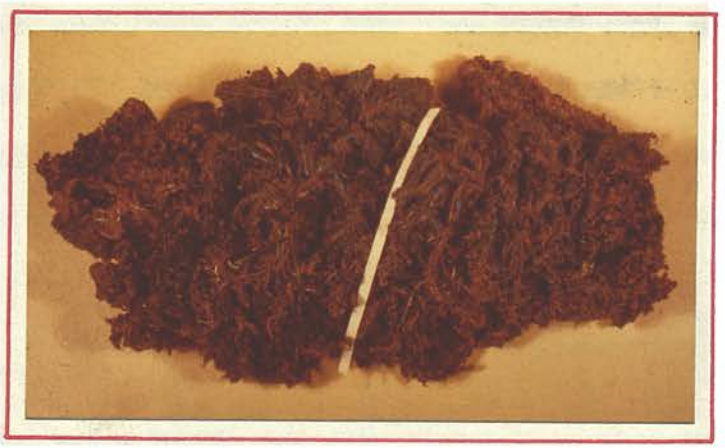

Fig. 2.- Illustrating the point of division between the right and left halves of the liver.

into the wound. Between 0.5 and 1 ml. in the rat and 5 ml. in the dog of Indian ink solution was then rapidly injected into the surface of the spleen. Discolouration of the liver by the dye was evident in a few seconds and the vessels of the lesser omentum were then occluded by artery forceps and the liver rapidly removed from the animal and immersed in 10 per cent. formalin. After fixation, serial sections were cut varying in thickness between 50 and 150 μ. This serial thick section technique proved to be more informative than the usual thin section method. By study of these preparations an attempt was made to develop a three-dimensional picture of the liver architecture and to correlate the observations made on the neoprene casts.

General Features of the Anatomy of the Human Liver, including Features of Surgical Importance

Sub-Divisions of the Liver on the Basis of its Afferent Blood Supply.- The dividing line between the right and left flow beds of the liver is situated to the right of the midline. This major fissure can be delineated by a curved, oblique line extending from the fossa for the gall bladder to the right margin for the fossa of the inferior vena cava (Fig. 2). Unfortunately for the surgeon, there is no corresponding fissure on the surface.

Rex (1888) and Cantlie (1898) were the first to describe the true plane of sub-division of the liver into right and left /

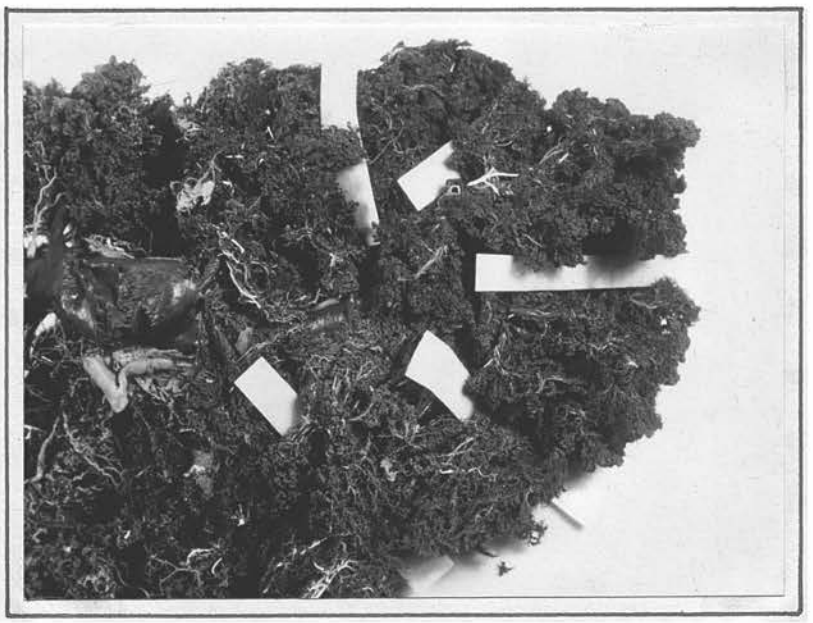

Fig. 3.- The segmental divisions of the right lobe of the human liver.

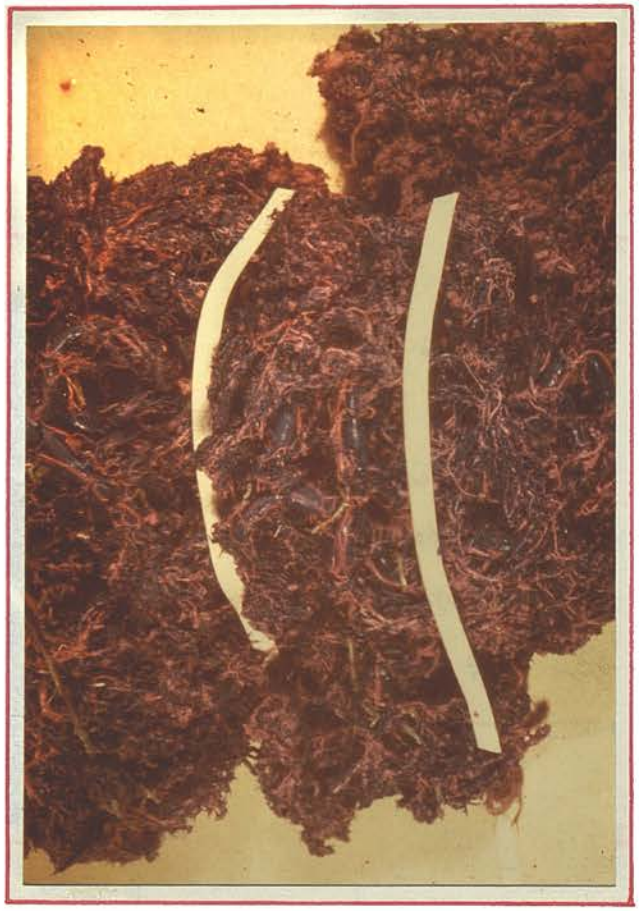

Fig. 4.- The two major fissures on the anterior surface of the liver are shown. The left branch of the portal vein supplies the quadrate and caudate lobes of the liver.

left halves. These findings have been confirmed by more recent workers (Hjortsjo, 1951; Elias and Petty, 1952; Couinan, 1954; Gans, 1957).

If the right and left branches of the portal vein are pursued from the central fissure, they are found to give rise at regular intervals to branches which supply discrete portions of liver tissue - the segments and sub-segments of the liver (Fig. 3). In the case of the left branch of the portal vein, this vessel is found to supply both the caudate and quadrate lobes before passing into the anatomical left lobe of the liver and dividing into a series of segments (Fig. 4).

The segmental anatomy of the intrahepatic blood vessels and ducts has been studied by Elias and Petty (1952), Gans (1955), Couinand (1957) and Hobsley (1958). Whilst a regular arrangement of the main branches of the portal vein can be readily discerned in a digested, injected cast, it seems unlikely that segmental resection of an isolated lesion within the liver is likely to prove a feasible surgical proposition and therefore these details will not be further considered.

When a segment of a neoprene cast is further dissected, the portal vein is found to give off a series of smaller branches, usually at right angles to the parent trunk, this branching process being continued usually to the sixth or seventh generation until a terminal portal venule is reached surrounded by a cluster of sinusoids. It is important to recognise /

Fig. 5.- The main bile duct of the quadrate lobe is shown to lie midway between the falciform ligament and the gallbladder fossa.

Fig. 6.- Showing the irregular distribution of the hepatic arteries within the liver.

recognise the fact that vascular connections between neighbouring portal venous segments and sub-segments do not exist, each small segment being entirely independent at least in respect of portal venous blood. It is not surprising, therefore, to find that occlusion of a branch of the portal vein leads to acute atrophy and congestion in the segments supplied known as a Zahn's infarct (Popper and Schaffner, 1957).

The distribution of the intrahepatic bile ducts follows closely on the sub-division of the liver in terms of the portal system. The central bile duct of the quadrate lobe (Fig. 5) possesses certain attractive possibilities in regard to short circuit operations between the intrahepatic biliary tract and the gastro-intestinal tract in that:-

(1) Its position is fairly constant;

(2) It lies near the anterior surface of the liver;

(3) It is not usually crossed by any important blood vessels;

(4) Its diameter, particularly after biliary obstruction, is adequate for anastomosis.

Although the hepatic artery follows closely on the segmental pattern dictated by the portal venous system, its branches pursue a meandering course to their destination and anastomoses between vessels on a segmental plane are fairly frequent (Fig. 6). Furthermore, whilst the portal venous segments are absolutely descrete, the arterial circulation of neighbouring segments intercommunicate through a fine but clearly /

Fig. 7.- The subcapsular arterial plexus, an important source of arterial anastomosis between the individual segments.

Fig. 8.- Showing the segmental distribution of the hepatic veins.

clearly defined sub-capsular arterial plexus (Fig. 7). This plexus, together with its extensive connections with the accessory extrahepatic arteries, may be a significant factor in permitting sufficient collateral arterial circulation to the right lobe of the liver following ligation of the right branch of the hepatic artery during cholecystectomy.

The Hepatic Veins.- The arrangement of the main hepatic veins in the liver of man is simple: three major vessels emerge from the postero-superior aspect of the liver; the right branch receives blood mainly from the right lobe of the liver, the left from the anatomical left lobe, i.e. that portion of the liver to the left of the falciform ligament, the remaining hepatic vein drains the central portion of the liver, i.e. the caudate and quadrate lobes. A few accessory veins frequently emerge from the posterior aspect of the right lobe of the liver and, after a short course, enter the anterior aspect of the inferior vena cava. These vessels are frequently encountered during surgical exposure of the right adrenal gland through the peritoneal cavity and may give rise to troublesome haemorrhage if not avoided or controlled.

Interdigitation of the Portal and Hepatic Venous Systems.- The liver is divided into segments and sub-segments by the regular branching of the portal venous and hepatic arterial systems. The hepatic venous system is also laid down on a segmental pattern (Fig. 8) but the anatomy is complicated by the /

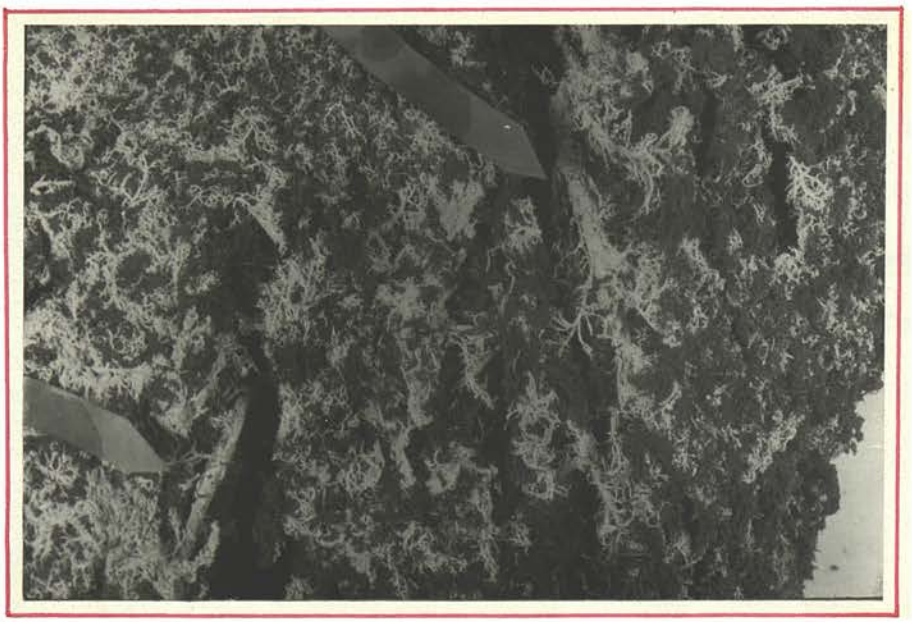

Fig. 9.- The two major fissures on the anterior surface of the liver are indicated, the main hepatic veins lie within these fissures.

Fig. 10.- The inter-digitation of the hepatic and portal venous systems in the right lobe of the liver is shown.

Fig. 11.- A close-up view of the inter-digitation of the venous systems in the liver.

Fig. 12.- Inter-digitation of the venous systems of the liver (x 15).

the fact that the portal venous and hepatic venous systems interdigitate with each other throughout the liver. No matter which two portal vein branches are selected a branch of the hepatic vein is always found lying between them (Figs. 10-12). An appreciation of the inter-relationship between the hepatic venous and portal venous systems is essential for a proper understanding of hepatic anatomy. From the surgical point of view the association is unfortunate since the hepatic veins must lie between the flow beds of the portal venous system or, in other words, exactly in the lines of potential cleavage dictated by the distribution of the afferent blood vessels of the liver. This means that surgical incisions along a main interlobar fissure must inevitably encounter large hepatic veins. Whilst this does not preclude the possibility of lobar resections based on the anatomy of the afferent vessels, the hepatic venous branches from the lobe which is to be removed must be ligated without damage to the major hepatic vein.

The blood supply of the common bile duct.- In the present study the blood supply of the common bile duct was investigated in one human subject at autopsy. The distal cut end of the common hepatic artery was cannulated and a solution of coloured neoprene latex injected into the vessel under high pressure. After removal and fixation of the organs the sources of arterial supply to the common bile duct were examined. The bile duct was found to have an extensive /

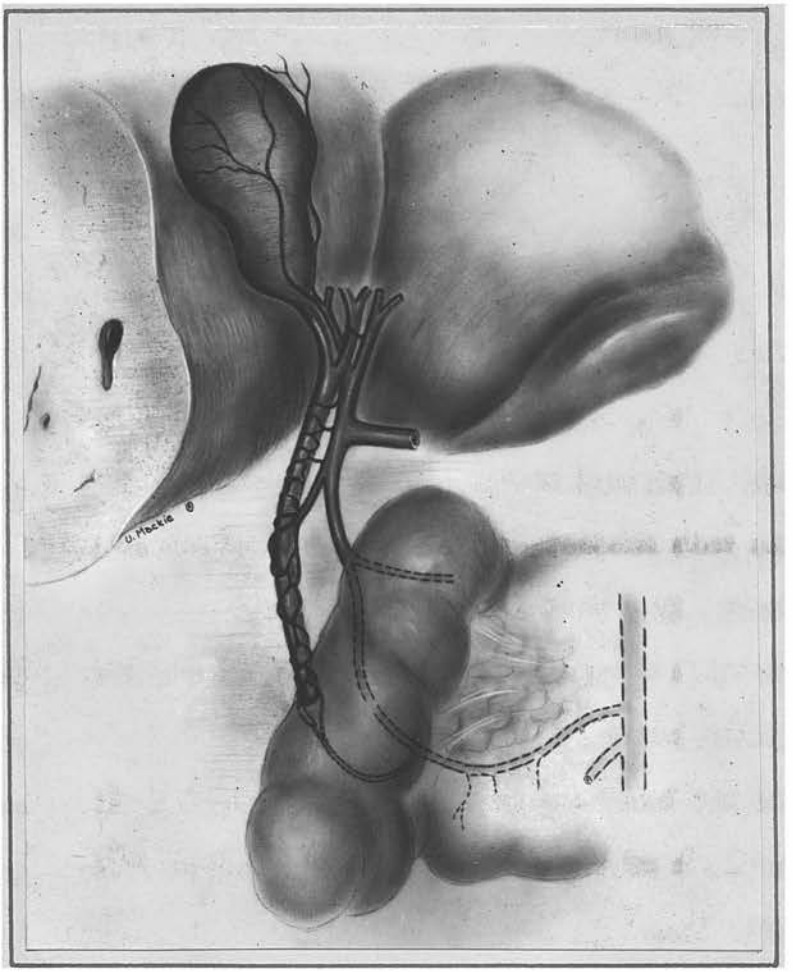

Fig. 13.- The blood supply of the common bile duct.

extensive arterial supply disposed in the form of a closely knit longitudinal plexus (Fig. 13). The supra-duodenal portion of the plexus received a series of contributions directly from the hepatic artery. The retro-duodenal portion of the plexus communicated with the retro-duodenal branch of the gastro-duodenal artery and, indeed, this was the most important source of arterial supply of the common duct in this subject. The terminal portion of the duct was surrounded by a ring of arterial vessels produced by the inosculation of the superior and inferior pancreatico-duodenal arteries.

It has been suggested by Henley (1955) that operative interruption of the retro-duodenal branch of the gastro-duodenal artery may lead to necrosis of the common bile duct and delayed stricture formation, particularly if the inferior pancreatico-duodenal contribution from the superior mesenteric artery is deficient. From the results obtained in the present limited study such an event appears to be unlikely in view of the extensive longitudinal arterial anastomosis along the duct fed by direct branches from the hepatic artery.

Blood supply of the gall bladder.- The cystic artery was found to divide into two branches close to the neck of the gall bladder: a superficial branch concerned entirely with the blood supply of the gall bladder and a deep branch which also contributed branches to the arterial plexus of the gall bladder, but also supplied arterial blood to the segments /

Fig. 14.- The blood supply of the gallbladder.

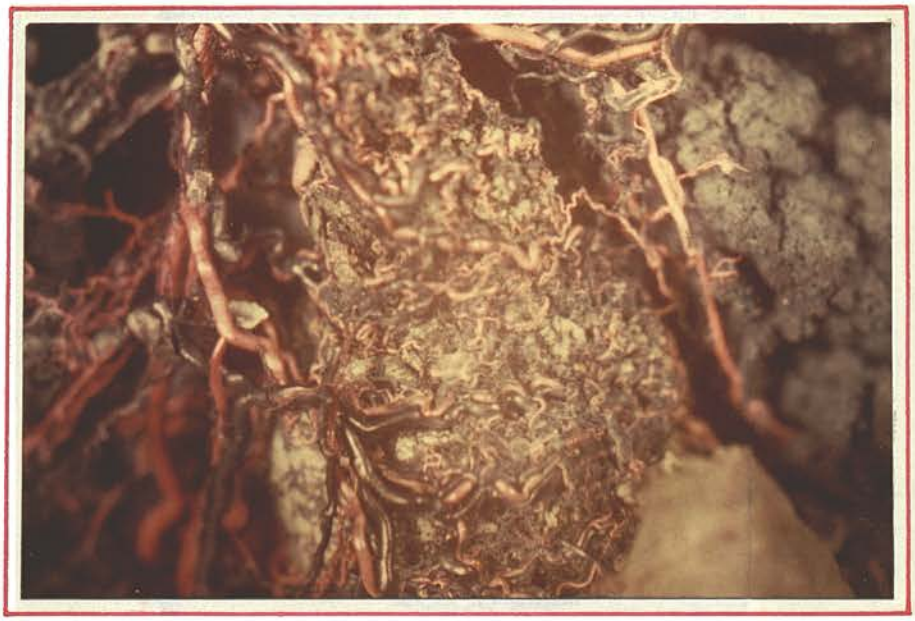

Fig. 15.- Showing the distribution of the deep branch of the cystic artery, and also the veins draining directly from the gallbladder into the liver.

segments of liver forming the gall bladder bed (Figs. 14 and 15). Further examination showed that the deep branch of the cystic artery was indeed the main source of arterial supply to the segments of liver, only a few collateral connections with the main intra-hepatic arterial system being present. It is, of course, a recognised clinical fact that only minimal back flow occurs from the distal cut end of the cystic artery during cholecystectomy. Since an adequate arterial supply is necessary for survival of liver cells, it seems likely that a varying degree of liver necrosis must occur in the gall bladder bed after cholecystectomy.

The venous drainage of the gall bladder was beautifully outlined by the neoprene technique (Figs. 14 and 15). A few fine veins were found to pass medially and terminate in the portal vein. The most important route of venous drainage of the gall bladder, however, was found to be through a series of large veins passing directly into the substance of the liver forming the bed of the gall bladder. These vessels finally terminated in an identical fashion to any other branch of the portal vein, by breaking up and supplying discrete clusters of sinusoids. Again, it seems certain that the liver tissue supplied by these veins must undergo severe reduction in its blood supply following cholecystectomy.

The /

The Fundamental Architectural Structure of the Liver

The mosaic of small polygonal areas in the liver of the pig, which can be discerned even with the naked eye, was observed by Kepfer in 1654 and he was undoubtedly the first to introduce the lobular concept of hepatic architecture which has persisted to this day. Much later, when techniques for microscopic examination of the liver became available, Kiernan (1833) reintroduced the lobular concept and noted that parenchymal trabeculae were orientated around what he called the central veins. Brissaud and Sabournin (1888) rejected Kiernan's vascular unit of liver architecture and since at that time little was known of the function of the liver except that it was capable of elaborating bile, they introduced the functional unit consisting of an area of liver tissue centred on a terminal bile ductule. With further advance of knowledge concerning the function of the liver it became obvious that the unit described by Brissaud and Sabournin lacked sufficient reality. Mall (1906) in a comprehensive review of the subject discarded the lobular concept and introduced in its place a unit of architecture based on the territory of supply of a terminal branch of the portal vein: the portal unit. From the functional point of view the introduction of the portal unit was a definite advance, but again it suffered from the fact that it could be delineated only by injection techniques and serial examination of thick sections.

Epplen (1922) was the next investigator to elaborate on /

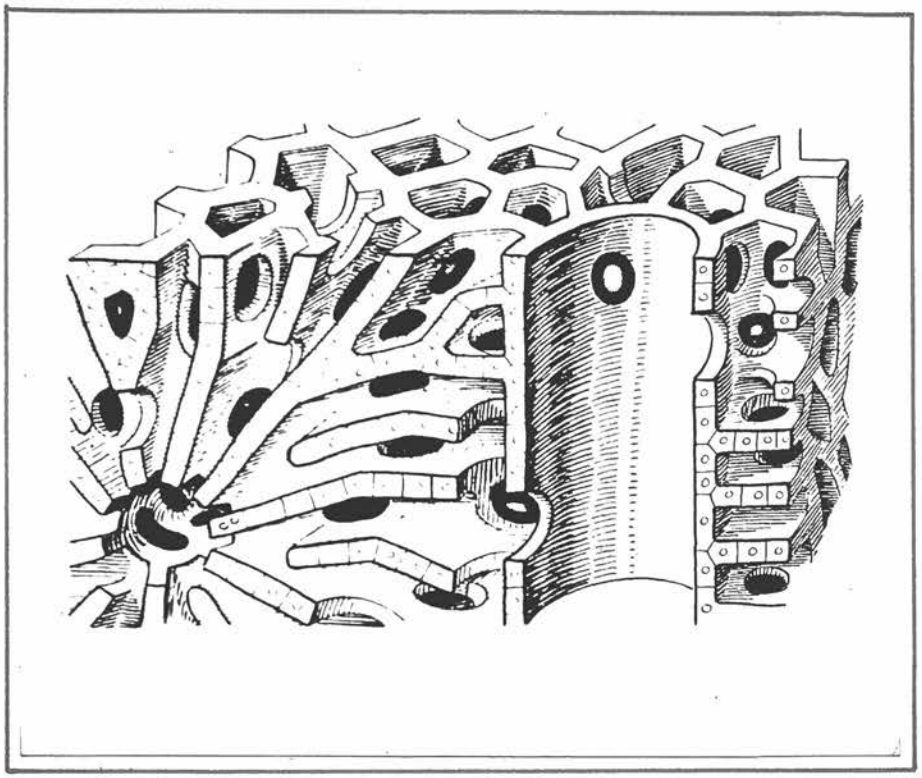

Fig. 16.- The arrangement of hepatic laminae bounding the sinusoidal spaces in the liver (Elias, Amer. J. Anat., 85, 1949).

on the minute anatomy of the liver and he reintroduced the lobular idea, the lobule being defined as "that mass of liver tissue enveloping a radicle of a hepatic vein". More recently, Elias (1949) undertook an intensive study into the minute structure of the liver, the technique employed being stereographic reconstruction from serial sections. It was established that instead of a series of sinusoids surrounded by the cords or trabeculae of cells, the parenchymal liver cells were arranged in laminae one cell thick and between the laminae were situated the sinusoids (Fig. 16). At the periphery of the lobule the cells are arranged to form a sheath for the structures of the portal unit, the sheath being penetrated in many places by lacunae through which the structures of the portal tract gain access to the interior of the lobule. When the lobule abuts against a neighbouring lobule the laminae inter-communicate so that the plates of cells, which he described, may pass as a continuous sheet across a large portion of the liver. Whilst this part of Elias' work has revised our ideas about the detailed anatomy of the liver cells and appears to rationalise intralobular anatomy, he retained the lobule as the final functional unit of liver architecture.

The use of the lobule as the final indivisible unit of architecture is certainly hallowed by the tradition of nearly one hundred and thirty years of intensive study. The varied attempts in the past to produce an alternative unit would appear to have been prompted by a sense of dissatisfaction /

dissatisfaction with the popular lobular concept. Examination of serial sections of liver of any animal, except perhaps the pig, leads to the inevitable conclusion that the lobule is an evasive unit, its outline only to be made out here and there, and only by the application of considerable imagination.

As Mall pointed out in 1906, the adoption of the lobular concept implies that the hepatic trabeculae are orientated in a radial fashion around a terminal branch of the hepatic vein. It would seem rational, therefore, that this orientation of the cells and the hepatic venous system must be an event occurring during the course of embryonic development of the liver, a view current in various text-books of embryology. If this is so, then the parenchymal cells of the liver must be unique amongst the tissues of the mammalian body since in other situations cellular growth differentiation are centred around afferent blood vessels. On a priori grounds, it seems unreasonable to postulate such an unlikely series of events which contradict the accepted biological growth processes of tissue cells. Apart from this biological objection to the lobular concept, further difficulties arise when one comes to orientate the portal tract surrounding a lobule with the vascular connections of the lobule. For instance, Elias (1949) and Maegraith et al. (1949) have described conducting veins which pass around the periphery of the lobule before passing inwards to feed the neighbouring sinusoids. Careful examination of a series of /

Fig. 17.- A terminal branch of the portal vein is shown to supply a single cluster of sinusoids. The inter-digitation of the portal and hepatic venous systems is also clearly shown on a microscopic scale (x 25).

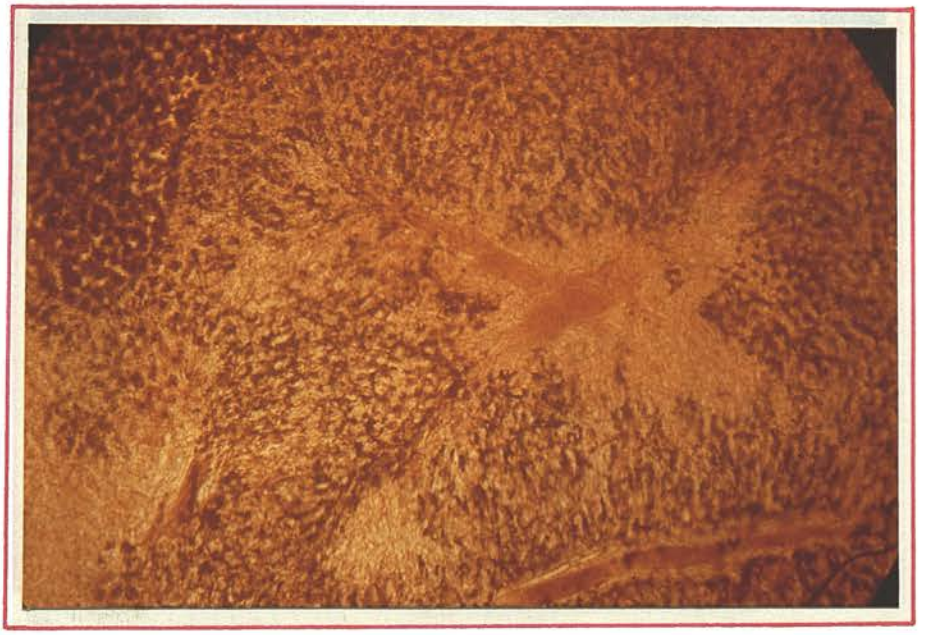

Fig. 18.- Intraportal injection of indian ink during life. Showing the terminal distribution of the portal venules which supply a single cluster of simusoids.

of fully injected neoprene casts and Indian ink injections of the liver has failed to demonstrate vessels corresponding to the conducting venous channels of these authors.

Turning to the implications of hepatic architecture on the interpretation of pathological processes in the liver, we again find that the lobular concept leaves much to be desired. Indeed, it seems that the present paucity of data regarding the intimate effects of liver disease on liver architecture has been greatly hampered by a lack of clear understanding of hepatic anatomy.

An interpretation of the micro-anatomy of the liver derived from a study of neoprene casts and intravital injections of Indian ink.- When selected portions removed from neoprene casts of the livers of dog and man are carefully examined under a binocular dissecting microscope, the minute branches of the portal veins are found to terminate abruptly by emptying into a single cluster-like group of sinusoids (Fig. 17). These clusters of sinusoids are readily separable from the clusters supplied by neighbouring adjacent, terminal portal vessels. This mode of termination can also be seen in intravital Indian ink preparations (Fig. 18). Conducting veins passing round the periphery of the clusters of sinusoids could not be discerned in any of the specimens examined. The integration of these terminal units of sinusoids, supplied by a single branch of the portal vein, into a unified concept of liver architecture provided considerable food for thought since it seemed at first /

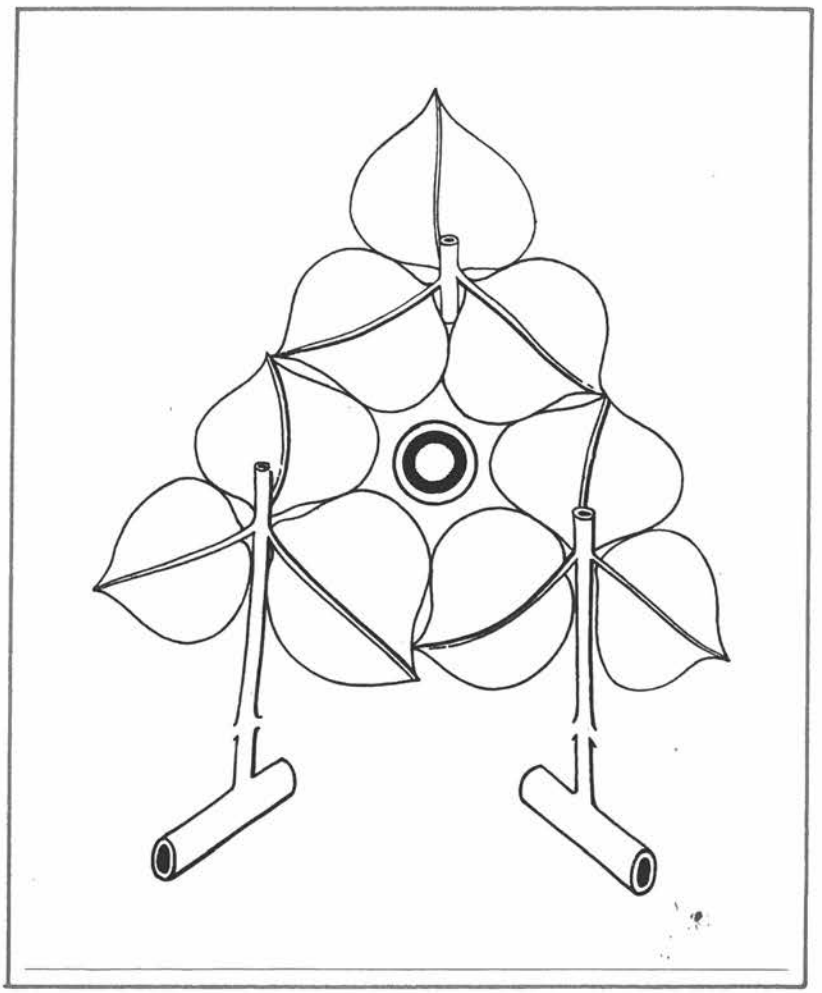

Fig. 19.- The fundamental architecture of the liver lobule. The arrangement of the various clusters of sinusoids supplied by the portal venules is shown (re-drawn after Rappaport et al., 1954).

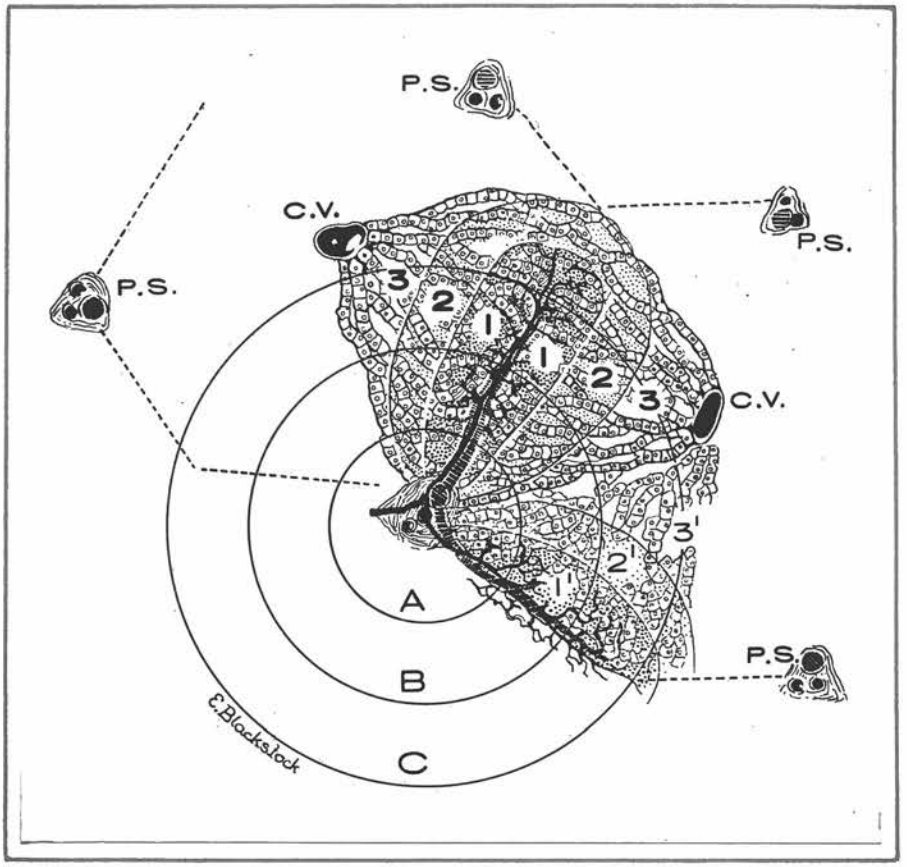

Fig. 20.- The cluster of sinusoids supplied by a terminal branch of the portal vein is distributed to adjacent lobules (after Rappaport et al., 1954).

first that this finding could not be equated with the findings of previous workers or with the appearances seen on haematoxylin and eosin sections of the liver. The problem was resolved, however, by careful examination of casts in which the hepatic venous system had also been fully injected. It was found that between each terminal cluster of sinusoids lay a terminal branch of a hepatic vein and that this vessel was in fact the structure described as the central veins by the adherents of the lobular concept. The orientation of various sinusoidal clusters around this central vein was then further examined when it became apparent that the appearance of a hepatic lobule was due to a special arrangement of the clusters around the central vein, in such a way that each lobule was made up by the contribution of four to six half-clusters, each half-cluster being orientated round the central vein of the lobule (Fig. 19). The remaining halves of the clusters then took part in forming parts of adjacent lobules (Fig. 20). In this way, the small masses of sinusoids became incorporated into the architecture of the liver so that any terminal branch of a portal vein supplied blood to portions of two adjacent hepatic lobules. Although the appearance of the neoprene casts suggests that the terminal clusters of sinusoids tend to be supplied entirely by their own afferent vessel, it seems likely that a considerable cross-flow from neighbouring lobular segments must take place so that blood may permeate under the influence of local controlling factors from one lobule to another /

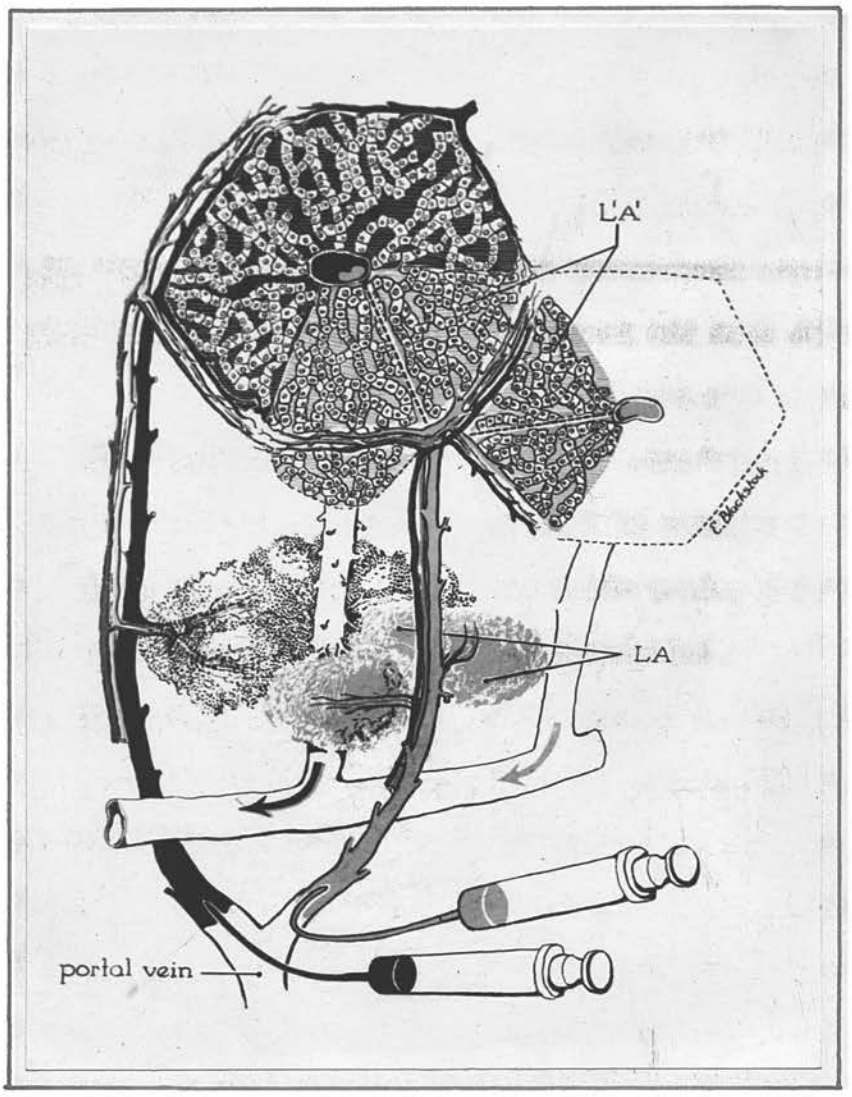

Fig. 21.- Injection of the terminal branches of the portal vein with solutions of differing colour clearly demonstrates the sub-divisions of the hepatic lobule (after Rappaport et al., 1954).

another and probably through relatively wide areas of liver tissue before gaining access to a temporarily patent central vein.

Since this concept of liver anatomy appeared to contradict the work of earlier workers, a further search of the literature was undertaken. It was then found that identical conclusions had been reached by Rappaport et al. in 1954 from the results of injections into neighbouring terminal branches of the portal vein with solutions of differing colour. They showed that it was possible to outline sectors of berry-shaped clumps of sinusoids of differing colour which were orientated in such a way that five to six half-sections became confluent around a terminal branch of the hepatic vein to produce the appearance of a lobule (Fig. 21).

Importance of this new concept for the understanding of hepatic anatomy and pathology.- If the cluster of sinusoids supplied by a terminal branch of a portal vein is accepted as the ultimate unit of liver structure, many of the difficulties in the interpretation of hepatic anatomy immediately disappear.

The liver cells can be regarded as being orientated in relation to the afferent rather than the efferent vessels, the collecting veins being situated at the periphery of the unit rather than the centre, bringing the liver into line with the biological behaviour of other tissues. The specialised appearance of the liver is produced by the interdigitation /

interdigitation of the hepatic venous and portal venous systems so that between every two portal branches within the liver a hepatic vein must reside. We have already seen this inter-relationship in the major and minor interlobar and inter-segmental fissures and an identical arrangement is apparent at the microscopical level if the new concept be accepted.

In the past it has been difficult to appreciate the three-dimensional anatomy of the lobule in detail: what were its longitudinal dimensions, how did it connect with neighbouring lobules, how did its afferent vessels penetrate and supply the circumference of the lobule when it was indeed impossible to locate these vessels. These and many other difficulties are resolved if the unit is reduced from the composite lobule to the solitary clusters of liver sinusoids supplied by a terminal portal venule.

Quite apart from rationalising the micro-anatomy of the liver, this concept has very important implications with regard to the interpretation of the histological effects of pathological processes. Since the lobule is a complex artefact produced by the integration of a series of clusters of sinusoids each with its separate afferent vessel, the periphery of each component in the lobule can be expected to be represented by a series of lines radiating through the central vein with the line being continued into adjacent lobules. One of the basic tenets of pathological interpretation of morbid processes within the liver is that the /

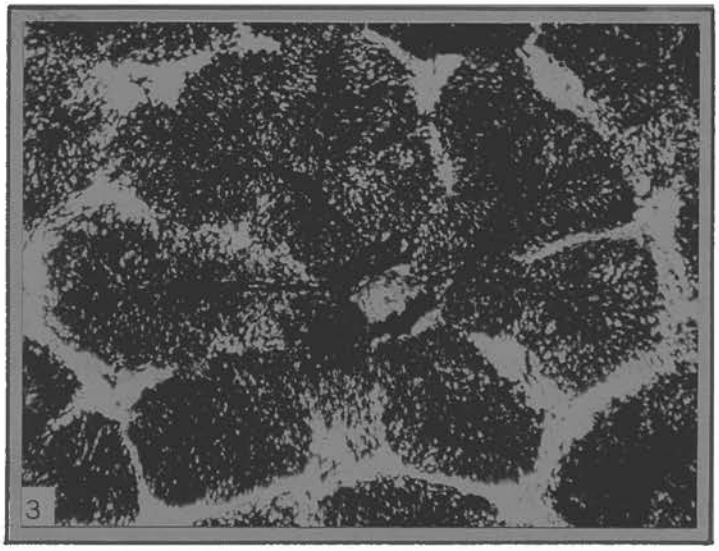

Fig. 22.- A case of diffuse hepatic fibrosis showing the dissection of the lobule by the pathological process. The periphery of the fundamental units of architecture are clearly outlined by strands of fibrous tissue.

the parenchymal cells situated at the point furthermost from the site of entry of the afferent blood vessel are more liable to damage by cytotoxic agents, metabolic derangements and the effects of anoxia than the cells in close proximity to the afferent blood vessel. On the basis of the classical concept of liver anatomy, this vulnerable area consists of the cells situated in the centre of the lobule, and thus accounts for the common occurrence of centrilobular necrosis. On the new concept, the vulnerable cells are situated not only in the centrilobular zone but also around the whole periphery of the fundamental unit of architecture. Examination of histological sections of livers affected by any form of acute parenchymal damage shows that in the majority of instances cellular necrosis is not confined to the centrilobular zone alone but also extends into the remainder of the lobule in an irregular fashion. It seems likely that this phenomenon can be accounted for by this new anatomical concept. Furthermore, in some forms of cirrhosis the lobules of the affected liver are dissected into separate islands of tissue by the laying down of collagen, fibroblasts and accompanying blood vessels. The pathological interpretation of this phenomenon has always defied adequate explanation but on the new concept the dissection can be described as being due to deposition of collagen and fibroblasts in response to episodes of cellular damage situated at the periphery of the ultimate units of the liver (Fig. 22). The outlining of the boundaries of the various units /

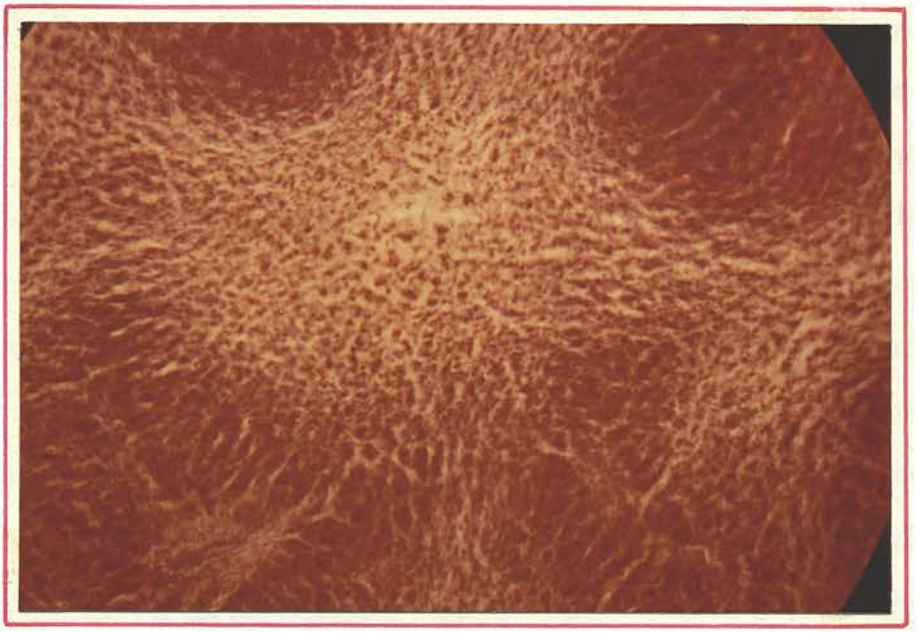

Fig. 23.- A case of veno-occlusive disease of the liver. The periphery of the terminal clusters of sinusoids supplied by various branches of the portal vein are clearly outlined by the areas of cellular necrosis within a lobule.

units of lobule may occasionally be very striking. Similarly, outlining of the units may also be seen in the presence of severe venous congestion of the liver, due either to right-sided cardiac failure or to obstruction to hepatic venous outflow. This feature was clearly shown on histological examination of the liver from a case of veno-occlusive disease (Fig. 23).

The distribution of the hepatic arteries within the liver.- Whilst the distribution of the hepatic arteries within the liver follows a segmental pattern like the portal venous system, the arrangement is far less regular. The portal veins pursue an extraordinarily regular and relentless course towards the periphery of the liver, each branch having a fixed destiny. The hepatic arteries, on the other hand, divide into numerous branches on the way and are dispersed like the tendrils of a vine around the portal venules and the intrahepatic bile ducts. Numerous anastomoses exist between these branches and, indeed, intra-segmental anastomoses are present at least in the hilum of each segment. Under the low power dissecting microscope the smaller hepatic arteries can be seen to pursue an identical meandering course throughout the minute sub-segments.

When the system of branching of the small hepatic arteries is studied with the aid of the dissecting microscope, a well-defined area of narrowing is frequently encountered at the origin of a small artery from its parent /

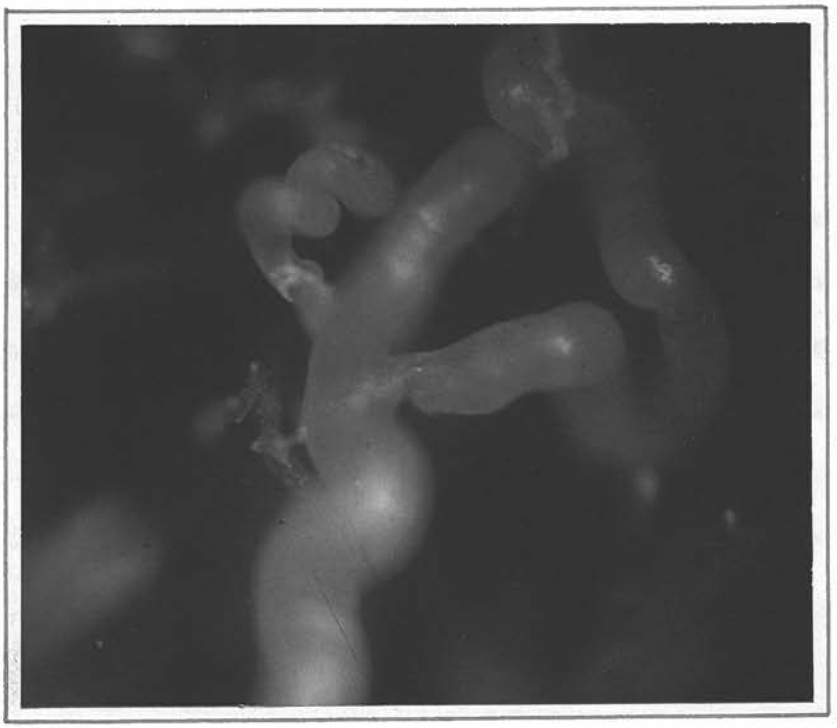

Fig. 24.- Showing the narrow segments at the origin of small hepatic arteries from their parent trunk (x 25).

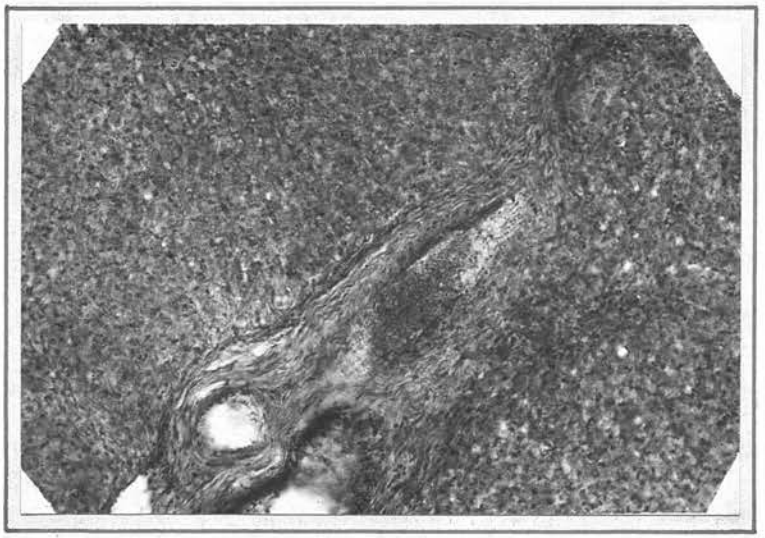

Fig. 25.- Showing an area of narrowing at the origin of a branch of the hepatic artery. This appears to be surrounded by a condensation of smooth muscle fibres. Haematoxylin and eosin (x 100).

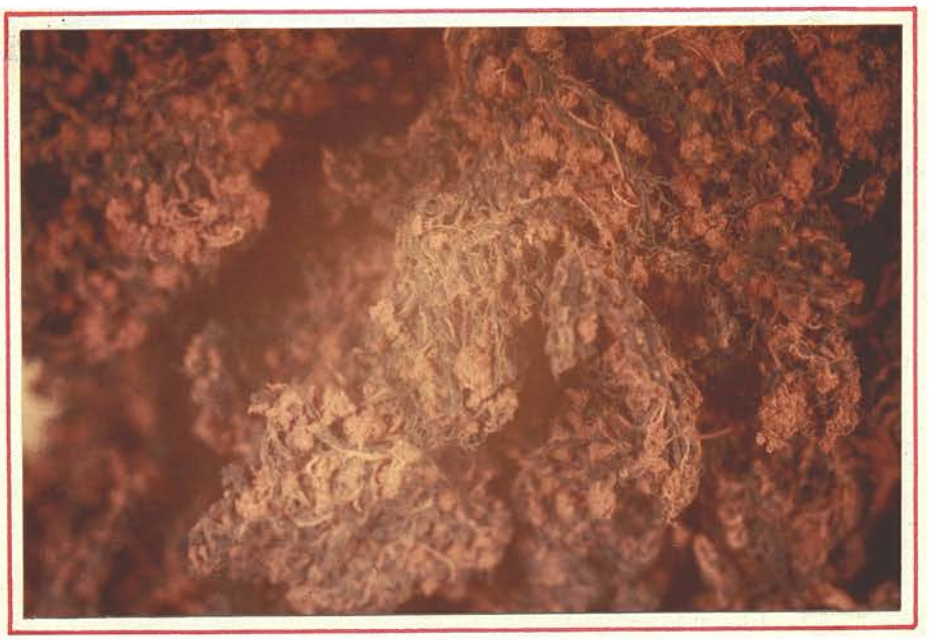

Fig. 26.- The distribution of the hepatic arteries to the sinusoidal circulation of the liver.

Fig. 27.- A small bile duct is shown surrounded by a dense arterial and venous plexus (x 25).

parent trunk (Fig. 24). This appearance is unlikely to be due to a hydrodynamic artefact during preparation of the cast since the injection was always continued until the flow of the neoprene solution had ceased. It may therefore indicate the presence of a sphincter or glomus body and confirmation of this idea is gained from examination of thick sections of liver stained with haematoxylin and eosin, when narrow areas at the site of the branching of the hepatic arteries can be made out surrounded by what appears to be a collar of pale staining smooth muscle cells (Fig. 25). In this situation a sphincter would be able to act with great mechanical advantage and by so doing regulate the distribution of the arterial blood within a sector of the liver.

When the finer branches of the hepatic arteries are followed to their termination, they are found to divide into separate pathways which conduct arterial blood either to a well-developed arterial plexus around the small bile ducts or, alternatively, into channels leading directly into clusters of sinusoids. The evidence obtained from the neoprene casts suggests that the latter forms by far the most important component of the arterial flow bed (Fig. 26).

The peribiliary arterial plexus has been described by previous investigators (Cameron and Mayes, 1930; Aunap, 1931; Maegraith et al., 1949) and is comparable with the dense arterial network which surrounds the extrahepatic bile ducts (Fig. 27). This is most clearly apparent in the blood /

Fig. 28.- A bile duct surrounded by a well-developed venous plexus (x 5).

Fig. 29.- The peri-biliary venous plexus (x 25).

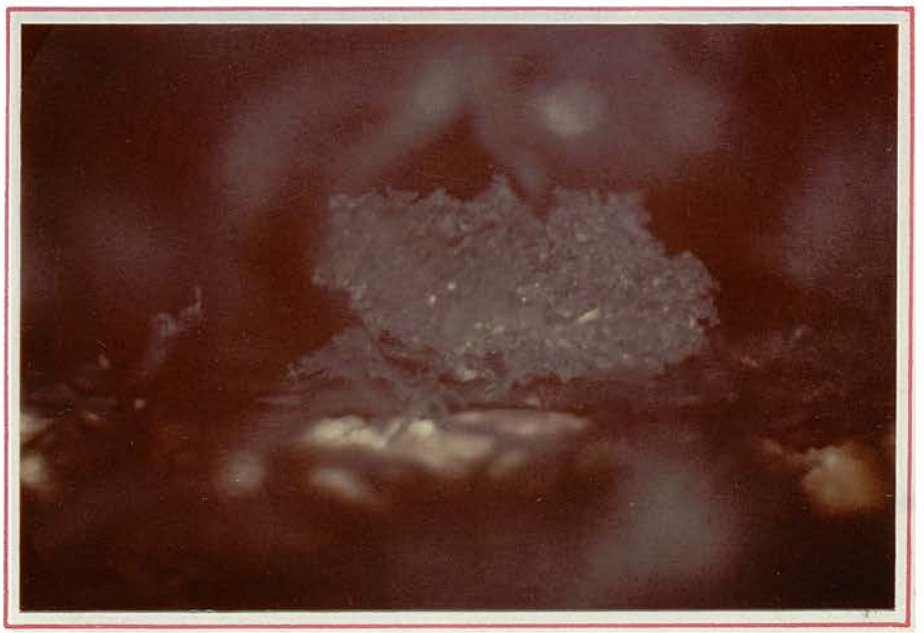

Fig. 30.- Showing the drainage of the peri-biliary venous plexus directly into the sinusoidal circulation of the liver.

blood supply of the gall bladder, the cystic artery corresponding to the fine arteries forming the peribiliary plexus within the liver. When the venous drainage of the intrahepatic bile ducts is examined it is found that the bile ducts (Figs. 28 and 29) are surrounded by a dense meshwork of venules which terminate in one of two ways: either by draining directly into a typical cluster of sinusoids (Fig. 30) identical to any other portal cluster or by passing directly into a small branch of a portal vein, which in turn delivers the peribiliary venous blood to the liver sinusoids. Of these two routes, the first appears to be of greater significance. The venous drainage of the intrahepatic ducts is therefore comparable to that of the gall bladder; those vessels draining directly into the liver sinusoids corresponding to the large veins passing from the deep surface of the gall bladder into the liver substance and the second route corresponding to the rather insignificant cystic veins which enter the main portal vein.

Function of the peribiliary plexus.- Why the bile ducts should receive such a rich arterial supply is not known. It has been suggested (Andrews et al., 1956), however, that the bile duct epithelium may have more important metabolic functions, particularly with regard to the excretion of bilirubin, than was hitherto believed. Experiments on the perfused dog liver have shown that the clearance of the dye bromsulphthalein from the perfusate takes place at a much faster rate from the hepatic arterial system than from the portal /

portal venous system, suggesting the possibility that other substances such as bilirubin may behave in a similar fashion. Andrews (1955) suggested that this selective clearance of bromsulphthalein may be due to activity of the bile duct epithelium supplied by the hepatic arterial branches of the peribiliary plexus.

The arteries of the peribiliary plexus also play an important part in supplying arterial blood to the other structures in the portal tracts. This source of arterial supply may become greatly augmented in hepatic cirrhosis because the vascular strands of connective tissue are supplied entirely by the hepatic artery.

Since the original studies of Kiernan in 1833, much discussion has centred round the problem of how and where the hepatic arterioles join the sinusoidal circulation. Kiernan believed that the hepatic arterioles communicated directly with the portal venules outside the lobule and that this mixed blood was then supplied directly to the sinusoids. Chrzonszczewsky in 1866 published the results of his studies on livers injected with ammoniated carmine and he was undoubtedly the first investigator to show conclusively that the hepatic arterioles were distributed directly to the sinusoidal circulation, mainly by fine vessels emptying into the central portion of the lobule. Mall (1906) studied this problem and came to the conclusion that the branches of the portal veins and hepatic arterioles enter the lobules of the liver directly. Mixing of the blood of the two circulations /

circulations was thought to occur within the lobule. Olds and Staffords (1930) also showed that the hepatic artery played an important role in the sinusoidal circulation, the vessels entering directly at the periphery of the lobule, and they were unable to detect any communication between the portal venules and hepatic arterioles within the portal space. This view was also shared by Maegraith et al. (1949). The terminal distribution of the hepatic arterioles was also studied by Elias (1949), using the method of three-dimensional reconstruction from serial sections of the liver. Many fine arterioles could be traced for a considerable distance within the lobule and he concluded, therefore, that the original observation of Chrzonszczewsky that the hepatic arterioles were distributed to the central parts of the lobule was indeed correct. These vessels which Elias termed arteriolar capillaries were considered to be important in that they could by nature of their small diameter and relative length impose a high resistance to blood flow, leading to equilibration of pressure between the hepatic arterial and portal venous systems. Elias postulated that these arteriolar capillaries, surrounded by smooth muscle cells and ganglion cells, produced a jet effect which might lead to directional control of arterial blood flow within the sinusoids.

Present studies of the arterial component of the sinusoidal circulation.- The neoprene cast method was found to produce suitable specimens for the examination of the terminal /

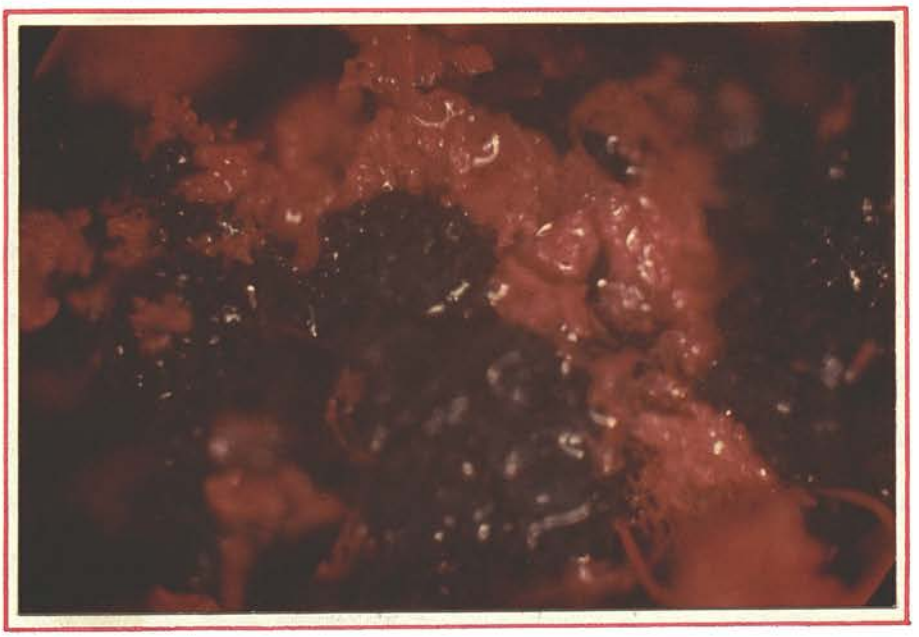

Fig. 31.- The distribution of the hepatic artery to the sinusoidal circulation (x 5).

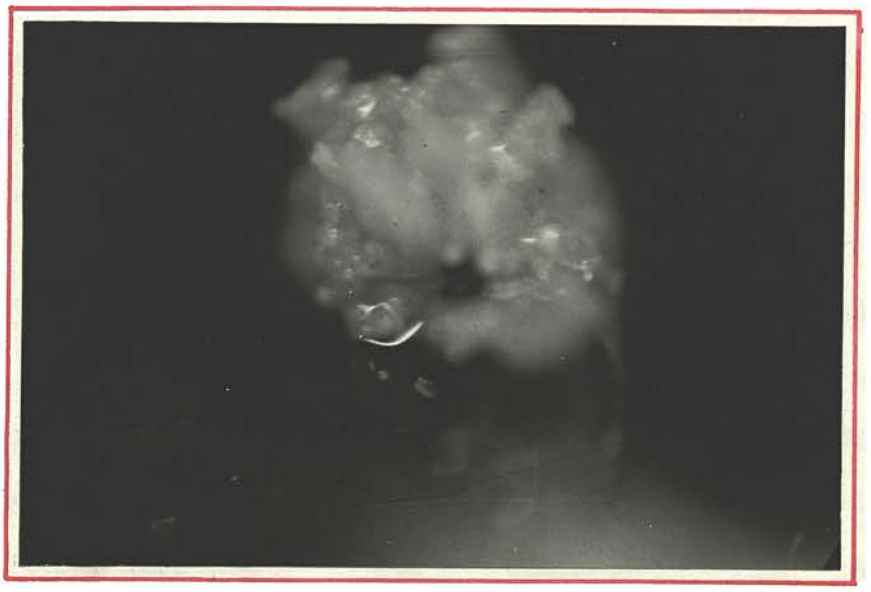

Fig. 32.- A cluster of sinusoids supplied by the hepatic artery. An adjacent group of sinusoids have been filled from the portal vein.

terminal distribution of the hepatic artery to the sinusoidal circulation. Fine vessels of the order of arterioles were found to be given off at intervals from the parent trunks. These arterioles were then seen to pass directly into the sinusoidal circulation, resulting in the filling of a cluster of sinusoids identical in appearance to those already described in connection with the portal venous system (Fig. 31). Frequently these arterial sinusoidal clusters were seen to abut against adjacent portal venous clusters to make up a lobule in exactly the same manner as the lobular component injected entirely from the portal venous system (Fig. 32). Despite long continued search, communications between the hepatic arterial and portal venous systems in the portal tracts were never observed and, indeed, the blood supply of the sinusoidal clusters appeared to be entirely independent. This finding suggests the existence of segments in the lobule perfused predominantly either by arterial or portal venous blood. Whilst these appearances produced by the injection of neoprene could be explained on the basis of capricious filling of the vessels by the latex, Wakim and Mann (1942), using a trans-illumination technique, also described the presence of arterial sinusoids in the liver.

In summary, three divergent concepts of the contributions of the arterial and venous system to the sinusoidal circulation have been presented: (1) that mixing of arterial and venous blood takes place in a perilobular plexus /

Fig. 33.- The arrangement of the smaller hepatic veins in man.

Fig. 34.- The hepatic veins in the dog surrounded by well-developed smooth muscle spirals (x 10).

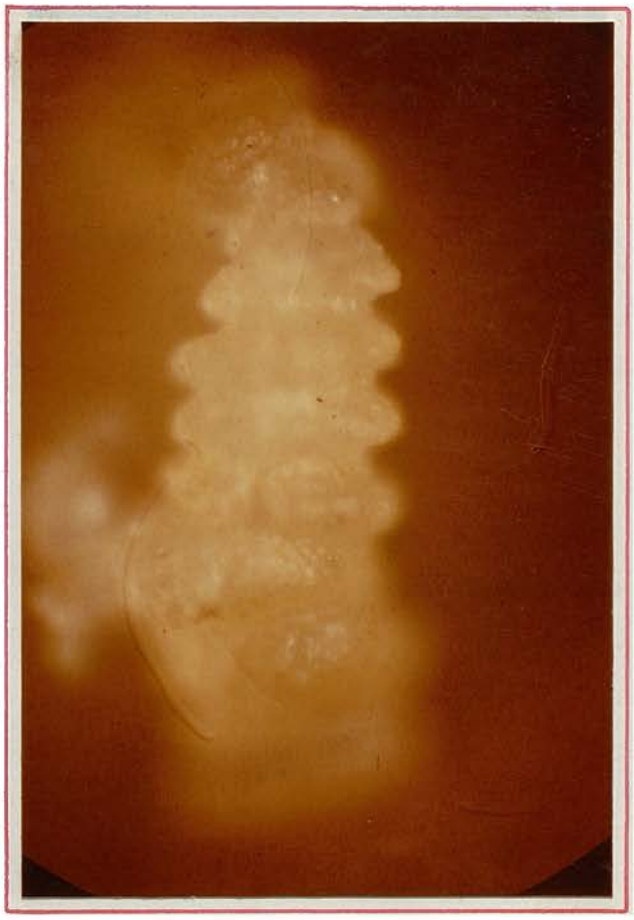

Fig. 35.- The muscular spirals in the small hepatic veins of the dog (x 25).

plexus whence it is distributed to the sinusoids; (2) that arterial and venous blood is delivered by separate vessels into the peripheral or central part of the lobule and that mixing takes place within the sinusoidal circulation; and (3) that clusters of sinusoids supplied entirely by branches of the portal vein or hepatic artery come together to form a lobule, implying therefore that only partial mixing of the two blood streams takes place within the lobule, the actual extent probably being governed by local dynamic conditions within the lobule.

The micro-anatomy of the hepatic venous system

In the section of the gross anatomy of the liver it was shown that the large hepatic veins are situated between the flow beds of two adjacent branches of the portal vein. This is perhaps the most fundamental and important single fact in the whole of hepatic anatomy, indeed this concept can be called the law of the hepatic vasculature. When we extend our examination from the major hepatic veins to the smaller vessels and finally down to the microscopic conducting and central veins of the lobule, an identical arrangement can be made out particularly if the lobule itself is sub-divided in the fashion already indicated in an earlier section. In man the hepatic veins present few features of special interest (Fig. 33) but in the dog the smaller hepatic veins (1-2 mm. in diameter) show a remarkably well developed series of regular spirals (Figs. 34 and 35). Examination of stained specimens /

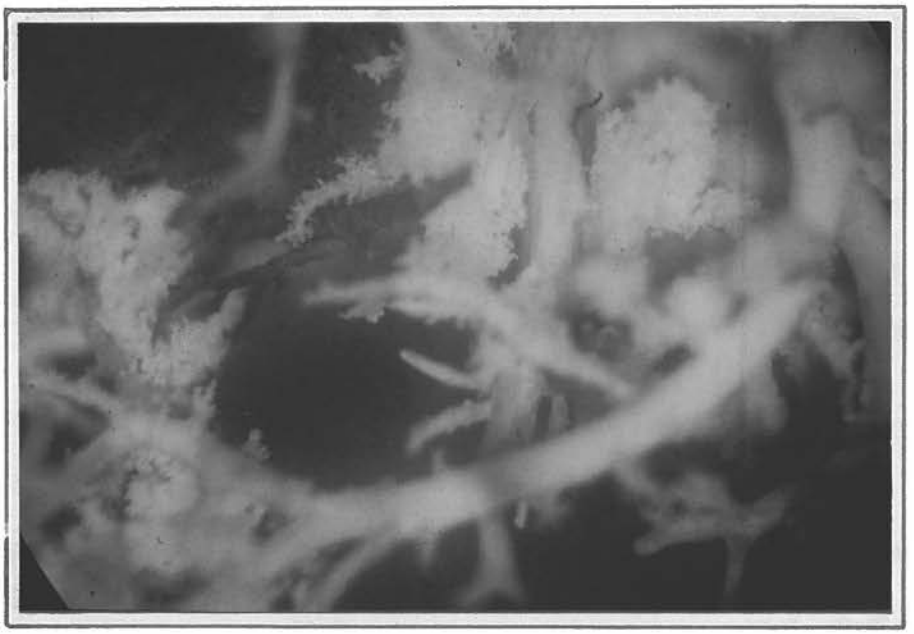

Fig. 36.- The smallest branches of the hepatic veins showing the mode of entrance of the simusoids into these vessels.

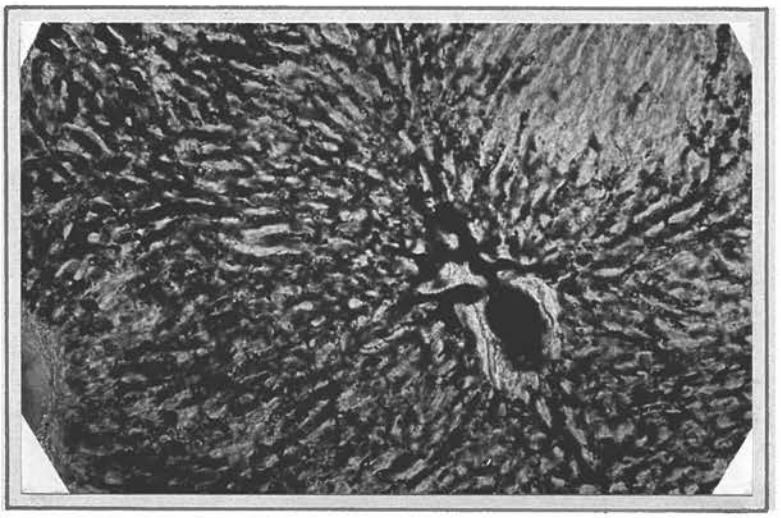

Fig. 37.- Intraportal injection of indian ink in the rat showing the sluice values at the point of entry of the sinusoids into the central vein.

specimens of dog liver injected with Indian ink shows beyond doubt that this appearance is due to the presence of closely knit spirals of smooth muscle fibres surrounding the vessels and producing obvious indentations on the intimal aspects. These structures were first described by Arey (1941), and in a comparative study the dog, the seal and the raccoon were shown to be unique in this respect amongst the various mammals studied. Why these animals alone should be supplied with these structures and what their exact physiological significance can be is not known but it seems reasonable to postulate that they play an important part in controlling the volume of blood within the liver.

Examination of the smallest hepatic veins, known by the adherents of the lobular concept as the central veins, shows that the sinusoids terminate directly in these vessels giving the appearance of a brush border (Fig. 36).

Deysach (1941) investigated the micro-anatomical features of the hepatic veins of the dog, opossum and bear and found evidence in each species of minute sphincters situated at the junction of the sinusoids and the central veins which he thought acted as a sluice valve mechanism (Fig. 37). These structures may be of great importance not only in regulation of sinusoidal blood flow and pressure but also in controlling hepatic blood volume.

Studies of the Living Hepatic Circulation by Trans-Illumination Techniques

So /

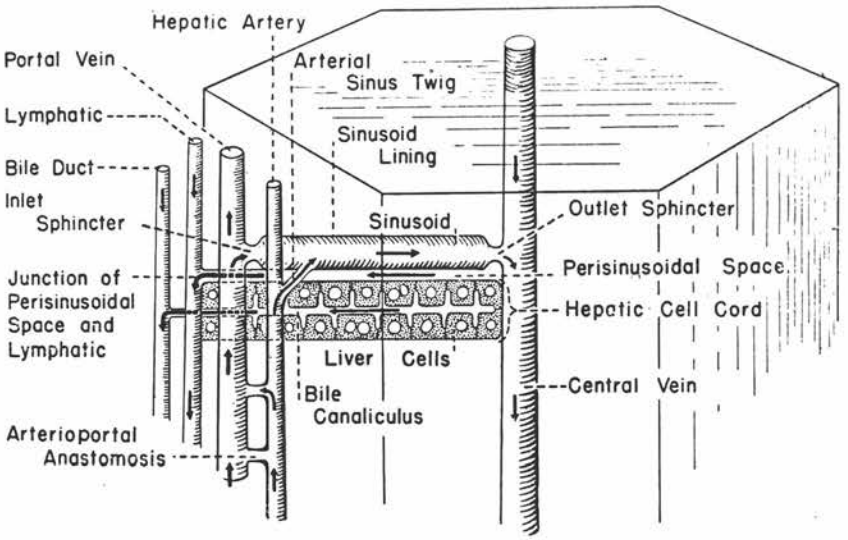

Fig. 38.- The vascular arrangement of the hepatic lobule (after Knisely and Bloch, 1948).

So far we have only considered micro-anatomical data obtained by study of the liver by injection methods. In order to gain further insight, particularly into the intimate control of the hepatic circulation, we must briefly consider the results of various workers who have employed trans-illumination techniques to study the hepatic circulation.

Knisely (1939) carried out an extensive investigation into the micro-anatomy of the liver of the frog. The results of his researches were finally in 1948 embodied into a composite diagram (Fig. 38) which illustrates his concept of the hepatic circulation. The portal venules at their point of entry into the sinusoidal bed were shown to be narrowed by the presence of small inlet sphincters. Similarly at the junction of the sinusoid and central vein an outlet sphincter was noted, probably similar in function to the sluice valve mechanism of Deysach. Two types of communication between the arterial and portal systems were found: direct arterio-portal communications in the portal tracts and arterio-sinusoidal communications in the lobules.

Wakim and Mann (1942) also studied the liver of amphibia and mammals by the trans-illumination technique. The circulation through the lobules was found to be in a constant state of flux, at one moment the sinusoidal circulation of a whole or part of a lobule might be rapid whilst at other times circulation became slow and sluggish and might even cease. This intermittency of circulatory activity was found to be present more frequently in the mammalian /

mammalian than in the amphibian liver. Physiological evidence however derived from studies of the hepatic circulation with the heated thermocouple flow recorder (Grayson, 1953; Torrance, 1957) strongly suggests that circulatory intermittency does not occur, at least on a micro segmental level. In other words the total rate of blood flow through any minute segment is constant, but within this segment of tissue alterations in circulatory activity may occur.

According to Wakim and Mann (1942) in the mammalian liver the terminal branches of the portal vein and hepatic artery break up into fine ramifications which usually empty independently into the sinusoids so that sectors of a lobule have a predominantly arterial or venous circulation. However, owing to the numerous collateral communications between adjacent sinusoids a variable degree of mixing of the two streams does occur. Direct communications between the hepatic artery and portal vein outside the sinusoidal bed were found in the mammalian liver, but much less frequently than in the liver of the frog. Frequently a Y-shaped sinusoid at the periphery of the lobule was seen to receive both arterial and venous connections. The concept that the blood derived from the two sources of afferent blood supply remains to a large extent unmixed was further elaborated by the differential injection of the portal vein and hepatic artery <u>in vivo</u>, and by studying the effects of occlusion of one or other of the vessels on the area of liver /

liver under the microscope. Seneviratne (1949) also studied the appearance of the trans-illuminated liver of various animals and his results confirm most of the findings of the earlier workers.

Alternative Circulatory Pathways within the Liver

While presinusoidal communications between the hepatic arterioles and portal venules have been described by many workers, the present concensus of opinion is that arterio-venous anastomoses are uncommon in the mammalian liver (Elias, 1949). The writer was unable to detect any evidence of such connections either in neoprene casts or in Indian ink preparations. Prinzmetal et al. (1948) injected glass spheres of varying diameter into the portal vein of dogs during life and recovered spheres varying in maximum diameter between 60 and 180 u from the lungs. They concluded that direct communications between the portal venous and hepatic venous systems are present in the liver of the dog. A direct connection between a portal venule and a small branch of a hepatic vein was convincingly demonstrated only in one single section in the present studies.

The anatomical and physiological evidence of the presence of an anastomosis between the hepatic artery and the hepatic veins has been presented by Andrews and Maegraith (1953). Following intra-arterial injection of latex they were able on occasion to fill the hepatic venules without filling the sinusoids, which suggests that direct connections between /

Fig. 39.- A small segment of a neoprene cast has been dissected showing that direct branches of clusters of sinusoids arise not only from the terminal branches of the portal vein, but also from the main conducting veins.

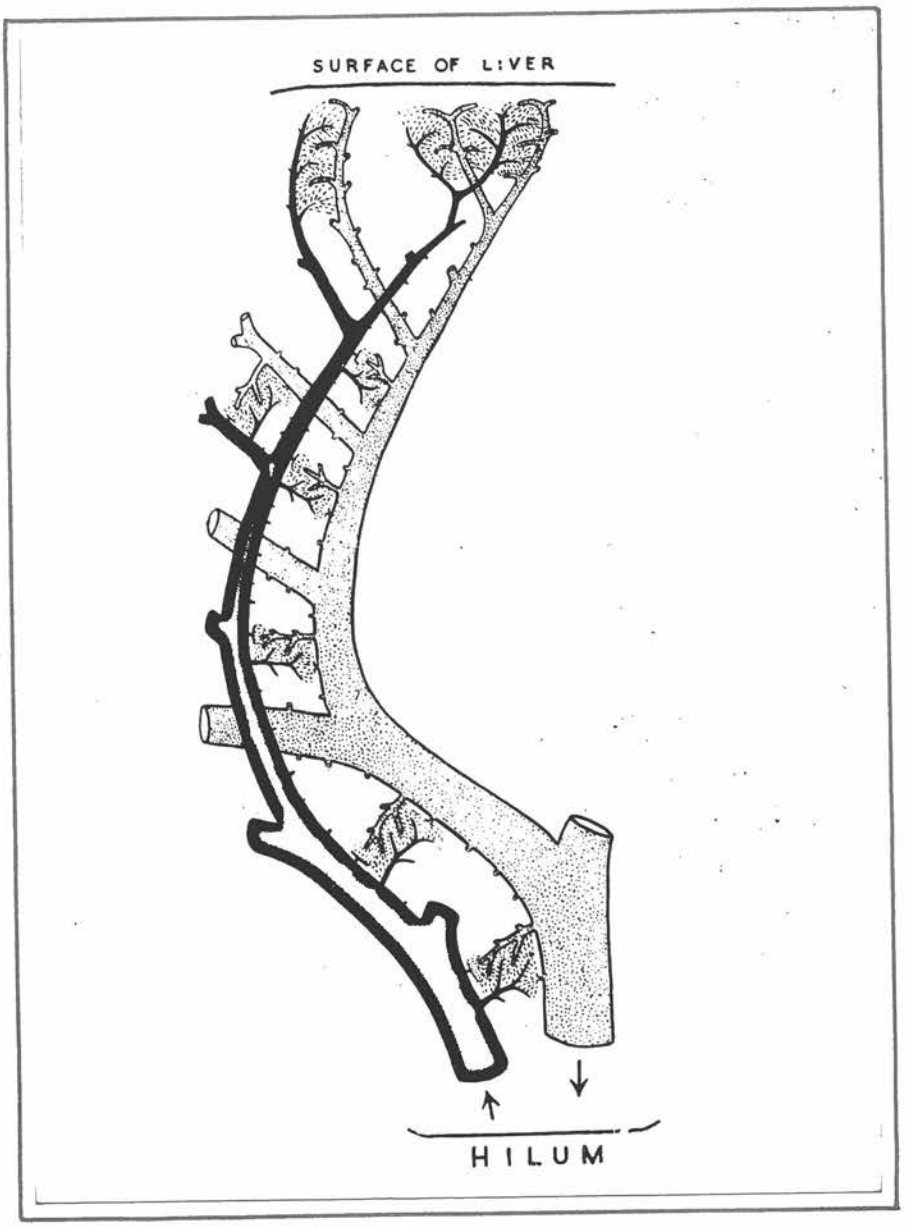

Fig. 40.- A diagram of the distribution of the venous pathways through the liver, illustrating the possible short circuit channels close to the hilum of a segment.

between the hepatic arterial and hepatic venous systems do exist. The vessels involved appeared to be arterioles and were demonstrated in the rat, guinea pig and rabbit. Despite careful search however the present studies failed to reveal any such vascular connections in the liver of the dog and man. It seems likely, therefore, that whilst direct communications between the various circulatory systems within the liver do occur they are unlikely to contribute materially to the intrinsic control of the hepatic circulation.

A further type of intrahepatic shunt has been described by Daniel and Prichard (1951a and b) which may prove to be a more significant factor in controlling the regional distribution of blood within the liver. The intrahepatic branches of the portal vein were outlined by cine radiography after the injection of thorotrast into the portal vein of anaesthetised rabbits. Following intraportal injection of adrenaline or stimulation of the hepatic arterial nerve plexus, blood flow through the liver was re-directed in such a way that the periphery of the liver was bypassed, and blood appeared to flow through preferential, short-circuit channels situated near the hilum of each lobe. Examination of dissected casts of the intrahepatic portal venous system showed a regular tree-like branching process with the accompanying sinusoidal clusters being supplied both from the terminal branches and from the main conducting trunks (Figs. 39 and 40), and it may be that those sinusoids arising /

arising from the relatively large veins together with the more proximally placed branches of the segment could under certain circumstances of vasomotor activity offer a lower resistance to flow than the more peripherally placed vessels. Evidence of a similar short-circuiting mechanism in the hepatic arterial system will be presented in a later section. This aspect of hepatic circulatory physiology is at present being studied by means of a radioisotope dilution technique.

PART II

THE CONTROL OF THE HEPATIC ARTERIAL CIRCULATION

PRESSURE AND FLOW RELATIONSHIPS IN THE SPLANCHNIC CIRCULATION

THE ACTIONS OF ADRENALINE AND NORADRENALINE ON THE SPLANCHNIC CIRCULATION

THE EFFECTS OF HAEMORRHAGE ON THE SPLANCHNIC CIRCULATION

THE EFFECTS OF THE INTRAVENOUS INFUSION OF NORADRENALINE ON SPLANCHNIC BLOOD FLOW IN HAEMORRHAGIC SHOCK

THE CONTROL OF THE HEPATIC ARTERIAL CIRCULATION

The classical studies of Burton-Opitz (1910) laid the foundation of modern knowledge concerning the physiological behaviour of the arterial circulation of the liver and despite sporadic attempts to gain more intimate information about it, a significant advance did not occur until recently when Grayson (see references) and his co-workers pursued a detailed investigation into the hepatic circulation in the rat.

The present investigations were undertaken to obtain more accurate data on the relationship between perfusion pressure and hepatic arterial blood flow in the dog.

Methods

Twenty-five healthy dogs varying in body weight between 9 and 25 kg were used in these experiments. Anaesthesia was induced by intravenous injection of sodium pentobarbital (nembutal, 30 mg/kg) and a free airway was maintained by an endotracheal tube.

Operative Procedures.- The abdomen was opened through an upper midline incision. Complete haemostasis was achieved either by diathermy coagulation or by ligature. The hepatic artery was exposed either in the free edge of the lesser omentum at a point distal to the origin of the gastro-duodenal artery, or at its origin from the coeliac artery, after ligation and division of the gastro-colic omentum. /

omentum. The periarterial nerve plexus was then carefully reflected, an occasional nerve fibre being sacrificed in order to expose approximately 2 cm of the artery. Collateral arterial vessels to the liver were then sought and the gastro-duodenal artery, the left gastric artery and the small arteries to the lesser curvature of the stomach were ligated. In a few experiments the common bile duct was ligated in order to occlude the fine arterial plexus which surrounds the duct and which may anastomose at a higher level with other branches of the hepatic artery.

Prior to cannulation of the various vessels, heparin (Liquemin Roche, 1.9 mg/kg body weight) was injected intravenously. The proximal portion of the exposed hepatic artery was ligated and after division of the vessel a wide bore glass cannula was inserted into the distal cut end, a procedure facilitated by the application to the vessel wall of a small quantity of pethidine (50 mg/ml.) which eliminated spasm produced by manipulation of the vessel.

In a few early experiments both ends of the divided artery were cannulated, blood flow being re-established through a flowmeter. This method presented certain technical difficulties and the pressure drop across the system was found to be unpredictable. It was therefore abandoned and in succeeding experiments the inflow connection of the flowmeter was connected to a wide bore polythene cannula inserted into the aorta through a femoral artery. All connections between the cannulae and the flowmeter /

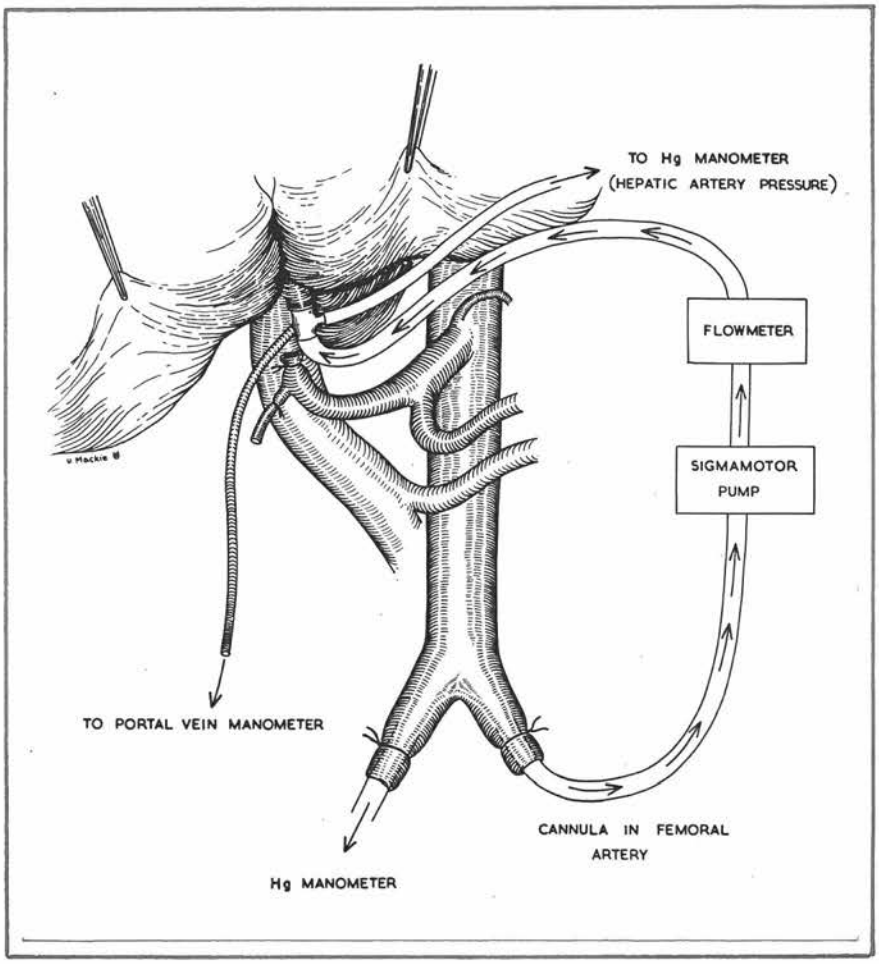

Fig. 41.- Details of the methods employed to measure hepatic arterial bloodflow and pressure.

flowmeter were of non-elastic siliconed plastic tubing which was frequently renewed. The complete circuit is shown in Fig. 41.

Blood Flow Estimation.- The rate of hepatic arterial blood flow was accurately measured by the density flowmeter described by Dawes, Mott and Vane (1953) (see Appendix A, p. 149). In place of the mechanical time base and the electro-magnetic counter used by the original authors, the time taken for 4 ml. of blood to flow through the metering chamber of the apparatus was measured in hundredths of seconds by a scaling unit with an A.C. mains time base (50 cycles/sec) which proved to be a convenient modification of the original method. The apparatus was found to be capable of measuring blood flows up to 175 ml./min, with an accuracy of ± 2 per cent. The pressure drop across the cannulae and the meter in a series of *in vitro* experiments using blood was found to be 10 to 15 mm.Hg at 100 ml./min.

Pressure Measurements.- Arterial blood pressures were recorded on a kymograph by mercury manometers. Systemic arterial pressure was recorded from a cannula tied into a femoral artery, and hepatic arterial pressure from a narrow side-arm in the arterial cannula. The anterior surface of the abdominal aorta was taken as the zero reference point for arterial pressure measurements. Pressure and flow recordings were correlated by means of an electro-magnetic marker on the kymograph, operating synchronously with the electro-magnetic tap on the flowmeter. In certain

experiments /

experiments portal venous pressure was measured from a polythene cannula inserted into the pancreatico-duodenal vein and recorded either by a saline manometer or by a new type of recording manometer (Simpson and Torrance, 1959; see Appendix C, p. 153) which proved to be more accurate and convenient. The ventral aspect of the vena cava was taken as the zero pressure reference point.

Steps were taken to maintain the temperature of the animal within normal limits:- when blood flow through the circuit was established, the abdominal incision was closed around the cannulae and by varying the temperature control of the operating table, intra-luminal oesophageal temperature, measured by a thermister, could be kept constant within narrow limits.

Determination of Pressure Flow Curves.- In the majority of experiments a Sigma motor pump, model TS6 with a Zero-Max control, was incorporated in the circuit proximal to the flowmeter so that the rate of blood flow could be controlled accurately within wide limits. In a few experiments hepatic arterial perfusion pressure was varied by the application of a screw clip to the input connection of the flowmeter.

In all experiments the absence of collateral vessels was demonstrated by measurement of the fall in pressure in the system distal to a point of complete occlusion. When the pressure fell to below 30 mm.Hg and did not increase in the subsequent few minutes, the absence of significant collateral /

collateral vessels was accepted. If these criteria were not fulfilled, either an attempt was made to eliminate the source of the collateral vessels or the experiment was discontinued.

Following each alteration in perfusion pressure, a few moments were allowed for conditions to become stabilised. The mean flow rate was then determined from a series of at least six flow determinations.

Results

Relationship between Perfusion Pressure and Blood Flow in the Hepatic Arterial System.- Curves relating perfusion pressure to rate of blood flow were studied in 25 successful experiments in which absence of significant collateral channels was confirmed. Two experiments were abandoned because large collateral vessels could not be controlled.

Since the wide variations in hepatic arterial flow, produced by variations in the output of the pump, did not have a significant effect on systemic blood pressure, it seems unlikely that interference by systemic baroreceptor reflexes can complicate the interpretation of pressure flow curves obtained by this technique.

For purposes of analysis the initial pressure flow curves from each individual experiment were selected. They showed that a non-linear relationship existed between perfusion pressure and blood flow in the hepatic arterial system. /

system. In general, the curves showed a predominant convexity towards the flow axis but in two instances curves convex to the pressure axis were found; in both experiments hepatic arterial resistance was unusually high - a finding which could not be accounted for by a mechanical defect in the perfusion circuit. In six experiments curves of definitely sigmoid shape were found, the apex of the convexity towards the pressure axis being situated around 40 mm.Hg and the apex of the convexity towards the flow axis in the region of 70 to 80 mm.Hg. In no instance did inflections in the pressure flow curves bear any relation to the systemic arterial pressure at the time of determination and this was taken as further evidence that collateral vessels had been satisfactorily occluded. In 17 experiments the curves were purely convex towards the flow axis.

The effects of rapid increase and decrease in perfusion pressure were studied but the changes in blood flow were similar to those following gradual alteration in perfusion pressure, and hysteresis effects could not be demonstrated by the technique employed.

So that a standardised P/F curve of the hepatic arterial system could be obtained, the results from each experiment were expressed as arterial flow per 100 g liver at the various levels of arterial pressure. Statistical justification for the expression of arterial flow in terms of units of liver weight is considered later. The standardised curve, with the standard deviation at each pressure /

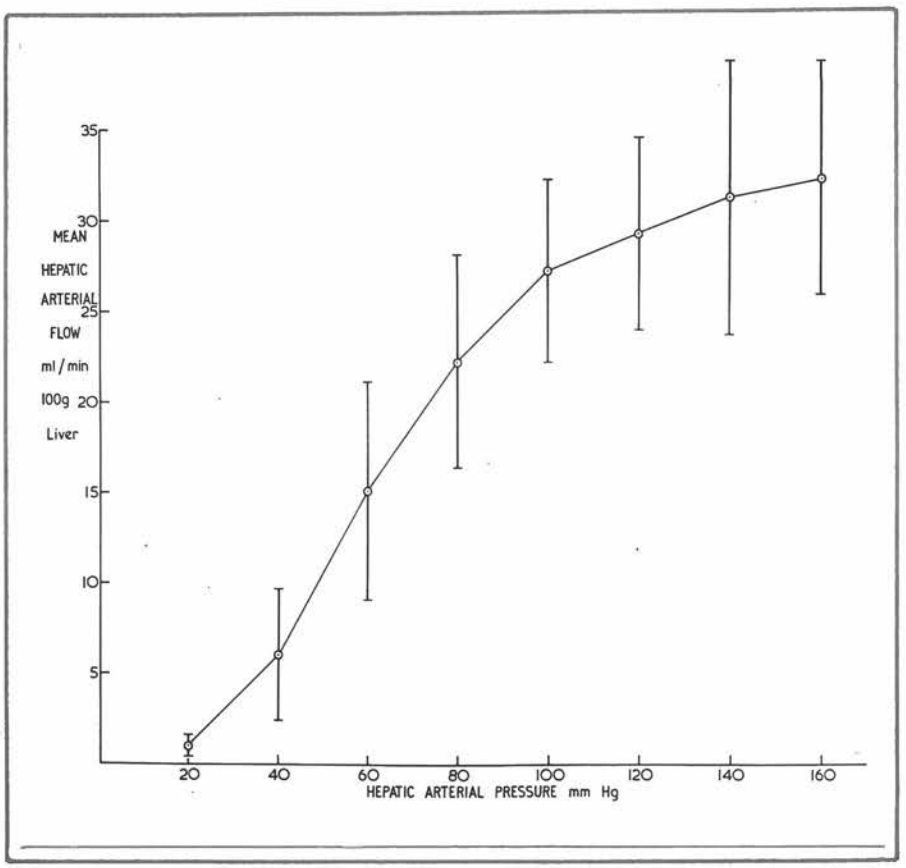

Fig. 42.- The standardised pressure flow diagram of the hepatic arterial circulation. The mean values and standard deviations were derived from 25 individual experiments.

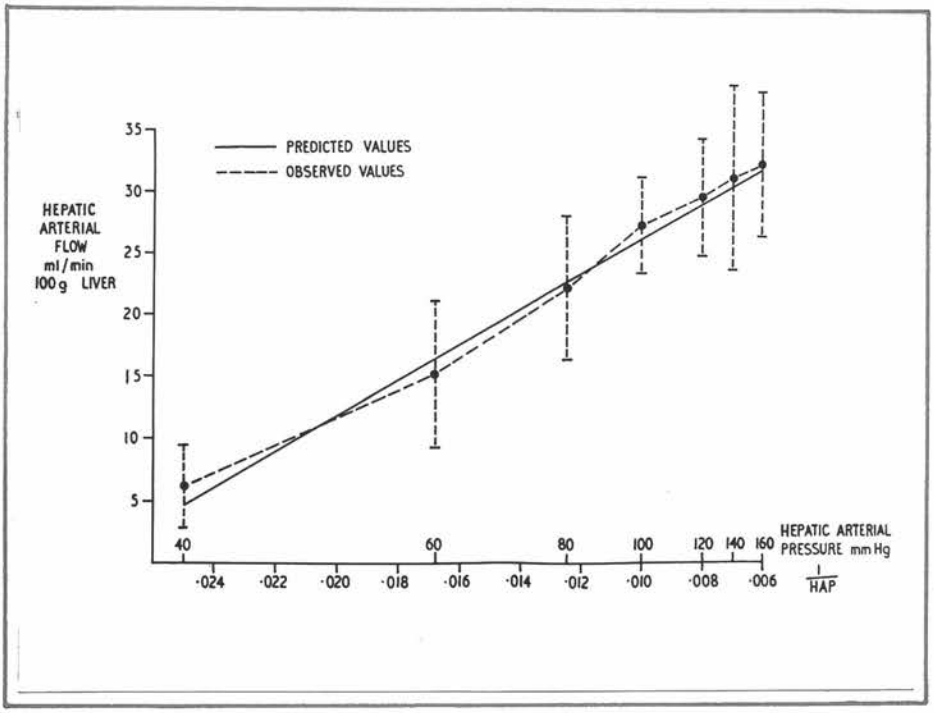

Fig. 43.- When hepatic arterial blood flows are plotted against hepatic arterial pressures on a reciprocal scale the observed relationships can be accurately predicted from the formula $HAF = 40.68 - \frac{1431}{HAP}$

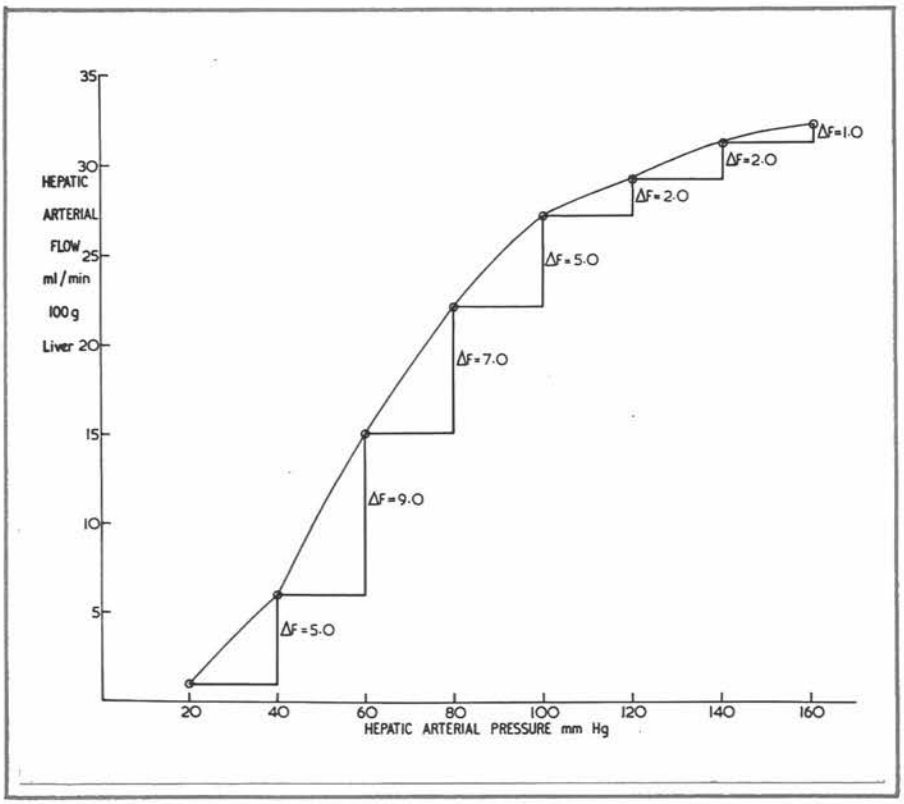

Fig. 44.- The increment in hepatic arterial blood flow (Δ F) for every 20 mm. Hg. increase in arterial pressure is found to become progressively diminished at pressures above 40 mm. Hg.

pressure level, is shown in Fig. 42. The curve is obviously convex towards the flow axis, the apex of the convexity being situated around 90 mm.Hg. Around 40 mm.Hg the curve deviates perceptibly towards the pressure axis, resulting in a sigmoid curve. The mean arterial perfusion pressure at which hepatic arterial flow fell to zero, i.e. the "critical closing pressure" was found to be 18 mm.Hg, S.D. ± 5.8. Significant differences between critical closing pressure and critical opening pressure were not demonstrated.

Mathematical analysis of the portion of the pressure flow curve above 40 mm.Hg shows that the relationship between pressure and flow can be accurately predicted from the formula:-

$$HAF = 40.68 - \frac{1431}{HAP}$$

The resulting straight line lies at all times within one standard deviation of the mean value (Fig. 43).

Effect of Variations in Arterial Pressure on Hepatic Arterial Flow.- When the increment in hepatic arterial flow (ΔF) for every 20 mm.Hg increase in arterial pressure is plotted on the standardised pressure flow curve, the changes are clearly apparent (Fig. 44). As the arterial pressure is increased from 40 mm.Hg, ΔF becomes steadily reduced until the increment in flow at the higher pressure levels, i.e. above 120 mm.Hg, becomes barely perceptible. It will be seen that the arterial blood pressure plays a much more important part in controlling hepatic arterial flow in the pressure /

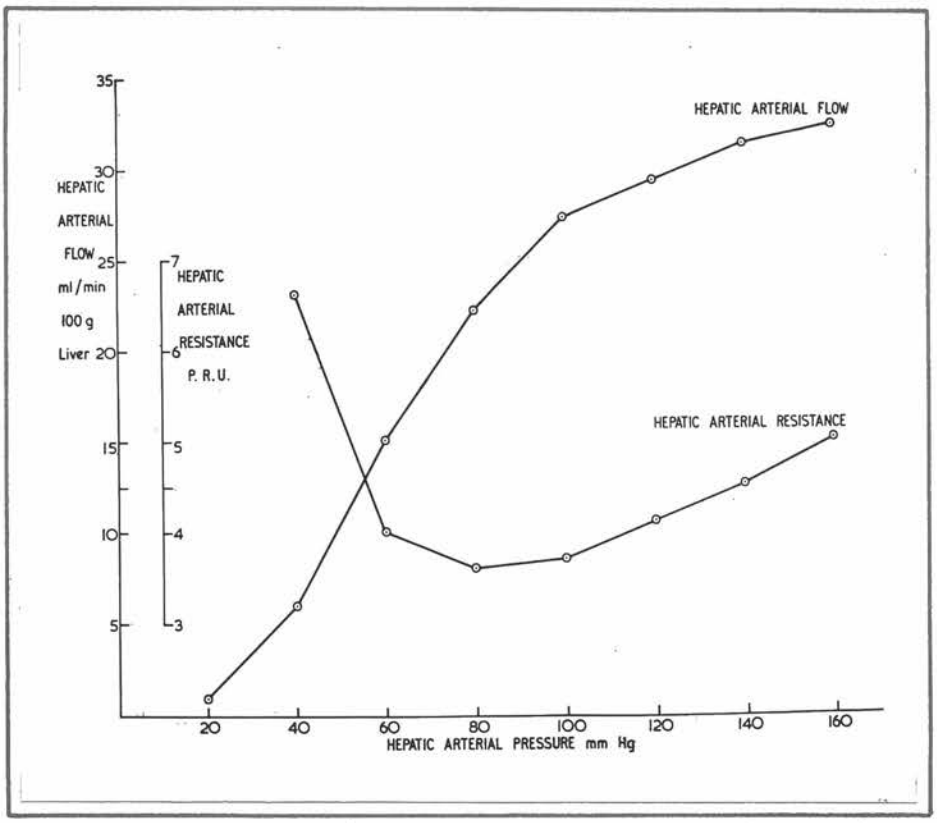

Fig. 45.- Showing the effects of variations in arterial pressure on hepatic arterial resistance (expressed in peripheral resistance units).

pressure range between 40 and 100 mm.Hg than in the higher pressure ranges. These results imply that arterial pressure plays an important part in controlling resistance to arterial inflow to the liver.

Hepatic arterial resistance was calculated from the formula $\frac{\text{Hepatic Arterial Pressure}}{\text{Hepatic Arterial Flow}}$, hepatic venous pressure being ignored in these calculations. Changes in the calculated arterial resistance at different perfusion pressures are shown in Fig. 45. It is evident that when hepatic arterial pressure is reduced from 160 to 100 mm.Hg arterial resistance steadily falls, but as the pressure is reduced below 80 mm.Hg the resistance begins to increase and below 60 mm.Hg the increase in hepatic arterial resistance becomes greatly exaggerated, finally reaching infinity at the critical closing pressure.

The Effects of Varying Period of Hepatic Arterial Occlusion on Hepatic Arterial Resistance.- Lest the non-linear relationships between hepatic arterial pressure and blood flow were due in part to the effects of the subnormal inflow on the liver, the results of different periods of arterial occlusion were studied. The inflow connection to the flowmeter was occluded for intervals varying from 1 to 10 minutes - the hepatic arterial resistance before and after this procedure was then calculated but significant alterations in vascular resistance could not be detected. The inhalation of a mixture of 5 per cent. carbon dioxide and /

and 95 per cent. oxygen has been shown in other experiments to lead to a profound fall in mesenteric vascular resistance, but this did not affect hepatic arterial resistance. It seems unlikely, therefore, that the increase in vascular resistance at the lower pressure and flow levels is due to the local effects of anoxia on the hepatic circulation.

The Effect of Ganglion Blockade, Nerve Block and Atropinisation on the Hepatic Arterial Pressure Flow Relationships.- In four experiments ganglion blockade was produced by intravenous injection of hexamethonium bromide (25 mg). Comparison of the P/F curves obtained 20 minutes after injection with control curves showed a significant deviation towards the flow axis in three out of four experiments but the general shape of the curves was not affected.

The peri-arterial nerve plexus was infiltrated with 2 per cent. xylocain through a fine hypodermic needle connected to a length of polythene tubing, the needle having been embedded in the nerve plexus after cannulation of the artery. The curves obtained 10 minutes after the injection of the local anaesthetic showed a suggestive deviation towards the flow axis but the original shape of the curve was retained.

The effects of an intravenous injection of atropine sulphate (3 mg) were also studied but no significant alteration was demonstrated either in the position relative to the flow axis or in the shape of the curves. It can be concluded, therefore, /

therefore, that the changes in vascular resistance induced by alterations in hepatic arterial pressure are not dependent on extrinsic autonomic nerve influences.

Relationship between Hepatic Arterial Flow and Pressure and Portal Venous Pressure.- In six experiments an attempt was made to determine the effect on portal venous pressure of variations in the hepatic arterial flow and pressure. Simultaneous measurement of portal venous flow by a rotameter, and of hepatic artery flow was accomplished only in one experiment, owing to the technical difficulties involved.

In every instance portal venous pressure fell when the hepatic arterial circulation was occluded, although the fall was by no means uniform. The mean decrease in pressure was 1.5 cm of saline with a range of 0.9 to 2.5 cm of saline, S.D. ± 0.47.

When hepatic arterial flow was varied, portal venous pressure increased or decreased directly with the changes in hepatic artery flow but the change in pressure was frequently delayed for 30 to 60 seconds and, occasionally, an increase or decrease towards the control value occurred, suggesting the possibility of a compensatory alteration in portal venous flow. Some support for such a mechanism was suggested by the experiment in which it was possible to measure the hepatic artery and the portal venous flows simultaneously.

Stable curves showing the effects of variation in hepatic artery flow and hepatic artery pressure on portal venous /

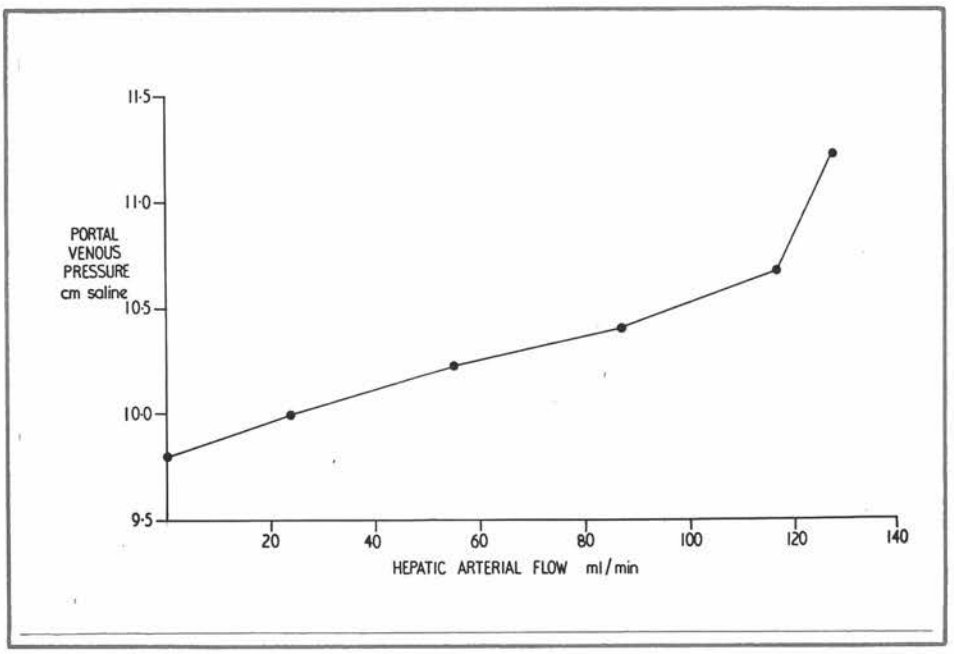

Fig. 46.- In this experiment the relationship between hepatic arterial blood flow and portal venous pressure was found to be linear except at maximal rates of flow.

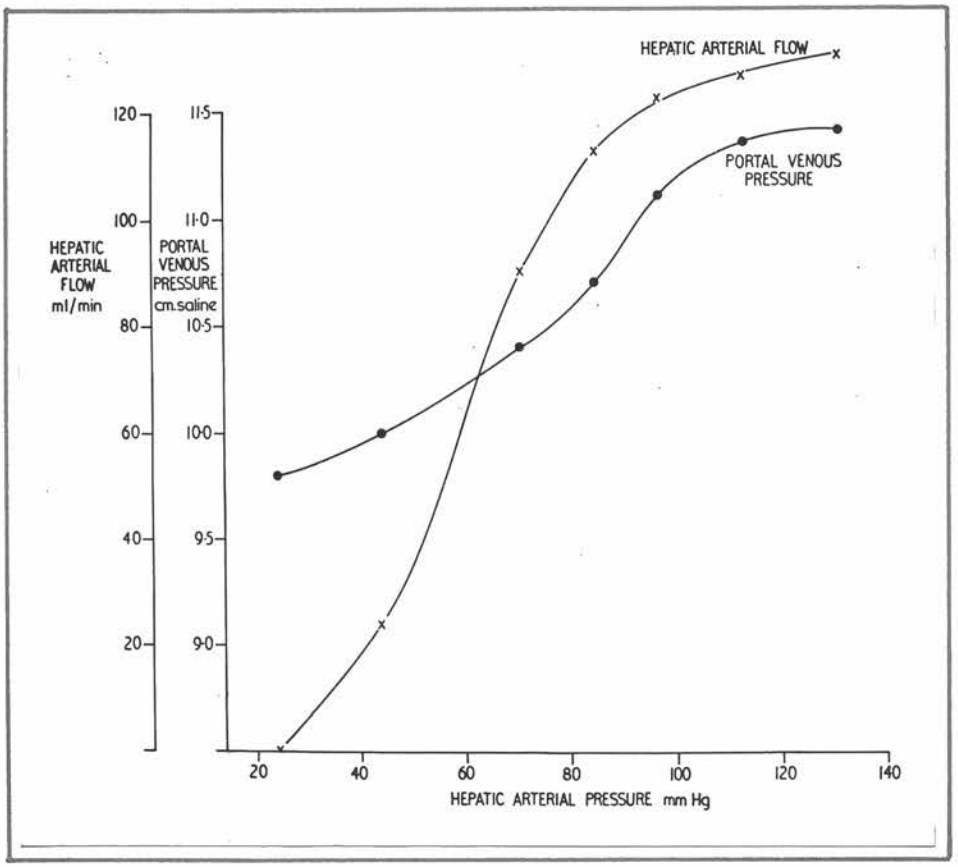

Fig. 47.- In this experiment the relationships between portal venous pressure and hepatic arterial pressure appeared to be non-linear, a finding which can probably be explained by the form of the hepatic arterial pressure flow relationship.

venous pressure were obtained in three out of six experiments. Portal venous pressure varied in an approximately linear fashion with that on the hepatic artery, except at maximal rates of flow, when a disproportionate increase in portal venous pressure occurred (Fig. 46). When hepatic arterial pressure was plotted against portal venous pressure, however, a sigmoid curve was obtained - the orientation of the curve being similar to that of the arterial P/F relationship (Fig. 47).

Spontaneous Variations in Hepatic Arterial Flow.- Throughout these experiments evidence was sought of spontaneous variations in hepatic arterial flow, but hepatic arterial resistance was found to remain constant within narrow limits over long periods, provided the systemic blood pressure was maintained. In those animals in which large phasic variations in blood pressure were present, hepatic artery flow showed corresponding fluctuations. When such variations in hepatic arterial flow were compared with a control P/F curve, it was obvious that they could be accounted for entirely by the passive effect of the rhythmic alterations in arterial pressure. These findings suggest that rhythmic changes in the autonomic nervous control of the hepatic arterial system are not the cause of spontaneous variations in hepatic arterial resistance.

Correlation of Hepatic Arterial Flow with Liver Weight.- At the conclusion of the experiments the liver was removed and weighed, no attempt being made to prevent blood loss from /

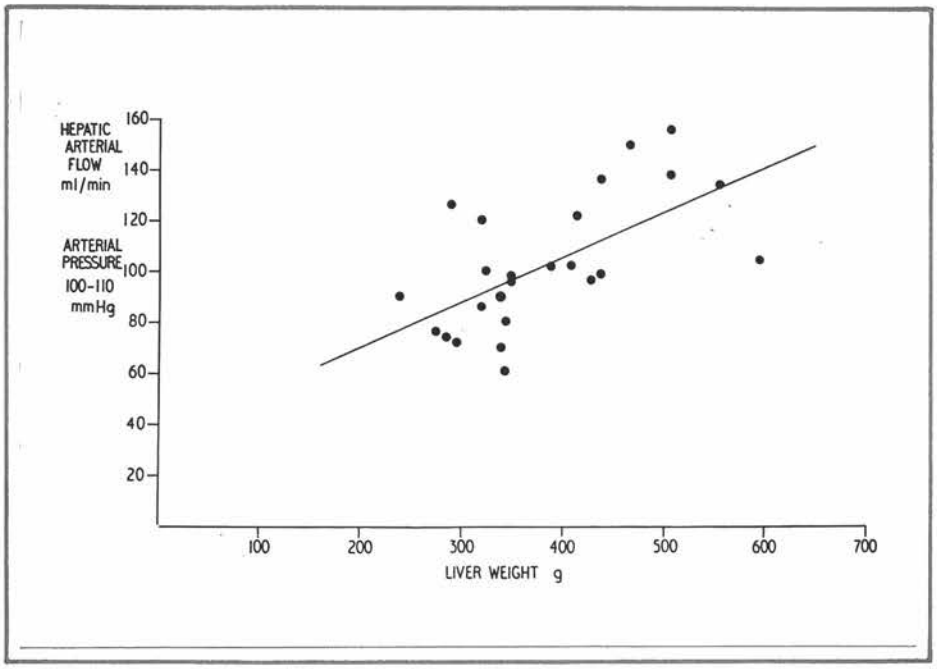

Fig. 48.- Diagram illustrating the relationship between hepatic arterial blood flow within a defined pressure range (100-110 mm. Hg.) and liver weight. The best fitting linear regression line is shown.

from the major blood vessels. The mean liver weight in this series of experiments was found to be 2.26 per cent. of the body weight, a figure in close agreement with that obtained by Grindlay and Bollmann (1952).

In order to establish an accurate correlation between hepatic artery flow and liver weight, the arterial flow within a closely defined pressure range of 100 to 110 mm.Hg was selected for the purposes of comparison. Statistical examination showed a highly significant correlation between hepatic arterial flow and liver weight ($t^2 = 12.21$, $P < 0.005$). A linear regression line was calculated, the best fitting line being expressed by the formula HAF = 0.166 LW + 38.69 (Fig. 48). The close correlation between arterial flow and liver weight justifies expression of hepatic arterial flow in terms of liver weight as used in the calculation of the standardised P/F curve.

The relationships between hepatic arterial flow, liver weight and body weight are shown in Table I. Mean hepatic arterial flow expressed in terms of units of liver weight was found to be 27.2 ml./min/100 g liver weight, S.D. = ± 5.6. Mean hepatic arterial flow expressed in terms of body weight was 6.9 ml./min/kg body weight, S.D. = ± 1.9.

Discussion

It has been recognised for some time that the relationship between perfusion pressure and blood flow in many vascular /

vascular beds is non-linear. The first indication that the splanchnic circulation also possessed non-linear pressure flow characteristics was provided by Ginsburg and Grayson (1954), and by Johnson (1954) who studied the effects of alterations in the systemic blood pressure on liver blood flow in the rat by the method of internal calorimetry (Grayson, 1952). They concluded that the hepatic circulation was endowed with an intrinsic auto-regulatory system so that blood flow through the liver could be maintained at a fairly constant level despite wide variations in systemic blood pressure. In their experiments, alterations in systemic blood pressure were evoked by bleeding into a blood pressure compensating reservoir, so that the purely passive effects of altered perfusion pressure could not be clearly dissociated from other possible effects of haemorrhage. Furthermore, with the methods employed, it was obviously difficult to obtain detailed information regarding participation of the various compartments of the splanchnic circulation in total hepatic blood flow; in particular, hepatic arterial flow could be measured only after elimination of portal venous inflow by evisceration or by ligation of the portal vein. The pressure and flow relationships in the intrahepatic portal venous system have been studied by Brauer, Leong, McElroy and Holloway (1956), using the isolated perfused rat liver, and by Riecker (1955), using the perfused dog liver. The haemodynamic behaviour of the arterial circulation of the liver /

liver, has not received the same attention, however.

The relationship between cardiac output and mean systemic blood pressure in intact dogs and in animals in which the carotid sinus and the aortic depressor nerves had been severed were studied by Levy, Brind, Brandlin and Phillips (1954). They established that the mean arterial blood pressure increased in a linear fashion with increasing cardiac output within a pressure range of 35 to 180 mm.Hg, when reflex changes originating in the carotid sinus and aortic arch baroreceptors were excluded. The recti-linear relationship between pressure and flow in their preparations was regarded as fortuitous, since the relationship between cardiac output and systemic arterial pressure is due to the geometric summation of the pressure-flow curves of the many vascular beds which are arranged in parallel circuits to comprise the systemic circulation.

According to Green, Lewis, Neckerson and Heller (1944), the pressure-flow curve of the skin is curvilinear and convex to the flow axis. On the other hand, skeletal muscle frequently shows a sigmoid pressure flow curve but under most conditions the relationship for the entire hind limb of the dog is parabolic and convex to the pressure axis. The pressure-flow relations of the renal circulation have been firmly established by various groups of workers (Selkurt, 1946; Shipley and Study, 1951; DeWardener and Miles, 1952), who have consistently found evidence of an intrinsic auto-regulatory system by which renal blood flow is kept fairly constant /

constant despite large changes in perfusion pressure. Recently, the pressure-flow relationship in the cerebral circulation has been studied in the rabbit by Carlyle and Grayson (1956), using the method of internal calorimetry. Their results indicate a striking non-linear relationship between perfusion pressure and blood flow, the curves being strongly convex to the flow axis. The pressure flow relationships of isolated segments of the small intestine have been investigated by Selkurt, Scibetta and Cull (1958) and of the mesenteric circulation as a whole by Trapold (1956b). Both groups of workers showed that mesenteric vascular resistance remained constant above 80 mm.Hg but below this level it was increased. The present investigation has clearly demonstrated that the non-linear pressure flow characteristics of the hepatic arterial circulation of the dog also produce curves convex to the flow axis, a finding which agrees with the work of Grayson and Mendel (1957) on the hepatic circulation of the rat.

From consideration of the published data and the results of the present experiments, it seems likely that the pressure flow diagrams of the cerebral, renal and hepatic arterial circulations are predominantly non-linear and markedly convex to the flow axis. This may be an important haemostatic mechanism for the government of blood flow through these organs.

Factors Involved in Producing Non-Linear Relationships between Pressure and Blood Flow.- The rheological interpretation /

interpretation of the results of experiments on the flow of blood through a rigid tube of uniform diameter is complex (Coulter and Pappenheimer, 1949). It is not surprising, therefore, that the haemodynamic proportion of a complete vascular bed endowed with a system of branching tubes of varying diameter, elasticity and contractility, perfused by a pulsatile stream of a complex suspension, remain obscure. The interpretation of the pressure flow diagram obtained from any vascular bed must therefore remain largely a matter for conjecture until further basic information has been accumulated and more advanced methods of haemodynamic analysis are available.

The formula derived by Poiseuille is applicable to laminar flow of a simple Newtonian fluid through a rigid, straight tube of uniform internal diameter, and relates perfusion pressure gradient to the rate of flow, the radius and length of the tube and the viscosity of the fluid. An increase in perfusion pressure gradient is accompanied by a directly proportional increase in flow, provided the radius and length of the tube and viscosity of the perfusate remain constant. On the other hand, if an increase in perfusion pressure gradient produces an increase in the radius of the tube or if the resulting increase in flow produces alterations in viscosity, the relationship of radius, length and viscosity that constitute the resistance to flow will not remain constant, and the perfusion pressure and flow relationship cannot be rectilinear.

It seems likely that the elastic properties, the anatomical distribution and connections of the vessels and the myogenic responses of the vessel wall, together with the anomalous viscosity of blood at differing flow rates, play a large part in producing non-linear pressure flow patterns in vivo.

It has been shown in this series of experiments that hepatic arterial resistance reaches infinity at a mean pressure of 18 mm.Hg. This fact can be explained on the basis of the critical closing pressure theory advanced by Burton (1951), who predicted from Laplace's Law on the tension equilibrium of cylindrical tubes that if the intraluminal pressure fell below a certain critical level, the vessel would close. Evidence supporting this theory has been provided by Nichol, Girling, Jerrard, Mason and Burton (1951) and in the human digit by Gaskell and Burton (1953), Yamada (1954) and Roddie and Shepherd (1957). The observations of Burton (1951) and Roddie and Shepherd (1957) are consistent with the thesis that the critical closing pressure varies directly with alterations in vasomotor tone.

A sigmoid type of pressure flow curve in the hepatic arterial system could be explained on the basis of a series of parallel vascular channels possessing critical closing pressures distributed between 18 and 100 mm.Hg, so that as the perfusion pressure increased above the critical opening pressure, the gradual opening of extra circuits would lead to a steady fall in vascular resistance as the

cross-sectional area of the vascular bed increased. It could be postulated that above 100 mm.Hg the majority of circulatory pathways are being perfused and the slight but steady increase in hepatic arterial resistance explained on the basis of a slight modification of Poiseuille's Law. Brauer et al. (1956) using the isolated perfused rat liver preparation suggested that this hypothesis would explain the results of their studies on the pressure flow relationships in the intra-hepatic portal venous system and the uptake of radioactive colloidal chromium by the liver.

The Importance of the Elastic Properties of the Vessel Wall and the Intrinsic Myogenic Responses to Stretch.- It has long been recognised that the diameter of the peripheral vessels may be modified by changes in trans-mural pressure. Isolated segments of aorta have been shown to possess elastomeric or rubber-like properties leading to sigmoid pressure volume curves (Roy, 1880; Hallock and Benson, 1937). Recently, it has been shown by the writer (unpublished observations) that the isolated main limb arteries of the dog behave in a similar manner. On the other hand, data are not available about the elastic properties of the smaller resistance vessels. If, in fact, these vessels behave in a similar fashion to the larger arteries then the pressure flow curve of the hepatic arterial circulation could be readily explained on this basis.

The response of the resistance vessels to varying trans-mural /

trans-mural pressure may be the result not only of the elastic properties of the vessel but also of intrinsic alterations in the intramural smooth muscle fibres. It has been suggested that when the pressure is increased the tendency to passive distension of the vessel is opposed by a myogenic constrictor reaction in the vessel wall (Bayliss, 1902; Folkow, 1949; Patterson and Shepherd, 1954; Coles and Greenfield, 1956). The evidence in favour of this concept has been accumulated entirely from studies of the circulation of the limb, however; it may not be applicable to the vessels of the visceral circulation.

Anomalous Viscosity Effects.- It has been shown beyond doubt (Bayliss, 1952) that the viscous behaviour of whole blood shows certain anomalous features, the apparent viscosity being dependent on the internal diameter of the tube and the rate of blood flow, i.e. on the linear velocity of blood flow. For a given rate of blood flow, the apparent viscosity diminishes as the radius of the tube decreases whilst the apparent viscosity increases when the mean velocity of flow falls below a certain critical level. In vivo the position is more complicated because of the passive distension of blood vessels so that the changes in viscosity will bear a complex relationship to perfusion pressure and rate of blood flow. It seems likely that the viscosity of blood plays some part in determining the shape of the pressure flow curves in any vascular bed. Recently, Selkurt et al. (1958) have compared the pressure flow curves /

curves in a denervated segment of small intestine, using blood and dextran as the perfusate. When the intestine was perfused with dextran at pressures above 100 mm.Hg, the vascular resistance remained constant, whereas with blood a steady increase in vascular resistance was found. It was concluded that this was an anomalous viscosity effect. In the present experiments vascular resistance has been shown to increase steadily above 100 mm.Hg, suggesting that fluctuations in viscosity do not play a large part in determining hepatic arterial resistance.

Relationship of Hepatic Arterial Flow and Pressure to Portal Venous Pressure.- The experiments on the relationship of hepatic arterial flow and pressure to portal venous pressure have shown that hepatic arterial flow and portal venous pressure are linearly related, whilst the relationship between hepatic arterial pressure and portal venous pressure appears to be sigmoid and generally of the same geometric shape as the pressure-flow curve of the hepatic arterial system. Thus arterio-venous anastomoses between the hepatic artery and portal vein do not appear to play any significant part in regulating the distribution of arterial blood flow within the liver of the dog, an increment or decrement in hepatic arterial flow producing the same effect on intra-hepatic portal venous dynamics as does a similar increase or decrease in portal venous blood flow.

Grayson and Mendel (1957) have shown that occlusion of the hepatic artery in the rat produces a fall in portal venous /

venous pressure which leads to a compensatory increase in portal venous flow. In one experiment in this series simultaneous measurements of hepatic arterial flow and portal venous flow were possible, and it was found that a significant increase in portal venous flow followed occlusion of the hepatic artery. Since the mean fall in portal venous pressure on occlusion of the hepatic artery was found to be 1.5 cm of saline - an alteration in portal venous pressure unlikely to exert any direct effect on the vascular beds which contribute to portal venous flow - this may indicate the presence of an intrinsic baroreceptor mechanism in the portal venous system which controls gastro-intestinal vascular resistance, possibly by means of a neurogenic reflex. Recently, Selkurt and Johnson (1958) have produced evidence of such a mechanism in the portal venous system of the dog.

The Importance of Pressure-Flow Curves - Analysis of Vascular Dynamics.- The importance of the factor of perfusion pressure in the production of changes in vascular resistance has been largely ignored until recently. For instance, Trapold (1956a) was led to erroneous conclusions regarding the effects of ganglion-blocking drugs on mesenteric vascular resistance because pressure flow curves before and after administration of the drug had not been compared. In a further investigation (Trapold, 1956b), however, this situation was remedied and it was then shown that ganglion-blocking drugs produced a significant shift towards /

towards the flow axis, indicating release of vasomotor tone. The earlier experiments had indicated a reverse effect, that in fact was due to the hypotensive effects of the drugs, which caused a passive increase in vascular resistance that was not compensated for by the vasomotor inhibition. It is obvious, therefore, that for accurate haemodynamic analysis of the vascular responses to any set of circumstances which result in a change in perfusion pressure, it is essential to compare the altered conditions of perfusion pressure and blood flow with a control pressure flow curve. Indeed, without the aid of such a yardstick, analysis of the effects of haemorrhage, ganglion blockade and such drugs as adrenaline and noradrenaline on a vascular bed become confused.

Relationship between Hepatic Arterial Flow and Liver Weight.- The expression of hepatic arterial flow in terms of units of liver weight has been employed in the past although a significant correlation between the two variables has never been clearly demonstrated. The present experiments have shown a highly significant statistical correlation when the relationship between hepatic arterial flow within a closely-defined range of arterial pressure, and liver weight is computed. If further work confirms that hepatic arterial flow and liver weight are related according to the regression equation $HAF = 0.166\ Lw + 38.7$, this, together with the equation derived from the standardised pressure flow curve, may provide a useful method /

method of computing hepatic arterial flow in terms of liver weight at any given perfusion pressure between 40 and 160 mm. Hg.

The magnitude of the arterial contribution to total hepatic blood flow obtained by previous workers is shown in Table II. Using a mechanical stromuhr, Burton-Opitz (1910) estimated hepatic arterial flow to be 26 ml./min/100 g liver and 7.4 ml./min/kg body weight. McLeod and Pearce (1914) estimated hepatic arterial flow by the effects of occlusion of the liver arteries on hepatic venous outflow and derived a mean value of 31 ml./min/100 g liver. Grodins, Osborne, Ivy and Goldman (1941) obtained a similar result (26 ml./min/100 g liver) using a thermostromuhr. The mean hepatic arterial flow in the present experiments was 27.2 ml./min/100 g liver, which agrees closely with the results of these earlier workers. On the other hand, the results obtained by Grab, Janssen and Rein (1929) and Grindlay, Herrick and Mann (1941), using thermostromuhrs and Blalock and Mason (1937), using a collection method indicated a much lower rate of hepatic arterial flow. It seems likely, however, that the methods employed to estimate the rate of arterial flow were inadequate and liable to error from extraneous uncontrolled factors.

TABLE I

Hepatic Arterial Flow Rates Expressed in Terms of Liver Weight and Body Weight

Hepatic arterial flow ml./min 100-110 mm.Hg	Body weight (kg)	Liver weight (g)	Hepatic arterial flow ml./min/100 g liver	Hepatic arterial flow ml./min/kg body weight
75	14.5	285	26.3	5.2
122	14.0	414	29.4	8.7
66	16.0	400	16.5	4.1
120	14.0	320	37.5	8.6
101	14.0	390	26.0	7.1
75	10.0	275	27.2	7.5
90	11.6	240	37.4	7.6
80	14.0	345	23.2	5.7
98	14.0	350	28.0	7.0
126	14.0	290	43.4	9.0

TABLE I (cont'd)

Hepatic arterial flow ml./min 100-110 mm.Hg	Body weight (kg)	Liver weight (g)	Hepatic arterial flow ml./min/100 g liver	Hepatic arterial flow ml./min/kg body weight
72	15.6	293	24.5	5.3
61	10.0	345	17.7	6.1
99	25.0	440	22.5	3.6
102	17.5	410	23.7	6.0
86	16.5	320	27.0	5.2
95	16.0	430	22.3	5.8
90	11.0	340	26.8	8.2
134	16.0	560	24.0	8.4
138	17.5	507	27.6	8.0
105	26.0	600	17.5	4.0
149	16.0	470	32.0	9.3

TABLE I (cont'd)

Hepatic arterial flow ml./min 100-110 mm.Hg	Body weight (kg)	Liver weight (g)	Hepatic arterial flow ml./min/100 g liver	Hepatic arterial flow ml./min/kg body weight
100	13.2	325	30.8	7.6
135	14.0	440	30.7	9.6
96	13.4	350	27.4	7.2
156	14.6	510	31.0	10.1

Mean = 27.2 S.D. ± 5.6

Mean = 6.9 S.D. ± 1.9

TABLE II

Hepatic Arterial Flow Rates Related to Liver Weight and Body Weight

The results of previous workers are compared with the present experiments

Author	Year	No. of observations	Method	Hepatic arterial flow ml./min/100 g liver	Hepatic arterial flow ml./min/kg body weight
Burton-Opitz	1910	9	Mechanical stromuhr	26.0	7.4
McLeod & Pierce	1914	6	Collection	31.0	-
Grab, Janssen & Rein	1929	5	Thermostromuhr	12.4	4.9
Blalock & Mason	1936	5	Collection	15.5	5.1
Grodins, Osborne, Ivy & Goldman	1941	28	Thermostromuhr	26.0	-
Present series		25	Density flowmeter	27.2 ± 5.6	6.9 ± 1.9

PRESSURE AND FLOW RELATIONSHIPS IN THE SPLANCHNIC CIRCULATION

It has become a well-established fact that the relationship between perfusion pressure and blood flow in most, if not all, vascular beds is non-linear. As might be expected, however, each bed exhibits its own individual behaviour, the integration of these curves resulting in a linear relationship between pressure and flow for the whole systemic circulation, at least in the dog (Levy et al., 1954). Whilst the splanchnic circulation receives approximately 25 per cent. of the cardiac output and indeed is one of the main factors in determining cardiac output, the pressure flow relationships in the various individual vascular compartments have not yet been completely elucidated. In this section the results of a group of experiments, designed to elucidate the relationship between pressure and flow in the superior mesenteric arterial system, the splenic arterial system and the intra-hepatic portal venous system are reported.

Methods

Healthy sheepdogs, varying in weight between 10 and 22 kg, were anaesthetised by intravenous administration of pentobarbitone (30 mg/kg body weight). A cuffed endotracheal tube was inserted to maintain a free air-way. In some /

some experiments respiration was controlled by means of a respiratory pump.

Determination of Blood Flow in the Superior Mesenteric Arterial and Splenic Arteries

The abdomen was opened through an upper mid-line incision, the skin, linea alba and peritoneum being divided by diathermy. Any remaining bleeding vessels were either coagulated by diathermy or controlled by the application of ligatures.

The superior mesenteric artery was exposed at its origin from the aorta by division of the peritoneum along the lower border of the pancreas. The thick, adventitial sheath of the artery was then incised and approximately one inch of the vessel carefully exposed with minimal damage to the peri-vascular nerve network. In order to exclude collateral vessels, the branches arising from the convex aspect of the parent trunk, which supply the transverse and ascending colon, were ligated. For a similar reason, the first and second jejunal arteries were also ligated. A ligature was then applied to the origin of the artery from the aorta and the vessel divided immediately distal to this point. A specially prepared wide bore glass cannula was then inserted into the open end of the vessel. In most instances, a minute quantity of pethidine was applied to the vessel wall prior to cannulation since this was found to facilitate the insertion of a wide bore cannula. Blood flow through the mesenteric bed was re-established by connecting /

connecting a wide bore polyethylene cannula inserted into the aorta through a femoral artery into the afferent limb of the density flowmeter. The cannula in the mesenteric artery was connected to the efferent limb of the flowmeter by a Portex tube. All connections and cannulae and also the interior of the flowmeter were thoroughly coated with silicone.

The splenic artery was exposed after ligation and division of the gastro-colic and gastro-splenic ligaments. In this way, all vascular connections between the spleen and stomach were severed. The sheath of the artery was entered close to its origin from the coeliac artery and the greatest care was taken to preserve intact the peri-arterial nerve plexus. The technique of cannulation and re-establishment of blood flow through the spleen were identical to those employed for the mesenteric system.

Portal Venous Flow

The abdomen was opened through an upper mid-line incision. Exposure of the portal vein was found to be facilitated by a transverse extension of this incision through the right rectus muscle and sheath. The portal vein was mobilised from its source to the point at which the vein divides into its individual branches. Occasionally a small hepatic duct and accompanying branch of the hepatic artery required to be ligated and divided to complete the exposure. The pancreatico-duodenal vein was divided and ligated /

Fig. 49.- The specially designed portal venous cannulae.

ligated close to the portal vein in every instance. Since the total length of portal vein available for cannulation was usually about one and a half inches, cannulae were specially designed which could be accommodated to this narrow space and at the same time produce minimal interference with portal venous flow. After considerable trial and error a pair of curved interlocking cannulae were prepared with fluted endings (Fig. 49). These cannulae could be inserted through a small, longitudinal slit in the vein and firmly fixed in position with ligatures within a period of two to three minutes. In order to reduce this period of portal venous occlusion to a minimum, after the cannulae had been filled with saline, they were immediately connected by a Portex tube and the clamps on the portal vein released. A few minutes later the Portex tubing was occluded proximally and distally and the tube divided at its mid-point and rapidly connected to a rotameter previously filled with saline. Blood flow through the system was then resumed after removal of the clamps.

A rotameter was employed to measure portal venous flow (Appendix B, p. 151) since <u>in vitro</u> calibration experiments had shown that this instrument gave an accurate measure of blood flow between 60 and 550 ml. a minute, at the same time producing minimal pressure drop across the cannulae and flowmeter. The measured pressure drop amounted to 3-5 cm of water at 300 ml. a minute. A specially designed perspex float was used in the rotameter so that the upper surface of the /

the float acted as a lens and the position of the float relative to a calibrated scale could be rapidly and accurately determined when the tube was trans-illuminated by means of a 500 Watt spot-light. Correlation of portal venous flow and portal venous pressure and systemic blood pressure was made by a manually-operated signal recording on the kymograph.

Pressure Measurements

Systemic blood pressure was recorded on a kymograph by a mercury manometer from a cannula in the femoral artery, the zero level being the anterior surface of the abdominal aorta. Superior mesenteric arterial pressure and splenic arterial pressure were also recorded by mercury manometers from side limbs in the cannulae connected to the arteries, and again the abdominal aorta was used as the zero reference. Portal venous pressure was measured from a side limb on the cephalic cannulae or from a polyethylene cannula inserted into a pancreatico-duodenal vein. Portal venous pressure was recorded either by a conventional water manometer recording on a kymograph or by means of a new type of recording manometer (Simpson and Torrance, 1959). The ventral surface of the portal vein was used as the zero reference point. Inferior vena caval pressure was measured by a polyethylene cannula inserted through a femoral vein to a point immediately above the diaphragm. The zero point used was the anterior surface of the cava.

Pressure Flow Determinations

The absence of significant collateral vessels was ensured in each experiment on the superior mesenteric and splenic arterial systems by occluding the efferent connection to the flowmeter and confirming that the pressure in the system distal to this point of occlusion fell to 15 mm.Hg or lower. In the majority of experiments on the mesenteric or splenic systems alterations in perfusion rate were accomplished by varying the output of a Sigma-Motor pump inserted into the circuit proximal to the flowmeter. This method permitted a very wide range of perfusion rates to be studied. Following each alteration in perfusion rate at least fifteen to twenty flow determinations were made, after a short period had been allowed to elapse for stabilisation to occur. In some experiments perfusion pressure was also varied by connecting a femoral arterial cannula to a blood pressure compensating reservoir. The latter method was also employed to study the effects of altered systemic blood pressure on portal venous flow and pressure so that the pressure flow relationships of the gastro-intestinal tract as a whole could be assessed.

In order to study the dynamics of the intra-hepatic portal venous circulation, portal venous blood flow was varied by applying an adjustable screw clamp to the proximal connection of the rotameter. Whilst this method suffers from the disadvantage that a varying amount of back pressure is produced within the portal venous system proximal to the cannulae, /

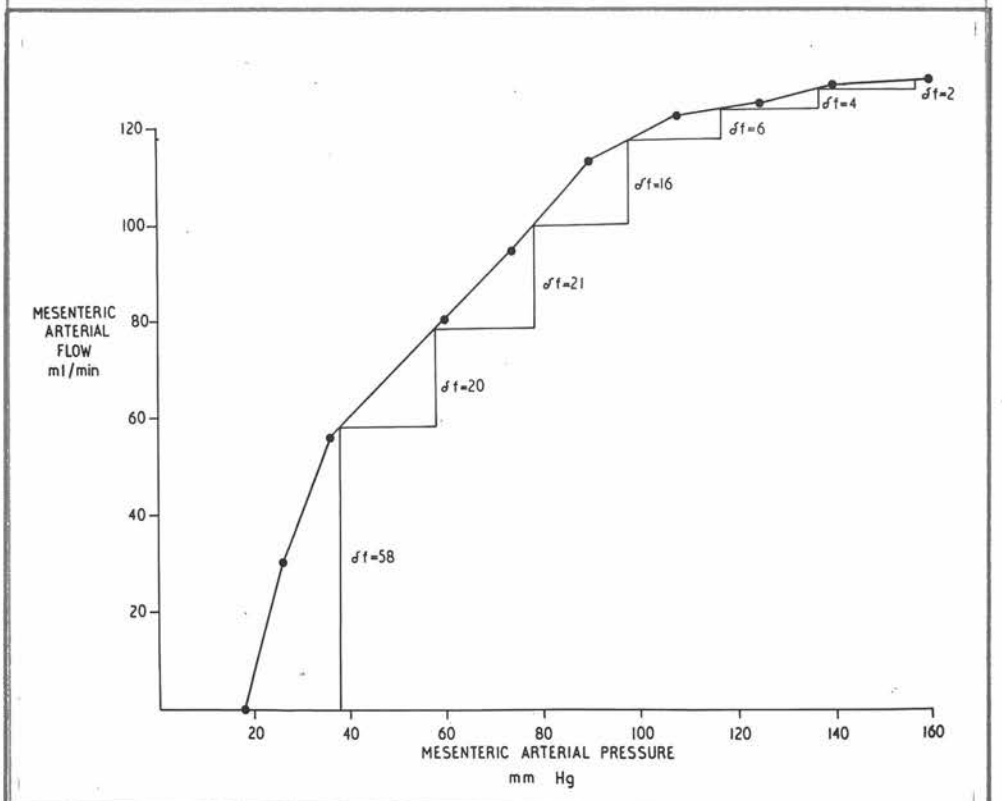

Fig. 50.- A typical pressure flow curve in the mesenteric arterial circulation. The increments in blood flow for every 20 mm. Hg. increase in pressure are shown.

cannulae, it was found that stable pressure flow curves could be obtained without significant effects on the systemic blood pressure so that interference effects produced by systemic baroreceptor responses were not likely to influence the results. Furthermore, this method eliminated the difficulties and complicating factors of the rather complex perfusion circuits employed by Riecker (1955).

Results

Pressure Flow Relationships in the Mesenteric and Gastro-Intestinal Vascular Systems

The relationship between perfusion pressure and blood flow in the mesenteric arterial system was studied in seven experiments where the absence of significant collateral channels had been clearly established. In six experiments the curves obtained were non-linear and showed a predominant convexity towards the flow axis, the degree of convexity varying considerably from experiment to experiment, and even during the course of an experiment (Fig. 50). In one experiment the relationship appeared to be virtually linear over a range of 40 to 145 mm.Hg. In three experiments the curves showed a smooth convexity between 15 and 160 mm.Hg. In two experiments the relationship between pressure and flow was virtually linear up to 80 mm.Hg but as the perfusion pressure was increased the curve deviated towards the pressure axis, giving a curve generally convex to the flow axis for the whole range. A sigmoid pressure flow relationship, /

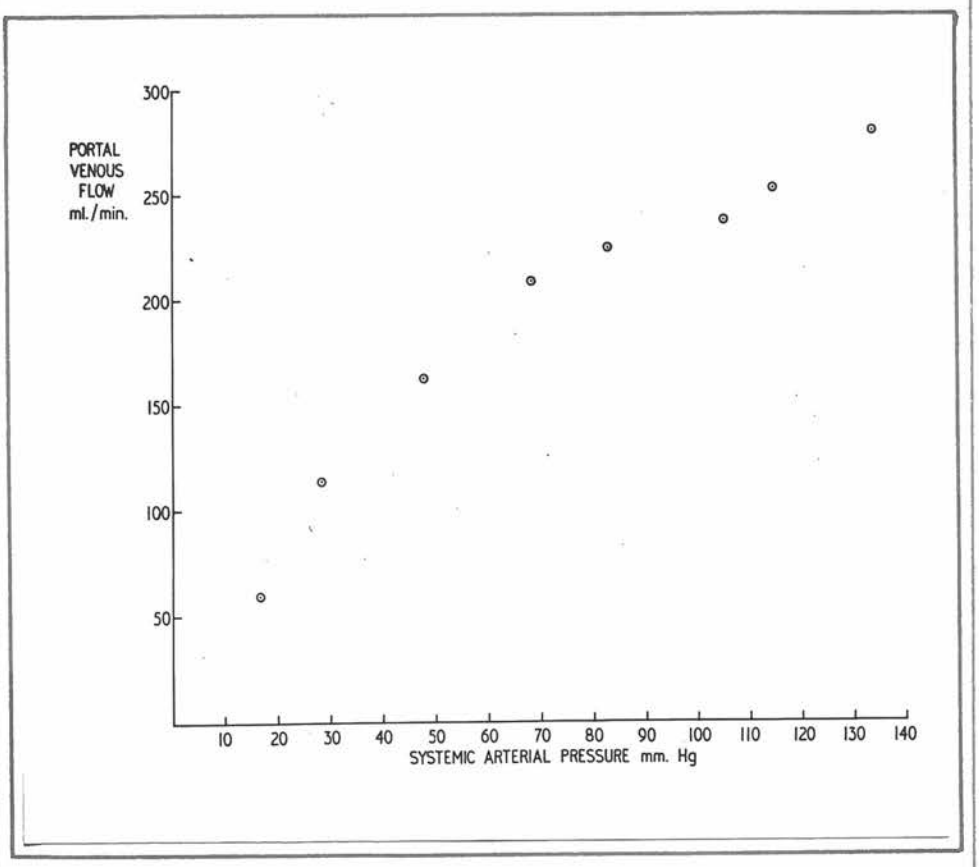

Fig. 51.- The relationship between systemic arterial pressure and portal venous blood flow.

relationship, such as was commonly present in the hepatic arterial system, was only observed on one occasion in this series of experiments.

The pressure gradient across the mesenteric bed at which blood flow ceased was found to vary from 6 to 20 mm.Hg with a mean value of 11 mm.Hg. This finding was also observed during the experiments on portal venous blood flow, when blood flow through the gastro-intestinal tract was found to continue until the systemic blood pressure finally fell below 10 mm.Hg, indicating the presence of certain low resistance vascular circuits within the gastro-intestinal circulation.

The pressure flow relationships of the gastro-intestinal circulation as a whole were studied by the method of controlled haemorrhagic hypotension, similar to the method employed by Grayson and Mendel (1957) in the rat. Systemic blood pressure was lowered by this means in stages of 10 to 15 mm.Hg and after stable conditions had returned, portal venous flow and pressure and systemic arterial pressures were accurately measured. The curves obtained by this method were found to be similar in many respects to those obtained from the mesenteric bed. In each experiment the general shape of the P/F curve was convex towards the flow axis and as already mentioned blood flow continued until the arterial pressure fell to around 10 mm.Hg (Fig. 51).

Changes /

Changes in Vascular Resistance in the Gastro-Intestinal Tract Induced by Alterations in Trans-mural Pressure

The changes in vascular resistance produced by alterations in trans-mural pressure were calculated as follows:

$$\text{Mesenteric resistance} = \frac{\text{mesenteric arterial pressure} - \text{portal venous pressure}}{\text{mesenteric arterial flow}}$$

$$\text{Gastro-intestinal resistance} = \frac{\text{aortic pressure} - \text{portal venous pressure}}{\text{portal venous flow}}$$

When mesneteric vascular resistance was plotted against mesenteric arterial pressure, the general shape of the curves was similar in each experiment except for the experiment in which the pressure flow relationship was found to be linear. In the experiments in which pressure flow curves convex to the flow axis were found relationships of vascular resistance and perfusion pressure were almost identical. At arterial pressures of above 95 mm.Hg, mesenteric vascular resistance steadily increased, and a more or less linear relationship between perfusion pressure and resistance was found. As the arterial pressure was reduced below 95 mm.Hg, mesenteric vascular resistance remained static in two experiments and decreased in three until the blood pressure fell to below 70 mm.Hg, when a further decrease in mesenteric vascular resistance was found, the portion of the curve between 30 and 70 mm.Hg again being linear. As the perfusion pressure fell below 30 mm.Hg, the resistance suddenly increased so that around

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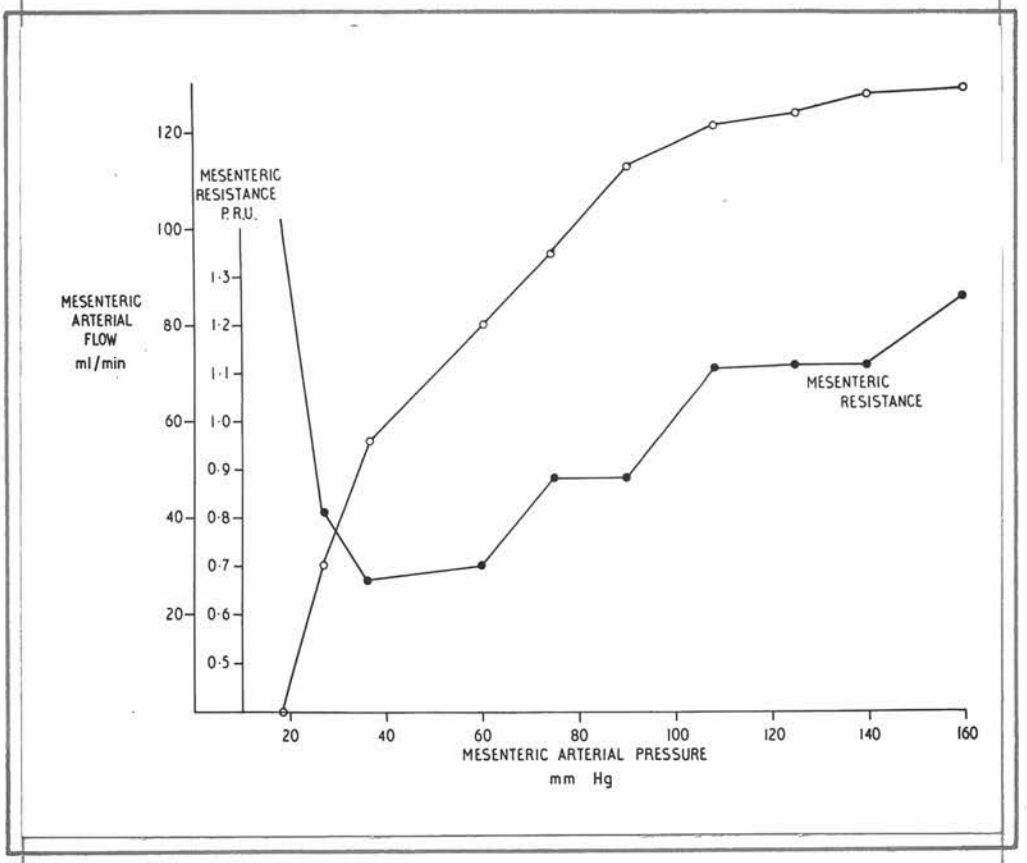

Fig. 52.- Showing the effects of variations in mesenteric arterial pressure on mesenteric vascular resistance. Note the secondary decrease in resistance below 70 mm. Hg.

22-26 mm.Hg resistance was similar to the portion of the curve between 70 and 95 mm.Hg. As the point of the critical closure was approached, resistance increased steeply to reach infinity (Fig. 52).

The vascular resistance of the gastro-intestinal tract at different pressure gradients was also calculated in each of four experiments. Despite the fact that systemic blood pressure was varied by graded haemorrhage into a reservoir, the resistance perfusion pressure gradient curves were similar in shape to those described in the superior mesenteric arterial system, though the higher pressure ranges, i.e. over 130 mm.Hg could not be fully investigated by the method employed.

The Effect of Anoxia on the Intestinal Vasculature

Since in the majority of experiments on the mesenteric system vascular resistance decreased as the perfusion pressure gradient fell below 70 mm.Hg before finally increasing as the critical closing pressure was reached, it seemed important to determine whether this fall in vascular resistance could be explained by the effects of intestinal anoxia on the mesenteric vasculature. This was studied on eighteen occasions in eight separate experiments by occluding the afferent connection to the flowmeter for periods varying from 60 to 75 seconds and obtaining serial measurements of mesenteric blood flow and pressure after a resumption of blood flow. In seventeen out of the eighteen experiments a definite fall in mesenteric resistance /

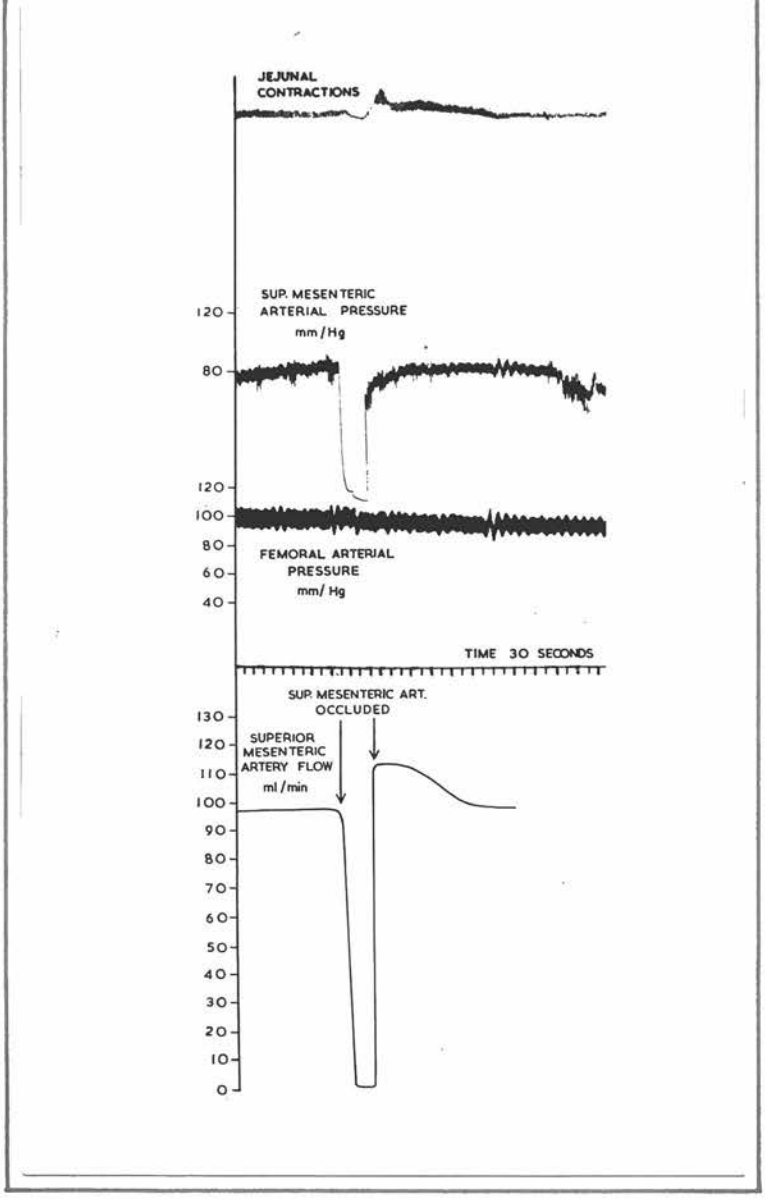

Fig. 53.- The effects of occlusion of the superior mesenteric artery. Note the increased flow and decreased mesenteric arterial pressure on resumption of blood flow.

resistance was apparent, which lasted for periods varying between one and two and a half minutes (Fig. 53). Longer periods of occlusion did not result in more prolonged post-occlusion hyperaemia. Calculation of the maximal drop in mesenteric resistance produced by arterial occlusion showed that in many cases the resistance fell by as much as 60 per cent. The time taken until the resistance returned to control levels averaged 90 seconds, and the curve relating resistance to time appeared to be an exponential function.

Ganglion blockade was affected by the intravenous administration of hexamethonium bromide (50 mg) in two experiments. Mesenteric occlusion for a period of 75 seconds produced an identical response to that obtained in the intact animal. Similarly, the preliminary intravenous administration of either atropine (3 mg) or dibenamine (50 mg) did not affect the intensity or duration of the post-occlusion hyperaemia.

The motor activity of the jejunum was recorded in each experiment by inserting a small balloon connected to a recording tambour into the lumen of the jejunum. Both the rate and magnitude of jejunal contractions were usually inhibited during the period of vascular occlusion and frequently the tone of the intestine also decreased, although, using a balloon recorder, it is impossible to be certain whether this may be caused by a decrease in intestinal blood volume rather than by an alteration in intestinal tone. On resumption of blood flow through the mesenteric artery the intestinal /

intestinal tone increased appreciably and after 10 to 15 seconds intestinal motor activity became markedly enhanced, both the magnitude and rate of the circular muscle contractions becoming greatly augmented, and then returning to control levels within 100 to 120 seconds after resumption of blood flow. These striking changes in gut motility cannot be due merely to augmented blood flow through the mesenteric artery because rapid increases in blood flow artificially produced by the pump did not produce any effect on gut motility and augmented motor activity was found to occur approximately 10 seconds after the onset of maximal hyperaemia. At first it seemed likely that the post-occlusion hyperaemia might be linked by a metabolic demand mechanism inaugurated by increased intestinal motor activity. However, it was found that following the intravenous injection of atropine (3 mg), the post-occlusion augmentation of the intestinal activity was prevented or reduced whereas vascular hyperaemia of a similar degree to that found before injection of atropine was still present. It seems likely therefore that the two phenomena are not necessarily functionally inter-related. On the other hand, both phenomena might be explained by the local accumulation of a substance whose action following resumption of blood flow leads to active dilatation of the mesenteric vascular bed and independently to an effect on the intestinal musculature.

A series of experiments were performed in which the effects /

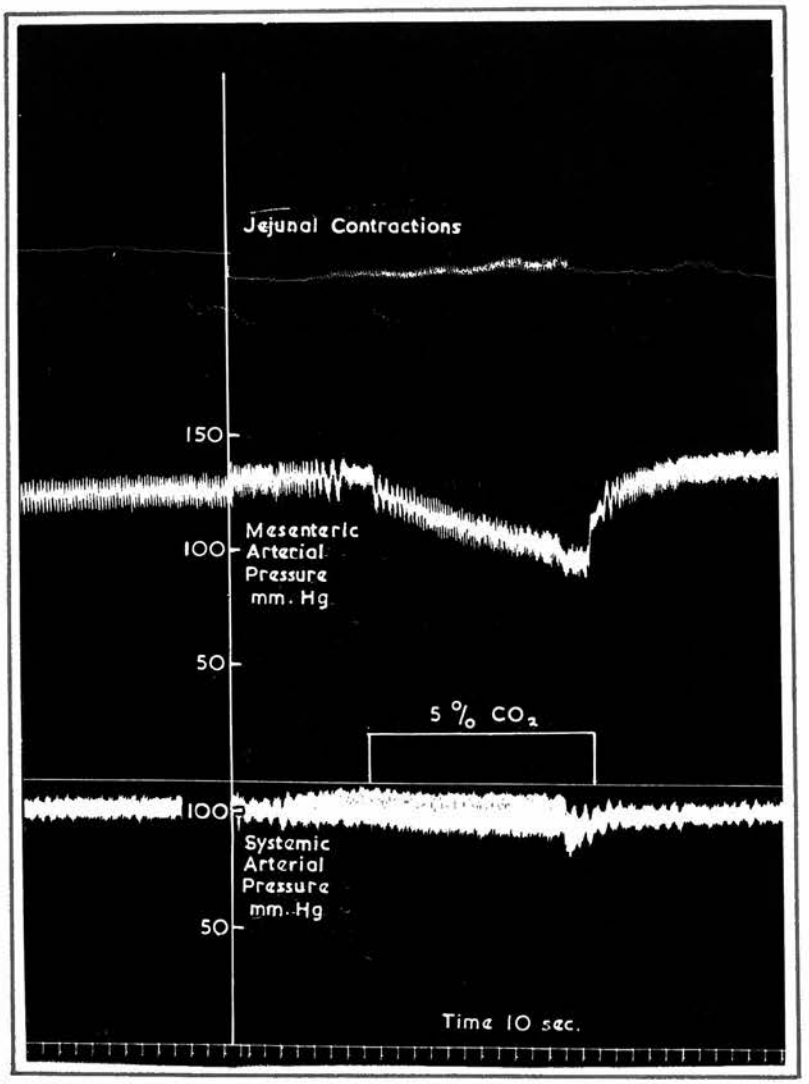

Fig. 54.- Mesenteric arterial flow maintained at a constant level by the perfusion pump. The inhalation of 5% carbon dioxide in 95% oxygen leads to a decrease in mesenteric arterial pressure indicating vaso-dilatation.

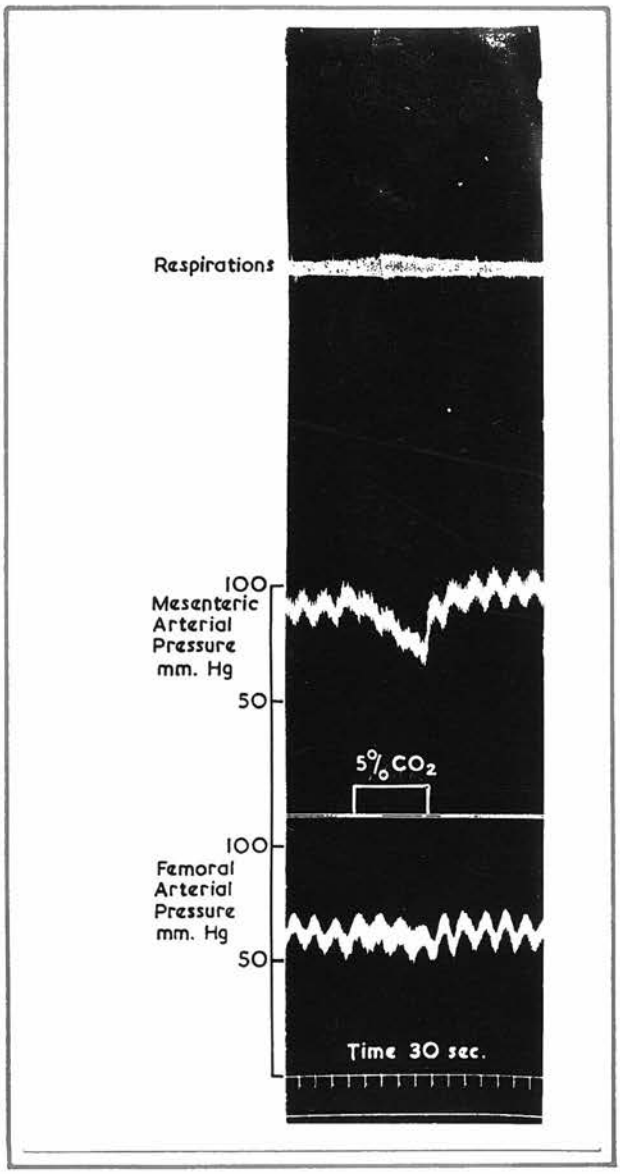

Fig. 55.- The effects of inhalation of 5% carbon dioxide following the intravenous injection of hexamethonium bromide. Ganglion blockade does not alter the response of the mesenteric circulation to inhalation of 5% carbon dioxide.

effects of inhalation of 5 per cent. carbon dioxide in 95 per cent. oxygen on mesenteric vascular resistance and intestinal motor activity were investigated. In every experiment, provided the general condition of the animal was satisfactory, a highly significant decrease in mesenteric vascular resistance was produced without significant effect on systemic blood pressure (Fig. 54). This effect was clearly apparent within 60 to 80 seconds after breathing carbon dioxide when mesenteric vascular resistance progressively decreased during the ensuing four to five minutes before a constant level was reached, the total decrease in calculated vascular resistance being about 40 per cent. On resumption of air breathing mesenteric resistance rapidly increased so that control values were reached within 30 to 40 seconds. Examination of simultaneous recordings of jejunal motor activity showed that the inhalation of 5 per cent. carbon dioxide in oxygen produced an increase in the size and number of jejunal contractions which returned to normal soon after resumption of air breathing. These effects of carbon dioxide on mesenteric vascular resistance were not affected by preliminary ganglion blockade (Fig. 55) and it can be concluded that the effects of increased arterial concentration of carbon dioxide on vascular resistance are produced by an intrinsic action on the blood vessels rather than by an extrinsic chemo-receptor reflex.

The effects of inhalation of 5 per cent. carbon dioxide /

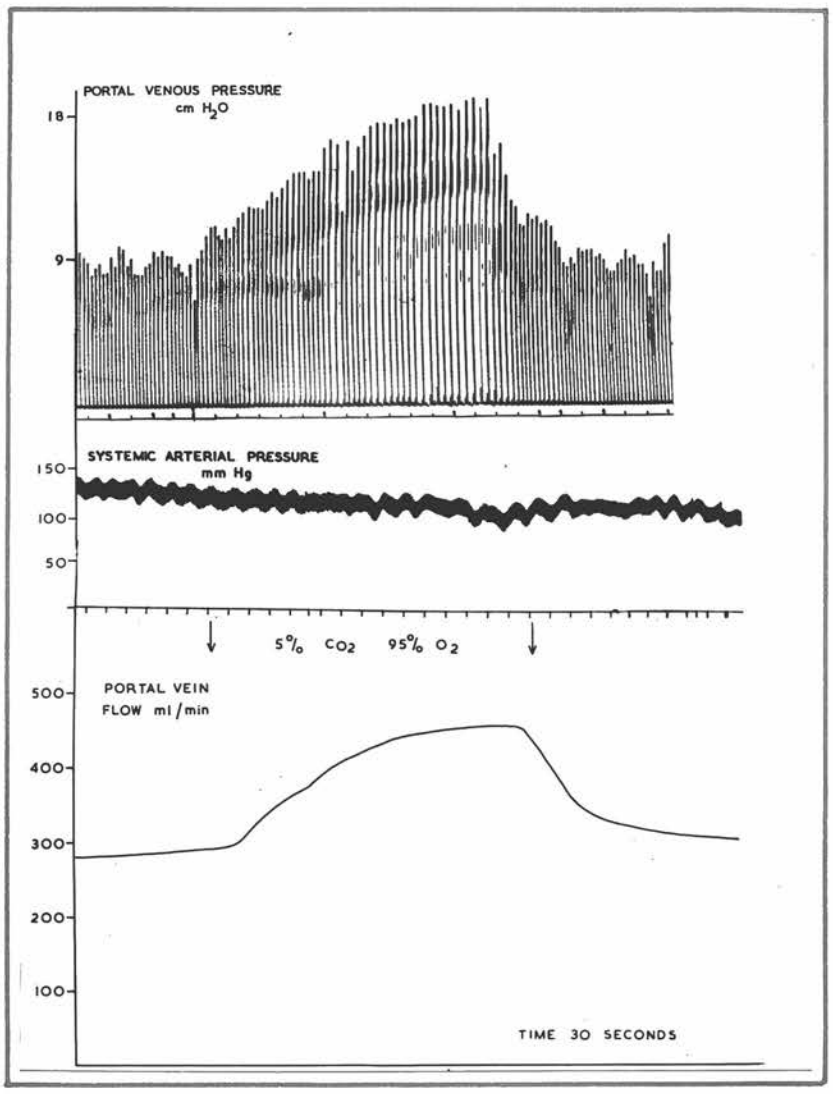

Fig. 56.- The effects of inhalation of 5% carbon dioxide on portal venous dynamics.

dioxide and 95 per cent. oxygen on the gastro-intestinal circulation as a whole were investigated in a series of experiments in which portal venous flow and pressure were measured. Provided the animal was in good condition and the systemic blood pressure was well maintained, a highly significant increase in portal venous flow occurred in every experiment (Fig. 56) which was accompanied by an increase in portal venous pressure. In two experiments correlation of the portal pressure and flow values during the inhalation of carbond dioxide with a control P/F curve of the intra-hepatic portal venous system indicated that the increase in portal venous pressure could be accounted for entirely by the increase in portal venous flow.

It can be concluded therefore that the arterial carbon dioxide concentration plays a large part in determining gastro-intestinal and mesenteric vascular resistance, and in turn influences the rate of portal venous inflow to the liver

Spontaneous variations in portal vein flow.- Phasic variations in portal venous flow during the respiratory cycle were noted in every experiment. During the inspiratory phase portal venous flow decreased whilst during expiration blood flow increased. The magnitude of these phasic changes in blood flow varied from animal tc animal and appeared to depend on the depth of respiration. In most instances, the variation in portal venous blood flow amounted to 30-40 ml./min, and coincided with a slight increase or decrease in portal venous pressure. Variations

in /

in portal venous flow were found to occur even with the abdomen widely opened so that it appears unlikely that changes in intra-abdominal pressure per se are responsible. In one experiment the portal vein was exposed through a thoraco-abdominal incision, the right leaf of the diaphragm being divided and respiration controlled by a mechanical pump. Under these circumstances when the effects of changes in intra-coelomic pressures were eliminated, definite variations in portal flow during the respiratory cycle were detected which disappeared when the respiratory pump was stopped. In case these effects were due to rhythmic variations in the rate of discharge of blood from the spleen, the effects of occlusion of the hilum of the spleen were studied in two experiments. This manoeuvre did not affect the magnitude or character of the respiratory variations in portal flow. Similarly, in other experiments when mesenteric blood flow was determined directly in the innervated preparation, rhythmic variations in mesenteric blood flow during the respiratory cycle were not detected. It seems, therefore, that the cause of the respiratory variations in portal flow cannot be entirely explained on the grounds of altered pressure gradients across the liver produced by changes in intra-thoracic and intra-abdominal pressure or, indeed, by the movement of the diaphragm.

In two experiments large variations in portal blood flow were found to coincide with large spontaneous variations /

variations in systemic blood pressure. In one experiment the mean portal venous flow was 220 ml./min but as the systemic pressure decreased portal venous flow fell to 130 ml./min and as the pressure increased, portal venous flow increased to 280 ml./min in stepwise gradations. These variations were not eliminated by occlusion of the hilum of the spleen.

Intra-hepatic portal dynamics.- The pressure flow relationships of the intra-hepatic portal circulation were studied in six experiments. The method of varying portal venous flow by applying a variable resistance to the inflow connection of the rotameter appeared to be the most accurate and simple method available, although suffering from the disadvantage that in order to study the lower flow ranges considerable back pressure on the portal bed was produced.

The effect on portal venous pressure of between 10 and 20 variations in the rate of portal blood flow were studied in each experiment. The P/F curves were found to be stable under these conditions and no significant deviations could be discerned between the points on the curve obtained during reduction in flow and those obtained during the phase of increasing blood flow.

Considerable variation in the shape and special relationships to the pressure and flow axes was found from experiment to experiment. For instance, in one experiment the initial curve was virtually linear over the middle and higher /

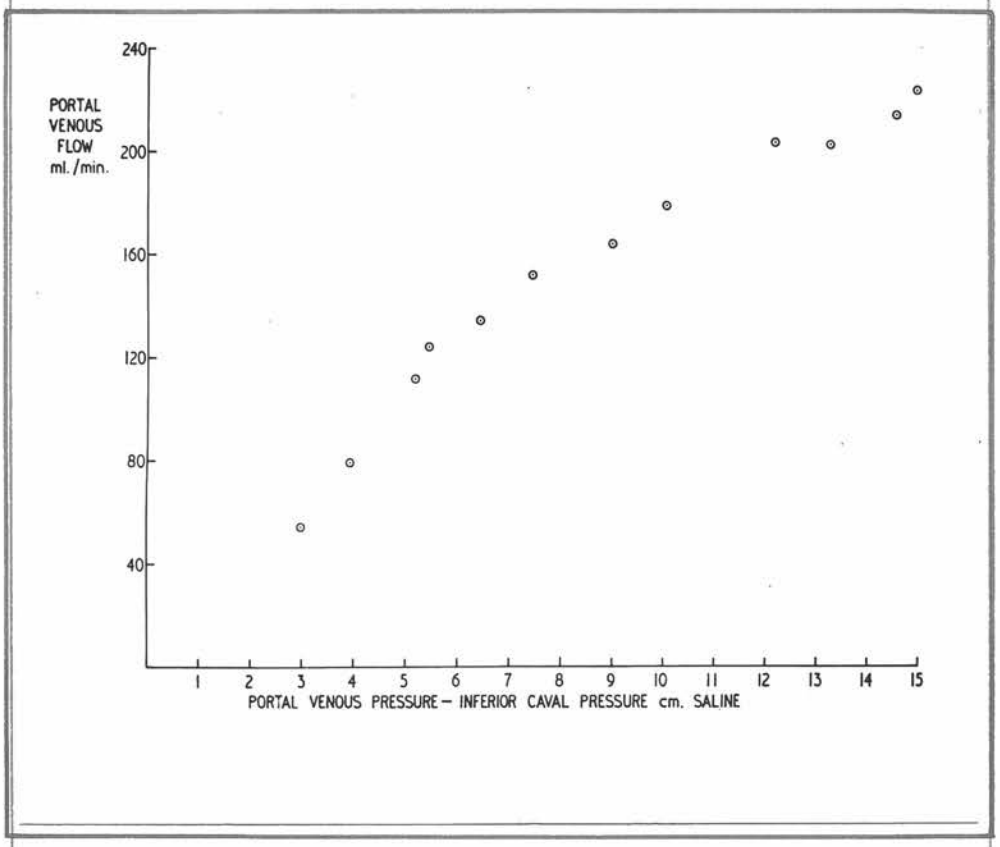

Fig. 57.- The relationship between portal venous flow and pressure. Note the general convexity towards the flow axis.

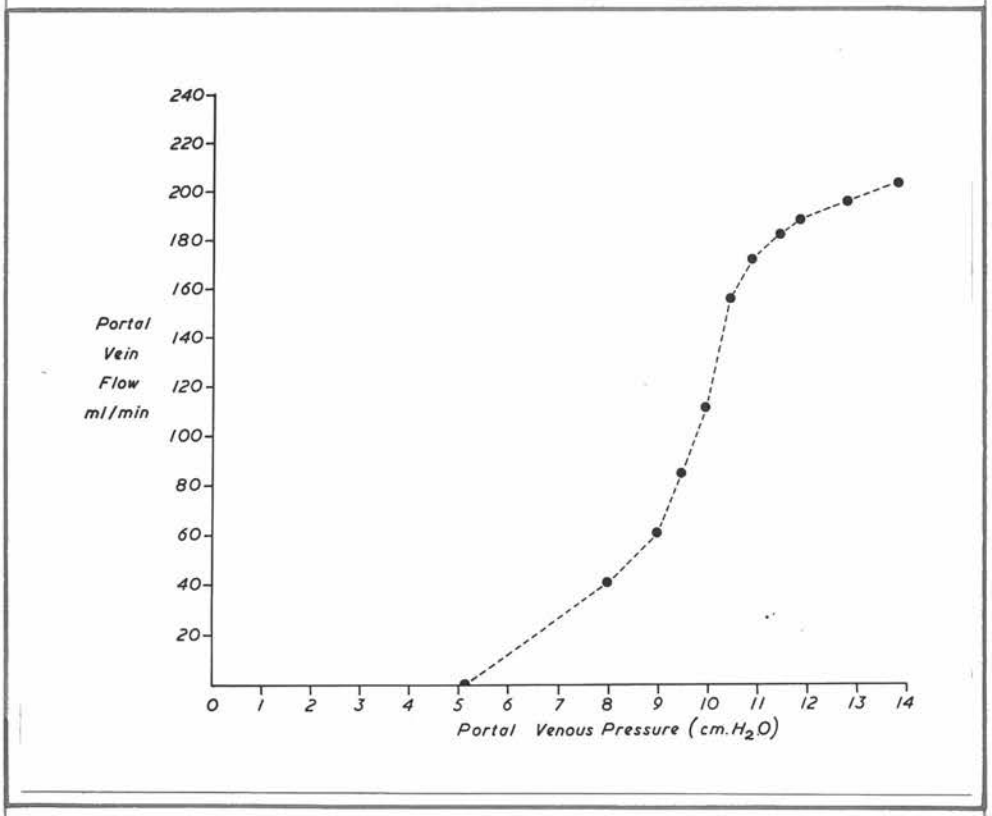

Fig. 58.- A sigmoid relationship between portal venous flow and pressure was demonstrated in two experiments.

higher flow ranges but deviated sharply towards the flow axis at flow levels below 90 ml./min. Later in this experiment, a few minutes after an arterial haemorrhage of 100 ml. which reduced the systemic blood pressure to 80 mm.Hg, the curve was found to be convex towards the flow axis and also shifted towards the flow axis, evidence that intra-hepatic portal resistance had decreased. In three experiments the pressure flow curves exhibited a smooth convexity towards the flow axis, the convexity being particularly well marked in two experiments so that an over-proportional increase in flow per unit increment in pressure at low flow levels occurred whereas the reverse situation obtained at high flow rates (Fig. 57). In two experiments a sigmoid relationship between pressure and flow was found similar to the results obtained from the hepatic arterial system (Fig. 58).

The critical closing pressure of the intra-hepatic portal venous system could not be accurately measured by the techniques employed but by extrapolation of the curves a positive pressure intercept was found, varying between 2 and 5 cm of saline.

Variations in intra-hepatic portal resistance with perfusion pressure.- The intra-hepatic portal vascular resistance was calculated and plotted against portal venous pressure. These curves followed a fairly uniform pattern. As perfusion pressure increased from the critical closing pressure vascular resistance declined steeply until at a critical /

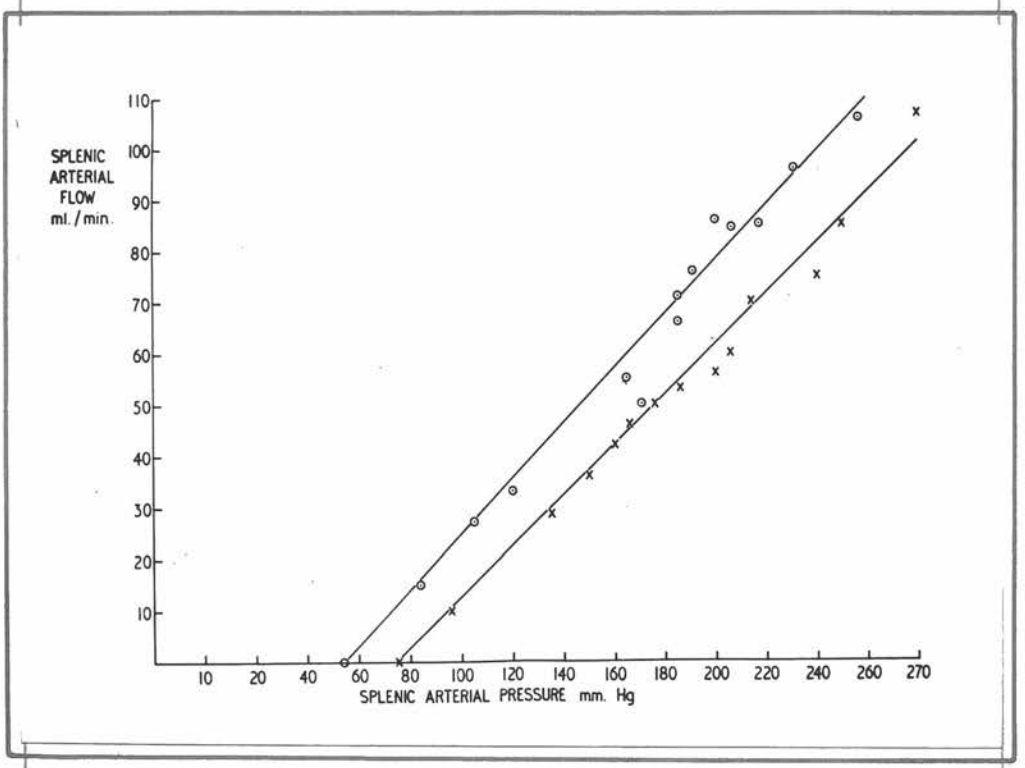

Fig. 59.- The relationships between splenic arterial pressure and blood flow from two separate experiments are illustrated.

critical pressure, varying between 6.5 and 10.5 cm of saline, vascular resistance remained constant up to the higher ranges of perfusion pressure.

Pressure flow relationships in the splenic arterial system.- Grindlay et al. (1939) using a thermostromuhr applied to the splenic artery detected rhythmic fluctuations in splenic arterial blood flow which coincided with rhythmic contractions of the spleen and which were observed even in the denervated spleen. This phenomenon was not detected in the present experiments, possibly because the spleen was in a contracted state due to the manipulations involved in cannulation of the splenic artery.

A series of pressure flow curves were obtained in four experiments in which the complete absence of collateral vessels was confirmed. In each instance an apparently linear relationship between pressure and flow was found between the critical opening pressure and 260 mm.Hg (Fig. 59). The critical closing pressure was found to be much higher in the spleen than elsewhere in the splanchnic bed, varying between 56 and 75 mm.Hg.

Discussion

The mesenteric circulation.- The behaviour of the mesenteric circulation during the course of haemorrhagic shock has provided a rich source of experimental investigation (Selkurt, 1946; Wiggers et al., 1946; Selkurt /

Selkurt and Brecher, 1956). These authors have clearly demonstrated that following re-infusion of shed blood in the dog portal venous flow becomes augmented in an over-proportional manner, frequently to levels higher than in the pre-haemorrhage period. These results, together with the studies of Lillehei (1956), Smith and Grace (1957), McRae et al. (1958) and Powers et al. (1958) on the important role of the intestinal circulation in the genesis of irreversible shock, emphasise the need for a better understanding of the fundamental haemodynamic properties of this vascular bed.

Trapold (1956b) studied the pressure flow relationships in the cranial mesenteric system of the dog as part of an investigation into the effects of ganglion-blocking agents on mesenteric vascular resistance. At arterial pressures above 60 mm.Hg the pressure flow relationship was found to be linear. Below this level, mesenteric resistance increased steeply. Since apparently no attempt was made to control the influence of collateral arterial vessels to the gut during these experiments, the results cannot be regarded as conclusive.

More recently, Selkurt et al. (1958) carried out a detailed series of experiments on the pressure flow relationships in isolated, denervated, perfused loops of canine small intestine. A standardised pressure flow curve was derived from 18 experiments, using oxygenated blood as the perfusate. This curve was found to be slightly convex towards /

towards the pressure axis. Calculations of mesenteric resistance showed that at pressures between 80 and 240 mm. Hg mesenteric resistance became gradually reduced whereas below 80 mm.Hg mesenteric resistance increased steeply, blood flow ceasing at around 20 mm.Hg. When a loop of intestine was perfused with oxygenated dextran the pressure flow relationships were considerably altered and, indeed, closely resemble the patterns demonstrated in the present experiments. Calculation of the mesenteric resistance during perfusion with dextran showed that at pressures above 50 mm.Hg resistance remained constant whereas below these levels resistance increased steeply. The critical closing pressure was not noticeably different from the experiments where the intestine was perfused with blood. The authors regarded the difference in the pressure flow curves as being due to the anomalous viscosity effects of the red cell suspension in blood, a factor which is, of course, likely to lead to alterations in vascular resistance only at high rates of blood flow.

The results of the present experiments, where the small intestine was perfused in vivo with an intact innervation, showed that the pressure flow curves of the small gut are predominantly convex to the flow axis. The fact that Selkurt et al. (1958) obtained somewhat different results in their experiments may be explained by the inevitable degree of trauma inflicted not only on the intestine but on its vascular pedicle during the process of isolation /

isolation and denervation. Grayson (1954) and Carlyle and Grayson (1956) have emphasised the fact that the pressure flow characteristics of the splanchnic and cerebral circulations may be greatly modified following interference with the afferent or efferent blood vessels of the part.

In the present experiments the pressure flow relationships in the gastro-intestinal tract as a whole were studied by measuring the effects on portal venous blood flow of graded haemorrhagic hypotension. Whilst the response of the portal circulation to haemorrhage undoubtedly involves numerous factors, it was interesting to observe a non-linear relationship between pressure and flow in this vascular territory under these circumstances so that portal venous flow was maintained at more or less normal levels until the blood pressure was reduced below a critical level of approximately 80 mm.Hg.

Johnson (1954) and Ginsburg and Grayson (1954) showed that equilibrium levels of liver blood flow in the rat, measured by the method of internal calorimetry, did not change significantly when the arterial blood pressure was lowered by controlled haemorrhage from normal levels to around 80 mm.Hg. Between 80 and 60 mm.Hg a fall in liver blood flow began and below 60 mm.Hg blood flow declined markedly. This phenomenon was designated "intrinsic autoregulation of liver blood flow". Grayson (1954) showed that portal venous flow was directly related to arterial blood pressure in the rat and that under conditions of /

of haemorrhagic hypotension underwent considerable reduction. Grayson and Mendel (1957) undertook a further study of this problem and compared the effects of graded haemorrhagic hypotension on liver blood flow in rats with an intact hepatic circulation and in animals in whom the hepatic artery had been occluded. A virtually linear relationship between portal blood flow and pressure and systemic blood pressure was demonstrated after ligation of the hepatic artery, indicating that the hepatic arterial component of the total hepatic blood flow becomes relatively increased as systemic blood pressure is reduced. This finding was further elucidated by studying the effects of repeated occlusion of the hepatic artery on hepatic blood flow during haemorrhage. Occlusion of the arterial supply to the liver resulted in a much greater decrease in hepatic blood flow at hypotensive levels than in the normotensive animal. It would appear, therefore, that the hepatic arterial circulation plays a very important part in the homeostatic control of hepatic blood flow in haemorrhagic hypotension.

In an earlier section the haemodynamic properties of the hepatic arterial system in the dog are reported and it was demonstrated that this system behaved in a similar fashion to that described by Grayson and Mendel (1957) in the rat. The present experiments on the portal venous system in the dog, however, have shown that the relationship between systemic blood pressure and portal venous flow is not linear, and indeed this bed also appears to possess the features /

features of intrinsic control to a high degree. It is concluded, therefore, at least in the dog, that the phenomenon of circulatory autoregulation of hepatic blood flow is provided not only by the hepatic arterial system but also by the venous outflow from the gastro-intestinal tract.

On release of a partial or complete interruption of the blood supply to a portion of small intestine, produced either by anastomosis clamps, mechanic obstruction or strangulation, it is a frequent surgical observation that the subserosal and submucosal blood vessels become greatly congested, and this is often accompanied by augmented motor activity in the involved area. Indeed, the sudden redistribution of blood volume produced by this phenomenon may lead to severe hypotension and even to death when a long loop of intestine is involved. Despite this clinical observation and the demonstration of the importance of the intestinal circulation in haemorrhagic shock, the direct effects of sub-normal blood flow on the intestine and the effects of carbon dioxide retention on the intestinal vasculature have not received sufficient attention in the past.

Bean and Sidky (1957), using perfused loops of canine small intestine, investigated the effects of lowered oxygen tension on intestinal blood flow, tonus and motility. When a denervated segment was perfused with blood at low oxygen tension, arterial inflow increased by about 30 per cent. Similarly, when innervated loops of bowel were perfused with hypoxic blood, vasodilatation was also evident, indicating that /

that the mechanism involved in the decrease in intestinal resistance is not mediated by an extrinsic chemoreceptor reflex. During these experiments intestinal tonus and motility were not affected so that neither the purely mechanical effects of the intestinal musculature (Bean and Mahomed, 1950) nor local metabolic agents produced by activity of the intestinal musculature appeared to be involved. The authors concluded that hypoxia produces dilatation of the intestinal vessels by a direct action.

The present experiments on the effects of interruption of arterial inflow on intestinal vascular resistance and motility produced somewhat different results to those of Bean and Sidky (1959) in that during the period of post-occlusion hyperaemia intestinal motor activity became greatly exaggerated in the majority of experiments and it was impossible to decide whether the effects on the intestinal circulation were due to a direct effect of anoxia or to a secondary demand mechanism, involving a metabolic by-product of smooth muscle activity. On the other hand, these two groups of experiments cannot be regarded as strictly comparable since the effects of hypoxia produced by interruption of the circulation and the effects of perfusion at a normal rate with hypoxic blood may be different. Products of intestinal metabolism are probably accumulated during circulatory arrest whereas they must be at least partially removed when the gut is perfused with hypoxic blood at normal flow rates. This possibility prompted further /

further experiments on the effects of the inhalation of 5 per cent. carbon dioxide in 95 per cent. oxygen on mesenteric and portal blood flows and on intestinal motor activity. This group of experiments showed beyond doubt that an increase in arterial carbon dioxide content produces a profound decrease in mesenteric resistance, which is accomapnied in the majority of instances by an increase in rate and magnitude of jejunal contractions. That this appears to be a direct effect on the intestinal vasculature rather than due to an extrinsic chemoreceptor reflex was shown by the production of identical results following full ganglion blockade with hexamethonium bromide.

Selkurt et al. (1958) have recently investigated the effects of various other substances present in the wall of the gut intestinal vasculature. Amongst the substances infused, adenosine triphosphate adenylic acid, adenosine and substance P (which has been isolated from the intestine and brain; Euler and Gaddum, 1931), produced significant vasodilatation in an isolated, denervated, perfused loop of small intestine. Further biochemical investigation will therefore be required to identify the metabolic factors responsible for the decrease in mesenteric vascular resistance produced by sub-normal arterial flow to the intestine.

It seems probable that a decrease in intestinal vascular resistance, associated with hypoxia, must play an important part in determining the form of the pressure flow curves /

curves of the mesenteric circulation at the lower flow rates. In most experiments when the arterial pressure was reduced below 60 mm.Hg, vascular resistance was found to decrease significantly as the pressure was reduced until a critical level was reached when vascular resistance increased steeply. The fact that this pattern of response was not detected by Selkurt et al. (1958) may have been due to a pre-existing state of partial hypoxia and vasodilatation in their isolated, perfused preparations.

Wiggers et al. (1946) have shown that in a dog in advanced haemorrhagic shock intravenous infusion of shed blood led to a profound increase in portal venous pressure. More recently, Selkurt and Brecher (1956), using direct flowmeters, showed that this phase of increased portal pressure was accompanied by a simultaneous increase in portal venous flow, due to a marked reduction in splanchnic vascular resistance, particularly in the mesenteric component. The results of the present experiments suggest that intestinal anoxia, increased arterial carbon dioxide tension and possibly acidosis may modify the response of the mesenteric vessels to produce an over-proportional increase in portal venous flow and pressure following re-infusion of blood. Clowes (1959; personal communication) has shown that portal venous pressure becomes noticeably increased during the course of experimental cardio-pulmonary by-pass. This increase was related to a decrease in arterial pH and it was thought that this in turn led to an increase in hepatic /

hepatic vascular resistance by a direct constrictor action on the hepatic veins. It may be, however, that these results could be explained by the effect of alterations in arterial pH on mesenteric vascular resistance.

The splenic circulation.- It was first suggested by Hargiss and Mann (1928) that the spleen might function as an arteriovenous connection between the aorta and portal vein, which might compensate under conditions of reduced gastro-intestinal outflow thus ensuring an adequate venous inflow to the liver under these conditions. On anatomical grounds, there is reason to believe that the ellipsoids of the spleen may act as short-circuit or arteriovenous shunts conveying either blood or plasma from the arterial capillaries to the venous sinusoids without reversing the pulp proper (Solnitzky, 1937; Lewis, 1957). The present experiments showed in each instance that the relationship between pressure and flow in the splenic arterial system was linear over a wide range of pressure. The findings suggest, therefore, that the changes in perfusion pressure per se do not lead to a decrease in arterial resistance with an increase in splenic blood flow under conditions of reduced arterial pressure. It may be, however, that the manipulations involved in cannulation of the splenic artery could invalidate the results of these experiments since in each instance the spleen was noticeably contracted.

Grayson and Mendel (1957) studied the splenic contribution to portal blood flow under varying conditions of /

of arterial pressure produced by haemorrhage and found that splenic blood flow increased when arterial pressure was reduced to 75 mm.Hg, thereafter diminishing to zero as the pressure was further reduced. In the next section of this thesis evidence is presented that splenic vascular resistance is reduced following the intravenous injection of adrenaline or noradrenaline. Since both adrenaline and noradrenaline have been shown to be released into the blood stream following acute blood loss (Saito, 1928; Armin and Grant, 1955; Lawrence, 1956; Manger et al., 1957), the increase in splenic blood flow in Grayson and Mendel's experiments may have been produced by these substances.

Intrahepatic portal venous system.- The present experiments on the relationship between portal venous flow and pressure in the innervated liver of the dog have produced pressure flow curves predominantly convex to the flow axis with an over-proportional increase in flow per unit increase in pressure in the lower pressure ranges and a gradually diminishing ΔF as the perfusion pressure is increased. These results confirm to a large extent the findings of Riecker (1955), who studied the pressure flow relationships in the perfused liver of the dog.

Brauer et al. (1956) undertook an elaborate study of the haemodynamic properties of the isolated rat liver. Their data indicate that the relationship between pressure and flow in this preparation is of sigmoid form, the shape of the curve being identical whether blood or plasma at an oxygen /

oxygen partial pressure of $2\frac{1}{2}$ atmospheres is used as the perfusion. It seems unlikely, therefore, that anomalous viscosity effects, due to the presence of circulating red blood cells, play an important part in controlling intra-hepatic portal dynamics. From calculations derived from changes in liver weight caused by alterations in pressure and flow through the isolated liver, the authors concluded that the form of the pressure flow diagram could be most readily explained on the basis of a series of parallel circulatory channels within the liver, with critical opening pressures distributed in such a way as to lead to non-linear pressure flow relationships. Further evidence for this view was accumulated from experiments on relationships between the uptake of colloidal chromium phosphate by the liver at differing perfusion rates. Zweifach and Benacerraf (1958) studied the uptake of colloidal graphite by the reticulo-endothelial system in the liver during haemorrhagic shock and concluded that under these conditions of reduced portal inflow blood flow through the liver was restricted to certain low resistance channels, the remainder of the liver being virtually deprived of a circulation. We have already seen in Part I of this thesis that there are reasonable anatomical grounds for accepting this new dynamic concept of the intra-hepatic portal circulation, and a series of experiments is at present being undertaken, using a radioactive dilution technique, to measure portal venous flow and circulation time characteristics through the liver under varying pressure /

pressure and flow relationships. It is too early as yet to say whether this method will provide sufficiently accurate data for such an analysis.

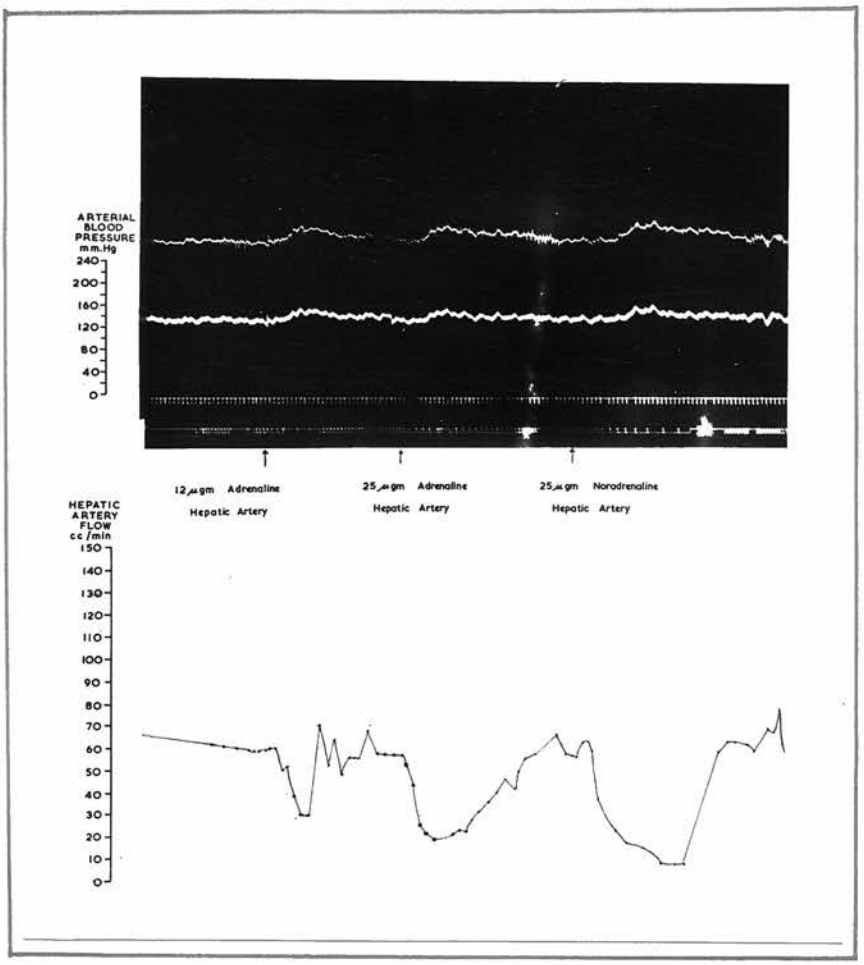

Fig. 60.- The effects of direct intra-arterial injections of adrenaline and noradrenaline on the hepatic arterial circulation.

THE ACTIONS OF ADRENALINE AND NORADRENALINE ON THE SPLANCHNIC CIRCULATION

Methods of Study

The methods employed to measure blood flow and pressure in the various compartments of the splanchnic circulation were identical to those previously described.

The adrenaline B.P. used in these studies was supplied as a 1/1000 solution by T. & H. Smith Ltd. and the noreadrenaline as Levophed 1 mg/ml. (Bayer). The continuous intravenous infusions of adrenaline or noradrenaline were administered either by a Palmer continuous infusion pump or by a standard intravenous drip set.

Hepatic Arterial System

The injection of varying doses of adrenaline and noradrenaline into the tubing proximal to the cannula in the hepatic artery led in every instance to a decrease in blood flow, indicating a direct vasoconstrictor action (Fig. 60). The response was usually completed within 15 seconds, when hepatic arterial flow returned to the control value. When the pump was incorporated in the circuit and made totally occlusive, i.e. giving a constant output against variable resistance, hepatic arterial pressure increased sharply following intra-arterial injection of adrenaline or noradrenaline. In a few instances a bi-phasic response was detected, initial vasoconstriction being followed by vasodilatation, but in these experiments it was found /

found that a few branches from the hepatic artery to the stomach had not been adequately occluded by ligatures, and it seems likely that the secondary dilator response was due to effects of adrenaline and noradrenaline on the blood vessels of the stomach.

The vasoconstrictor effects of adrenaline and noradrenaline on the hepatic arterial circulation were compared by alternate injection of varying doses. Noradrenaline was found to possess more potent vasoconstrictor properties than adrenaline, the ratio being approximately 1.5 to 1.

The effect of preliminary intravenous injection of dibenamine (50 mg) on the response to the intra-arterial injection of adrenaline or noradrenaline was studied in two experiments. Twenty minutes later the vasoconstrictor effects of these substances were completely abolished.

Dose response relationships were studied by means of the increase in hepatic arterial pressure produced, whilst hepatic arterial flow was maintained at a constant level by the pump. The minimal dose of adrenaline and noradrenaline required to produce a vasoconstrictor effect was found to vary from 0.1 to 0.5 µg.

The effects of intraportal injections of adrenaline and noradrenaline on hepatic arterial dynamics

On six occasions in three separate experiments adrenaline and noradrenaline were injected into the portal vein through a cannula inserted into the pancreatico-duodenal /

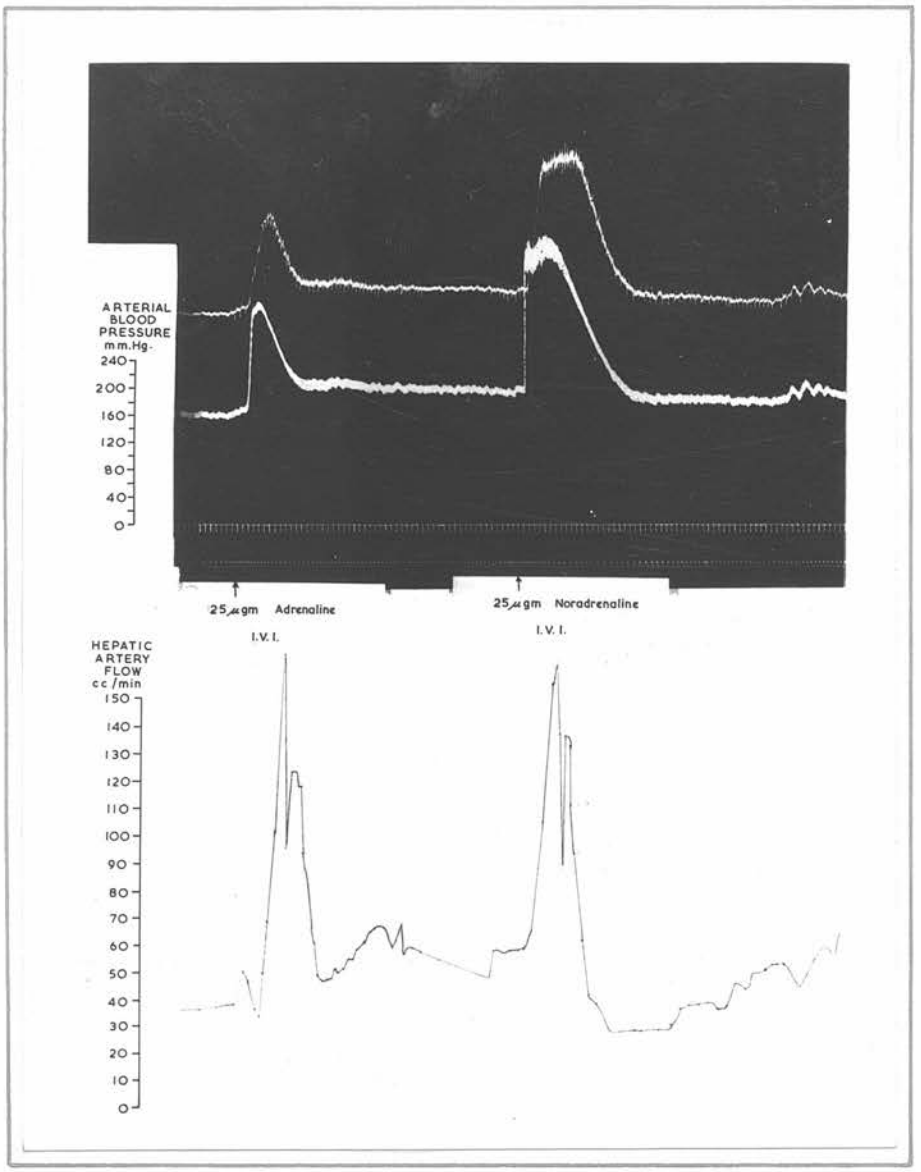

Fig. 61.- The effects of intravenous injections of adrenaline and noradrenaline on the hepatic arterial circulation.

duodenal vein. In each instance, an increase in hepatic arterial resistance was apparent but of lesser degree than after an equivalent dose injected directly into the hepatic artery; this was followed by a decrease in hepatic arterial resistance which tended to persist for longer than the vasoconstrictor phase. In these experiments the intra-arterial injection of adrenaline and noradrenaline in comparable doses was shown to produce only vasoconstriction.

The effects of intravenous injections of adrenaline and noradrenaline on the hepatic arterial circulation

The effects of intravenous injection of adrenaline and noradrenaline on the hepatic arterial circulation were modified by the dead space produced by the flowmeter and its connections (approximately 40 ml.). The intravenous injection of both adrenaline and noradrenaline in doses between 10 and 50 μg elicited a bi-phasic effect, owing to the delayed arrival of the drug in the hepatic arterial system (Fig. 61). During the period of increased systemic blood pressure hepatic arterial flow increased, but as systemic pressure decreased a sudden decrease in hepatic arterial flow appeared, apparently due to the delayed arrival of the substance in the liver. This effect was usually short-lived, hepatic arterial flow returning towards control values without any period of decreased hepatic arterial resistance.

It was interesting to examine the pressure flow relationships during the first part of the response since any systemic /

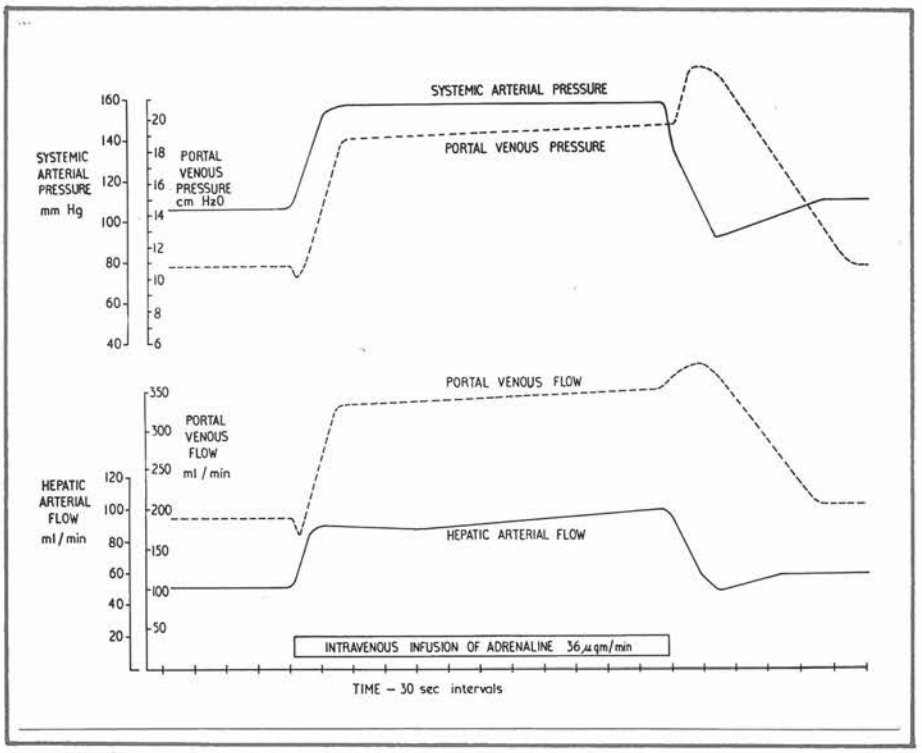

Fig. 62.- The effect of an intravenous infusion of adrenaline on hepatic arterial and portal venous flows from an experiment in which blood flow through both vessels were measured simultaneously.

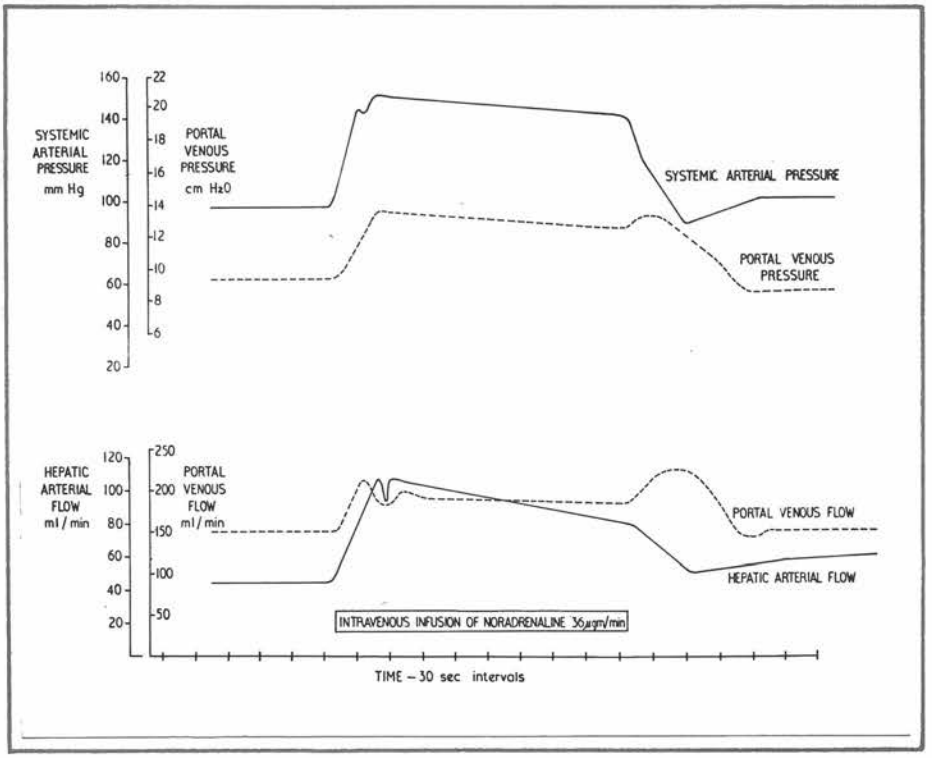

Fig. 63.- The effects of a continuous intravenous infusion of noradrenaline on hepatic arterial and portal venous flows. The increase in hepatic arterial flow in this experiment was greater than usually encountered.

systemic baroreceptor reflex response involving the hepatic arterial system might be expected to occur during this period uncomplicated by the presence of adrenaline or noradrenaline in the hepatic arterial system. In the majority of instances hepatic arterial resistance either remained constant or increased during the increase in systemic blood pressure. Comparison of the pressure flow values obtained in these experiments with control pressure values showed no evidence of a shift towards the flow axis, which would be apparent if reflex baroreceptor inhibition of vasomotor tone or active reflex vasodilatation (Ginsburg and Grayson, 1954) played a part in this response.

The effects of continuous intravenous infusions of adrenaline and noradrenaline on the hepatic arterial system

The effects of continuous infusions of adrenaline and noradrenaline in doses varying between 12 and 72 µg/min were compared in a total of 12 experiments. In every instance, the infusion of adrenaline resulted in an increase in hepatic arterial flow, provided a significant increase in blood pressure was produced (Fig. 62). On the other hand, the effects of noradrenaline infusions were somewhat unpredictable (Fig. 63). In the majority of instances a slight increase in hepatic arterial flow was produced but it was noted that if the animal's blood pressure became reduced, i.e. below 80 mm.Hg, the infusion of noradrenaline produced a more marked increase in arterial flow. Reference to control pressure curves provided an explanation of this difference /

difference in response, since it was shown that the extent of the increase in hepatic arterial flow produced by a unit increase in hepatic arterial pressure tended to be considerably greater below 80 mm.Hg than in the normotensive range. Even in the presence of an increased level of circulating noradrenaline it seems likely that these differing pressure flow relationships can explain the varying effects of noradrenaline infusions.

The effects of adrenaline and noradrenaline on hepatic arterial dynamics were investigated following the intravenous injection of atropine (3 mg). Comparison of the effects with control curves did not disclose any modification of the response to either substance. Similarly, the prior administration of hexamethonium bromide (50 mg) did not materially alter the response. It was concluded therefore that systemic baroreceptor reflexes do not play an important part in determining the effects of intravenous infusions of adrenaline or noradrenaline on the hepatic arterial circulation.

The effects of intravenous injections of adrenaline and noradrenaline on portal venous dynamics

A total of 35 intravenous injections of adrenaline or noradrenaline were studied, the dose varying between 5 and 75 µg. Provided a significant increase in systemic blood pressure was produced, a constant pattern of response in the portal venous circulation was obtained. In the vast majority of instances the response was clearly tri-phasic (Figs. /

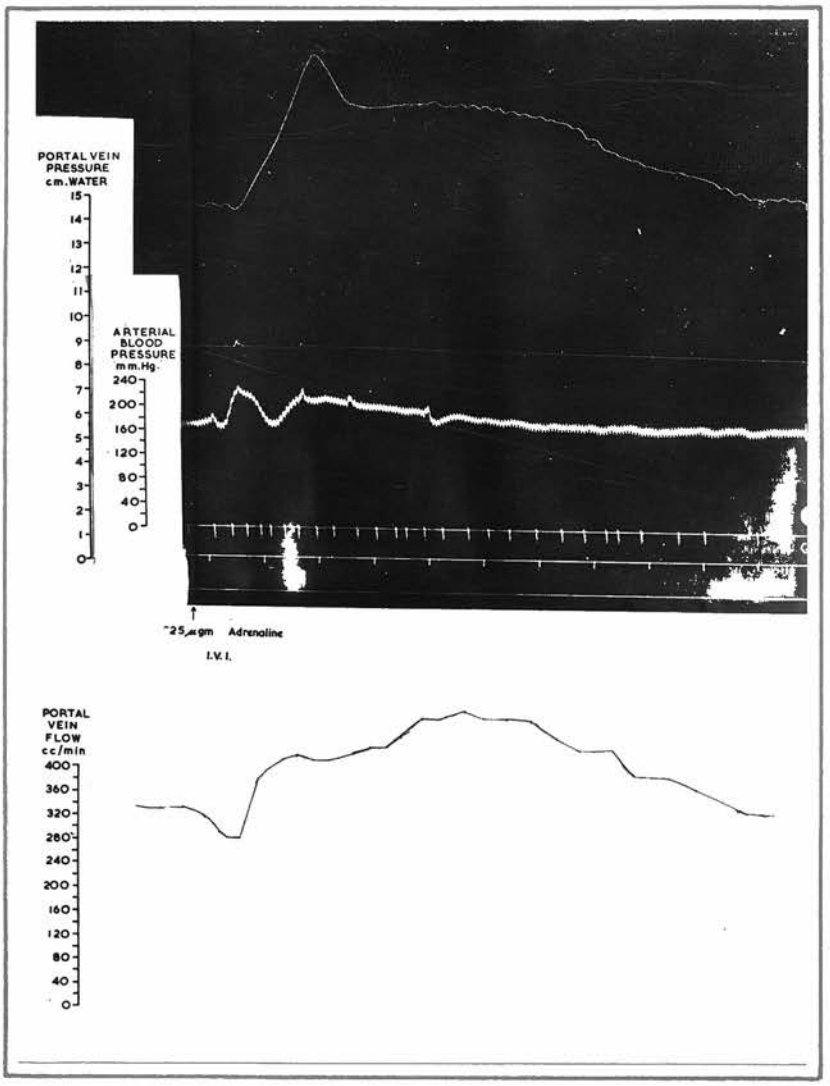

Fig. 64.- The effects of an intravenous injection of adrenaline on portal venous dynamics.

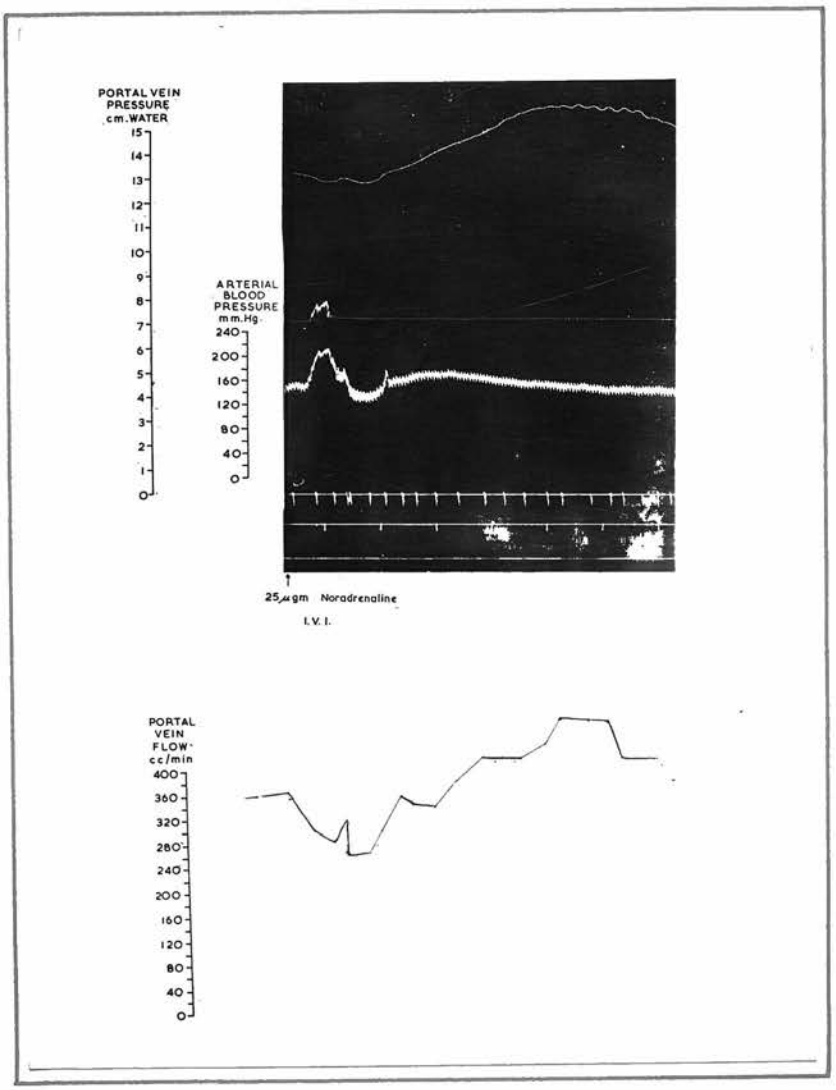

Fig. 65.- The effects of an intravenous injection of noradrenaline on portal venous dynamics.

(Figs. 64 and 65). During the initial increase in systemic blood pressure produced by intravenous injection of adrenaline portal venous flow became slightly reduced. This was accompanied by a synchronous decrease in portal venous pressure, indicating mild vasoconstriction in the gastro-intestinal circulation but no effect on the intra-hepatic portal resistance. This phase was immediately followed by an increase in portal venous flow and a slight increase in portal venous pressure occurring during the peak of the increase in systemic blood pressure. This was followed by a slow decrease towards the pre-injection levels as the blood pressure decreased. However, the most significant effect on the portal circulation became apparent a few seconds later when systemic blood pressure had usually fallen slightly below the control values. During this tertiary phase of the response portal venous flow and pressure became greatly augmented and did not return to the pre-injection levels for periods varying from 30 seconds to $2\frac{1}{2}$ minutes. In order to determine whether this tertiary response could be due to an effect of adrenaline on the splenic circulation, the hilum of the spleen was occluded by an occlusion clamp in two experiments. In both instances, pronounced vaso-dilatation was produced during the post-pressor phase following the intravenous injection of adrenaline or noradrenaline, suggesting that the splenic circulation did not play an essential role in this part of the response of the portal venous system to the intravenous injection of adrenaline /

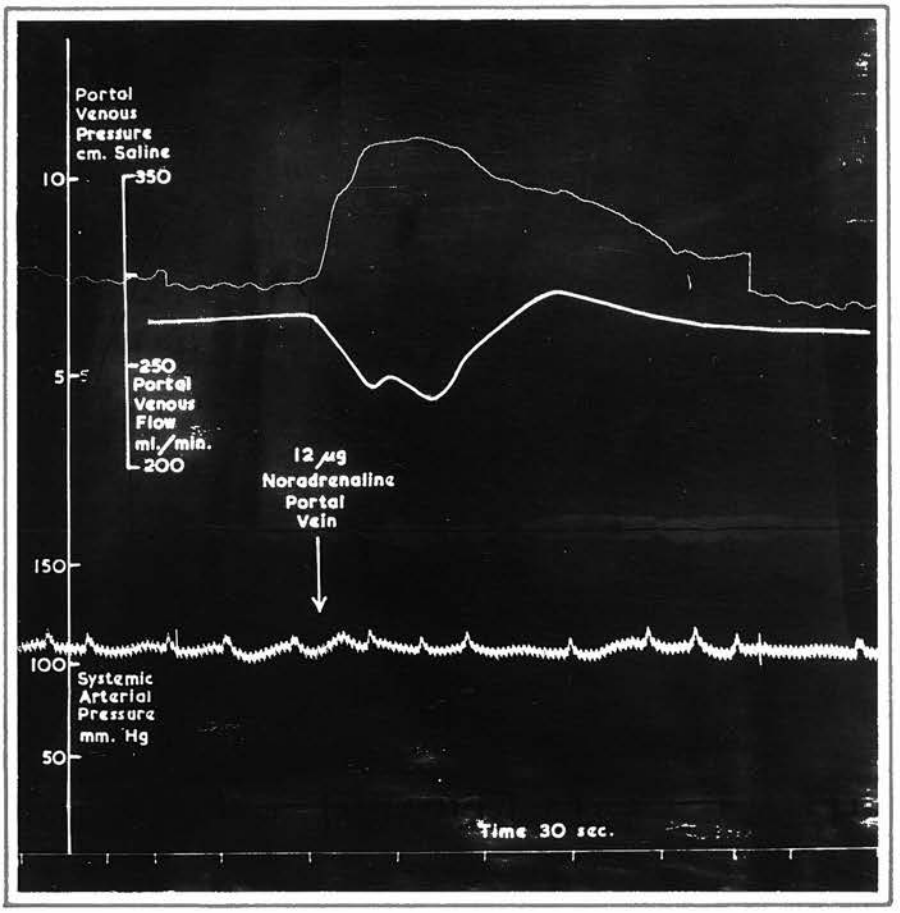

Fig. 66.- The effects of an intra-portal injection of noradrenaline on portal venous dynamics.

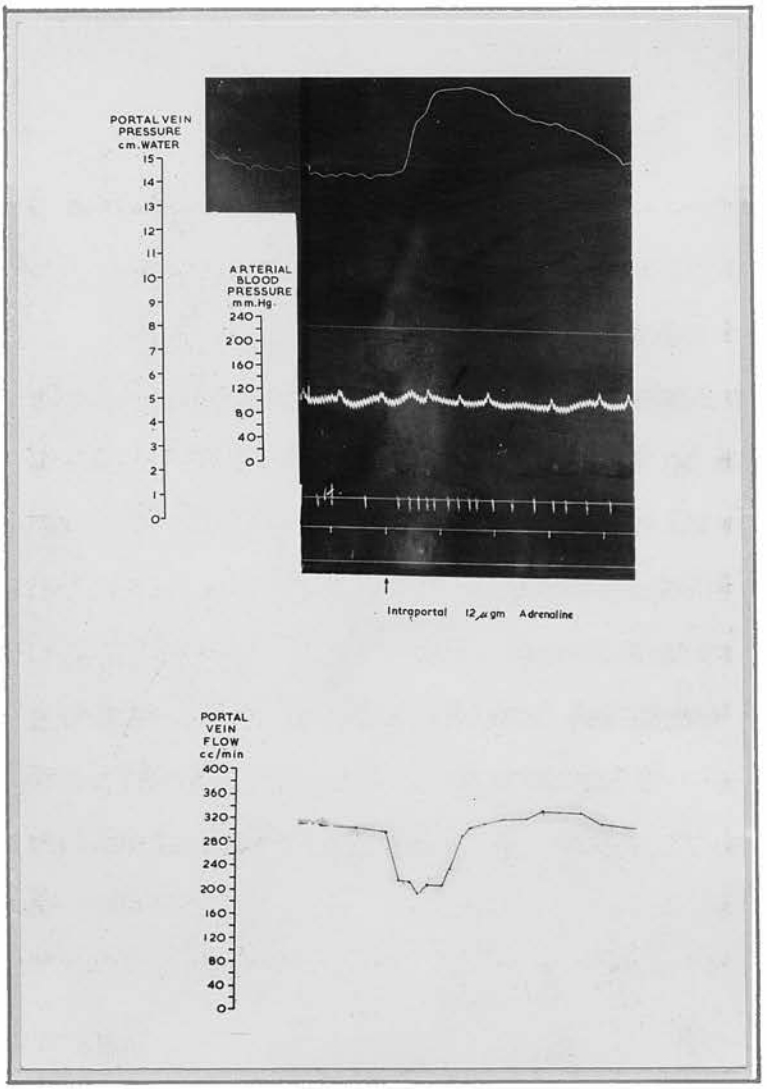

Fig. 67.- The effects of an intra-portal injection of adrenaline on portal venous dynamics.

adrenaline or noradrenaline.

The effects of intraportal injections of adrenaline and noradrenaline on portal venous dynamics

Immediately after an intraportal injection of either adrenaline or noradrenaline portal venous pressure increased and this was accompanied by a decrease in portal venous flow (Figs. 66 and 67).

The decrease in portal venous flow cannot be fully explained by the moderate increase in intrahepatic resistance since portal venous pressure increased by only 3 to 4 cm saline, which is unlikely to lead to an increase in gastro-intestinal resistance. Selkurt and Johnson (1958) have recently suggested that elevation of portal venous pressure evokes a local baroreceptor reflex which in turn leads to an increase in gastro-intestinal resistance and this factor may account for the decrease in portal blood flow following the intraportal injection of adrenaline or noradrenaline. If the dose was sufficient to produce an increase in systemic blood pressure, a secondary increase in portal flow and pressure appeared similar to the effects of systemic intravenous injection of these substances.

The effects of intravenous injections of noradrenaline on portal venous dynamics were found to be more or less identical to the effects of comparable doses of adrenaline. During the phase of increased systemic blood pressure, however, portal venous flow usually decreased and the delayed dilator effects although still obvious were not so well /

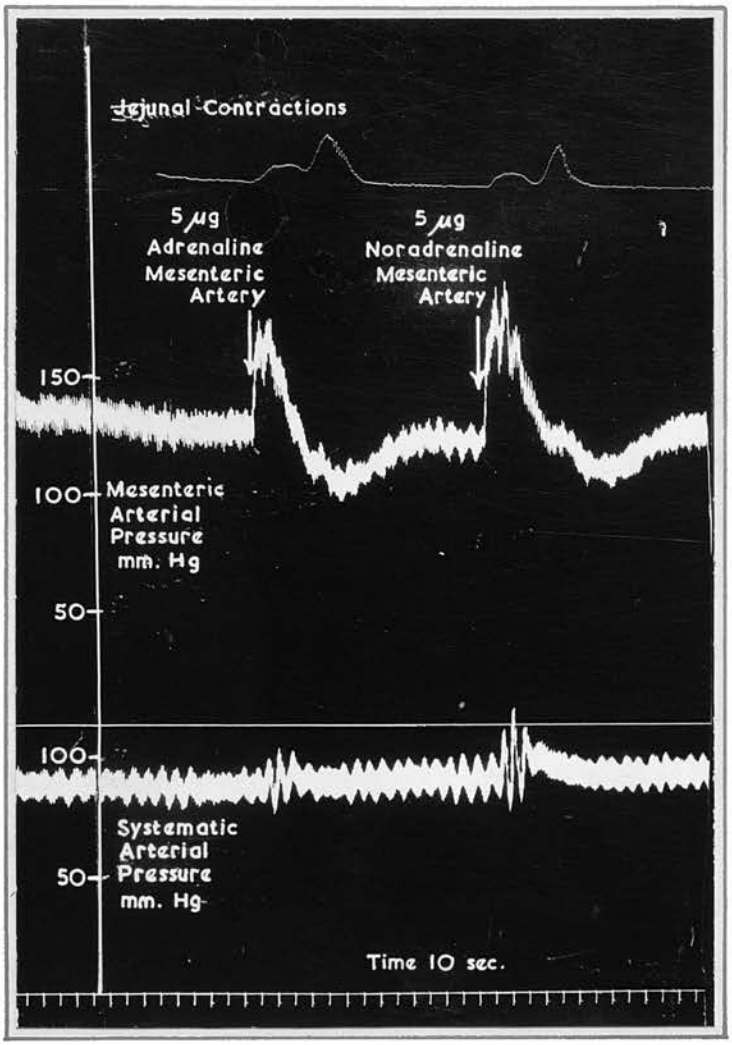

Fig. 68.- Mesenteric blood flow was maintained at a constant level by the perfusion pump. The biphasic effects of the direct intra-arterial injections of adrenaline and noradrenaline are shown.

well marked as following the intravenous injection of adrenaline.

The effects of adrenaline and noradrenaline on the mesenteric circulation

The injection of adrenaline in doses varying between 1 and 25 µg directly into the mesenteric arterical circulation led in every instance to a bi-phasic response: immediate vasoconstriction followed by a period of vasodilatation, the duration of each phase being approximately equal (Fig. 68). Direct intra-arterial injection of nor-adrenaline produced comparable effects except that the dilator response was less well marked.

The minimal dose of adrenaline or noradrenaline, which on intra-arterial injection elicited a vasoconstrictor response, was found to be about 0.005 µg for each substance. Comparison of the effects of larger doses on the mesenteric circulation, however, suggested that noradrenaline appeared to be a more powerful vasoconstrictor.

In two experiments the effects of a preliminary intravenous injection of dibenamine (50 mg) on the response of the mesenteric circulation to direct intra-arterial injection of adrenaline or noradrenaline was studied. Approximately 30 minutes after the injection of dibenamine the intra-arterial injection of adrenaline or noradrenaline led to pronounced vasodilation followed by a brief vasoconstrictor response or, in other words, reversal of the effect found in the same experiment prior to the administration /

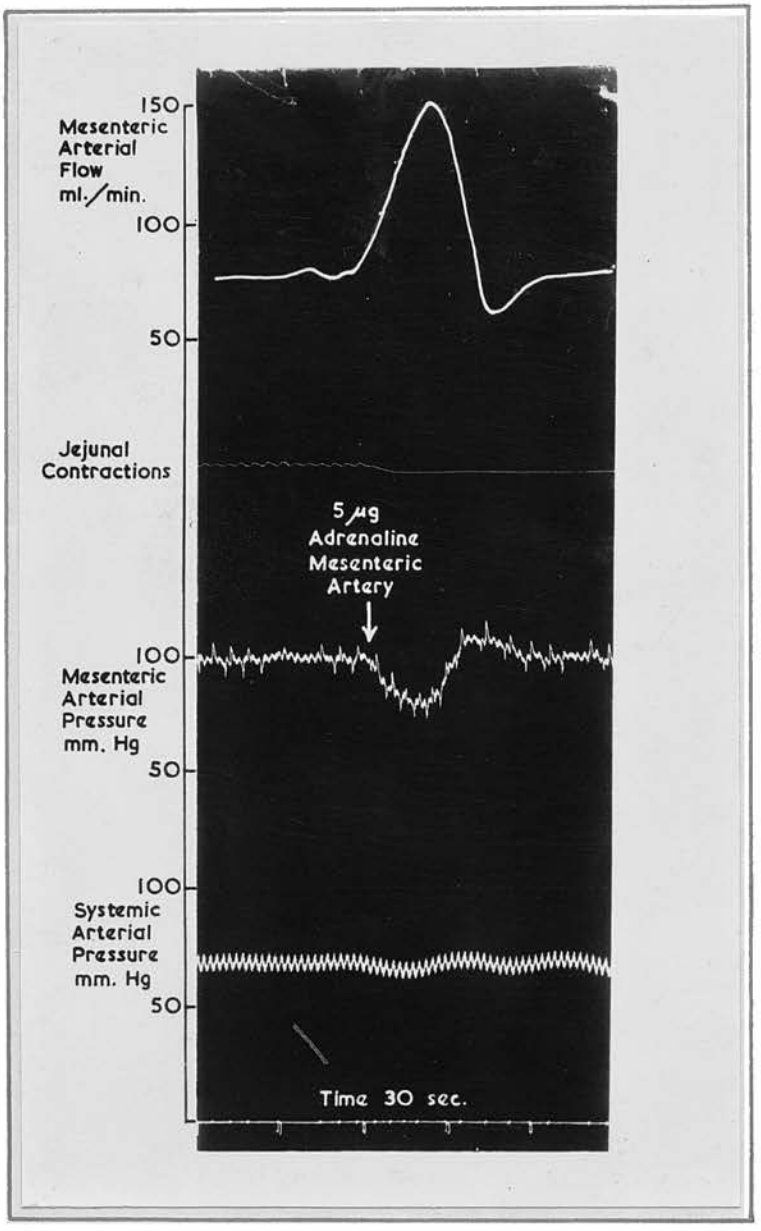

Fig. 69.- Thirty minutes after an intravenous injection of dibenamine (50 mg.) the biphasic effects of an intra-arterial injection of adrenaline are reversed.

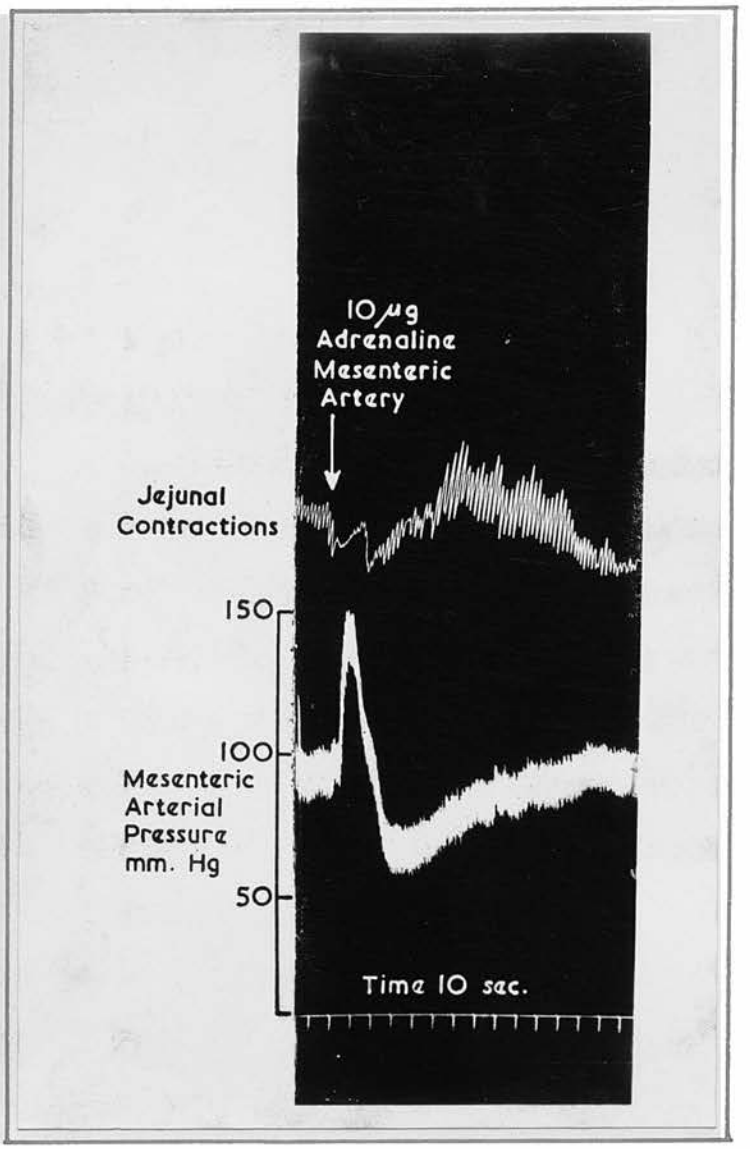

Fig. 70.- Showing the correlation between the biphasic effects of an intra-arterial injection of adrenaline on the mesenteric circulation and intestinal motor activity.

administration of dibenamine (Fig. 69).

The responses to intra-arterial injection of adrenaline or noradrenaline were also investigated following the intravenous injection of atropine (3 mg) or hexamethonium bromide (50 mg) and were found to be identical to the findings prior to the administration of these drugs, i.e. vasoconstriction followed by vasodilatation.

Simultaneous recordings of jejunal motor activity were obtained in each experiment. During the immediate constrictor phase intestinal tonus and contractions were usually inhibited. The apparent decrease in intestinal tonus may, of course, be partly due to an associated decrease in intestinal blood volume. During the secondary dilator phase intestinal movements became greatly augmented but it is important to note that the mesenteric vascular resistance had usually reached its lowest level 10 to 20 seconds before the onset of augmented motor activity (Fig. 70). Occasionally, a well developed secondary vasodilator response was obtained without any significant effect on gut motility. These facts suggest, therefore, that the dilator phase is not due primarily, at least, to an effect of these substances on the intestinal musculature.

The intravenous injection of adrenaline or noradrenaline in doses varying between 5 and 50 µg produced a somewhat complicated effect on the mesenteric circulation due to the dead space produced by the flowmeter and its connections. During the initial increase in systemic blood pressure mesenteric /

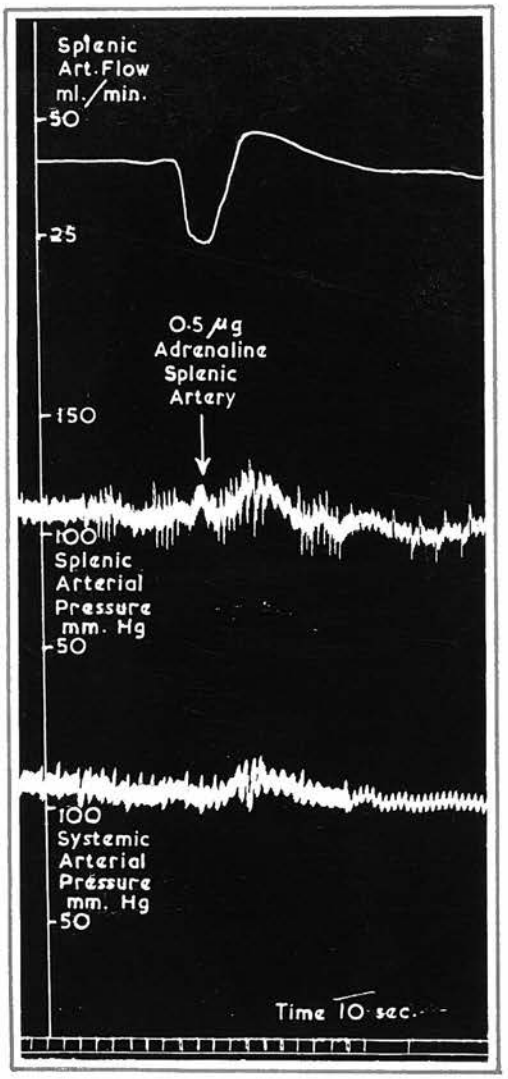

Fig. 71.- The effects of a direct intra-arterial injection of adrenaline on splenic arterial flow.

mesenteric blood flow increased in most instances and remained elevated following the injection of adrenaline. In the case of noradrenaline, however, mesenteric blood flow was frequently curtailed at the peak of the systemic blood pressure response. As the arterial blood pressure decreased a well marked vasodilator response was found in the mesenteric circulation, identical to the effects produced by direct intra-arterial injection.

Continuous intravenous infusions of adrenaline and noradrenaline in doses sufficient to produce a considerable elevation of the systemic blood pressure produced somewhat variable results. In most instances, the infusion of adrenaline was accompanied by a significant increase in mesenteric blood flow, whereas during the infusion of noradrenaline mesenteric blood flow tended to remain around the pre-infusion level.

The effects of adrenaline and noradrenaline on the splenic circulation

The effects of direct injection of adrenaline or noradrenaline into the splenic artery were studied in three separate experiments. In every instance this led to purely constrictor effects (Fig. 71). The splenic arterial system was found to be extremely sensitive to these substances: for instance, a dose of 15 µg injected into the splenic artery resulted in complete cessation of splenic blood flow for approximately 10 minutes. The injection of adrenaline or noradrenaline into the splenic artery in doses insufficient /

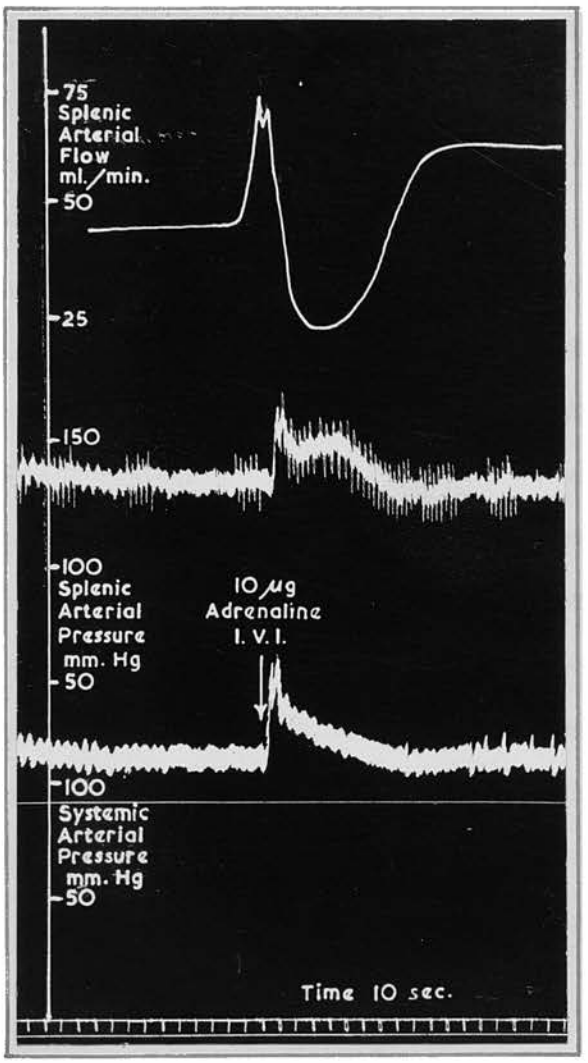

Fig. 72.- The effects of an intravenous injection of adrenaline on the splenic circulation.

insufficient to produce a systemic pressor response when injected either into a systemic vein or a portal vein were in fact found to produce significant elevations of systemic blood pressure (Fig. 71). Granaat (1953) obtained similar results in the dog and cat and provided evidence that the injection of adrenaline or noradrenaline into the splenic artery released further quantities of noradrenaline and an unidentified vasoactive substance into the splenic venous blood.

The intravenous injection of adrenaline or noradrenaline in doses between 10 and 25 µg produced in each instance a significant increase in splenic blood flow during the initial pressor response. A decrease occurred as the drugs reached the splenic circulation and finally, as the blood pressure declined an increase in splenic blood flow due to a fall in splenic vascular resistance, which frequently persisted for up to five minutes. This dilator phase was particularly well marked following the intravenous injection of adrenaline (Fig. 72).

Discussion

Previous work has clearly demonstrated that the intravenous administration of adrenaline results in an increase in hepatic blood flow (Burton-Opitz, 1912; Bearn et al., 1951; Grayson and Johnson, 1953) whereas the action of adrenaline locally on the liver vessels is vasoconstrictor /

vasoconstrictor (Burton-Opitz, 1912; Clark, 1928; Bauer et al., 1932; Charkravarti and Tripod, 1940; Andrews et al., 1955). In contrast, the systemic administration of noradrenaline has frequently been shown to lead to a reduction in liver blood flow in the rat (Grayson and Johnson, 1953) and in man (Bearn et al., 1951). The present experiments have shown that hepatic arterial flow is increased during the continuous infusion of adrenaline, which confirms the early work of Burton-Opitz (1912). The infusion of noradrenaline, on the other hand, produced only a small increase in hepatic arterial flow in the normotensive animal. Distinct differences can also be demonstrated between the effects of adrenaline and noradrenaline administered systemically on portal venous flow which is usually increased by adrenaline and reduced by noradrenaline. The overall effect on hepatic blood flow is therefore an increase in total flow with an increase in the relative contribution of the hepatic artery during the infusion of adrenaline and a reduction in total flow with noradrenaline, but again with a significantly increased contribution from the hepatic artery.

Grayson and Johnson (1953) concluded from their investigation into the effects of adrenaline and noradrenaline on the splanchnic circulation of the rat that two conflicting mechanisms determine the resulting effects on hepatic blood flow: first, a direct local constrictor action on the hepatic vessels and, secondly, a reflex

action due to the effects of increased systemic blood pressure acting on the carotid sinus and the aortic arch baroreceptors. With intravenous adrenaline, the reflex effect predominates with a resultant increase in liver flow. With noradrenaline, a more even balance is struck; the local effect on the liver is dominant and overcomes the reflex vasodilator effect. Following the administration of atropine, the effects of adrenaline were shown to be reversed. It was concluded therefore that the efferent arc of the vasodilator reflex was mediated by cholinergic nerve fibres, mainly concerned in controlling hepatic arterial resistance. The present experiments have failed to detect a vasodilator reflex involving the hepatic circulation in the dog since neither preliminary atropinisation nor ganglion blockade materially affected the response to the intravenous injection of adrenaline or noradrenaline.

The purely constrictor effect of both adrenaline and noradrenaline has been demonstrated in the hepatic arterial and portal venous circulations within the liver. The threshold dose required to produce constriction within the arterial system was found to be between 0.1 and 0.5 µg. Andrews et al. (1955) found the minimum dose in the isolated perfused liver of the dog to be 0.1 to 1 µg. The portal circulation, on the other hand, appears to be more resistant, the threshold dose being between 5 and 10 µg.

Injection of adrenaline or noradrenaline into the portal vein has been shown to produce an increase in hepatic arterial /

arterial resistance. Since on anatomical and physiological grounds connections between the portal veins and pre-sinusoidal terminations of the hepatic artery are unlikely to exist, this effect must be due to constriction of the hepatic veins. Bauer et al. (1932) and Andrews et al. (1955) showed that injection of adrenaline produces a decrease in liver volume consistent with the theory that the hepatic veins are contracted by adrenaline. The secondary increase in hepatic arterial flow after initial constriction following intraportal injection of adrenaline suggests, however, that these substances may have a bi-phasic effect on the hepatic veins.

McMichael (1932) concluded from his observations on the effects of adrenaline on the portal circulation that the resulting complex changes in portal venous pressure could be accounted for by changes in mesenteric and hepatic resistance and the effects of increased hepatic arterial pressure and its effects on the portal circulation. The present experiments have clearly demonstrated a tri-phasic response in the portal circulation following the intravenous injection of adrenaline or noradrenaline. The most interesting part of this response is the delayed decrease in gastro-intestinal vascular resistance, resulting in a striking increase in portal venous flow and pressure. This has been shown to be due to a bi-phasic effect of these substances on the mesenteric circulation. Deal and Green (1956) also showed that adrenaline and noradrenaline had bi-phasic /

bi-phasic effects on the mesenteric bed and furthermore obtained identical results to the present experiments, when preliminary administration of dibenamine resulted in reversal of the bi-phasic response to either substance.

Correlation between alterations in small intestinal motor activity and decrease in vascular resistance during the dilator phase suggested that the decrease in mesenteric vascular resistance was secondary to these motor effects, possibly linked by a metabolic demand mechanism. On further examination, however, it was clear that the decrease in vascular resistance appeared appreciably before the increase in intestinal activity. Furthermore, identical vascular responses were detected in the absence of changes in intestinal activity. Since it had been shown that intestinal anoxia led to a decrease in vascular resistance in the gut, it seemed possible that the dilator phase following adrenaline or noradrenaline was due to transient tissue anoxia during the constrictor phase. That this could not be the explanation is shown by the dibenamine experiments, when adrenaline and noradrenaline resulted in preliminary vasodilatation. The existing evidence therefore suggests that these substances exert a direct bi-phasic effect on the intestinal blood vessels.

THE EFFECTS OF HAEMORRHAGE ON THE SPLANCHNIC CIRCULATION

A great deal of experimental investigation has been undertaken to elucidate the part played by the splanchnic circulation not only in the genesis of irreversible shock but also in the compensatory adjustments produced by haemorrhage and trauma. This aspect of the problem has recently been reviewed by the writer (Torrance, 1958). Investigations on the effect of haemorrhage on splanchnic haemodynamics have been carried out using the dye-clearance method (Werner et al., 1952; Hamrick and Myers, 1953; Heinemann et al., 1953; Reynell et al., 1955; Sapirstein et al., 1955) which enables a fairly reliable estimation of hepatic blood flow to be made (Selkurt, 1954), but cannot be applied to a detailed investigation of the changes in vascular resistance in the various compartments of the splanchnic circulation. Another limitation of the indirect technique includes the fact that continuous flow-recording is not possible.

More direct methods of studying changes in splanchnic haemodynamics in shock have yielded considerable information, but it must be admitted that our present knowledge is still incomplete. Blalock and Levy (1937) determined the effect of haemorrhage on hepatic venous outflow by means of an ingenious collecting device, but continuous flow recordings were not possible and the manipulations involved tend to invalidate their results. Wiggers et al. (1946), employing delicate /

delicate optical manometers to record changes in portal venous, inferior venal caval and systemic arterial pressures, reached certain conclusions regarding splanchnic vascular resistance changes in shock. Selkurt et al. (1947) measured portal vein flow following haemorrhage by intermittent occlusion of the portal vein after splenectomy and measured the rate of outflow from the splenic vein. This rather cumbersome technique did not lend itself to repeated flow estimations. More recently Johnston (1954) and Grayson and Mendel (1957) have applied the heated thermocouple flow recorder to study the effects of haemorrhage and hypotension on liver blood flow in the rat. Selkurt and Brecher (1956) investigated splanchnic haemodynamics in haemorrhagic shock by measuring blood flow through the hepatic artery and portal vein with bristle flowmeters, a method which afforded continuous recording of blood flow.

Since a great deal still remains to be learned about the mechanisms which regulate splanchnic blood flow under normal conditions it is not surprising that the changes induced by haemorrhagic shock are even more obscure. In order to investigate some of these problems the writer undertook a study of the effects of haemorrhage on the splanchnic circulation in 42 acute experiments on dogs.

Methods

Three methods of producing controlled haemorrhage were employed /

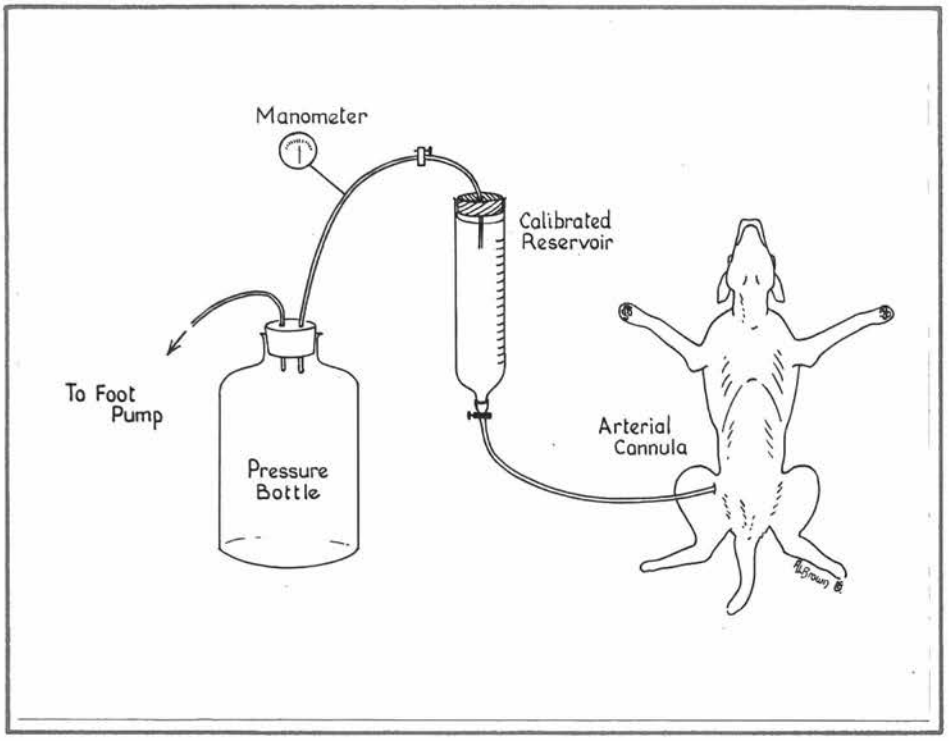

Fig. 73.- A diagram of the blood pressure compensating apparatus.

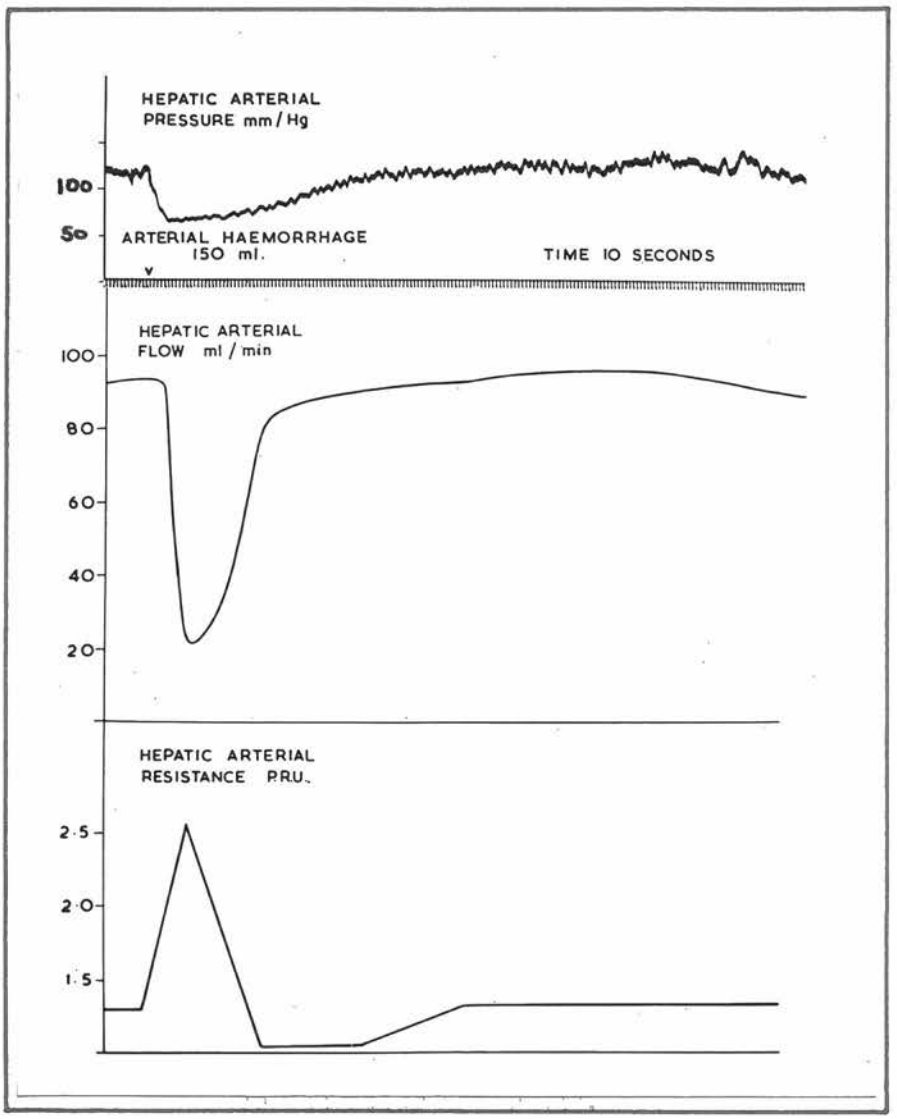

Fig. 74.- The effects of haemorrhage on the hepatic arterial circulation.

employed: (1) bleeding into a compensating reservoir maintained at a pre-determined pressure level (Fig. 73); (2) bleeding to a selected level of arterial pressure and allowing the animal to compensate for this degree of blood loss; and (3) bleeding in 50 ml. samples or multiples of 50 ml., depending on the body weight of the animal.

Blood flows and pressures in the various compartments of the splanchnic circulation were measured by the techniques already described.

The effects of haemorrhage on the hepatic arterial circulation

Rapid arterial haemorrhage sufficient to reduce the systemic blood pressure to 50 to 60 mm.Hg led in most instances to an immediate and significant increase in hepatic arterial resistance (Fig. 74). During the ensuing two to three minutes the resistance fell slightly below control levels, slowly returning to around the pre-haemorrhage level over the next 10 to 20 minutes, provided the animal's blood pressure recovered. On the other hand, if the animal failed to compensate for the blood loss, and passed into a state of established haemorrhagic shock, hepatic arterial resistance tended to remain slightly below control levels.

It seems likely therefore that a compensatory mechanism associated with haemorrhage leads to a decrease in hepatic artery resistance so that hepatic arterial flow is maintained at a somewhat higher level than might be expected. The possible /

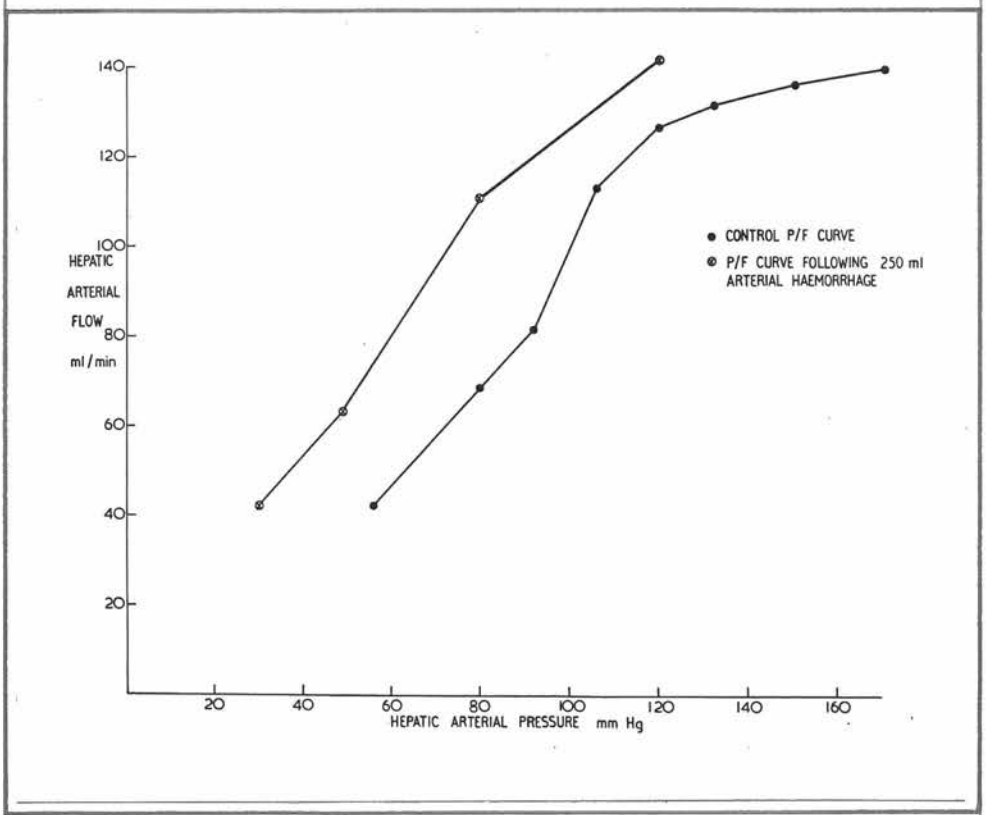

Fig. 75.- Comparison of the pressure flow curves in the hepatic arterial circulation before and after haemorrhage.

possible reasons for the apparent vasodilatation following haemorrhage were investigated in some detail.

Since it had already been shown that a passive decrease in hepatic artery pressure below 80 mm.Hg led to an increase in arterial resistance within the liver (see p. 39), it was interesting to compare the P/F curves obtained immediately before and five minutes after a haemorrhage sufficient to reduce the systemic blood pressure to around 40 mm.Hg (Fig. 75). Comparison showed that there was a suggestive shift to the left which indicated that vasodilatation had occurred following haemorrhage.

Since local tissue hypoxia or carbon dioxide retention might be the factors responsible, the effects of periods of hepatic artery occlusion and the inhalation of 5 per cent. carbon dioxide and 95 per cent. oxygen on the hepatic arterial circulation were studied. Occlusion of the hepatic artery for periods up to 10 minutes had no effect on vascular resistance on resumption of blood flow. Similarly, the inhalation of 5 per cent. carbon dioxide did not affect the hepatic arterial circulation.

<u>The effects of haemorrhage on the mesenteric arterial and portal venous components of the splanchnic circulation</u>

The effects of haemorrhage on the mesenteric circulation were fundamentally similar to those found in the hepatic arterial system. Immediate vasoconstriction during the course of the haemorrhage was followed by significant vasodilatation, particularly if the systemic blood pressure fell /

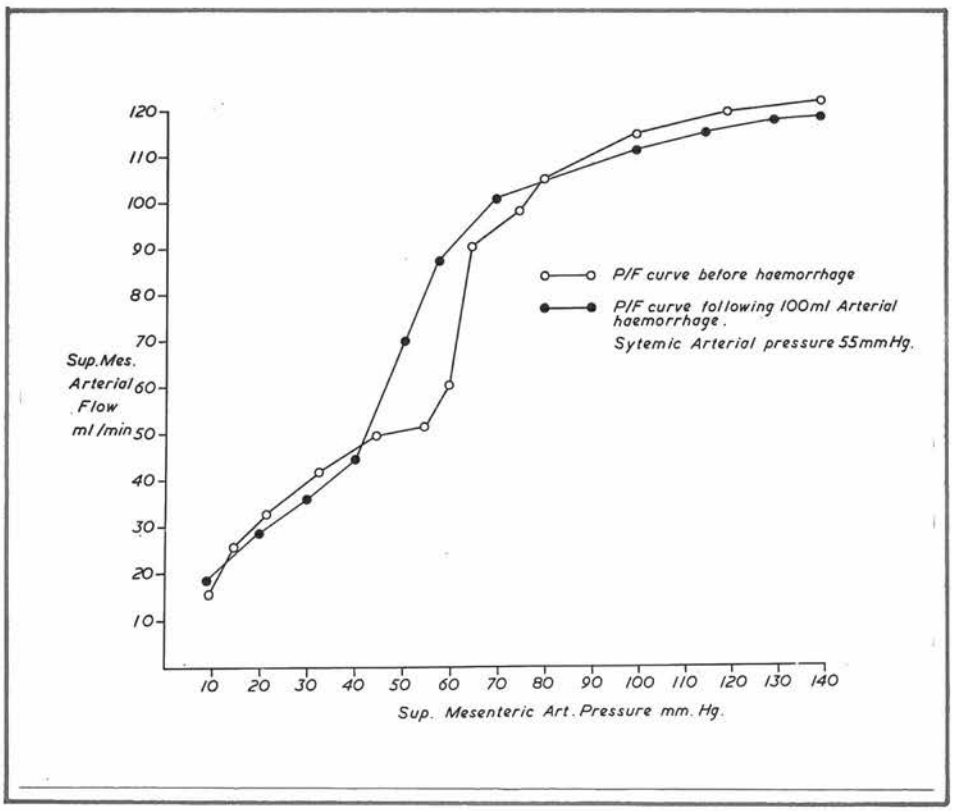

Fig. 76.- Comparison of the pressure flow curves in the mesenteric circulation before and after haemorrhage.

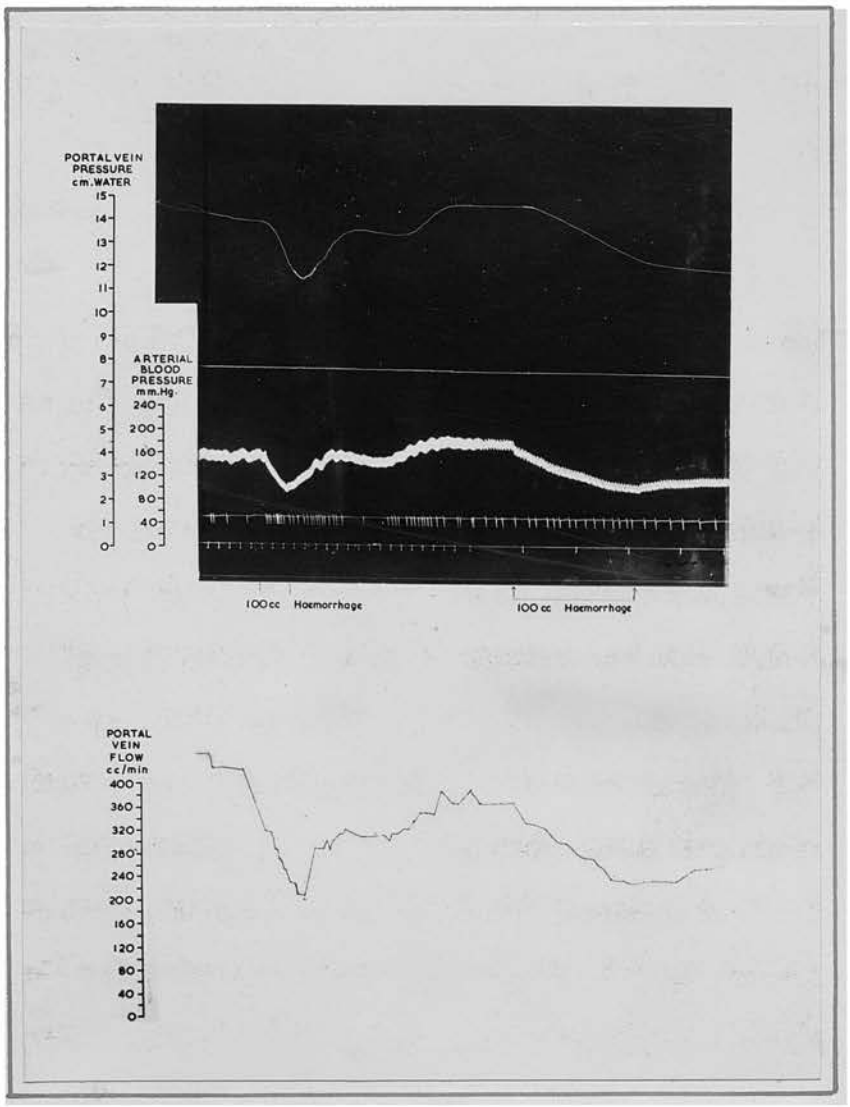

Fig. 77.- The effects of haemorrhage on portal venous flow and pressure.

fell below 50 mm.Hg. Comparison of the pressure flow curves obtained immediately before and 10 minutes after a haemorrhage of sufficient volume to reduce systemic pressure to 55 mm.Hg confirmed that there was no evidence of vaso-constriction, and indeed if anything a slight shift to the left indicating vasodilatation (Fig. 76). Since hypoxia produced by artificial reduction in superior mesenteric artery flow has been shown to lead to a decrease in mesenteric resistance, it seems likely that the vasodilatation associated with haemorrhage is also a consequence of intestinal hypoxia. Stagnant anoxia may exert its effect by local accumulation of carbon dioxide and other metabolites; the effects of inhalation of 5 per cent. carbon dioxide on mesenteric resistance following haemorrhage were examined. Significant dilator effects were not observed under these circumstances, possibly because the tissues were already maximally dilated.

Measurement of portal venous flow and pressure before and after haemorrhage (Fig. 77) permitted calculation of changes in both mesenteric and intra-hepatic portal resistance. Stepwise reductions in systemic arterial pressure were produced by the use of the compensating reservoir, and portal venous pressure and flow were measured at each level. The patterns of response of the gastro-intestinal circulation to haemorrhage were similar in most instances to those found in the mesenteric circulation, i.e. reduction of arterial pressure from normal levels to around

80 /

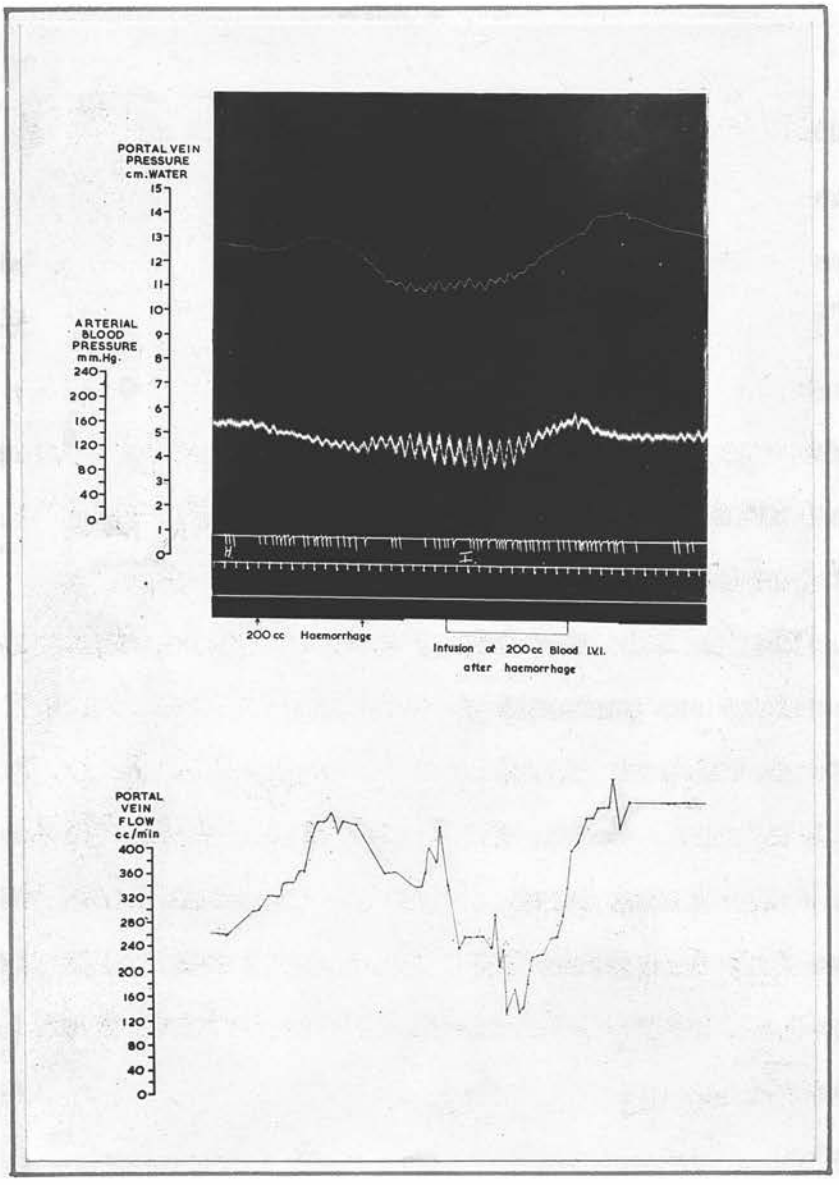

Fig. 78.- In this experiment haemorrhage was accompanied by an increase in portal venous flow and a slight increase in portal venous pressure. Rapid re-infusion of blood led to a considerable increase in gastro-intestinal vascular resistance.

80 mm.Hg did not produce a significant effect on portal venous blood flow; indeed in some instances the portal venous flow did not become reduced until the arterial pressure fell below 60 mm.Hg. In one experiment portal venous flow became significantly increased after a 200 ml. haemorrhage (Fig. 78). The pressure flow curves of the gastro-intestinal circulation obtained by this technique confirmed the presence of a striking degree of auto-regulation in this circulatory system. In two experiments splenectomy was performed prior to haemorrhage in order to determine the part played by the splenic circulation in this response. Curves similar to those obtained in the intact animal were found, and it was therefore concluded that an increase in splenic blood flow was not responsible for these auto-regulatory changes in the gastro-intestinal circulation.

The changes in intra-hepatic portal venous resistance following haemorrhage were found to be less predictable than the changes in the gastro-intestinal circulation. In most instances portal venous pressure fell pari passu with the fall in portal venous flow, the calculated resistance to flow remaining around the pre-haemorrhage level. Occasionally, however, a significant increase in intra-hepatic resistance was produced. Comparison of the flow and pressure measurements with previously determined pressure flow curves showed that haemorrhage produced either no change or only a slight increase in intra-hepatic portal venous /

venous resistance.

Summary of the immediate effects of haemorrhage on the splanchnic circulation

Certain conclusions can be drawn from these experiments regarding the immediate effects of a large arterial haemorrhage sufficient to reduce the blood pressure to 40-50 mm.Hg.

(1) In the anaesthetised dog neurogenic vasoconstrictor reflexes mediated through the carotid and the aortic baroreceptor mechanisms do not appear to play an important part in determining the responses of the splanchnic circulation to haemorrhage.

(2) The splanchnic circulation possesses a high degree of intrinsic auto-regulation, which protects the viscera from stagnant anoxia. However, below a critical arterial blood pressure this compensatory mechanism breaks down and blood flow becomes considerably reduced.

(3) Compensatory vasodilatation has been demonstrated in the hepatic arterial and mesenteric circulations during haemorrhagic hypotension; consequently blood flow is maintained at a higher level than predicted from a pressure flow curve obtained from these vascular beds before haemorrhage. Investigation of the cause of this vaso-dilatation has implicated intestinal anoxia, and possibly local carbon dioxide retention.

The /

The effects of prolonged haemorrhagic hypotension

Haemorrhage of sufficient volume to reduce the blood pressure to around 40 mm.Hg was produced and the blood pressure maintained constant at this level by the compensating reservoir. Progressive failure of the circulation could then be followed by determining the volume of blood automatically re-infused as the animal progressed into a state of shock. In other experiments the blood pressure fell spontaneously one to two hours after the experiment was started, because of a steady ooze from the abdominal wound, the consequences of abdominal manipulation, and probably a degree of bacterial infection. The haemodynamic observations in these two groups of experiments showed no significant differences. Calculations of vascular resistance were made in the various components of the splanchnic circulation throughout the period of observation which extended in some instances up to six hours. Analysis of the results of this study can be briefly summarised as follows:

The vasodilatation produced by the initial haemorrhage in the hepatic artery and mesenteric circulations persisted, indeed the vascular resistance of the hepatic arterial system sometimes became further reduced as the animal's condition deteriorated. The resistance of the mesenteric circulation, however, tended to remain constant throughout this period. Although portal venous flow remained constant provided systemic blood pressure was maintained, portal venous /

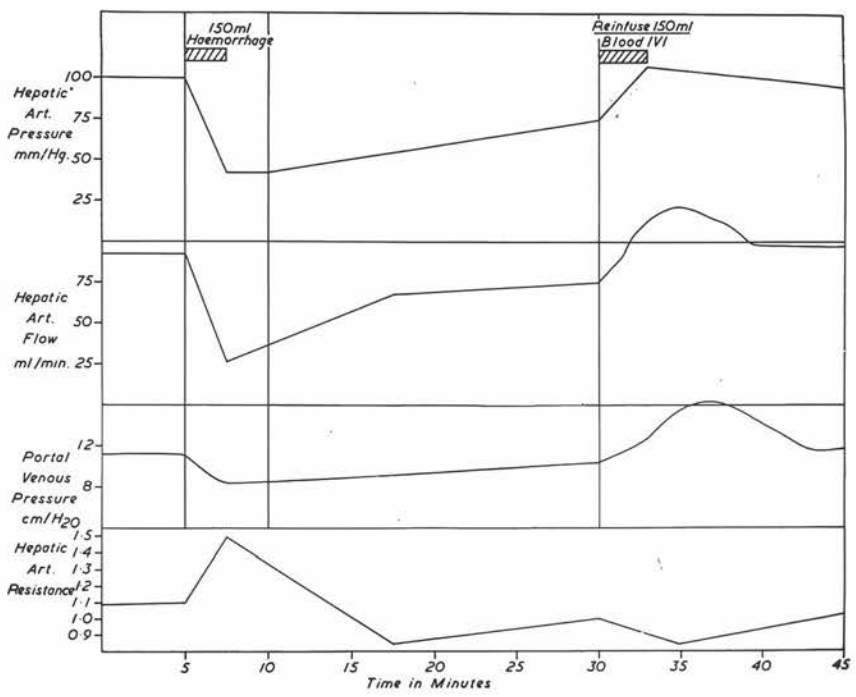

Fig. 79.- A diagram summarizing the effects of haemorrhage on the splanchnic circulation observed in these experiments.

venous pressure showed a tendency to rise - evidence of a slight increase in intra-hepatic portal resistance. Since inferior vena-caval pressure did not increase during this period, the increased resistance to portal flow must reside within the liver.

It can therefore be concluded that following an initial haemorrhage rapid compensatory changes take place in the splanchnic circulation. These changes persist throughout the period of progressive shock and indeed the hepatic arterial resistance may decrease whilst the portal venous resistance shows a tendency to increase (Fig. 79).

The effects of re-infusion of blood

Restoration of the blood volume by the intravenous re-infusion of blood produced certain interesting alterations in splanchnic blood flow. The infusion of 100-200 ml. of blood at 37°C. over a period of three to five minutes produced a significant rise in systemic blood pressure, which was accompanied by an increase in hepatic arterial and portal venous blood flow, with a slight fall in calculated hepatic arterial and mesenteric arterial resistances. Pari passu with the increase in portal venous flow, portal venous pressure increased and frequently exceeded the pre-haemorrhage level, although portal venous flow had not shown a parallel increase. Towards the end of the infusion, as the systemic blood pressure became stabilised at its new level, portal venous flow became greatly augmented as a result /

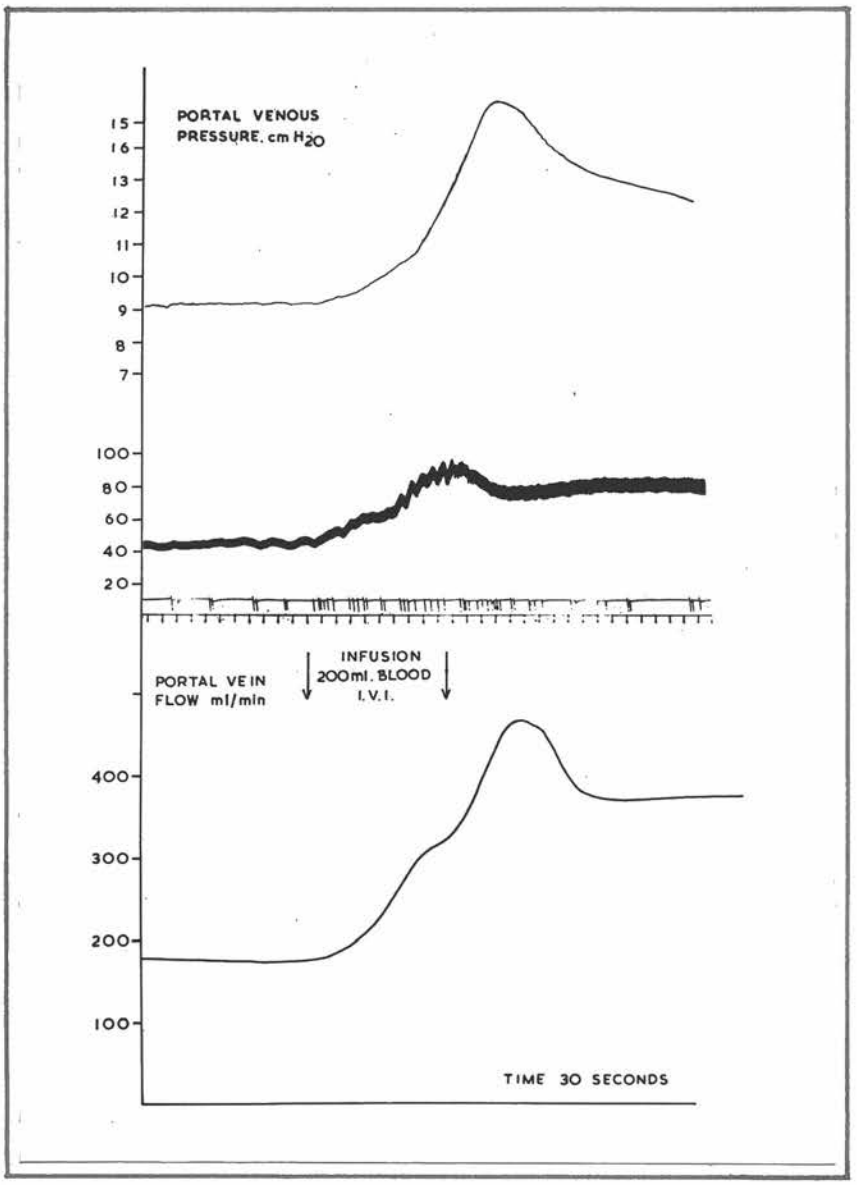

Fig. 80.- The effects of re-infusion of blood on portal venous dynamics. Note the delayed fall in gastro-intestinal resistance associated with an increase in portal venous flow and pressure.

result of a further fall in gastro-intestinal resistance (Fig. 80). Portal venous pressure also increased, and in five out of fifteen observations rose to levels considerably higher than before haemorrhage, indicating an increase in intra-hepatic portal resistance. The explanation of this increase in intra-hepatic resistance in the face of a decrease in gastro-intestinal resistance could not be determined by the present techniques.

The sequence of events following re-infusion of blood depended entirely on the state of the animal. Provided the systemic blood pressure was maintained, portal venous flow slowly decreased during the next few minutes and became stabilised at a new level, significantly higher than before the infusion. In the five experiments where portal pressure increased above control values this tended to be maintained throughout the remainder of the experiment. In other experiments portal venous pressure fell parallel with the decrease in portal venous flow and became stabilised within five to ten minutes after completion of the infusion. If re-infusion of shed blood was carried out when the animal was in the resistant or irreversible stage of haemorrhagic shock then little or no effect on systemic blood pressure was produced, and the changes in splanchnic dynamics were equally unimpressive.

Discussion /

Discussion

Whilst direct determination of splanchnic blood flow offers many advantages over the indirect dye clearance method the results obtained by the two procedures are complementary. The consequences of operative trauma and possible damage to the peri-arterial nerve plexuses do not complicate the interpretation of the results obtained by the B.S.P. clearance method, but the number of flow determinations which can be performed is limited, rapid alterations in blood flow cannot be appreciated, the actual determination of flow itself is less accurate, and the effects of re-infusion of blood cannot be studied owing to alterations in the arterial concentrations of the dye. It is therefore of interest to compare the results obtained by these two different methods of study. Reynell *et al.* (1955), using the B.S.P. dye clearance, studied the effects of acute and prolonged haemorrhagic hypotension on splanchnic haemodynamics in dogs, and found that total peripheral resistance increased following haemorrhage but that splanchnic resistance either decreased or showed no significant change. They concluded that the splanchnic circulation does not participate in the generalised arterial vasoconstriction associated with haemorrhage. Similar results have been reported by Werner and McCannon (1952), Hamrick and Myers (1953), Heinemann *et al.* (1953) and Sapirstein and Buckley (1955).

Selkurt and Brecher (1956) employed bristle flowmeters to /

to measure blood flow and resistance changes in the splanchnic circulation during haemorrhagic shock, and found that splanchnic vascular resistance remained about the control level during the hypotensive period. Following the re-infusion of shed blood, however, a phase of marked reduction in splanchnic resistance was produced which was particularly noticeable in the mesenteric compartment. The present series of experiments have also failed to reveal evidence of vasoconstriction in the splanchnic circulation following haemorrhage: indeed hepatic arterial and mesenteric blood flows appear to be maintained at a higher level than can be accounted for by passive changes in arterial blood pressure.

Splanchnic oxygen consumption during haemorrhagic shock

The observation has been made that following haemorrhage, an increase in the arterio-venous oxygen gradient across the splanchnic bed continues to provide the liver with a reasonably constant supply of oxygen, despite reduction in blood flow (Werner et al., 1952; Hamrick and Myers, 1955; Selkurt and Brecher, 1956). Total splanchnic oxygen consumption remains within the normal range until shock is well advanced when oxygen consumption becomes reduced. Presumably when the oxygen saturation of the portal venous blood reaches a critical level, the liver will receive blood in which the degree of unsaturation is such that no further extraction can occur.

Under /

Under normal conditions, the hepatic artery supplies about 70 per cent. of the oxygen available to the liver. Selkurt (1956) has provided evidence which suggests that the alterations in splanchnic haemodynamics in shock lead to changes in the relative contributions of the hepatic artery and portal vein to hepatic blood flow so that the liver becomes even more dependent on its arterial supply for adequate oxygenation. The results of the present experiments tend to confirm these findings.

Such mechanisms appear to play a part in protecting the viscera against the deleterious effects of anoxia.

Compensatory changes in splanchnic blood volume in shock

So far only the compensatory changes in blood flow and oxygen utilisation which occur in the splanchnic bed following haemorrhage have been considered. The volume of blood in the splanchnic bed of the anaesthetised dog was estimated by Delorme et al. (1952) to be between 20 and 50 per cent. and by Horvath et al. (1957) as 21 per cent. of the total blood volume. A reduction in splanchnic blood volume following haemorrhage could therefore play an important part in maintaining cardiac output in oligaemic states.

The evidence concerning alterations in splanchnic blood volume during haemorrhage has been obtained by direct plethysmography of the liver and spleen, radiographic visualisation of the portal venous system, measurement of the soft tissue shadow of the liver and spleen on X-ray films and more recently by radioactive dilution techniques.

Griffiths /

Griffiths and Emery (1950) showed by direct liver plethysmography that the liver volume became reduced following haemorrhage and that this effect was diminished by splanchnicectomy or bilateral adrenalectomy. The classical experiments of Barcroft et al. (1925), clearly demonstrated that the spleen contracted after haemorrhage. The problem has recently been investigated in man (Glasser et al., 1954), by measuring the changes in the size of the soft tissue shadows cast by the liver and spleen on X-ray films before and after haemorrhage. A significant decrease in the size of both organs was demonstrated suggesting that the volume of blood contained within these organs had been reduced. Friedman et al. (1951) carried out a series of experiments using a radiographic technique for the study of the portal and hepatic venous systems following haemorrhage in the dog. Haemorrhagic hypotension was shown to produce a decrease in the diameter of the portal and hepatic veins of between 10 and 55 per cent. of the control diameter. Haemorrhagic shock, four to six weeks after bilateral splanchnicectomy, produced a slightly lesser degree of venoconstriction than in the intact dog, suggesting that constriction of these vessels was mediated in part by the sympathetic nervous system. Direct measurement of the diameter of the portal vein of the dog in haemorrhagic shock (Engstrand, 1950) also showed considerable constriction of this vessel. Recently Reynell et al. (1955) have developed a radioactive dilution technique for the calculation of splanchnic blood volume, and /

and together with determinations of hepatic blood flow by the dye-clearance technique have demonstrated a striking reduction in splanchnic blood volume in haemorrhagic shock, despite the fact that the splanchnic vascular resistance was usually below the control level.

From this evidence it can be concluded that following haemorrhage the circulating blood volume becomes redistributed in an attempt to augment cardiac output. Since the largest proportion of the splanchnic blood volume resides within the portal venous system and its ramifications such as the spleen, widespread venoconstriction diverts a large volume of blood from the venous to the arterial and capillary circulation. Since a considerable reduction in calibre of the low pressure portal venous system can occur without leading to a significant increase in mesenteric resistance, this mechanism appears to allow two important compensatory changes in the splanchnic circulation to occur: maintenance of adequate blood flow to the liver, and redistribution of circulating blood volume from the venous to the arterial circulation. Two apparently separate mechanisms are therefore at work, mesenteric resistance and blood flow being determined by the response of the splanchnic arterioles, whilst the splanchnic blood volume is regulated either by passive or active changes in venous capacity. The evidence suggests that the mechanisms are to a certain extent under independent control.

The /

The importance of portal hypertension in shock

In 1943, Wiggers and his colleagues put forward the hypothesis that stagnation of blood in the splanchnic bed was an important factor in producing or perpetuating irreversible shock. While measuring portal venous pressure, inferior vena caval pressure and systemic arterial pressure in dogs subjected to standardised haemorrhagic shock they found that portal venous pressure fell immediately after the haemorrhage but soon rose towards control values. As the dog passed into the irreversible state portal venous pressure tended to rise above control values. Following re-infusion of shed blood the portal venous pressure became greatly elevated, occasionally to twice the normal level. They concluded that the intra-hepatic resistance to portal venous flow had become increased and by reason of this back pressure led to progressive stagnation of blood in the venous side of the splanchnic circulation. The sequestration of this volume of blood from the circulation was held to be largely responsible for the development of irreversible shock. Selkurt (1946) and Zanetti (1952) repeated these experiments and found that the intra-hepatic portal venous resistance became increased during the irreversible stage of shock. The present experiments disclosed a similar trend of events. The cause of the increase in intra-hepatic portal venous resistance in irreversible shock has still not been completely elucidated but various underlying factors have been suggested:-

(1) /

(1) Spasm of the hepatic veins.- Maegraith of Liverpool and his colleagues (Maegraith and Findlay, 1944; Maegraith et al., 1947; Maegraith, 1948) have suggested that in shock, active constriction of the hepatic veins may take place probably through neurogenic reflex action. Hepatic venous constriction leads to sinusoidal congestion and a degree of stagnant anoxia which, if severe and prolonged, results in hepatic centrilobular necrosis. The evidence in favour of the presence of nervous control of the hepatic venous system has been presented by Andrews et al. (1954). not given.

Maegraith et al. (1949) have clearly demonstrated hepatic venous constriction during anaphylactic shock in the experimental animal, but the evidence regarding the participation of this mechanism in shock due to other causes is by no means complete. Unfortunately, the majority of these experimental investigations have been carried out in the dog, in whom well developed hepatic venous smooth muscle spirals have been demonstrated (Arey, 1941).

(2) A direct result of liver anoxia.- It seems possible that the increase in intra-hepatic venous resistance in shock is caused by the direct effects of cellular anoxia, leading to swelling of the parenchymal cells, cellular sinusoidal narrowing and stagnation of blood flow. In the perfused liver of the dog and monkey for instance, Andrews et al. (1954) noticed that following a period of circulatory arrest the liver became congested and cyanotic and the resistance to flow increased, an effect which was usually /

usually irreversible. Similar changes in the human liver have been noted during hypotensive anaesthesia by Bromage (1952).

(3) Intra-hepatic portal venous constriction.- The experiments of Friedman et al. (1951) have clearly demonstrated that the diameter and capacity of the intra-hepatic portal venous system become reduced after haemorrhage. It is unlikely, however, that this mechanism alone could account for the striking increase late in the course of haemorrhagic shock.

(4) Intra-hepatic embolism.- Crowell and Reid (1955) demonstrated minute emboli in the liver and lungs of experimental animals following re-infusion of shed blood. These authors believe that small thrombi form in the stagnant circulation during the hypotensive period and become washed into the liver and lungs following re-infusion of blood, and this may account for the increase in portal venous resistance following re-infusion of blood.

Whilst an increase in the resistance to portal blood flow through the liver may be present in the terminal stage of shock, it is doubtful whether this factor plays a part in determining the final outcome. The hypothesis of splanchnic congestion as a cause of irreversible shock was put to experimental test by Frank et al. (1951) who studied the course of haemorrhagic shock in dogs in whom an Eck fistula had been performed. If splanchnic congestion had been an important factor then these dogs should have been unusually tolerant /

tolerant to haemorrhagic shock. No significant difference was detected between the control and the treated group, suggesting that splanchnic congestion was not a factor of importance in shock.

THE EFFECTS OF THE INTRAVENOUS INFUSION OF NORADRENALINE ON SPLANCHNIC BLOOD FLOW IN HAEMORRHAGIC SHOCK

Despite the widespread use of intravenous noradrenaline therapy in the treatment of hypotensive states associated with coronary thrombosis, trauma, overwhelming infection, refractory haemorrhagic shock and post-adrenalectomy hypotension, the fundamental haemodynamic consequences of such therapy remain ill-understood.

Since experimental evidence has closely implicated the splanchnic circulation in the genesis of irreversible shock, it seemed worthwhile to investigate the effects of noradrenaline therapy on the various compartments of the splanchnic circulation in haemorrhagic shock.

Methods

Thirty-three healthy dogs, varying in body weight between 9 and 25 kg were used in these experiments. The methods of anaesthesia and of determination of blood flow and pressures in the various compartments of the splanchnic circulation were identical to those previously described.

The systemic blood pressure of the animal was reduced to the desired level by graded haemorrhage as described in the preceding section. In these experiments the blood pressure was reduced to between 30 and 75 mm.Hg and maintained at this level for periods varying from twenty minutes to one and a half hours. Since it was desired to investigate the effects /

effects of noradrenaline infusions in circumstances comparable with clinical practice, i.e. in the presence of an apparently adequate circulating blood volume, at the conclusion of the hypovolaemic phase of the experiment the blood in the reservoir was slowly re-infused by a catheter inserted into a femoral vein. In most instances, the blood pressure increased following the re-infusion of blood but the equilibrium pressure remained considerably below normal (mean 82 mm.Hg). If the blood pressure returned to normal levels further haemorrhage was induced until on re-infusion the blood pressure became stabilised between 30 and 80 mm. Hg, a state which can be described as normovolaemic haemorrhagic shock (Wiggers, 1950). When the blood pressure had become stabilised, a series of control observations on blood flow and pressure were made and by incorporating the Sigma-motor pump into the circuit, control arterial pressure flow curves were determined.

An intravenous infusion of noradrenaline (Levophed Bayer) was then administered through a polythene cannula inserted into a femoral vein, the rate of infusion being adjusted to maintain the mean systemic blood pressure between 100 and 140 mm.Hg. The dose required was found to vary considerably, even during the course of the same experiment. Furthermore, despite the constant rate of infusion, after a varying interval the blood pressure tended to return towards the pre-infusion level. For the purposes of these experiments the observations on the altered

dynamics /

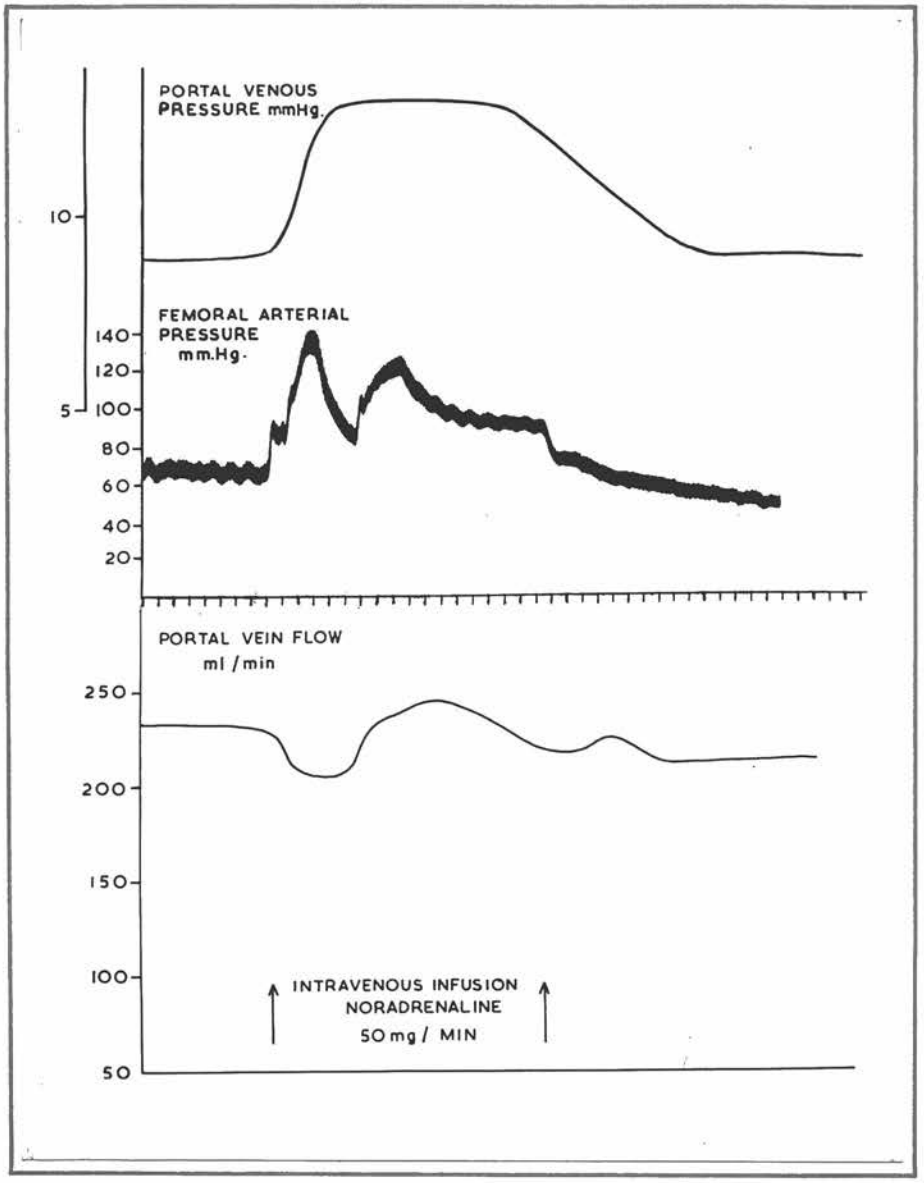

Fig. 81.- The effects of an intravenous infusion of noradrenaline on portal venous blood flow and pressure.

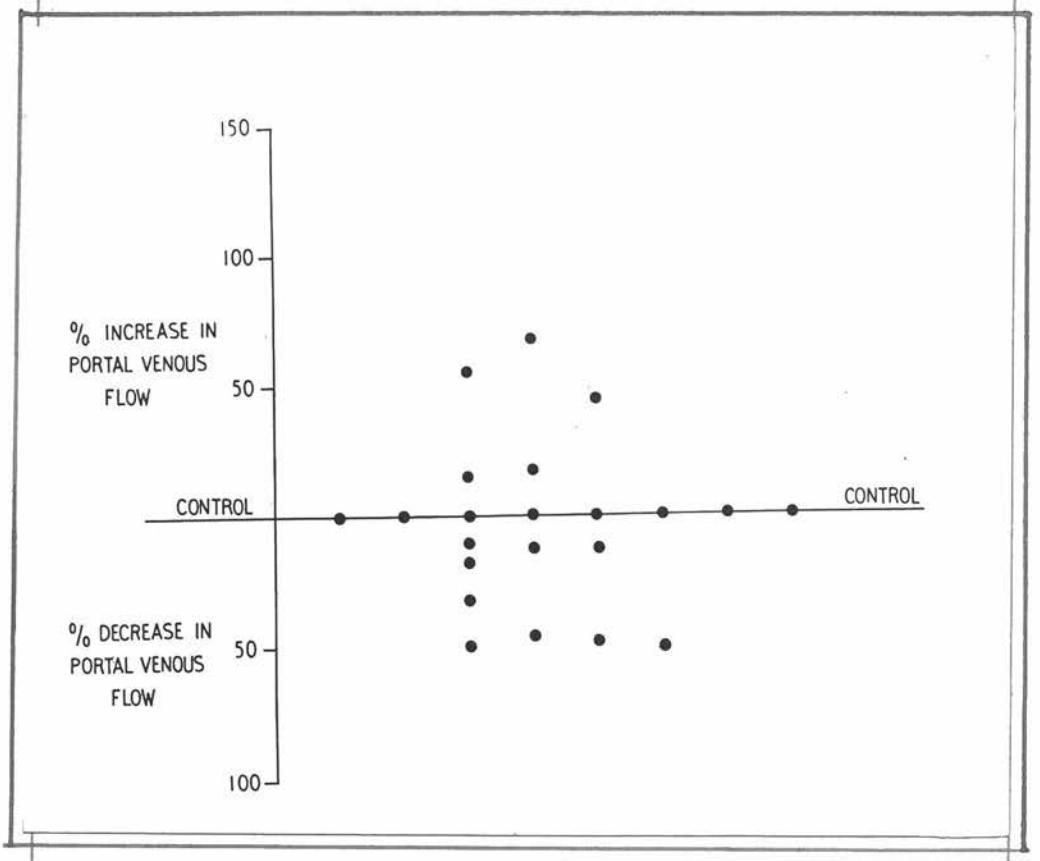

Fig. 82.- The effects of 22 infusions of noradrenaline on portal venous blood flow in haemorrhagic shock.

dynamics of the splanchnic circulation were made within a few minutes of starting the infusion before the spontaneous decrease in blood pressure appeared. The infusions were continued for periods varying from ten to forty-five minutes, and the rate of administration was varied to maintain a more or less normotensive state. During this period further blood flow determinations were made and repeated after the infusion had been discontinued.

Results

The effects of intravenous noradrenaline infusions on portal venous dynamics

The effects of 22 infusions in nine separate animals were investigated. Any alteration in portal venous flow less than ± 10 per cent. of the control pre-infusion rate was disregarded. The results can be briefly presented as follows:-

On eight occasions, the infusion of noradrenaline had no significant effect on portal venous flow ($p = 0.36$) (Fig. 81). Portal venous blood flow was significantly reduced on nine occasions ($p = 0.41$) with a maximum decrease of 50 per cent. of the pre-infusion level, and significantly increased following five infusions ($p = 0.23$) with a maximum increase of 64 per cent. of the control value. The mean effect on the rate of portal venous flow for the entire series of experiments was a reduction of 3 per cent. (Fig. 82). In two experiments variable effects of portal venous flow /

flow were noted. For instance, in one experiment an infusion of noradrenaline at 36 µg/min resulted in an increase in blood pressure from 70 to 150 mm.Hg but had no effect on portal venous flow. A second infusion at the rate of 72 µg/min increased the blood pressure from 70 to 120 mm.Hg and resulted in a decrease of portal venous flow from 300 to 200 ml./min but a further infusion at the rate of 72 µg/min produced an increase in blood pressure from 60 to 125 mm.Hg, but led to a significant increase in portal venous flow from 140 to 220 ml./min. These results probably indicate that the inherent sensitivity of the gastro-intestinal vascular system to circulating noradrenaline varies in a rather unpredictable fashion.

Calculations of the changes in vascular resistance indicated a significant increase in gastro-intestinal resistance during the course of each infusion in this series. There is no doubt, therefore, that the increased level of circulating noradrenaline exerts a potent vasoconstrictor action on the tissues drained by the portal vein. A similar constrictor effect on the intra-hepatic portal circulation was also evident since portal venous pressure was found to be consistently increased in the majority of experiments, even when portal venous flow was diminished.

The effects of noradrenaline infusion on superior mesenteric and splenic arterial dynamics

Since measurement of portal venous flow had shown that noradrenaline infusions had no significant effect, further

experiments /

experiments on the mesenteric splenic arterial systems were undertaken in order to elucidate their behaviour in more detail and, in particular, to determine their contribution to portal venous flow under these circumstances.

The behaviour of the mesenteric circulation was investigated in five separate experiments. No significant effect was detected in two experiments whereas in the remaining three experiments a slight but significant decrease in blood flow was detected. The mean effect in this group of experiments was a reduction of 12 per cent. below the control blood flow level. Comparison of control P/F curves with the pressure and flow values during the intravenous infusion of noradrenaline disclosed without exception a highly significant shift towards the right, indicating vasoconstriction produced by the increased level of circulating noradrenaline.

Splenic arterial blood flow was determined in two experiments. In both instances, splenic blood flow was found to be significantly increased. In one of these experiments blood flow through the spleen was increased during four separate infusions, and this was accompanied by a decrease in the calculated splenic vascular resistance. Comparison of the pressure and flow values during the infusion with a control pressure flow curve indicated that the decrease in splenic vascular resistance could not be accounted for entirely by the passive haemodynamic effects of increased perfusion pressure.

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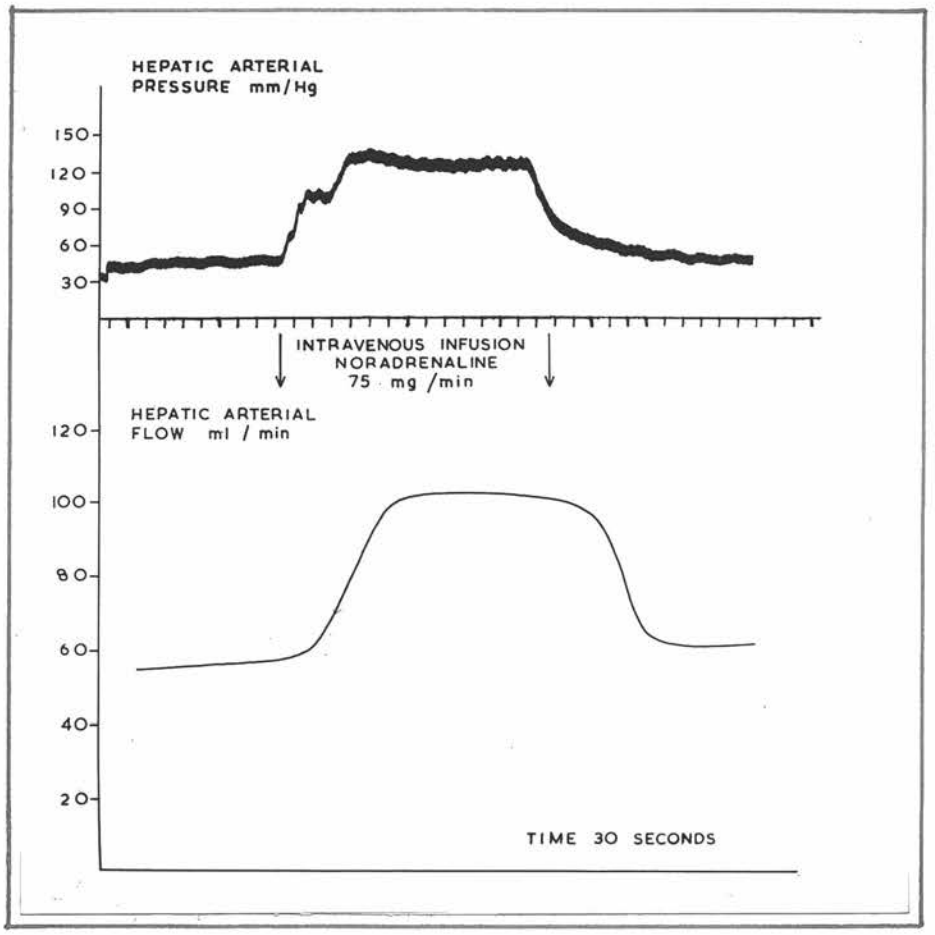

Fig. 83.- The effects of an infusion of noradrenaline on hepatic arterial flow.

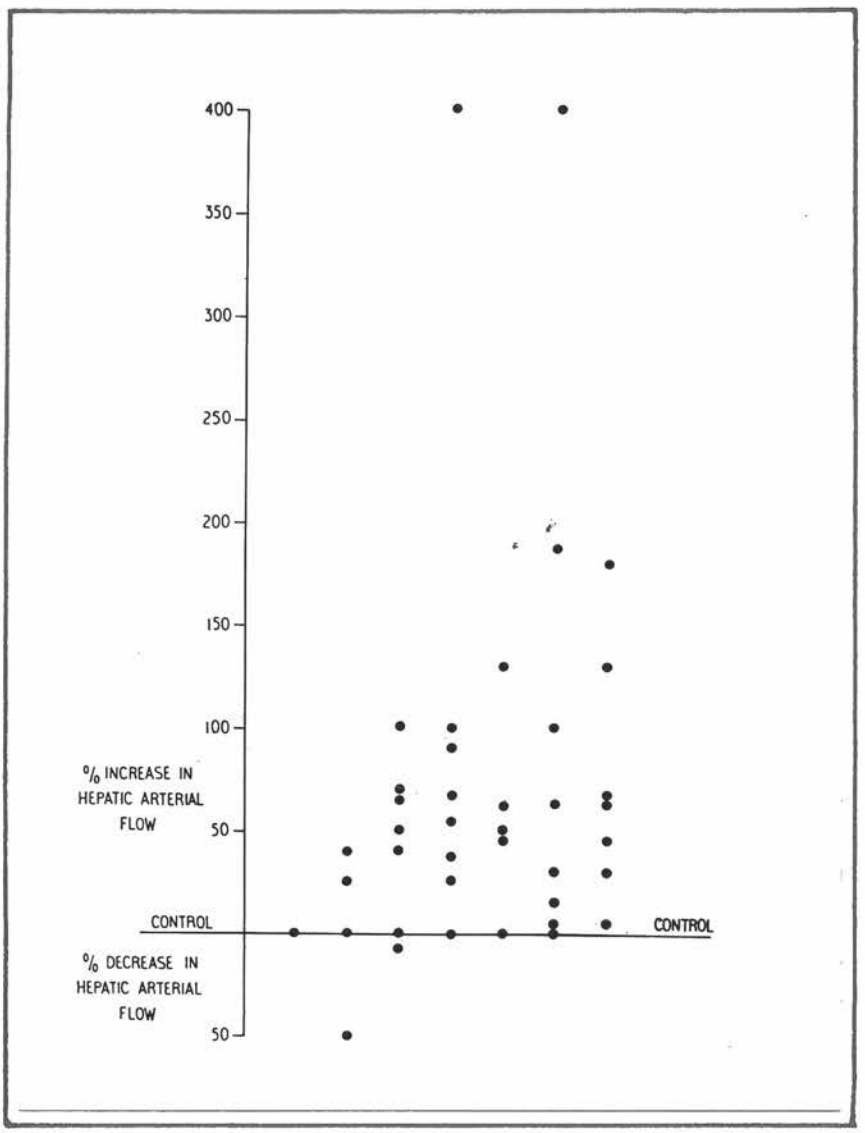

Fig. 84.- The effects of 41 infusions of noradrenaline on hepatic arterial flow.

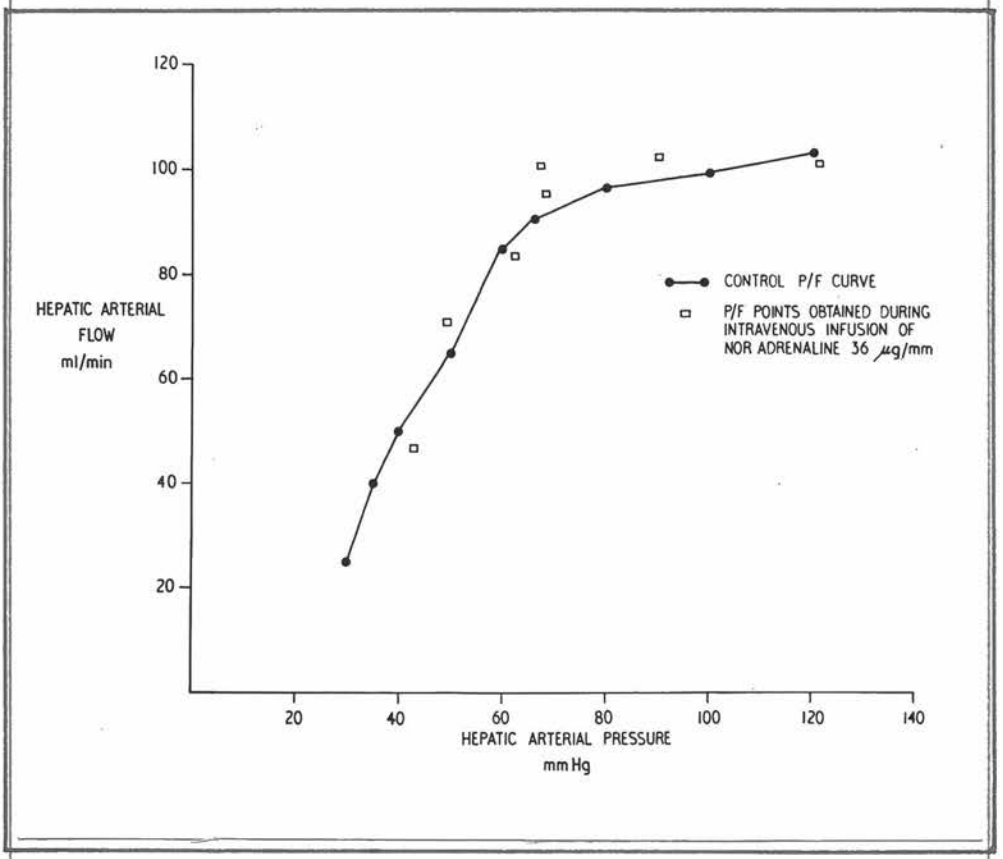

Fig. 85.- Comparison of the pressure flow values during intravenous infusion of noradrenaline with a control pressure flow curve. In this experiment there was no evidence of a direct vasoconstrictor effect of noradrenaline on the hepatic arterial circulation.

The hepatic arterial system.- The influence of noradrenaline infusions on hepatic arterial flow was investigated in 18 separate experiments, a total of 41 infusions being administered. Hepatic arterial flow was not significantly affected during eight of these infusions ($p = 0.185$), was decreased in two ($p. = 0.049$), and increased in thirty-one ($p = 0.756$) (Fig. 83), the mean effect being an increase in arterial flow of 73 per cent. (Fig. 84).

Since the probability of an increase in hepatic arterial flow during a noradrenaline infusion is 0.756 whereas the p value of an increase in portal venous flow is 0.23, this indicates a significant difference in response of the two vascular systems of the liver. The results cannot be explained on the basis of differing pre-infusion blood pressures or the rate of administration of noradrenaline since the range and mean values of these parameters were for all purposes identical in the two groups of experiments.

Comparison of the observed hepatic arterial blood flow and arterial pressure values with control pre-infusion pressure flow curves showed that in those experiments in which a large increase in hepatic arterial flow occurred during the infusion, the pressure and flow values closely corresponded to the values predicted from the control curve (Fig. 85). This finding indicates that in these experiments the increased level of circulating noradrenaline did not lead to vasoconstriction within the hepatic arterial system or, alternatively, that a direct constrictor effect was being

countered /

Fig. 86.- Injection of indian ink into the hepatic artery during a noradrenaline infusion. Note the patchy distribution of the dye.

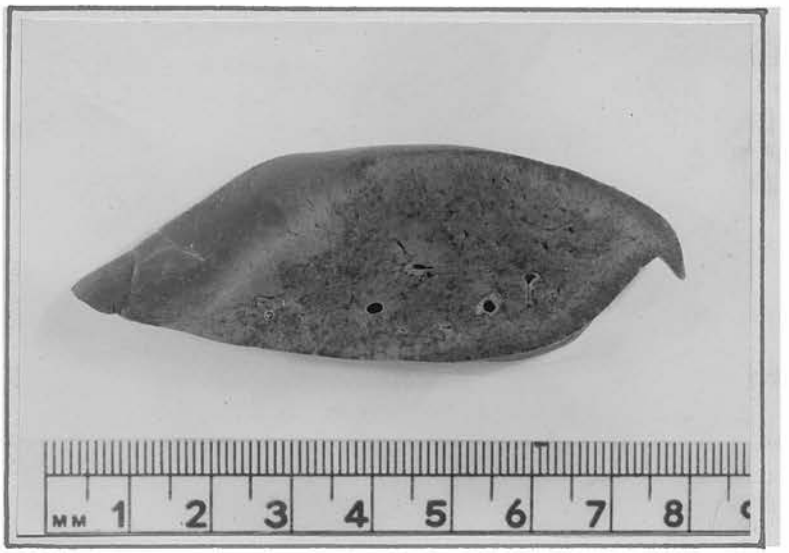

Fig. 87.- Cut surface of a lobe of the liver following injection of indian ink during an infusion of noradrenaline. Note the apparent restriction of the circulation to the deeper parts of the lobe.

countered by a reflex vasodilator response (Ginsburg and Grayson, 1954).

On conclusion of a few experiments while the blood pressure and hepatic arterial blood flow were well maintained by the noradrenaline infusion, 5 ml. of concentrated Indian ink solution were injected into the perfusion system. A few seconds later the circuit was occluded, the animal killed by an intravenous injection of nembutal and the liver removed and immersed in a solution of 10 per cent. formol saline. Examination of the liver after fixation showed an extraordinary patchy distribution of the dye (Fig. 86). In one instance there was no evidence of penetration of the dye into the periphery of a lobe whereas the hilar region was heavily stained (Fig. 87). Irregular perfusion of the liver was also demonstrated on histological examination. If this method of study is regarded as giving a valid impression of circulatory pathways through the liver, it appears likely that even with a rate of blood flow within the normal range, under certain circumstances the blood delivered by the hepatic artery may be diverted from certain parts of the liver, possibly through low resistance short circuit channels.

Discussion

The results of these experiments have shown that the intravenous infusion of noradrenaline in dogs made hypotensive by /

by severe haemorrhage followed by re-infusion of the shed blood leads in most instances to a significant increase in hepatic arterial flow but has little effect on portal venous flow. Whilst oxygen tensions within the liver were not estimated in these experiments it seems likely that the oxygen saturation of the sinusoidal blood must be improved by this alteration in the contribution of the hepatic artery and portal vein to total hepatic blood flow. A considerable body of experimental evidence has been accumulated which clearly implicates anoxic damage to the liver as one factor in the dissolution of tissue function associated with irreversible shock. From this point of view, in the majority of instances the exhibition of noradrenaline therapy may be expected to lead to prolongation of survival. On the other hand, the evidence provided by the intravital injection of Indian ink during the infusion of noradrenaline suggests that the hepatic arterial blood might perfuse only irregular portions of the liver, leaving other areas devoid of an arterial supply. The effects on liver function as a whole may not therefore be as beneficial as might have been suggested by the measurement of hepatic arterial flow alone. The importance of the gastro-intestinal circulation in the genesis of irreversible shock has recently been evaluated by Lillehei (1956). It was shown that diminished blood flow through the mesenteric circulation plays an important part in producing the decreased vascular reactivity associated with irreversible shock. /

shock. The present work has shown that the infusion of noradrenaline leads in the majority of instances to a slight reduction in mesenteric blood flow. The fact that the infusion of noradrenaline is unlikely to improve the blood supply of the gastro-intestinal tract may offer one explanation of the frequent failure of such therapy to improve the general condition of the experimental animal.

The effects of noradrenaline infusions in haemorrhagic shock on the circulatory dynamics of the heart, the kidneys and the brain have been investigated by various workers. Examination of these reports discloses remarkably divergent views on the possible consequences of this therapy. Frank et al. (1956) reported that the intravenous infusion of noradrenaline produces a significant increase in cardiac output in animals made hypotensive by haemorrhage and these results have been confirmed by Levy and Brind (1957). It seems likely that an increase in cardiac output is a result of a direct action on the myocardium and also of an increase in the potentially circulating blood volume from mobilisation of venous blood by veno-constriction (Tyrer, 1953). It has been pointed out, however (Levy and Brind, 1957), that owing to differences in the cardio-dynamic action of this drug in dog and man, similar facilitation of cardiac output may not occur in the hypotensive human.

The renal effects of noradrenaline therapy in haemorrhagic hypotension have received close attention. Moyer et al. (1954) found a significant increase in renal blood /

blood flow in dogs previously made hypotensive by haemorrhage. This result has not been confirmed by other workers. Recently Tait (1958; unpublished observations) studied the effects of noradrenaline on renal blood flow in haemorrhagic hypotension and could not detect any significant elevation in renal blood flow when the blood pressure was restored to normal levels by the infusion of noradrenaline. Similarly, the writer (unpublished observations) in three experiments in dogs found a profound decrease in renal blood flow during the administration of noradrenaline in haemorrhagic hypotension.

Green and Denison (1956) demonstrated that doses of noradrenaline, sufficient to cause marked vasomotor activity on all other vascular beds, produce minimal effects on the intracranial circulation. On a priori grounds the infusion of noradrenaline in haemorrhagic hypotension would thus lead to an increase in cerebral blood flow.

It seems likely, therefore, that the effects of an infusion of noradrenaline in a dog made hypotensive by haemorrhage lead to an increase in cardiac output, a reduction in renal blood flow, no significant effect on portal venous flow but a significant increase in hepatic arterial flow and probably also in cerebral blood flow. Whether these circulatory effects of noradrenaline result in a substantial benefit to the subject or whether they are merely temporary and would give rise to eventual disruption of tissue function, remain problems for further study.

PART III

LIVER BLOOD FLOW DURING OPERATIONS ON THE UPPER ABDOMEN

LIVER BLOOD FLOW DURING OPERATIONS ON THE UPPER ABDOMEN

In recent years the vascular and metabolic responses of the body during and after surgical procedures have aroused the interest of both anaesthetists and surgeons. This study is concerned with one aspect of the problem - the hepatic circulation during abdominal operations. In previous investigations of liver blood flow the bromsulphthalein clearance technique of Bradley et al. (1945) has been widely used, and much valuable information has been obtained. The method requires catheterisation of the hepatic veins, however, and is not suitable for the observation of rapid changes in the hepatic circulation.

Grayson (1952) showed that hepatic blood flow in animals could be recorded by the use of a heated thermocouple device inserted into the liver parenchyma, and recently this technique has been employed by Carlyle and Grayson (1956) in the study of the cerebral circulation.

In the present report the technique as applied to the human liver is discussed, and the observations recorded during a series of 27 operations on the upper abdomen are presented.

Method

Physical Considerations

The /

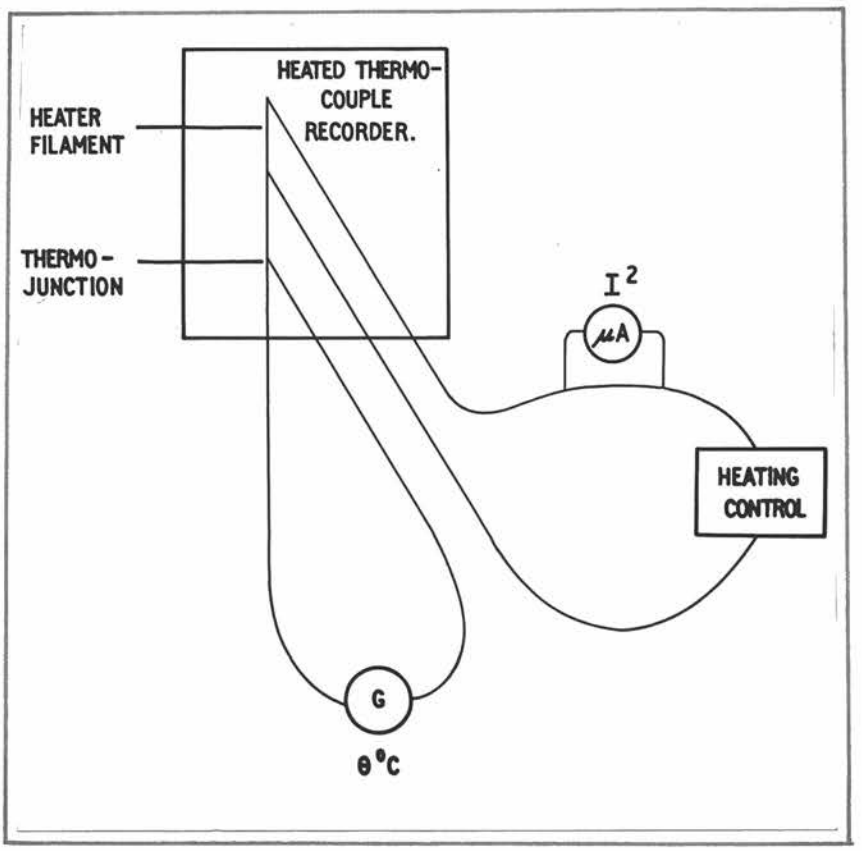

Fig. 95.- Simplified diagram of heated thermo-couple blood flow recorder.

The recorder consists of four fine wires joined at a standard distance apart, so that the distal junction acts as a small heater filament and the proximal one as a copper-constantin thermocouple (Fig. 95). In order to produce recorders of uniform dimensions, three fine copper wires are soldered to a constantin wire using a Dural jig. The recording unit is then carefully insulated by immersion in a solution of lampblack in amyl-acetate.

When an electric current is passed through the heater filament the temperature rises. This sets up a secondary current in the thermocouple which is connected to a sensitive galvanometer calibrated in degrees Centigrade. The current flowing through the heater circuit is accurately controlled by means of a Variac transformer, and the heating effect of this current is measured by a secondary circuit which contains a Cambridge Vacuo junction. The electrical current produced by the thermocouple in the Vacuo junction is estimated by a sensitive microammeter. By this means the square of the current in the heating circuit can be measured.

The heat-output of the heater filament is measured by the equation

$$H = CI^2R$$

(where C is a constant, I is the current in amperes, and R the resistance of the wires in ohms)

It follows, therefore, that the value I^2 obtained from the microammeter represents the heat-output by the heater filament in the recorder.

When /

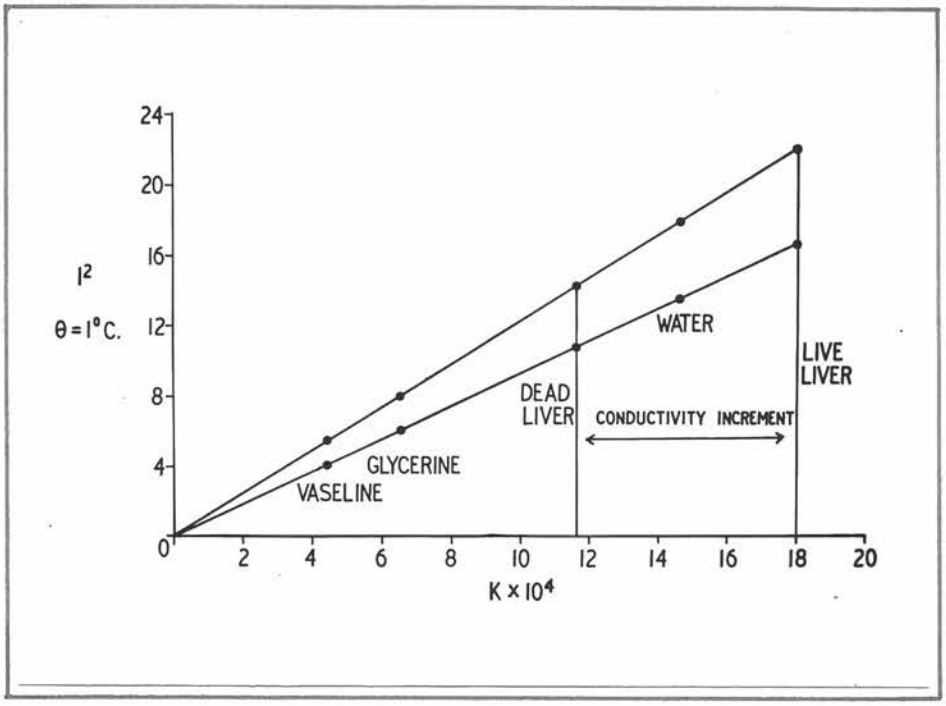

Fig. 96.- Illustrating linear relationship between I^2 and the thermal conductivity of various substances.

When the recorder is immersed in a series of semi-solid substances and a fixed temperature increment ($1^{\circ}C.$) induced in the heater filament, heat is lost by direct conduction to the surrounding medium until thermal equilibrium is established.

Carslaw's formula for the conduction of heat in semi-solids may now be applied:

$$I^2R = K4\pi r$$

(where K is the thermal conductivity of the substance, r the radius of a sphere of equivalent thermal properties to the heater, and ? is the fixed temperature increment)

Since $4\pi r$ and R are constants it follows that the square of the current required to heat the filament by a constant increment is a linear function of the thermal conductivity of the substance in which the recorder is immersed. This theoretical statement can be verified experimentally by determining the I^2 values for a series of substances of known thermal conductivity. When these results are plotted graphically (Fig. 96) a straight line results, proving that the relationship $\frac{I^2}{K}$ is a constant. Using "Vaseline" as the test substance, this constant can be determined for each recorder. With this constant known, the thermal conductivity of any other semi-solid can be determined by estimating the value of I^2 when the same temperature increment is applied.

By this method the thermal conductivity of dead liver has been determined in man, rabbits, cats and rats and found to be constant within narrow limits. The mean figure obtained was 11.9×10^{-4}.

When /

When the recorder is inserted into the liver of a living animal the presence of circulating blood produces an apparent increase in the thermal conductivity of the tissue. In a rabbit's liver the apparent thermal conductivity was 24.0×10^{-4}, an increase of 13.1×10^{-4} above the conductivity of dead liver. This increment in thermal conductivity can be employed to estimate the rate of blood flow in the vicinity of the recorder. The faster the rate of blood flow the greater the rate of heat loss from the recorder, and, therefore, the greater the current that must be supplied to the heater filament to maintain the constant temperature increment.

The rate of blood flow can be determined so rapidly by this method that it is possible to follow changes in the hepatic circulation from minute to minute. Grayson (1952) has shown that the presence of the recorder in the liver substance does not produce a demonstrable upset in the local circulation, even when it is left in situ for a period of days.

It must be appreciated that this technique estimates the rate of blood flow only in the small area of liver in the vicinity of the recorder.

The implantation of the recorder.- In small animals the implantation of the recorder is easily accomplished by direct puncture of the liver parenchyma, but unless great care is taken to ensure that the heater filament is deeply embedded, heat is transferred not only to the liver and its blood /

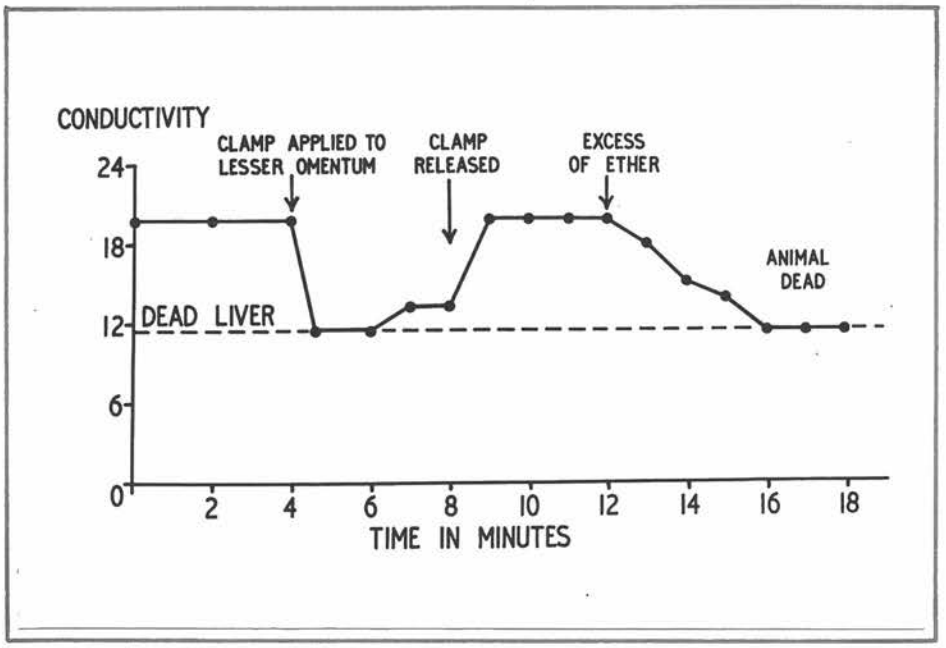

Fig. 97.- The effect of occlusion of the portal vein and hepatic artery on liver blood flow (Rabbit).

blood stream but also to adjacent structures, and fallaciously low recordings are obtained.

In man, if the implantation is carried out at right angles to the surface of the liver and the sharp inferior margin is avoided, this difficulty does not arise. Owing to the thickness of the investing capsule, however, direct puncture of the human liver at operation is not satisfactory.

The practice adopted in this study was first to puncture the liver with a fine hydrocele trocar and cannula, enabling the recorder to be inserted easily along the track to a distance of at least 2 cm. After insertion, the wires were anchored to the capsule of the liver by a fine suture, and the leads connected to the recording apparatus. The whole procedure involves minimal damage to the liver and there have been no obvious ill effects after operation.

Preliminary Experiments

As a preliminary, various animal experiments were performed to confirm the validity and the safety of the method. The results are briefly reported:

(1) The effect of occluding the afferent vessels of the liver in the lesser omentum of the rat is shown in Fig. 97. The conductivity measurement drops to the figure obtained in the dead liver, but when the clamp is released, the readings are immediately restored to the original level.

(2) In the dog the effect of establishing a shunt, through which the portal circulation is augmented by the total quantity of blood flowing through the inferior vena cava /

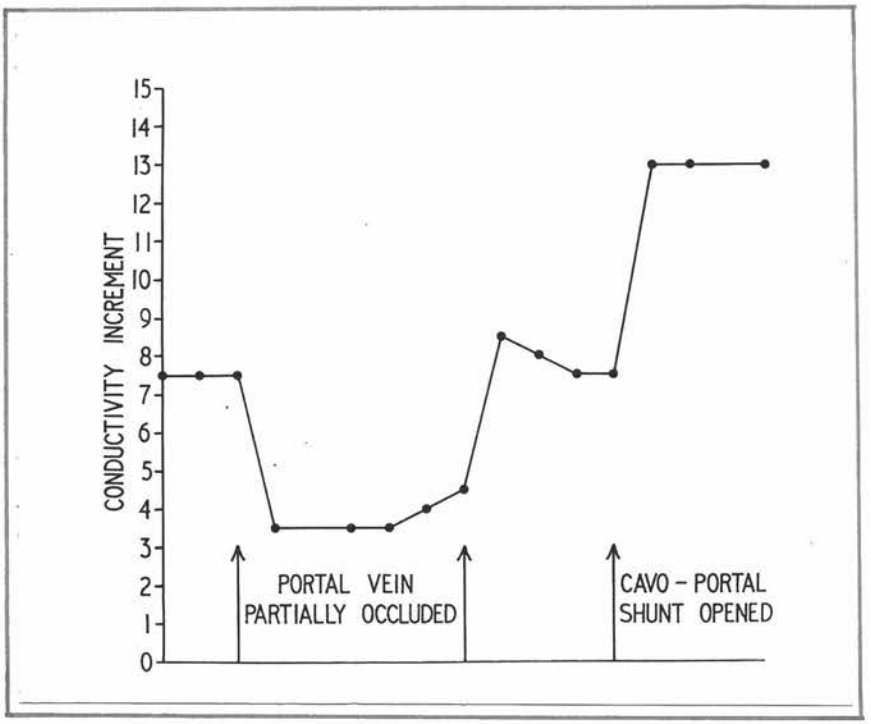

Fig. 98.- The effect on liver blood flow produced by establishing a cavo-portal shunt.

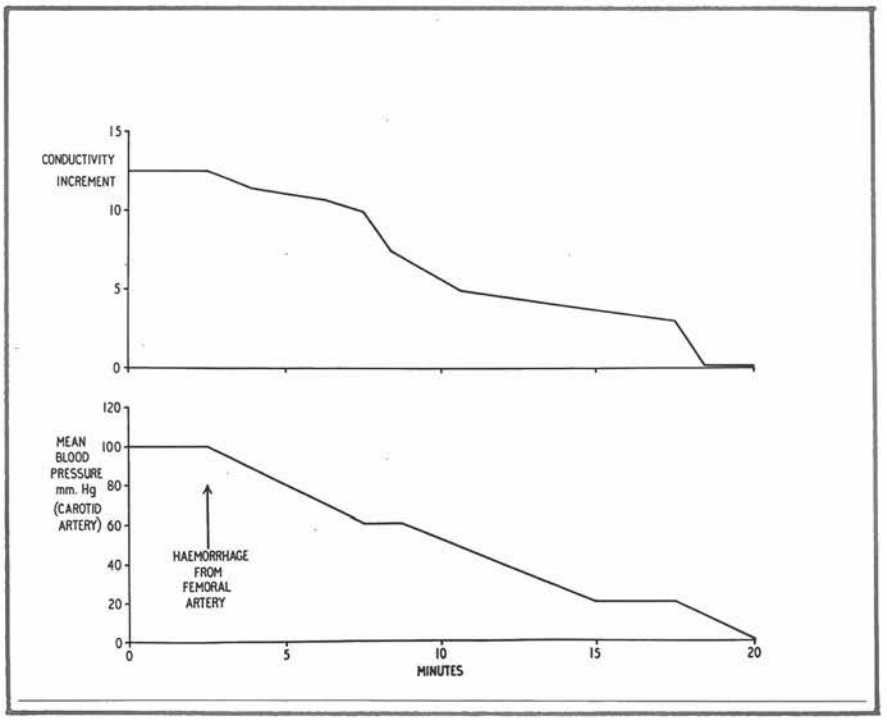

Fig. 99.- The effect of haemorrhage on liver blood flow (Rabbit).

cava below the level of the hepatic veins is shown in Fig. 98 . The diminution in the apparent thermal conductivity of the liver during temporary occlusion of the portal vein, and the high readings obtained after opening the shunt, are striking.

(3) The readings of increment in conductivity, and the records of blood pressure, in a rabbit subjected to progressive haemorrhage are shown in Fig. 99 . The liver blood flow is maintained until a severe degree of hypotension exists. At a critical level (approximately 60 mm.Hg), the readings become greatly diminished, eventually reaching the level obtained from dead liver.

There can be no doubt, therefore, that the increase in the apparent thermal conductivity of the liver above the value obtained from dead liver can be used as an indirect measure of the rate of blood flow in the vicinity of the recorder.

Whether the conductivity increment can be used as an accurate quantitative measure of blood flow in an organ is more difficult to assess. Grayson (1952) has shown by perfusion studies of the liver that the conductivity increment has a linear relationship to blood flow. On the other hand, Linzell (1953) by perfusing artificial "model organs," and also liver and spleen, found that the relationship of conductivity increment and blood flow may not necessarily remain linear over the complete physiological range. More recently Hensel et al. (1954) have shown that

a /

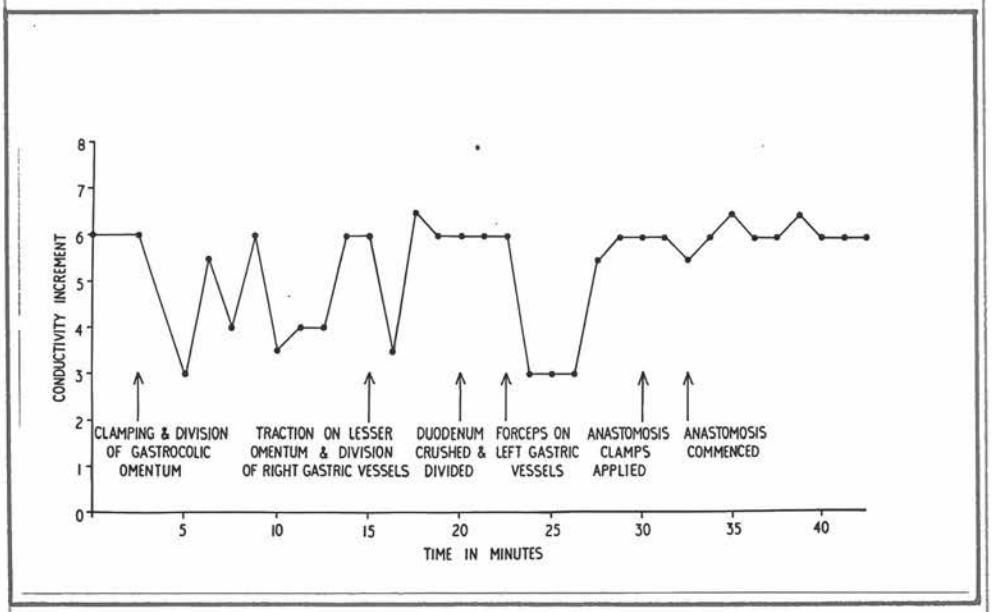

Fig. 100.- Typical variations in liver blood flow during partial gastrectomy.

a definite linear relationship exists between blood flow and conductivity increment in the perfused spleen. Similar findings have been reported by Carlyle and Grayson (1956) in studies of the cerebral circulation.

Material

Twenty-seven patients undergoing abdominal operations were studied by this technique. The usual premedication was omnopon gr. $\frac{1}{3}$ and hyoscine gr. 1/150. Anaesthesia was induced by intravenous pentothal, sometimes supplemented by pethidine, and continued by closed-circuit cyclopropane. Relaxation was obtained by means of an intravenous scoline drip.

As soon as the abdomen was opened and a suitable site chosen, the recorder was inserted into the liver and fixed in position. The operation then proceeded according to plan.

The types of operation during which these studies were made were as follows: gastrectomy, 18; vagotomy and gastro-enterostomy, 5; cholecystectomy and choledochotomy, 3; and splenectomy, 1.

Results

Early in the investigation it became apparent that alterations in the intra-hepatic circulation occurred after stimulation of certain structures in the upper abdomen. For instance during a partial gastrectomy (Fig. 100) striking reduction in blood flow occurred immediately after the /

the application of artery forceps to the gastro-colic omentum. This change was relatively shortlived, usually lasting 1 to 2 minutes. Following the application of a ligature and release of the forceps the blood flow was almost immediately restored to normal level. A similar reduction in flow followed the application of forceps to the right and left gastric vessels, and to the cystic artery during cholecystectomy. Traction on the left gastric vessels or on the gall-bladder also resulted in a definite reduction in liver blood flow.

This response apparently is evoked when blood vessels are clamped or dragged upon; of these stimuli, traction appears to be the more important.

During mobilisation of the stomach and duodenum in the course of gastrectomy, there were numerous episodes of reduced blood flow, and stability was not recorded until the anastomosis was begun.

Stimulation of certain visceral blood vessels in the upper abdomen constantly produced this response, whereas manipulation of the viscera produced no demonstrable effect. Thus when the duodenum or the stomach was clamped, the liver circulation was not affected, and division of the duodenum or stomach by scalpel or diathermy produced no detectable alteration.

These recurrent restrictions in hepatic blood flow were found in all patients undergoing partial gastrectomy, though the extent varied from subject to subject. In some patients diminution /

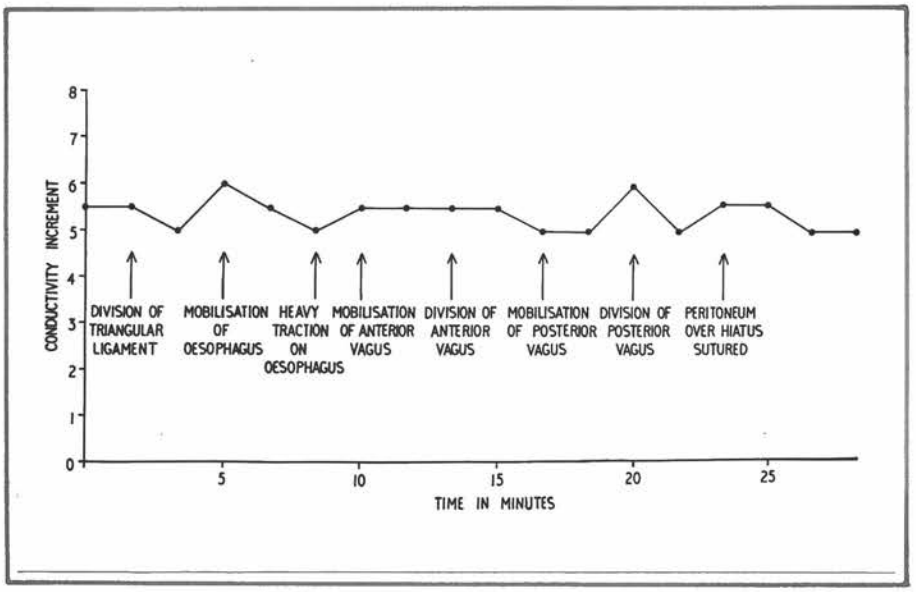

Fig. 101.- Liver blood flow recordings obtained during vagotomy.

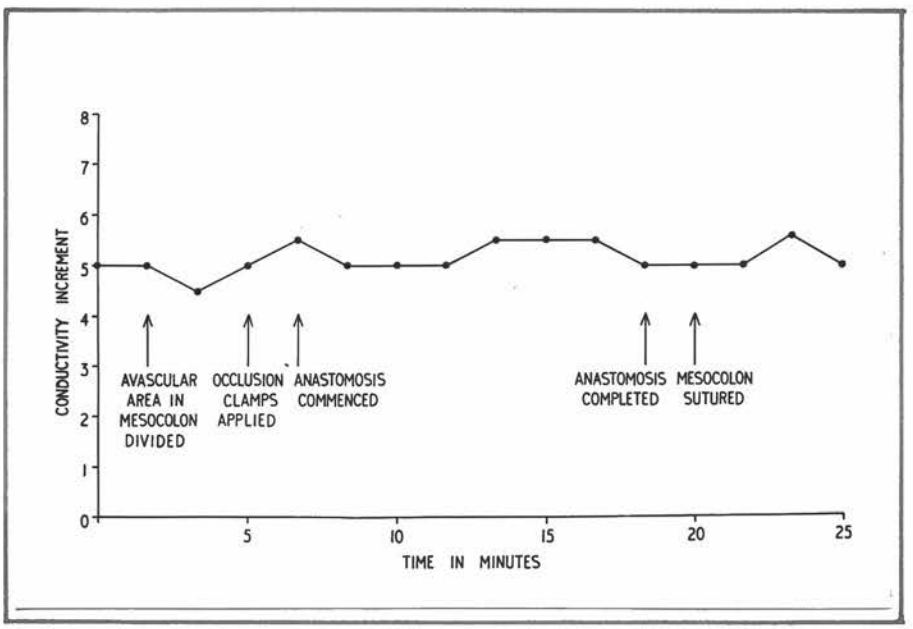

Fig. 102.- Liver blood flow recordings obtained during gastro-enterostomy.

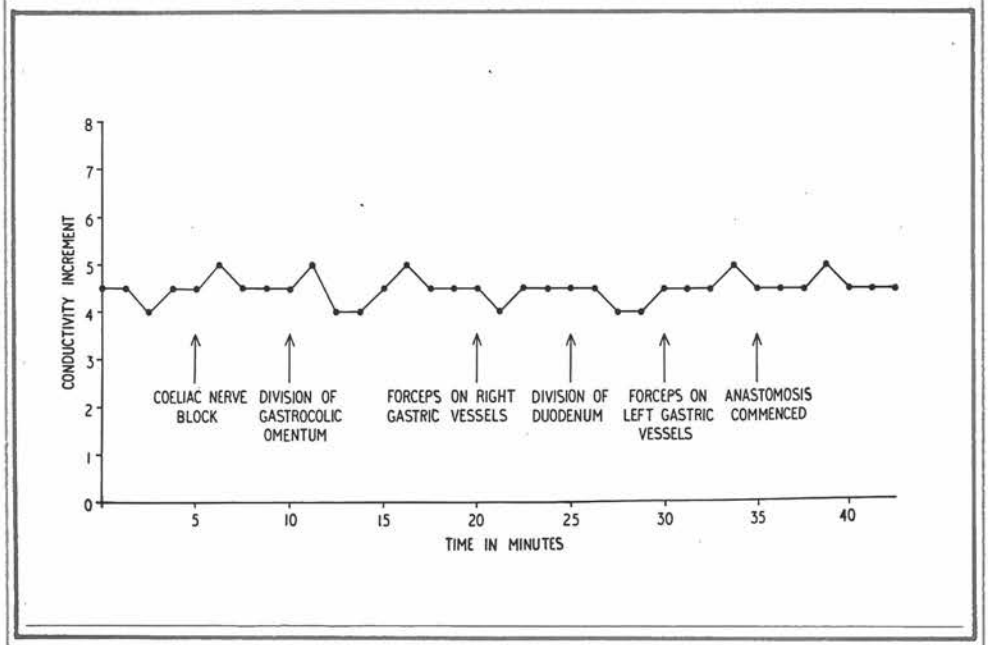

Fig. 103.- Liver blood flow recordings obtained during partial gastrectomy following coeliac nerve block.

diminution in flow up to 50 per cent. of the resting level was recorded; in others the changes were smaller. No correlation was found between the depth of anaesthesia and the magnitude of these responses, but it did appear that those subjects who became hypertensive during the course of the operation showed the greatest variations.

In contrast, the findings in a series of patients undergoing vagotomy and gastro-enterostomy are striking (Figs. 101 and 102). Marked variations were not found during the course of these operations, possibly because there was no traction or clamping of the vessels in the neighbourhood of the stomach. It is interesting to note that neither traction nor crushing, nor division of the vagus nerves produced any demonstrable effect on the resting liver blood flow (Fig.102).

In six patients about to undergo partial gastrectomy the coeliac plexus and the tissues of the lesser omentum were infiltrated with 50 ml. of 0.5 per cent. procaine. Following this, the application of artery forceps to the gastro-colic omentum did not alter the blood flow which remained constant throughout the mobilisation of the stomach and duodenum and even during heavy traction on the left gastric vessels (Fig. 103).

During the course of these direct recordings in patients, a careful watch was kept to determine whether spontaneous variations in blood flow, unassociated with trauma or variations in blood pressure, occurred as have been described in animals by Wakim and Mann (1942), and by Seneviratne /

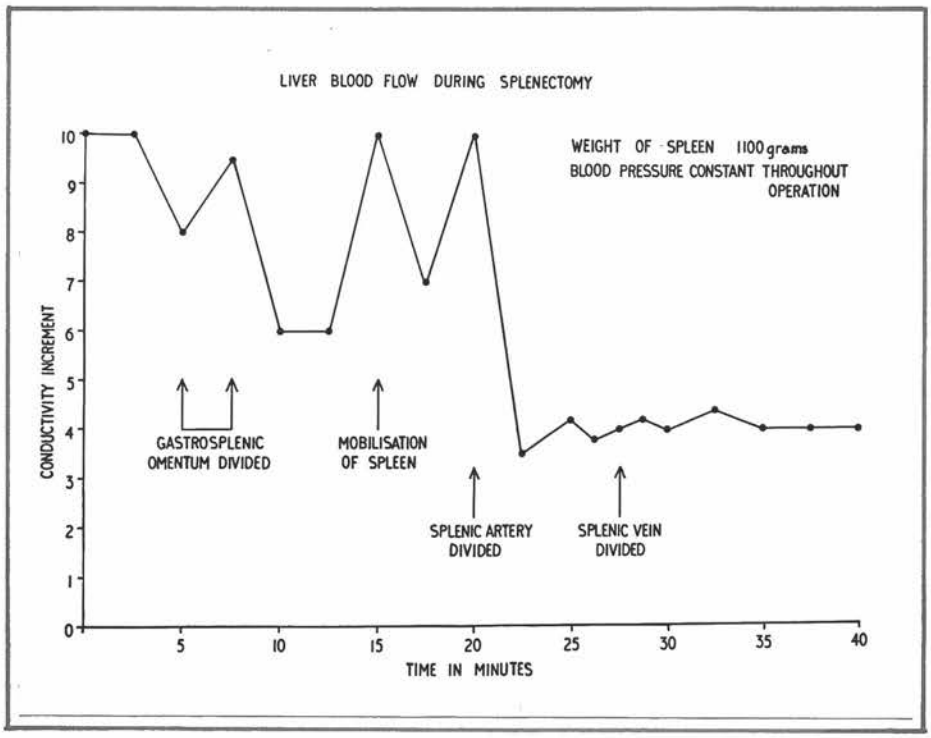

Fig. 104.- The effect of splenectomy on liver blood flow.

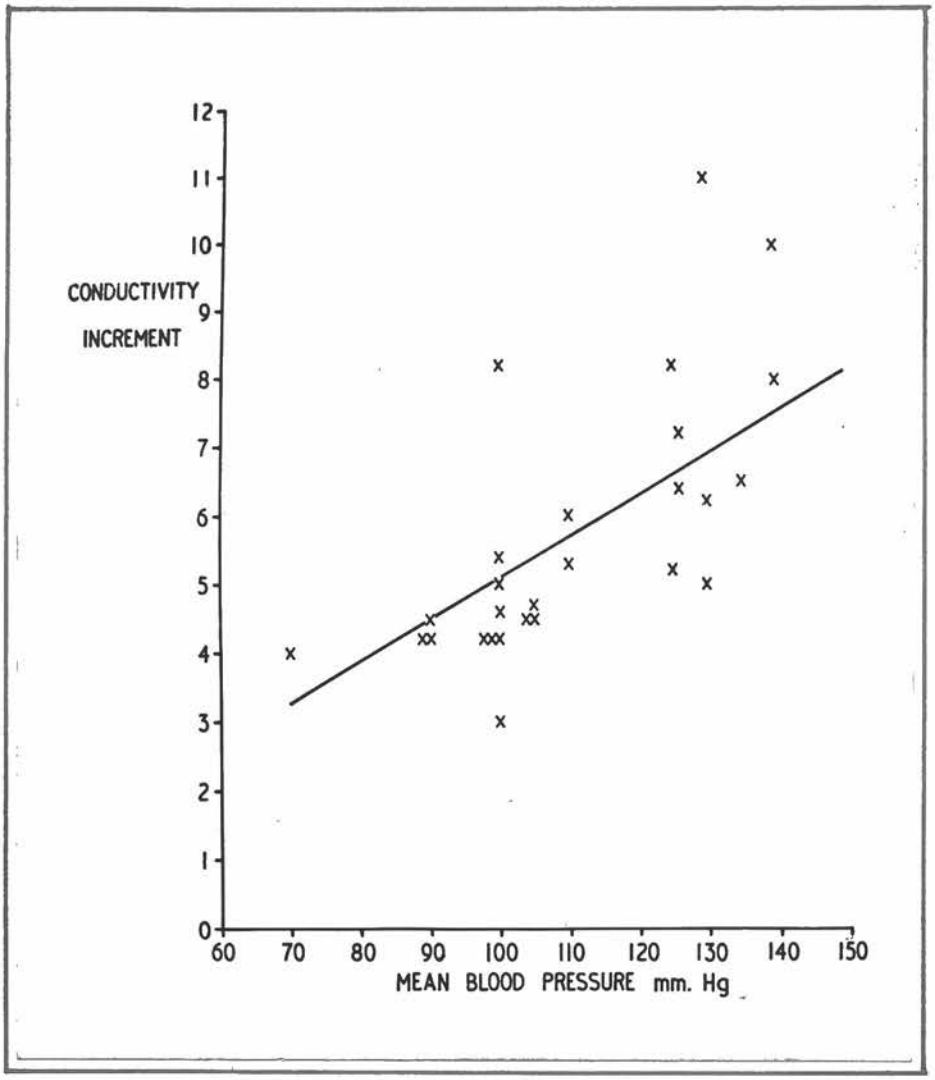

Fig. 105.- Showing relationship between liver blood flow and mean blood pressure. A linear regression line has been calculated.

Seneviratne (1949). This phasic variability in the local circulation was not detected in any case in the present series, one of the features of the recordings being the remarkable constancy of the resting flow readings. This observation does not disprove the existence of a similar mechanism in the human liver, as the volume of liver tissue under study is small and within it changing rates of flow may occur in one series of sinusoids along with compensatory changes in neighbouring sinusoids. It is certain, however, that cyclical alterations in circulatory activity do not occur on a segmental scale in the liver of man.

Liver blood flow recordings were obtained during the course of splenectomy in a patient suffering from monocytic leukaemia, with a greatly enlarged spleen (1,100 g). Histological examination did not disclose any involvement of the liver. The changes in liver flow produced by clamping the vessels in the gastro-splenic omentum are similar (Fig. 104) to those occurring during gastrectomy; the great reduction in liver flow after occlusion of the splenic artery is well shown.

In all the patients studied, serial determinations of blood pressure were made with a Pachon oscillometer. When the mean conductivity increment is plotted against the mean blood pressure determinations over a 10-minute period, an interesting relationship emerges (Fig. 105). There is a significant relationship between liver flow and mean blood pressure /

pressure ($P < .001$). In this series no patient developed a marked degree of hypotension, and these lower levels as yet remain unexplored by this technique.

In some cases a large increase in mean blood pressure occurred in the later stages of operation, and this allowed a comparison to be made between the liver flow readings during the normotensive and hypertensive states in the same patient. In all cases where this occurred a definite increase in liver flow readings was found, the increase being roughly proportional to the degree of hypertension present. Similarly, when a patient became hypertensive soon after the operative procedure had begun, any later fall in pressure could usually be predicted from the liver flow readings.

Discussion

It has been shown that reduction in hepatic blood flow can be produced either by traction or by crushing certain structures in the upper abdomen, but it is relatively short-lived and disappears immediately after the application of a ligature or release of traction. That an intact nerve supply is necessary is shown by the effect on the pattern of the recordings obtained during gastrectomy after coeliac nerve block, when alterations in flow are eliminated. These observations suggest that stimulation of perivascular afferent nerve fibres is the stimulus for the production of this reflex. Whether the efferent arc of the reflex produces a diffuse vasoconstriction in the splanchnic bed, or /

or whether the effect is confined to the hepatic blood vessels, cannot be determined from the present experimental work.

Daniel and Prichard (1951a) studied the portal circulation in the rat and cat by means of serial cineradiography after intraportal injection of thorotrast, and found that a restricted type of circulation occurred in a certain percentage of animals. The portal flow was diverted from the periphery of the liver through short channels directly into the hepatic veins in the hilar portions of the lobes, and there was an associated fall in the transhepatic circulation time. This phenomenon was noted in approximately one-third of the animals studied, although no operative procedure had been undertaken other than the limited laparotomy for injection of the contrast medium.

Daniel and Prichard (1951b) also found that in a high proportion of animals subjected to partial hepatectomy a similar restricted type of circulation was present, and they suggested that the ligature compressing the stumps of the excised lobes might have acted as an irritant, thereby setting up a neurovascular reflex. Attempts were made to reproduce these circulatory changes by electrical stimulation of the distal end of the divided hepatic nerve plexus. In every case this resulted in constriction of the portal radicles, and in some animals, in the short-circuit type of blood flow. Although traumatic stimulation of the hepatic nerve plexus was not studied by Daniel and Prichard, it is reasonable /

reasonable to suppose that a similar response would have been obtained.

Experiments performed by the writer disclosed no obvious reduction in hepatic blood flow in the rat or rabbit after the application of artery forceps to the gastric blood vessels, a stimulus which regularly produces reduction of flow in man. In order to obtain satisfactory recordings in animals, however, the heater filament must be deeply embedded in a lobe of the liver, and this of necessity places the recorder in close proximity to the large hilar vessels. Further evidence of the differing response obtained in man and in animals is provided by a comparison of the average flow readings obtained from the human and the animal liver. In a series of experiments on rats Grayson and Johnson (1953) reported a mean conductivity increment of 14.9×10^{-4}, and in an independent series a similar result was obtained by the writer. The mean conductivity increment obtained from the twenty-seven observations in man was 5.7×10^{-4}. Since there is no reason to suppose that the total relative hepatic blood flow is greater in the rat than in man, it would appear that the recordings obtained from the liver of a small animal represent not only the local sinusoidal flow, but also a varying proportion of the circulation through the hilar vessels supplying the lobe. Reduction in circulation resulting from trauma may, therefore, be masked when the heated thermocouple technique is used, by the shunting of blood through short hilar channels /

channels directly into hepatic veins in proximity to the heater filament in the recorder. In the present study, all recordings during operation were obtained from the peripheral portions of the liver, as the heated thermocouple technique is not suitable for the study of the deeper tissues in man. If short circuits between the portal and hepatic venules exist in man, restrictions in flow through the peripheral portions of the liver following trauma may depend on the opening of these shunts, which would deprive the peripheral sinusoids of portal blood. Unfortunately, information about the behaviour of the hepatic arterial system under similar circumstances is not yet known.

Habif et al. (1951) investigated the circulatory effect of anaesthesia on hepatic blood flow by catheterisation of the hepatic veins. They found a decrease in blood flow in four out of five patients after induction of anaesthesia by means of thiopentone and cyclopropane. Similar results were reported by Shackman, Graber and Melrose (1953), who found a decreased hepatic blood flow equivalent to 30 per cent. of the pre-anaesthetic level in 18 patients anaesthetised by thiopentone, cyclopropane, curare and oxygen, before the start of abdominal operations. In the present series, estimations of liver blood flow in the pre-anaesthetic period were not obtained since the introduction of the recorder into the liver can be accomplished only under direct vision. If it is correct that general anaesthesia produces a definite reduction in hepatic /

hepatic blood flow, the further restrictions associated with trauma during operation become even more significant.

Boyce and McFettridge (1938) emphasised the importance of damage to the liver by general anaesthesia and surgical operation; and Cantarow, Gartman and Ricchiuti (1935), in a study of liver function before and after simple cholecystectomy in patients without jaundice, found that in over 50 per cent. there was a varying degree of increased dye retention lasting for four days. Schmidt et al. (1942), using the hippuric acid test, carried out a similar study and found evidence of liver damage in a considerable percentage of patients after abdominal operations. It is interesting to note that those patients who had received a spinal anaesthetic showed the least derangement of hippuric acid synthesis.

Tagnon, Robbins and Nichols (1948) studied a group of 20 patients subjected to extra-abdominal operations, and in 14 a significant increase in dye retention which persisted for a few days, was found. No change was detected in the cephalin cholesterol flocculation test or thymol turbidity test during this period. They suggested that the impairment in liver function may have been due to anoxia during anaesthesia, or possibly to the toxic effect of the anaesthetic agent.

It is probable, therefore, that operations - particularly those involving much manipulation - may produce a degree of liver damage. In the majority of cases this is occult /

occult, but when patients with pre-existing liver damage from nutritional deficiency, biliary tract disease or neoplastic invasion are submitted to operation, the hepatic parenchyma may be unable to discharge its functions efficiently in the post-operative period.

The demonstration of recurring diminution in blood flow affecting the liver during the course of operations suggests that this may be a mechanism in the production of hepatic damage. Furthermore, it has been shown (Shorr et al., 1945) that hepatic anoxia leads to the release from the liver cells of a vaso-depressor material which in turn produces wide-spread vascular paralysis throughout the body, and leads to a condition akin to traumatic shock.

Coeliac nerve block, having been shown to be highly effective in preventing this neurovascular reflex, would appear to be a simple method of maintaining a constant hepatic blood flow during operation and of avoiding anoxic damage to the liver and the effects of this on the vascular and metabolic economy of the patient in the post-operative period.

APPENDIX A

The Density Flowmeter

APPENDIX B

A Rotameter for Measurement of Portal Venous Blood Flow

APPENDIX C

A New Type of Recording Manometer

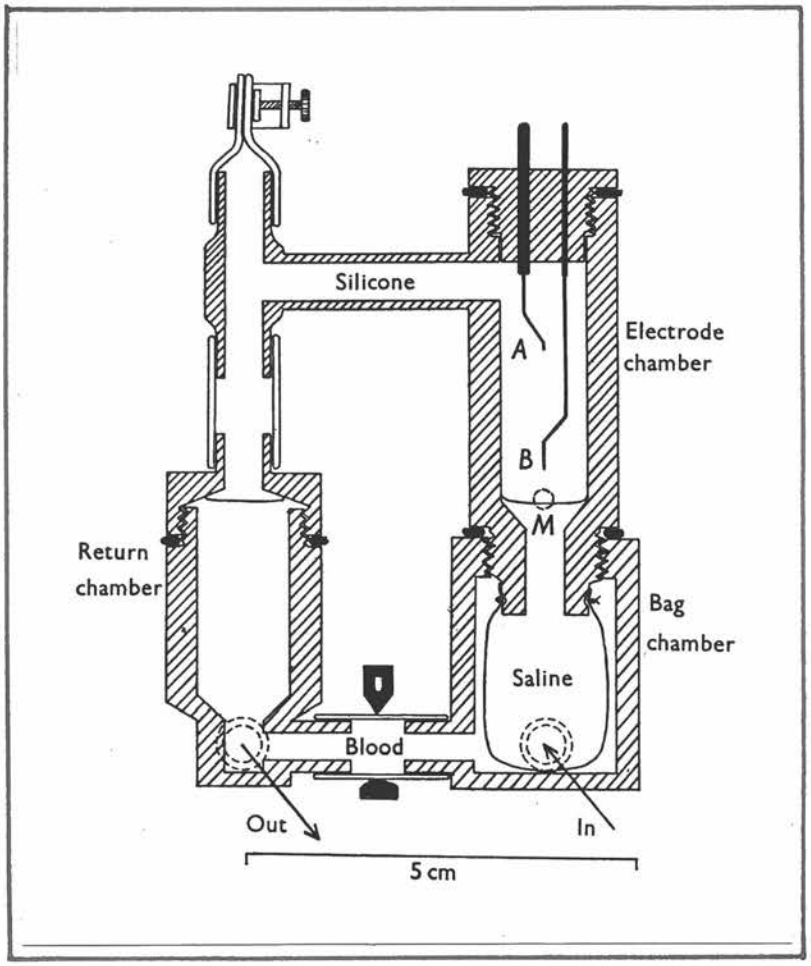

Fig. 88.- Cross sectional diagram of the density flowmeter (Dawes et al., 1953).

APPENDIX A

The Density Flowmeter

Of the many available methods for measuring blood flow, few rely on direct measurement of volume and time. Volkmann in 1850 designed an apparatus to time the volume change in a metering chamber after diversion of blood flow from the main stream into the chamber. Various modifications of the original method have appeared in an attempt to simplify the operation of the flowmeter but the apparatus has remained bulky and inconvenient.

Dawes, Mott and Vane (1955) devised a flowmeter based on the Volkmann principle but with the great advantage that the cycle of events during a blood flow estimation and the estimation itself are carried out automatically by an electronic control unit. The apparatus is illustrated in Figs. 88-90.

Blood flows continuously through the apparatus. During the "resting" phase the direction of flow is through the lower of the two inter-connecting cross-pieces. The remainder of the apparatus is filled to a suitable level with silicone DC 200/0.65 cs, specific gravity 0.75, viscosity 0.49 cP at 25°C., made by Midland Silicones Ltd. This substance is colourless and has a low viscosity, specific gravity and electrical conductivity and forms a well-defined meniscus with blood.

When /

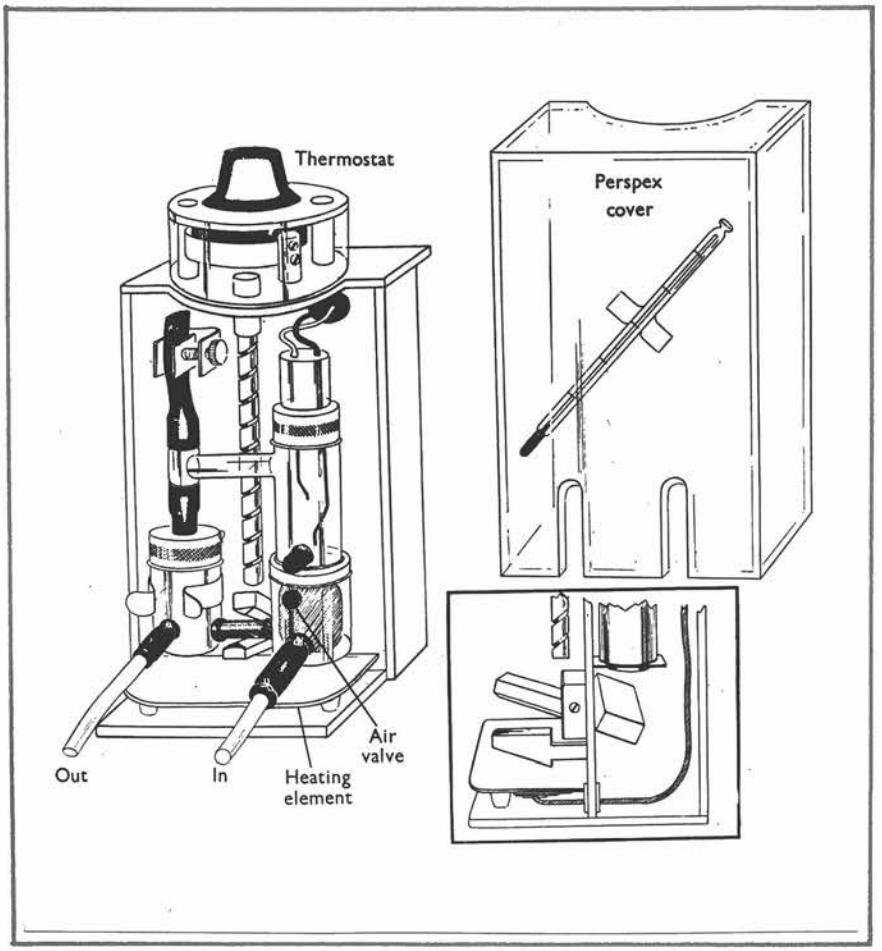

Fig. 89.- Diagram to illustrate the details of the density flowmeter (Dawes et al., 1953).

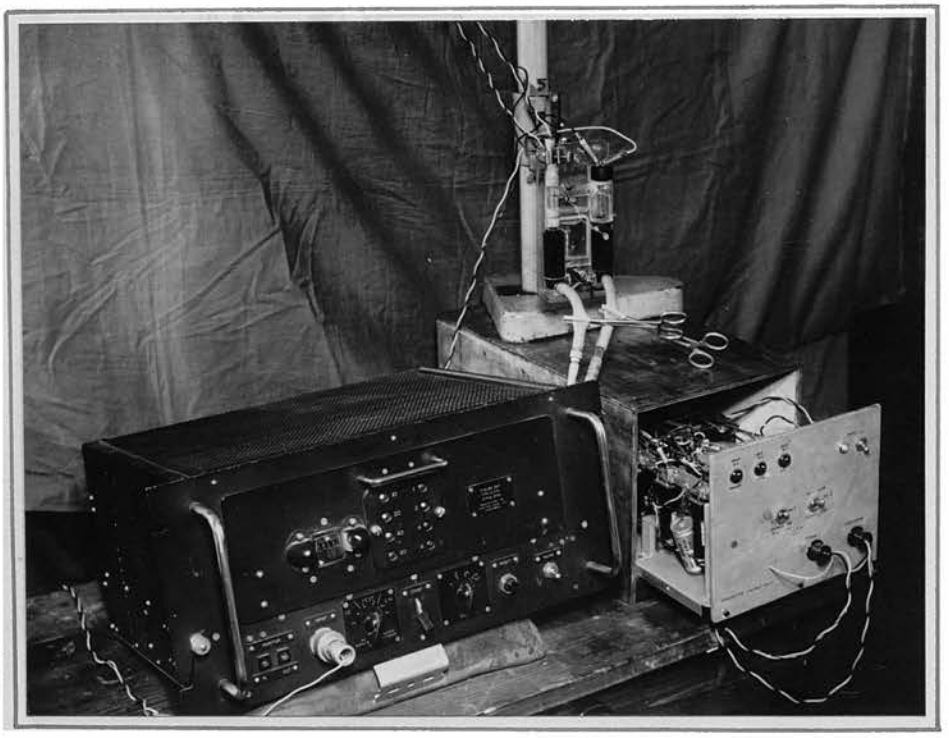

Fig. 20.- The assembled flowmeter with control unit on the right and scaling unit on the left.

When the direction of blood flow is diverted by closure of an electro-magnetic tap the blood silicone meniscus rises in the right-hand chamber, whose volume has been accurately determined. The time taken for the meniscus to pass between two points in the metering chamber is measured electrically. When the surface of the meniscus is broken by the tip of electrode B an electronic counting unit is set in motion, which continues to count until the tip of electrode A breaks the surface of the meniscus. Immediately the circuit maintaining closure of the electro-magnetic tap is broken, the tap opens and the menisci return to their original positions. Dawes, Mott and Vane employ a Post Office type electro-magnetic counter with a mechanical time base to record the inter-electrode flow time. The author, however, encountered considerable difficulty in obtaining a sufficiently high counting rate with this timing device. A more convenient technique was therefore devised, employing a scaling unit counting in 1/100 sec with an a.c. mains time base (50 cycles/sec). The electrical control unit was so arranged that either single or repeated measurements of blood flow could be effected. For the purposes of these experiments, an inter-electrode volume of 4 ml. was found to provide a useful measuring range up to 160 ml./min with an accuracy of approximately ± 2 ml./min.

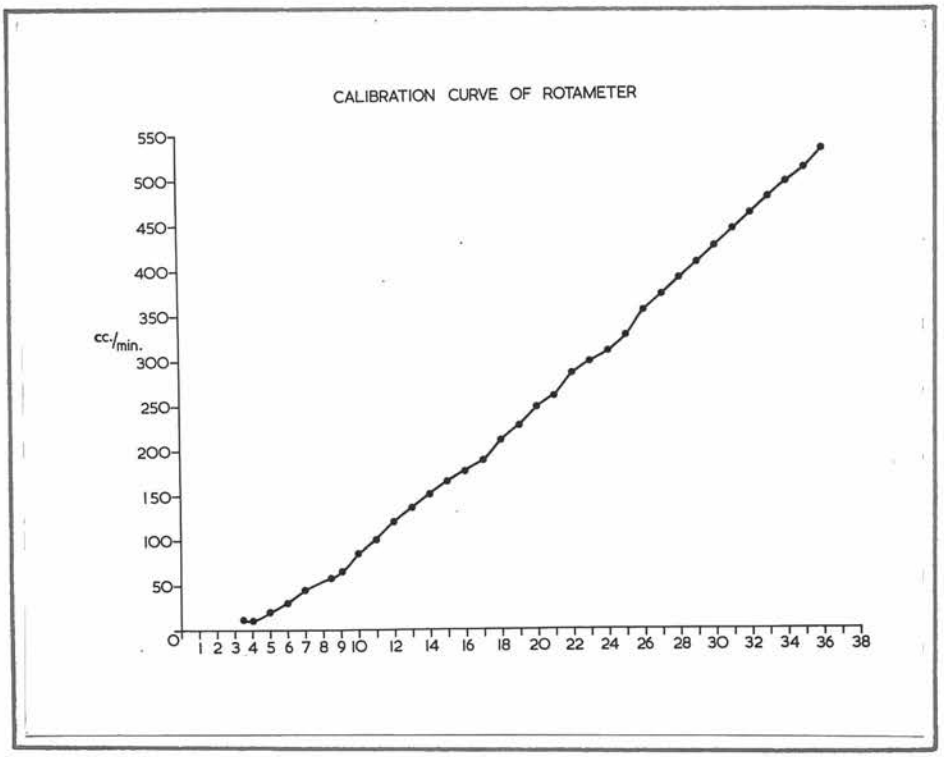

Fig. 91.- The results of a calibration experiment with the rotameter perfused with dog blood at 37°C.

APPENDIX B

A Rotameter for Measurement of Portal Venous Blood Flow

The rotameter described by Shipley (1950) was selected as the most suitable method for measuring portal venous blood flow, because of its inherent low resistance to flow, its accuracy and stability and its ease of application over a wide flow range.

The rotameter tube was machined on a lathe from a solid cylinder of perspex, using a tapered drill. The internal surface of the tube was then very carefully smoothed and polished to eliminate any irregularities in its surface. The effective length of the measuring chamber was 10 cm. A float was also machined, its head being specially polished to act as a lens so that its relative position could be easily determined when the tube was trans-illuminated by a 500 Watt spot-light.

Calibration experiments were carried out, using dog blood, and the weight of the float was adjusted until the apparatus was capable of accurate flow measurements between 60 and 550 ml./min. The rotameter was then mounted on a stainless steel case, to which an arbitrary scale was attached.

Numerous in vitro calibration experiments were carried out in order to test the apparatus at different temperatures and varying haematocrits (Fig. 91). Alterations of the temperature or haematocrit of the perfusate likely to be encountered /

encountered *in vivo* did not materially affect the calibration of the instrument. The pressure drop across the meter and its connections was found to be 3-5 cm of saline at 300 ml./min. In practice, the rotameter was found to provide a versatile, accurate and simple technique for measuring portal venous flow.

APPENDIX C

A New Type of Recording Manometer

The majority of pressure recording systems are designed to measure the distortion or deflection of a diaphragm. In these systems a change in volume corresponds to a change in pressure and unless amplification is used the ratio of volume change to the corresponding pressure change (Frank's volume elasticity coefficient; Frank, 1903), may be large when an attempt is made to record from low pressure systems, thereby severely limiting the method. However, if the problem is approached from another angle, it is possible to devise a method which obviates this difficulty. In many physiological and clinical circumstances it is possible and convenient to perfuse a system and derive the pressure by direct measurement of the rate of flow of the perfusate.

Poiseuille's Law states that the volume of fluid flowing through a tube in unit time is proportionate to the pressure difference between the ends of the tube and the fourth power of its radius; and inversely to the length of the tube and the co-efficient of viscosity of the fluid.

If, therefore, one end of a given tube can be maintained at a given pressure P while the other end is in a region of unknown pressure Px, then with a liquid of constant viscosity, the difference in pressure between the ends can be found from the expression:-

pressure difference $(P - Px) = kv$, where v is the rate /

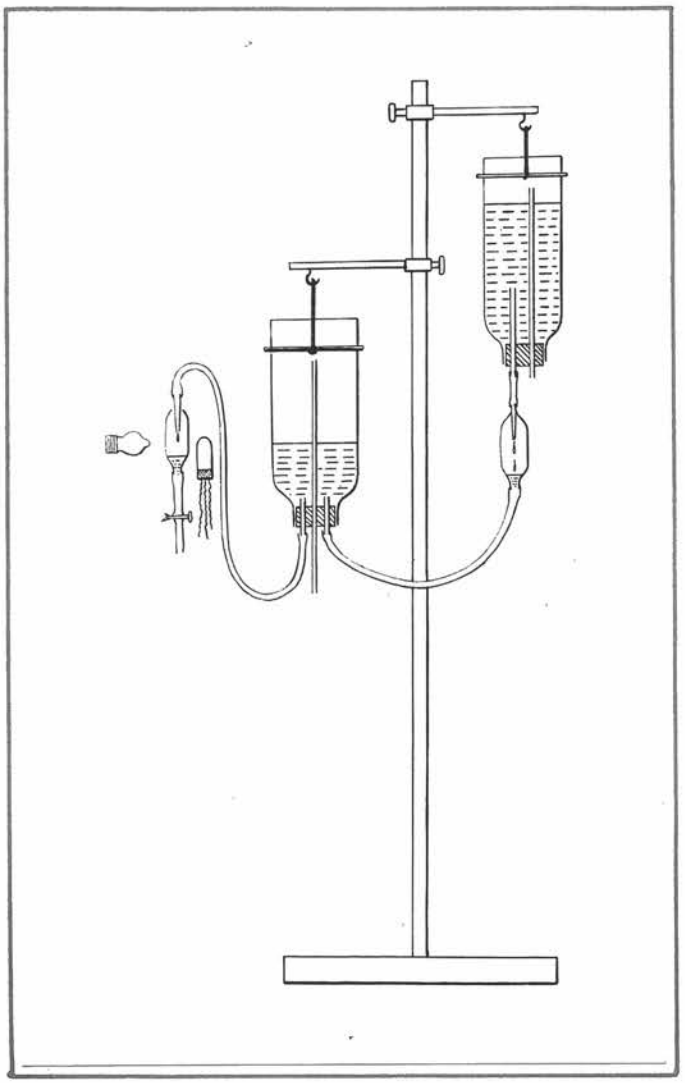

Fig. 92.- The perfusion circuit and photo-transistor drip rate recorder.

rate of flow.

If the rate of flow is expressed in terms of number of drops per second, then

$v = \frac{1}{t}$ where t is the time interval between the drops,

i.e. pressure difference $= \frac{k}{t}$

Px can be determined from the time interval between drops because P is known to be the difference in centimetres between the level of the fluid in a constant level reservoir and the point at which the determination is being made.

The method is straightforward. Two bottles of saline are connected through a drip chamber as shown in Fig. 92. The first acts as a reservoir to maintain the level in the second, the latter being connected through a further drip chamber to the unknown pressure system by relatively large bore tubing. The flow from both bottles is controlled by screw clips, and the constant level bottle has a third tube, open to the atmosphere, thus preventing any build-up of pressure in the bottle.

The rate of flow is set at a suitable value, as described below, and the flow from the reservoir is set to approximately the same rate. From time to time it is necessary to re-adjust the latter but changes in level occur very slowly. The light from a 2.5 v lens type bulb passes through the second drip chamber and falls on to an OCP71 photo-transistor. Each drop interrupts the beam, and the change in the transistor's current operates a relay (Telephone Manufacturing Co. Ltd. Carpenter Relay, Type 3117).

3117).

The drip rate is recorded by a method similar to that described by Gaddum (1938). A pen is driven by a synchronous electric motor through a magnetic clutch and draws a line whose length is proportional to the duration of time the clutch is engaged. Each drop operates the relay, which releases the clutch, and the pen returns to its former position; there it waits for a certain time, depending on electrical constants in the circuit, after which the clutch automatically re-engages and the pen again traverses the paper. By a suitable choice of waiting period, and the linkage operating the pen, the relationship between pressure and displacement of the pen can be made approximately linear. The pen will record only if the time interval between drops is greater than the pre-set waiting period. By adjusting the clip the same rate of flow can be obtained with almost any pressure difference between the two ends of the tube, but once set, equal deflections can be obtained for equal proportional changes in pressure. The inoperative period is the equivalent of the "backing off" of a meter and so the scale can be varied over a wide range. The same instrument can equally well be used to measure changes of the order of 1 cm H_2O or of 100 cm H_2O.

Calibration is carried out against a centimetre scale using a suitable base line. If large changes in pressure occur during an experiment, alteration in the scale can be accomplished simply by alteration in the height of the constant /

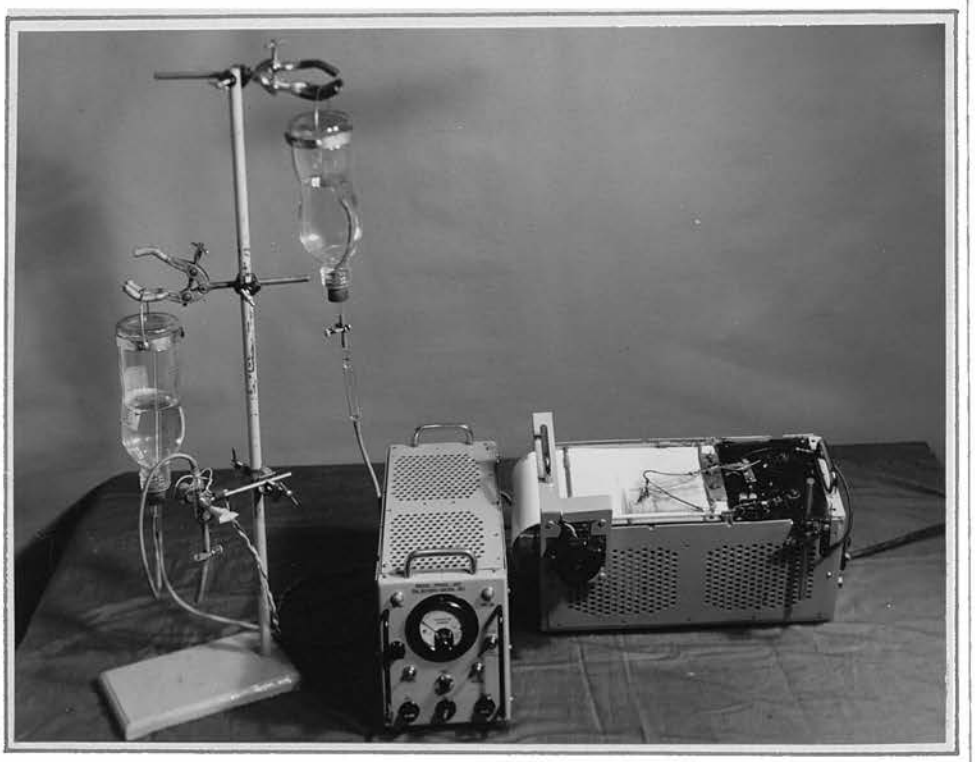

Fig. 93.- The assembled manometer with control unit and linear pen recorder.

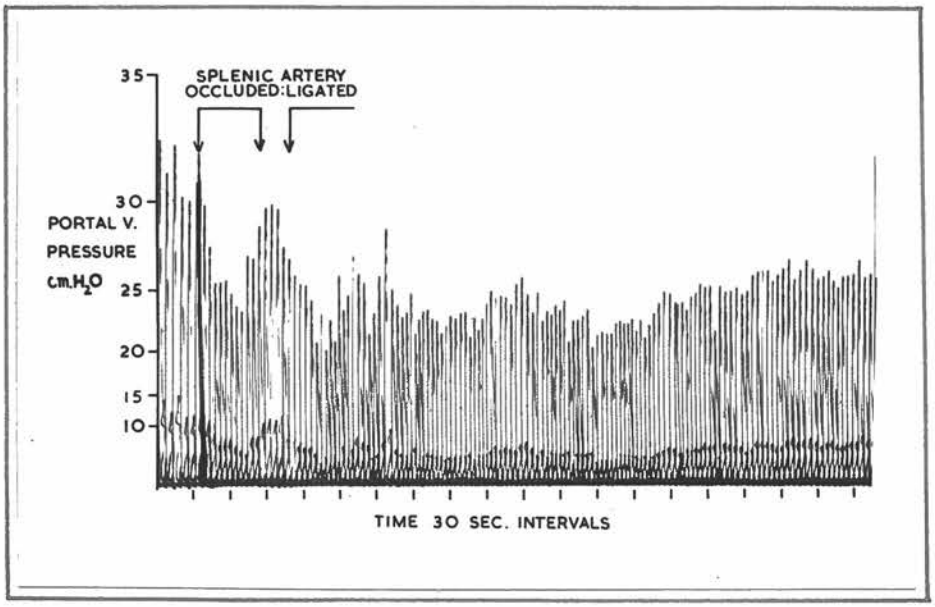

Fig. 94.- The effect of occlusion of the splenic artery on portal venous pressure in a patient with portal hypertension.

constant level reservoir, provided the actual movement from its initial position is subsequently added or subtracted from the calibration line.

The electrical and mechanical components of the control and recording units are of robust construction and this, together with the absence of valves, makes the apparatus portable and easy to maintain (Fig. 93). In its present form, the machine is not capable of recording rapid phasic changes in pressure such as occur in the arterial system. For non-pulsatile low pressure systems, however, it appears to possess many advantages, not the least being its simplicity and lack of drift.

This apparatus has been employed to obtain continuous recording of portal venous pressure in the dog and also during the course of various abdominal operations in man (Fig. 94).

This apparatus was designed in collaboration with Dr D.C. Simpson of the Department of Medical Physics, University of Edinburgh.

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