

THE HEPATIC VEINS IN HEALTH AND DISEASE

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V O L U M E 1

Chapters I to IV.

PREFACE

"La phlébite domine toute la pathologie" wrote Cruveilhier in his great work on morbid anatomy more than a hundred years ago. Since then venous disease has become of less account. No modern writer could make Cruveilhier's claim, and diseases of veins now receive less attention than they deserve. In many parts of the body compensation for temporary or permanent venous occlusions is readily achieved and functional perfection of the venous system masks the presence of extensive lesions. But this is not the case in the liver. Such channels as exist collateral to the hepatic veins are totally inadequate for the great flow of blood through the liver, and the organ is more affected than most other viscera by venous occlusions.

Where hepatic-venous occlusions are extensive compensatory readjustments of circulation may suffice for a while to obscure the severe congestion of the liver, but the clinical manifestations are eventually striking. This occurs in the Budd-Chiari Syndrome, and a chapter of this thesis is devoted to cases of that condition in which the occlusions were not secondary to disease of other organs. In another chapter experimentally induced venous congestion of the liver of the rat is described. Although the Budd-Chiari Syndrome is rare, these instances of severe venous congestion are of general interest in relation to other and commoner hepatic conditions. Passive venous congestion of the liver is a frequent sequel to heart failure. The simplicity of pathogenesis in the conditions studied here however, and, in many instances, the slow tempo of their

advance make them useful standards of comparison in any investigation of the more complex pathogenesis of portal cirrhosis and of the phenomena of ascites. Further, the recent descriptions of "Veno-occlusive disease" in Jamaica and possibly elsewhere makes it desirable to reassess the causes and effects of occlusions of the hepatic veins as they are encountered in this country.

To understand the causes of hepatic-venous occlusions and their effects on the liver it is necessary to consider some of the less known facts and some debatable theories concerning the normal structure and the function of the hepatic-venous system in health and these form the subject in the earlier chapters of the thesis. The afferent portions of the hepatic circulation have been studied widely in the past few decades in connection with diseases of the liver, but the efferent portions have been relatively neglected. Accordingly some of the scattered information on the structure of the hepatic veins of man has been reviewed and checked by personal observations. Similar studies on animals are of almost equal importance because structural differences exist between species which render it impossible to extrapolate unreservedly to human problems the results of observations on the hepatic circulation in animals. While observations on structure cannot be translated directly into functional terms, function can be understood only in the context of structure, whether that be gross, microscopical or ultra-microscopical. Where direct measurements of flow, pressure and other elements are few or unreliable, as in the case of the

hepatic veins and their small radicles, useful deductions regarding the action of the vessels and the flow through them can still be drawn from a sufficiently comprehensive examination of their structure.

ACKNOWLEDGEMENTS

The work for this thesis was carried out in the Departments of Pathology of Glasgow University at the Western Infirmary and of the Queen's University, Belfast. It is a pleasure to acknowledge my indebtedness to Professors D. F. Cappell & J. H. Biggart for their encouragement and criticism as well as for the provision of facilities. To the technical staffs of the two departments I am greatly obliged for the preparation of histological sections and for assistance with animal experiments. The files of the two departments have provided most of the clinical data and autopsy material used in this thesis but I am also obliged to clinical colleagues for free access to their records. Dr. J. E. Morison of Belfast, Dr. T. G. Milliken of Dungannon, Dr. W. A. Hopkins of Londonderry & Dr. J. Higginson lately of Johannesburg, South Africa have also kindly sent me material or clinical data.

My thanks are due to colleagues in other departments of the Queen's University, Belfast whose valued assistance at various stages in the work has been recorded in the appropriate places. I am also grateful to Mr. D. W. Neill for carrying out electrophoresis of proteins in some of the experiments and for other assistance on biochemical questions.

I wish to thank Mr. D. McA Mehafeey of Belfast for printing the black and white photographs and for making the negatives of many of them. A few of the photographs were taken

by Mr. S. Kerr of Glasgow and other photographs and most of the drawings are the work of the author. Figures 148 and 149 were drawn by Mr. George Smith of Belfast and figure 118a by Mr. Gabriel Donald of Glasgow. Where figures have been copied from the published work of others, due acknowledgement has been made in the captions. For the typing I am obliged to Miss R. McGurk and Miss A. Quinn. The colour prints are commercial productions.

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CHAPTER I

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THE HEPATIC VEINS IN MAN

Glisson depicted the anatomy of the hepatic venous system accurately in 1654 (Fig. 1) and Rex (1888) made important contributions to our knowledge by his detailed investigation of the liver blood vessels from the viewpoint of comparative anatomy. Few anatomists, however, devoted much attention to the hepatic veins till interest was rekindled recently by the search for safe planes for surgical excision of portions of the liver. The studies of Elias and Petty (1952) and of Gans (1955) on polyvinylite casts of the blood vessels were undertaken with this in mind and now provide a basis for more adequate knowledge. These authors described the location and composition of the main hepatic veins and reviewed most of the previous literature, but they directed their closest attention to the structures of Glisson's capsule. The gross studies reported here were carried out in large part before the two recent works were published. They confirm many of the findings in the latter, in so far as they go, but since the present investigation was intended chiefly to elucidate pathological findings, more attention has been paid to structures that could act as venous barriers.

The microanatomy of the hepatic veins of man has not been described adequately elsewhere. Franklin's review (1937) of the findings of a number of workers in this field and Andrews' more recent (1957) but much briefer summary reveal a diversity of findings and many gaps in knowledge. Variations in terminology have also obscured the subject. The most useful accounts of the structure of the larger hepatic veins are

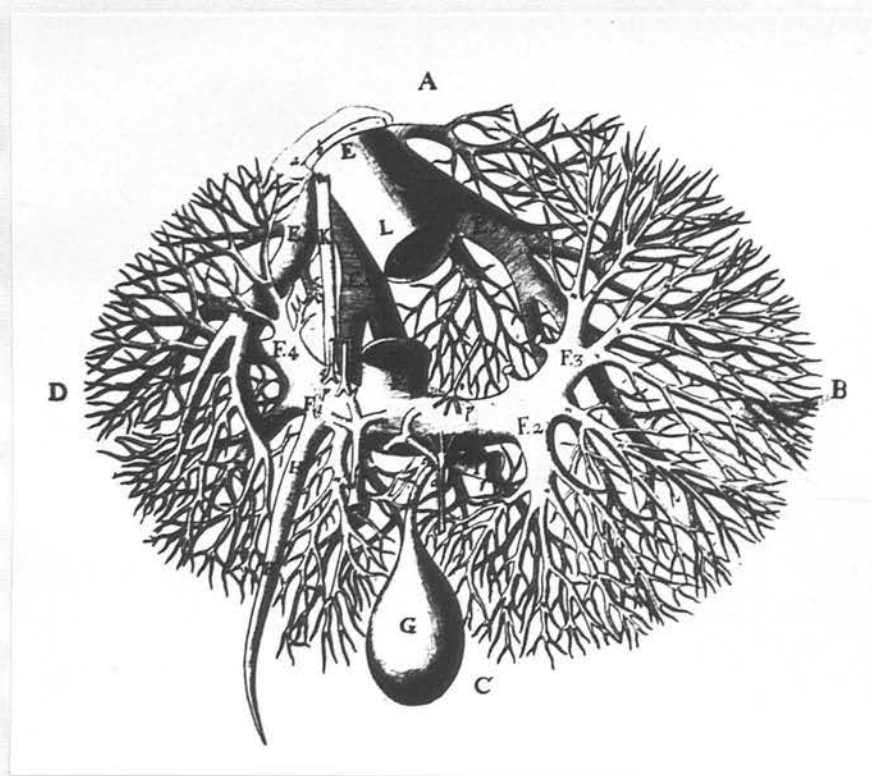


Fig., 1. Glisson's pictures of the portal and hepatic venous systems in man published in 1654. They have been recopied from Gans (1955) and show an anterior (above) and a posterior view (below).

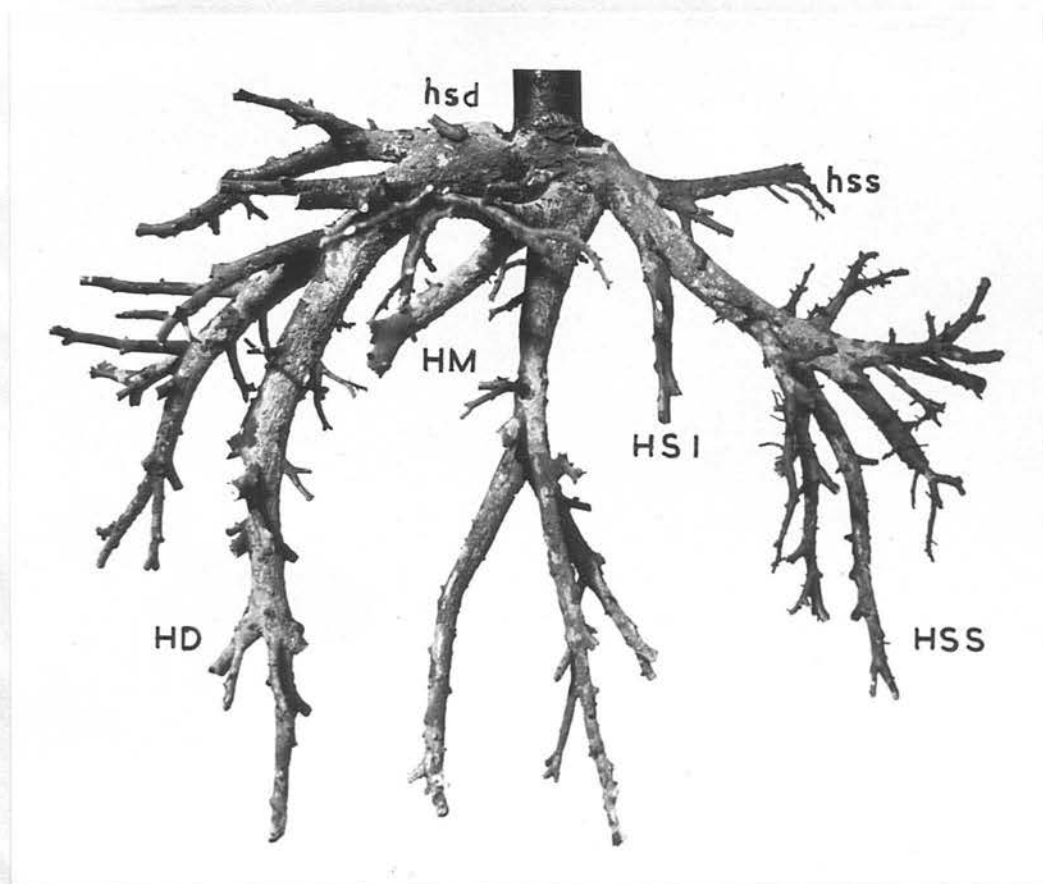


Fig., 2. An anterior view of a plastic cast of the hepatic veins injected from the inferior vena cava above. The veins have been labelled according to Elias & Petty (1952).

HD.	vena	hepatica	dextra.
HM	"	"	media.
HSI	"	"	sinistra inferior.
HSS	"	"	" superior.
hsd.	venula	superior	dextra.
hss.	venula	superior	sinistra.

those by Miyake (1928 - 30) & Tischendorf (1939) but they are deficient in many particulars, while some of the statements in Pfuhl's (1922) generally excellent account of the smaller veins require correction or amplification. The purposes of this fresh investigation are to remedy some of the deficiencies of the available accounts in description and illustration, to define the characters of the various veins by measurements and by study of their composition and so to reconcile where possible the views of others.

In the following account the hepatic veins are described throughout their courses and attention has been directed particularly to those aspects of structure which may have a bearing on normal function and on pathological processes. To avoid undue repetition the findings of others have been discussed pari passu with a systematic description of the author's own findings.

MATERIALS AND METHODS OF INVESTIGATION

A large number of casual observations on gross and microscopical anatomy have been made on upwards of 1000 autopsies performed over the past 10 years in which I have been interested in the subject. In addition about 100 blocks selected from the autopsy material have been specially stained by the picro-Mallory (Lendrum & McFarlane, 1940) method for muscle, supplemented by stains for elastica, reticulin, nervous elements and other structures in many instances.

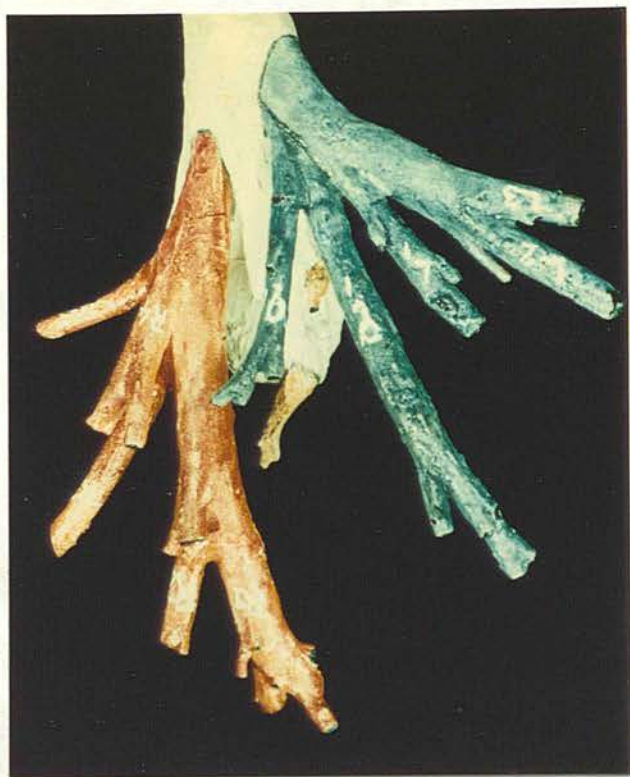


Fig., 3. A plaster-of-paris cast of the inferior vena cava (white) and proximal portions of the hepatic veins (coloured), viewed anteriorly. The radicles of the right ostium, marked R1 etc., are on the left. On the right the veins from the left lobe are marked L1 (HSI) and L2 and L3 (HSS). The radicles from the quadrate lobe q1 and q2 make up HM. At the lower end of the cava is seen the short stem of HCD.

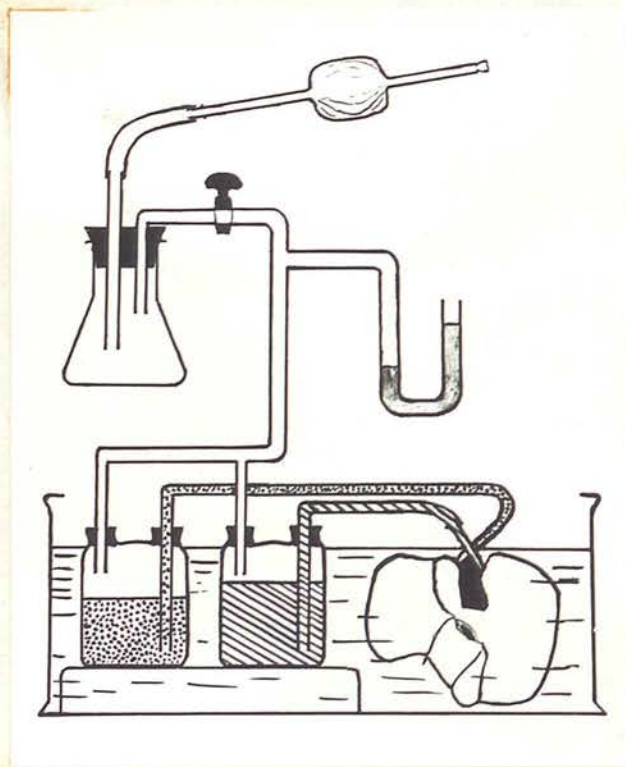


Fig., 4. Diagram of the apparatus used for injection of warm coloured-gelatine masses into the hepatic veins of human livers. The liver is supported in saline at 37°C . in a large bath which also accommodates Woulffe's bottles containing the injection masses. Air pressure is supplied by a Higginson's syringe, buffered and controlled as necessary.

Injection preparations: Studies were made of 14 retrograde-injection preparations of normal livers including the livers of a foetus of 1900 gm. and of a 3-day-old infant. Single casts were made in plastic of unknown composition (Fig. 2) and plaster-of-paris (Fig. 3). In five cases neoprene latex was injected (Fig. 17) and in seven warm coloured gelatine was used (Fig. 10). Injections were made into either the vena cava or hepatic veins after canulation and ligation of appropriate vessels, the portal vein and hepatic artery being left open till the injection was completed. Most of the blood was cleared from the livers by brief preliminary perfusion through the canulae with water or saline. Prolonged perfusion led to cellular damage and swelling. The depth of penetration varied with the media and from one cast to another (e.g. Fig. 17), but this was not disadvantageous within the limits of the information sought, and different structures were shown to advantage in different casts. Except for the plaster-of-paris cast, all livers were supported in fluid during injection, hardening and digestion. Pressures of 15 - 22 mm. Hg. were employed, usually by elevating the reservoir. For gelatine injections, the liver and gelatine reservoirs were put together in a bath of warm saline and the pressure supplied intermittently by a Higginson's syringe and damped down by an intervening air reservoir (Fig. 4); the resulting pressures were 5 - 15 mm. Hg. Although the pressures used were higher than those prevailing normally in the veins (6 mm. Hg.) they were desirable for rapid penetration and produced no evident damage. Even with the pressures used, the only material that entered the sinusoids

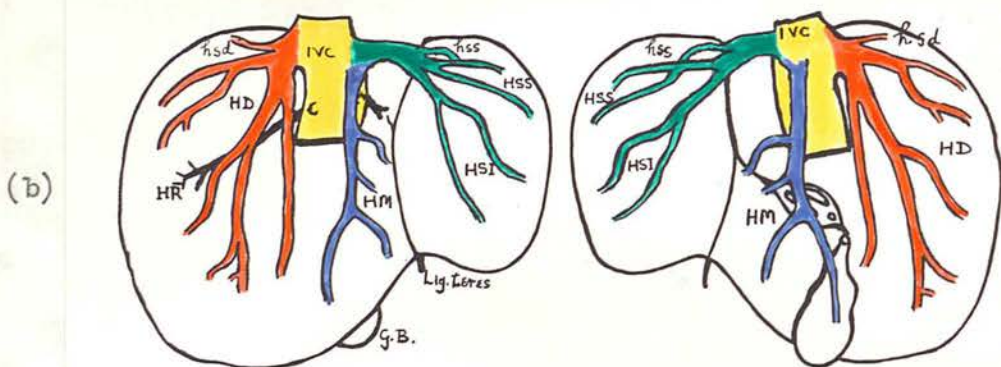
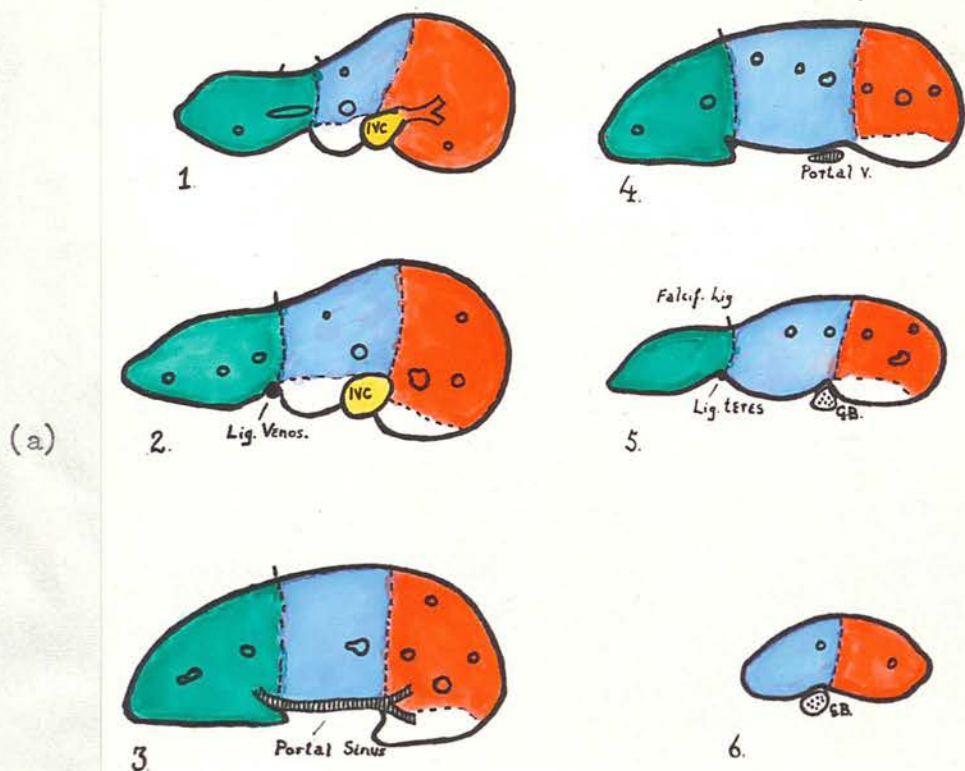


Fig., 5. Sections (a) and reconstruction (b) of the hepatic veins and the territories they drain, from a gelatine injection preparation. The veins have been labelled according to Elias & Petty (1952).

HD.	vena hepatica dextra.
HM.	" " media.
HSI.	" " sinistra inferior.
HSS.	" " " superior.
HR.	" " dorsalis.
hsd.	venula superior dextra.
hss.	" " sinistra.

at all was neoprene and when this penetrated into the lobules it did not go far.

Livers injected with neoprene were fixed overnight in acidified formalin to preserve their shape and immersed in strong commercial hydrochloric acid for varying periods up to 3 days. The casts were washed intermittently in water to clean them and examined grossly; portions for microscopical study were removed by teasing or else cut out in blocks and sectioned on a freezing microtome at thicknesses of about 200 μ . A shrinkage of about one quarter occurred in neoprene casts of the larger vessels. Photography is unsuitable for recording findings in such thick sections and camera-lucida drawings were made instead (Figs. 24-26 and 32-34). The coloured-gelatine-injection technique was used to map grossly the territories of the various hepatic veins and to trace the relations of the veins to the liver parenchyma. The injected livers were hardened in cold formalin and sectioned in either sagittal or horizontal planes at intervals of 1 cm. or more. Drawings were made of each section and transposed on to outline diagrams of the liver. An example is shown in Fig. 5. A few thick frozen sections were cut for microscopical examination. They proved more difficult to interpret microscopically than the latex casts and little information was obtained from them in comparison.

Gross terminology: The veins were originally denominated in the reconstructions by letters indicating to which of the main hepatic-vein groups, right, quadrate or left they belonged and by numbers corresponding roughly to the sites of termination

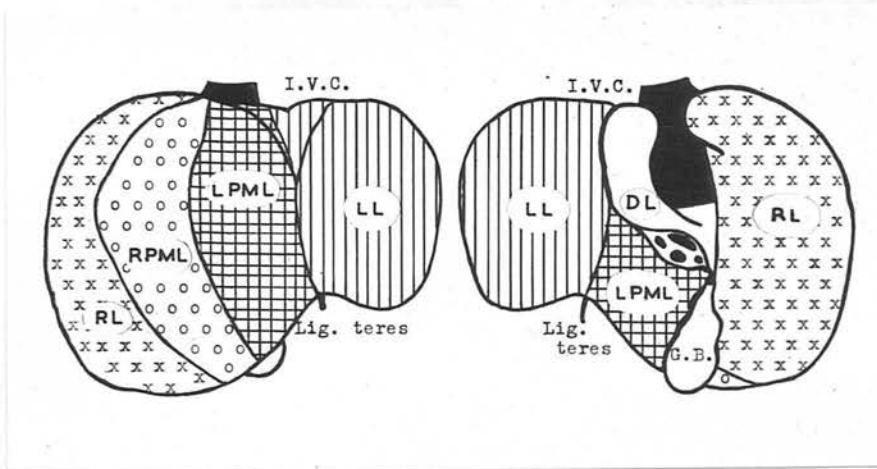


Fig., 6 (a), shows the lobation of the liver according to Gans (1955) but simplified. Rex (1888) illustrated similar boundaries in his figure 10, labelling the territories according to their portal supply. His terminology is shown after the names used by Gans, as follows:-

Right lobe	- R. arcuatus et descendens	- RL
Right paramedian lobe	- R. arcuatus	- RPML
Left paramedian lobe	- rechtes Astwerk	- LPML
Left lobe	- linkes Astwerk	- LL
Dorsal lobes		- DL

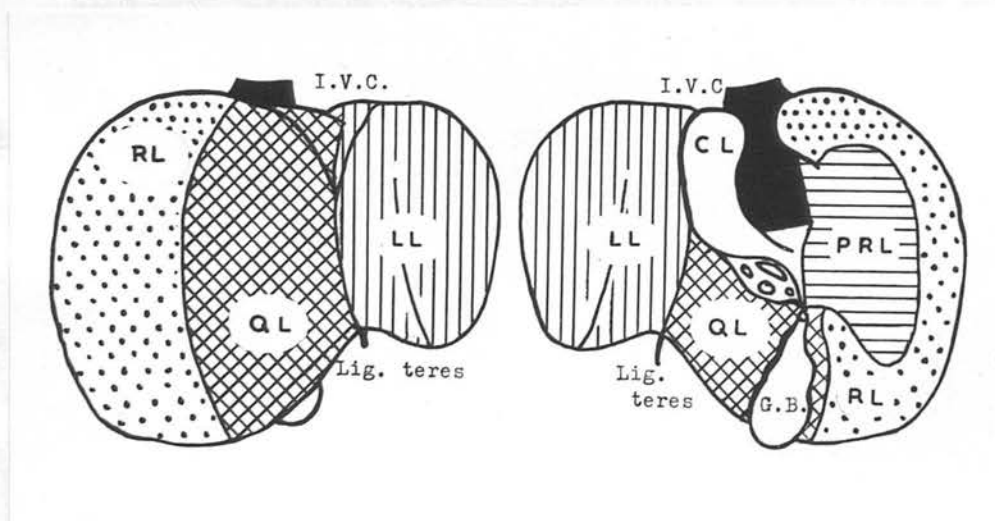


Fig., 6 (b), shows the vascular territories drained by separate hepatic veins as mapped out for this thesis. The territories have been denominated as follows:-

RL - right lobe; QL - quadrate lobe;
 CL - caudate lobe and process;
 PRL - paracaval portion of right lobe.

in the main trunk (Fig. 3). Although this terminology has advantages in comparing the individual veins in one preparation with those in another, it has been abandoned here in favour of that introduced by Rex and adopted by Elias and Petty and by Gans, because the latter gives a more exact indication of the territory drained. The ostia were found to be constant individually with small variations, but the amount of variety encountered in the make-up of their immediate radicles was so great that they have not been classified fully.

Several schemes of lobation of the human liver have been put forward. Although the Basle Nomina Anatomica (1895) are too widely employed to be abandoned here, use is also made of a scheme (Fig. 6a) put forward by Gans. Like some others to which its author refers, the scheme is based on the courses of the afferent blood vessels.

LOBATION OF THE LIVER

The plane of the falciform and round ligaments appears as the basic plane in the B.N.A. but, since it perpetuates the course of the embryonic left umbilical vein, it is not in a true sense a mid-line structure. Studies on animals (Chapter II) also indicate that the falciform-ligament plane does not divide the liver into comparable halves. Cantlie in 1898 (Fig. 7) was the first to state clearly the position of the other plane in man. He claimed that "The gall-bladder occupies a central position in the liver; that on either side of it lie the right and left lobes of the liver and that a line from the fundus of the gall-bladder to the exit of the

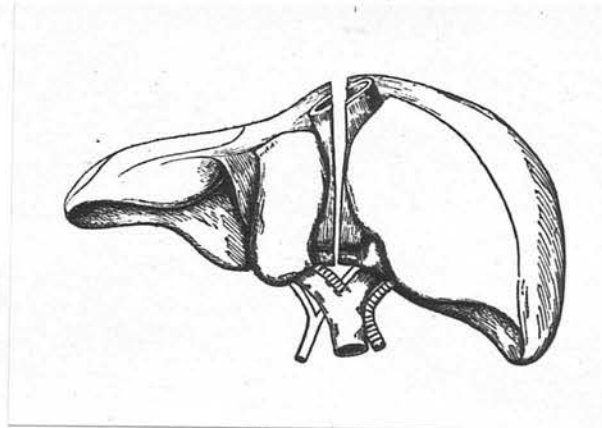
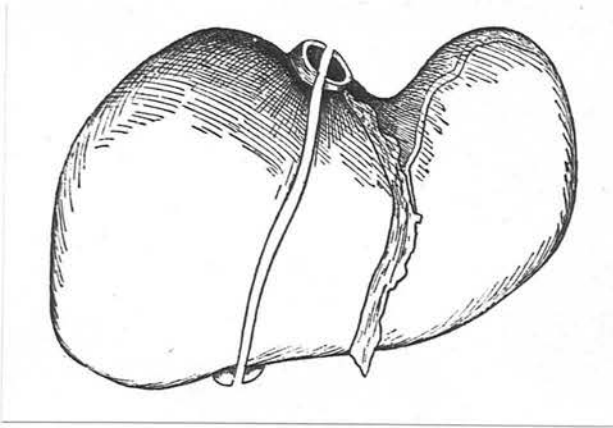


Fig., 7. A copy of Cantlie's (1898) original illustrations of the plane bisecting the liver. The line of division on the anterior surface of the liver is often called the "line of Cantlie".

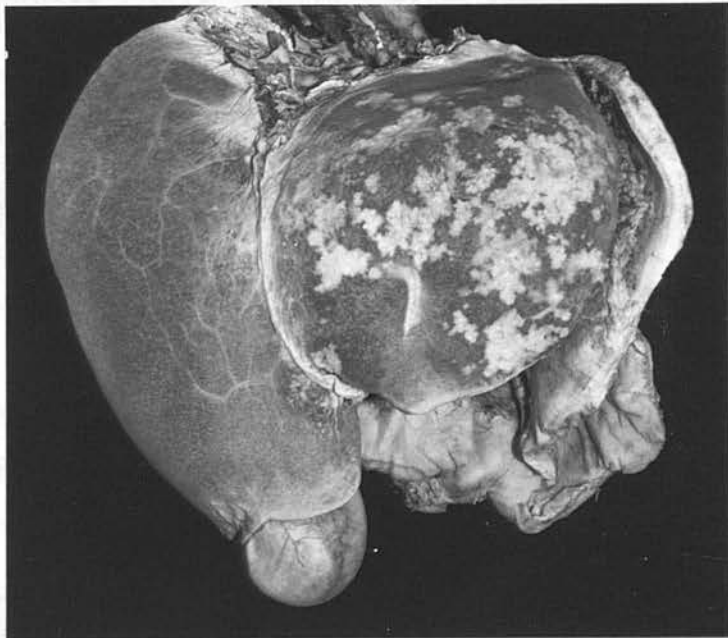


Fig., 8. A carcinoma of the stomach seen infiltrating the gastric wall on the right of the picture has metastasised to the left but not to the right lobe of the liver. In this case the portal blood from the gastric field which was carrying tumour seems to have reached the left lobe only. Direct spread to the liver had not taken place.

hepatic veins divides the liver into equal portions as shown by injections, by weighings, by developmental, by pathological and by clinical observations". Although Cantlie is usually given the credit for describing this "line of Cantlie", Rex (1888) illustrated it in his diagram of the portal-venous territories which is similar to that shown in Fig. 6a.

Cantlie's findings have often been confirmed since in relation to the portal distribution. Sérégé (1901), who described the same line of division in the liver stated that the tissue to the left of the line received its portal blood from the splenic vein and the tissue to the right from the superior mesenteric. He was of the opinion that the two streams mixed very little in the portal stem and so he was the first to enunciate the principle of portal streamlines. The truth of this principle has been disputed; occasional pathological findings tend to support its validity. An example is shown in Fig. 8. Portal venography via the spleen, however, usually fills the portal branches of the right lobe better than those on the left.

Quadrate lobe: As the term is used in this thesis, it corresponds rather approximately to the left paramedian lobe in Gans' scheme of lobation (Figs. 6a & 6b) and may be roughly defined as the liver tissue on the anterior and posterior surfaces of the liver between the falciform, round and venous ligaments on the left and the plane of Cantlie on the right. Though apparently a middle lobe in man, this central liver mass is more closely related to the left side. Both left and quadrate lobes derive their portal blood from the left part of

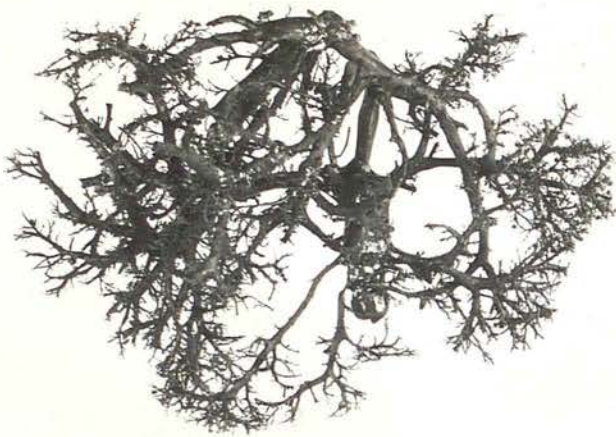
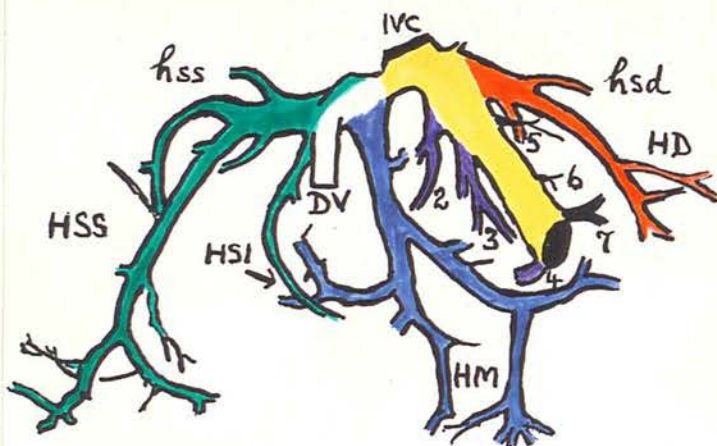
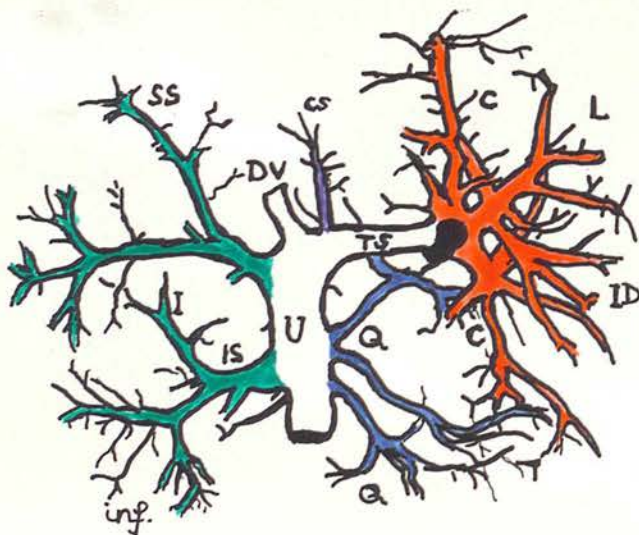


Fig., 9. (a) Neoprene latex cast of the hepatic cava and veins in an 1800 gm., fetus. The portal vein and its branches have filled through the ductus venosus. The cast is shown here complete and viewed anteriorly.



(b) A sketch of cava and hepatic veins in the above cast, viewed posteriorly. The hepatic veins have been separated from the portal veins by section of the ductus venosus. A key to the lettering is given opposite.



(c) A sketch of the portal and umbilical-vein branches in the above cast viewed posteriorly. The termination of the portal vein in the sinus is shown in black. The rami centrales of the right lobe (c) arise in man to the right of this termination.

Fig. 9. Key to lettering. The terminology is that of Elias & Petty (1952) which is based on Rex (1888).

Hepatic System.

- | | |
|--|--|
| HSS - vena hepatica sinistra superior. | 2. hcs - venula hepatica caudata superior. |
| HSI - " " " inferior. | 3. hci - " " caudata inferior. |
| hss - venula hepatica sinistra superior aut cranialis. | 4. hc " " processi caudati. |
| DV - ductus venosus. | 5. HDL - vena hepatica dorso-lateralis dextra. |
| HD - vena hepatica dextra. | 6. HR - vena hepatica dorsalis. |
| HM - vena hepatica media and radicles. | 7. HCD - vena hepatica dorso-caudalis. |
| hsd - venula hepatica dextra superior aut cranialis | |

Portal System.

- | | |
|---|--|
| SS - ramus cranialis aut superior lobi sinistri. | Q. - rami quadrati. |
| IS - truncus communis ramorum intermedi et caudalis aut inferior lobi sinistri. | C. - rami centrales lobi dextri. |
| I - ramus intermedius. | L - ramus lateralis dexter. |
| inf. - ramus caudalis aut inf. dexter. | ID - ramus caudalis aut inferior dexter. |
| U - pars umbilicalis trunci sinistri; it leads from the vena umbilicalis below: U in the adult is the recessus umbilicalis of the left portal vein (Rex). | |
| TS - pars transversa trunci sinistri. | |
| DV - ductus venosus. | |
| cs - ramulus caudatus sinister. | |

In black - termination of portal vein.

the portal sinus (Elias & Petty; Gans) and this can be traced back to the embryonic vascular arrangements, when both lobes form parts of the pars umbilicalis or portion of the developing liver supplied with umbilical and not with portal blood. Fig. 9, a cast made from a foetus at the end of the 8th month when the left lobe is still large, shows that the quadrate lobe is supplied by the branches (Q) on the right side of the pars umbilicalis trunci sinistri (U). The left lobe derives its blood from the left-sided branches (IS and SS).

The vein draining the quadrate lobe shares the left ostium with the left hepatic vein for a centimetre or so (Figs. 2, 3 & 5) although it is to a large extent autonomous. The preparations by gelatine injection into the hepatic ostia (Figs. 5, 10 & 14) show that the "watershed" of venous drainage to the main ostia lies 2-4 cm. to the right of the line of Cantlie on the anterior surface of the liver. This watershed varies somewhat from one liver to another and, on account of small anastomoses, liver tissue for 3-4 cm. can drain to either ostium, but chiefly to the left.

Caudate lobe (lobus Spigeli) and process: In injection preparations this is found to extend anteriorly in the substance of the liver to the levels of the portal sinus below (Fig. 10b) and of the anterior surface of the cava above (Fig. 5). The lobe and process are autonomous in venous drainage and comprise the two dorsal lobes of Gans' scheme.

Right lobe: On the basis of the Glissonian capsule and the distribution of the elements in it, the tissue to the right of

the line of Cantlie is divided into two parts by Gans, a right and a right paramedian lobe (Fig 6a). On the basis of the venous drainage, one can also separate the posterior surface of the classical right lobe from the rest, since much of this tissue drains or can drain by individual veins directly into the cava. The territories served by the inflow and outflow vessels do not, however, correspond closely enough to allow one to use Gans's terms, and the area with a separate drainage has been called the "paracaval portion of the right lobe" (Figs. 6b and 15) in this thesis. Most of the classical right lobe drains into the right ostium and the venous drainage on this side of the liver does not distinguish between lateral and paramedian portions as clearly as on the left.

Rex stated that the territories of venous drainage of the liver correspond to the territories of portal supply, i.e. the lobes he defined on comparative grounds. Gans found in man, on the other hand, that main hepatic veins or major radicles of them run between areas supplied by the major portal veins. Torrance (1957) points out that radicles of the hepatic vein lie at all levels between the corresponding branches of the portal vein and Couinaud (1954) shows the main hepatic veins running between his numbered portal segments.

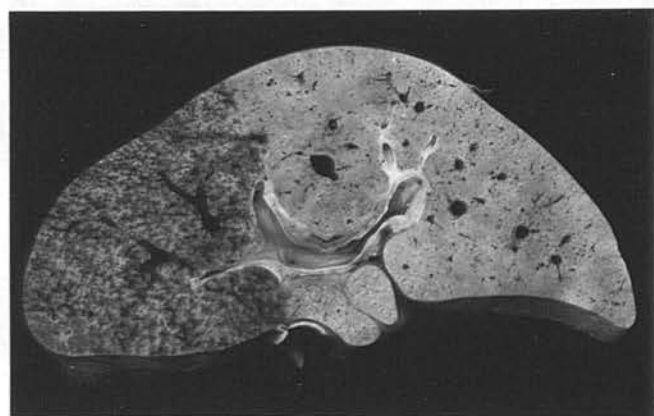
Knopp(1953) denies that the line of Cantlie divides the liver into portions of equal weight. He divided the liver, exclusive of the caudate lobe, in 3 root territories ("Wurzelgebiete") corresponding to the 3 chief hepatic veins HD, HM and HS and weighing on the average respectively 675, 365 and 285 gm. He states that the plane of hemisection of the liver lies between the first and the latter two territories



(a)

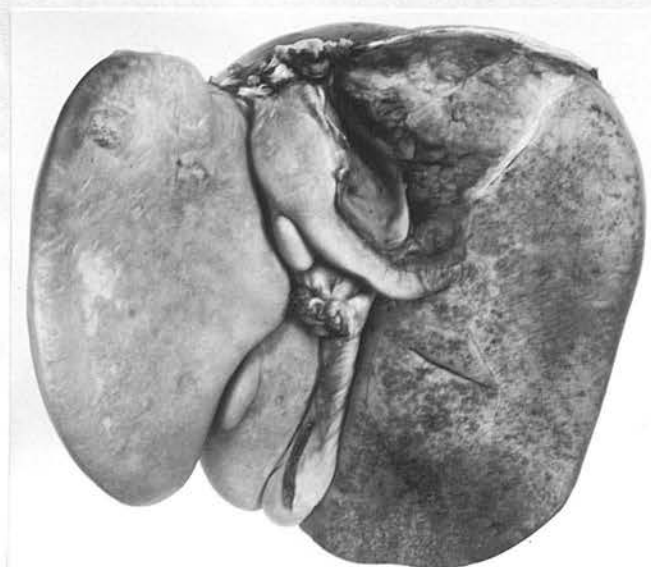
Fig., 10. A liver after injection of warm carmine gelatine into the right hepatic ostium and Berlin-blue gelatine into the left ostium. The carmine gelatine has penetrated deeper.

In the anterior view (a), it can be seen that the line of division between the territories of the two ostia lies 2-4 cm., to the right of the line of Cantlie.



(b)

In the mid section (b), the portal sinus (empty) has been cut longitudinally while most of the hepatic veins have been cut transversely. The caudate-lobe veins have not been injected.



In the posterior view (c), the paracaval portion of the right lobe is stained by the carmine gelatine which has entered this part as well as the main part of the lobe. The accessory ostia were not injected.

as shown in Figs. 6b & 10. The weights of the root territories bore a roughly constant relationship (the lumen index) to the cross-sectional areas of the veins at their terminations but Knopp's measurements of the latter are smaller than those given in this thesis (Table I) & in Nishikawa's paper (1918). Knopp does not seem to have allowed for the special drainage of the paracaval portion of the right lobe. The boundaries of his territories were found to vary, but the results approximated to those defined in the present work as shown in Fig. 6b.

Since there is so much variation between the portal- and hepatic-venous territories a modification of the conventional terminology of the liver has been used in this thesis and not one of the schemes of lobation based on portal-venous distribution.

Surgical considerations: In planning surgical incisions, the hepatic veins deserve close attention. Avoidance of medium-sized or large hepatic veins, which cannot collapse, decreases the danger of air embolism. The interdigitations of the portal and hepatic systems must also be kept in mind. The ramifications of the 2 systems alternate in any given plane and in the human liver they run in directions that are approximately at right angles to each other. The illustrations of Goldsmith and Woodburne (1957) give the most straightforward exposition of this and are confirmed by the more detailed observations on the hepatic veins in this thesis.

Left lobectomy through the plane of the falciform and venous ligaments avoids large and medium-sized hepatic veins,

and since the liver narrows there, often considerably, this incision will give less trouble from sinusoidal bleeding than others. It is advantageous however to cut a centimetre or two to the right of the falciform and ligamentum-venosum plane, because the left half of the portal sinus curves downwards terminally along this line. This umbilical portion of the portal sinus is marked U in the cast illustrated in Fig. 9.

A major difficulty in performing right hepatectomies lies in visualising the courses of the vessels when the whole outline of the liver cannot be seen at once. The landmarks used by Gans are not easy to recognize under operative conditions and this makes his scheme difficult to apply (Hobsley, 1957). The right ostium is not the only efferent vein from the right lobe, others being present lower in the cava. Finally the line of Cantlie is likely to prove too far medial to avoid H M or some of its large radicles (Fig. 10). Lloyd-Davies and Angell (1957) describe a successful right lobectomy through this plane and refer to some of the surgical literature. They report a wider variation in hepatic-venous drainage than what my experience or the scanty literature on the subject would indicate. As in the case of left hepatectomy, a compromise solution must be accepted and I am in agreement with Goldsmith and Woodburne in favouring a line 2 or 3 cm. to the right of the line of Cantlie. Couinaud depicts the lines of section in 8 different hepatectomies planned on segmental principles.

THE HEPATIC OSTIA

The main ostia, the right and left, are common terminal



Fig., 11. Junction of the right hepatic ostium (right) with the hepatic cava. The right ostium has been fixed partly dilated; many small veins join it. Part of the entrance of HM into the left ostium is seen.

The adventitial muscle bands of the cava cause striation of its inner surface. The loose attachment of the cava to the liver can be seen over the caudate lobe bottom left. The distal lip of the right ostium has a particularly loose attachment to the liver. It projects upwards as a fold which is made up partly of the caval and partly of the ostial wall x 1.6.

channels each made up by the junction of several large hepatic veins. Like the rest of the hepatic venous system they have no true valves. The right ostium (Fig. 11) is about 1.5 cm. wide and about 4 cm. long. The left is a little narrower (1.3 cm.) and shorter. It is less defined than the right because the two systems of veins that it receives unite close to the cava (Figs. 2 & 3). The proximal parts of the ostia are outside the liver. This free portion is short in the case of the right ostium but about 1 cm. of the upper part can be seen under the peritoneum when a little loose connective tissue above it is removed. The left ostium has only a partial investment of liver tissue, mostly round its lower surface. The horizontal portion of the left ostium lies above and slightly behind the superior convexity of the caudate lobe. It is extrahepatic in most of its course, separated only by loose connective tissue from the diaphragm and is not directly related to peritoneum. Small anterior portions of the left ostium derived from the quadrate lobe vein (HM) may however be visible directly under the peritoneum. Where the ostia lie within the liver they are loosely attached to the parenchyma by a mantle of lax connective tissue which is slightly thinner than that round the hepatic cava. Thus the ostia have partial freedom of movement throughout.

The loose attachments of the ostia permit indrawings of the walls to form annular constrictions along their lines of junction with the cava. These constrictions are inconspicuous, though present, at the proximal arcs of attachment (Fig. 20) but are readily seen along the distal lips where the angles of junction are more acute (Figs. 11, 12 & 21). At the lower

lip of each ostium a loosely slung fold is formed half by the caval and half by the ostial wall and it projects upwards. The middle part of this fold is loose-textured fibrous tissue with wide lymphatics in it (Fig. 21). As seen after careful fixation by ordinary methods the folds cause definite but not marked narrowing. They are less distinct in casts or when the vessels are otherwise dilated in fixation. The major hepatic veins though more firmly attached to the liver parenchyma than the ostia are not entirely immobile and, at the terminations of the major veins in the ostia where their attachments are loosest, there are distinct folds also. The small ostia accessoria located below the main ostia in the cava possess indistinct folds (Figs. 12). By fixation in hot formalin Elias & Feller (1931) were able to accentuate the folds at each end of the major ostia sufficiently to obstruct half the lumen. In fresh specimens, faradic stimulation or injection of pituitrin, ergot or barium chloride solutions had the same effect. The authors considered that the folds act as throttles to the venous outflow and Fig. 13, copied from Franklin, shows the method and effect of this action.

Left ostium: This drains the tissue from the quadrate and left lobes, that is to say the tissue to the left of the watershed shown in Fig. 10, with the exception of the caudate lobe and its process. The two large veins that drain the quadrate and the left lobe are the vena hepatica media (HM) and the vena hepatica sinistra (HS) and they unite close to their terminations to form the left ostium (Figs. 2 & 3). The extent of their union in the ostium is variable but they

are very rarely completely separate and the degree of variation is overemphasised in the simplified drawings of Lloyd-Davies and Angell. The veins are otherwise independent of one another in a manner roughly comparable to the anterior interventricular and left circumflex coronary arteries; injection of HM alone stains little more than the quadrate lobe. HM enters the ostium about 1 cm. from its junction with the cava. The left ostium is derived from the embryonic subdiaphragmatic anastomosis (Fig. 35) and the ductus venosus is attached to its lower aspect a short distance lateral to HM. An inconspicuous dimple can sometimes be found at this point in HS in the adult. The venula hepatica superior sinistra draining the most cranial portion of the left lobe (hss in Figs. 5 & 9) usually enters the ostium. It differs in its developments from other radicles of the ostium (Fig. 35) and Gans has observed a single instance where it emptied directly into the cava. The mouth of this variant is easy to distinguish however from that of a left phrenic vein which sometimes runs to join the cava about the same place. Phrenic veins have small valves at their mouths (Fig. 88), while valves are absent from all hepatic veins. A phrenic vein is more often seen on the right.

THE COURSES AND COMPOSITION OF THE HEPATIC VEINS

The main radicle from the quadrate lobe (HM) follows a vertical course directly in front of the cava 2-3 cm. from it (Fig. 5). One or two large veins from the superior portion of the lobe enter its upper part, but the most regular character of this system of veins consists in the prominent

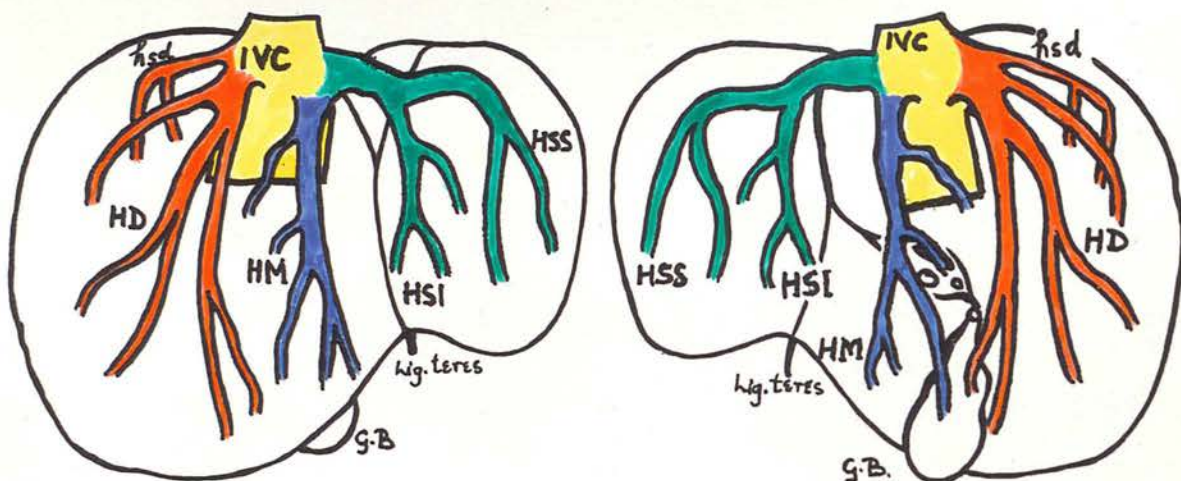


Fig., 14. Reconstruction of the hepatic veins from a gelatine-injection preparation. The veins are labelled as in previous figures. HSI is well developed in this liver and the fork on HM is present but not conspicuous.

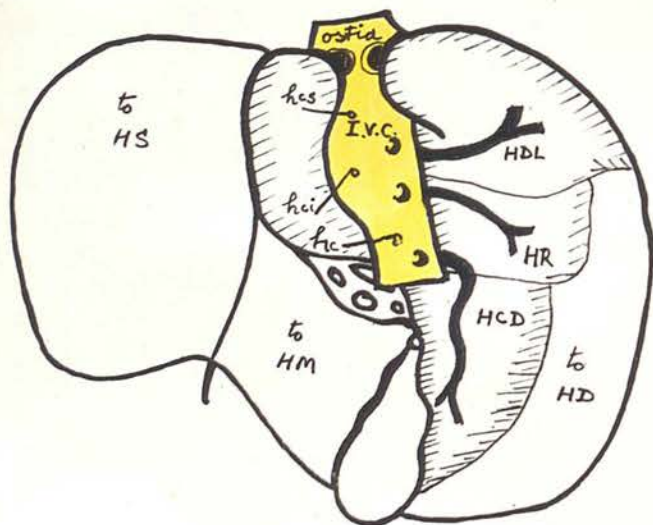


Fig., 15. The cava has been opened from behind and the ostia accessoria can be seen. Their territories are also shown. Elias & Petty (1952) named these vessels as follows:-

caudate lobe

- hcs - vena hepatica caudata superior.
- hci - vena hepatica caudata inferior.
- hc - vena hepatica processu caudati.

right lobe (paracaval portion).

- HDL - vena hepatica dorsolateralis dextra.
- HR - vena hepatica dorsalis.
- HCD - vena hepatica dorsocaudalis.

fork made by the junction of the two veins that give origin to HM inferiorly. This fork (the left and right branches noted by Rex) lies in a coronal plane and may perhaps serve to identify HM in radiographs of the hepatic veins. It is sometimes encountered in the corresponding veins in the rat and more often in the dog in which the two arms pass to opposite sides of the gall-bladder as they usually do in man. This peculiarity was depicted by Glisson (Fig. 1) in 1654 and may be seen clearly in Figs. 2, 5 and 14.

The main hepatic vein from the left lobe (HS) in the upper part of its course receives variable tributaries from the outer and upper portions of the left lobe as well as the small vein hss (Figs. 5 & 9) which is fairly constant and which drains the small amount of tissue above the level of the ostium. HS is made up of two main complexes, HSS from the intermediate and lateral zone and HSI from the lower and medial parts of the lobe (Fig. 6b). HSI may be as big as HSS (Figs. 5 & 14) or a small vein (Fig. 2). In the latter case some of the inferior parts of the lobe are drained by HSS. HSI runs upwards in the middle of the liver about 3 cm. distant from the right margin of the left lobe and enters HS proximally (Figs. 2 & 3 L 1).

The caudate lobe and caudate process are served by a number of veins (venae breves, Figs. 12 and 15) terminating as accessory ostia which empty directly into the left side of the cava. The ostia are somewhat constricted at their caval junctions. The vessels, though variable, have been named separately by Elias and Petty as the venulae hepaticae caudatae (hcs and hci) and the venula processu caudalis (hc).



Fig., 16. An intravital venogram of HD showing the contours of the main vein and some of its radicles which enter chiefly from a lateral direction. (Figs., 16 & 18 have been copied from X-rays kindly lent me by Prof. G. M. Bull and Dr. H. Shephard.)

The largest venous territory of the fully developed human liver is that on the right. It drains chiefly into the large vena hepatica dextra (HD) which is derived from the right vena revehens (Fig. 36) and terminates as the right ostium partly buried in the liver. It receives the small vein hsd (Figs. 9, 12 & 14) from the tissue above and lateral to it. The ostium is made up by the confluence of a number of large veins with HD. It is directed upwards and a little medially so that it continues on the course of HD which starts to the right of the gallbladder and runs in an upward and slightly leftward direction (Figs. 5 & 14). Most of the radicles thus enter HD on its lateral and ventro-lateral aspects. This was shown in Glisson's drawings (Fig. 1) and is visible in casts (Figs. 2 & 3) and in radiographs (Fig. 16) of the vessel.

A considerable proportion of the right lobe, the paracaval territory which includes much of the right lobe of Gans, sends at least part of its blood by a number of small veins with their own little ostia (the ostia accessoria) directly into the cava. These vessels, which are variable, are grouped by Gans with the caudate lobe veins as the venae breves but they have been named separately by Elias and Petty (Figs. 12 & 15). The third and lowest, the v. hepatica dorsocaudalis (HCD), is extrahepatic in the last centimetre of its course and the others may be partially so.

Anastomoses between venous territories: In the gelatine-injection preparations filled from the main ostia only, it was common to find more or less complete spread from the main part

of the right lobe into the neighbouring paracaval portion drained by *venae breves* (Fig. 10c) and this part of the liver seems to enjoy an exceptionally favourable venous drainage by partial duplication. Elias & Petty refer to many small anastomoses in this region. There is also an overlap in drainage amounting to a few centimetres where the right lobe joins the quadrate lobe above the gallbladder. This is visible most easily when the injection mass enters the sinusoids but it can be made out even when the veins only are filled. The sinusoidal network intercommunicates freely throughout the liver irrespective of lobular or lobar boundaries and, if the vessels of only one lobe are injected and those of its neighbour left empty, a moderate amount of diffusion may occur at this level. Under the usual conditions of injection in this study with equal pressures in neighbouring territories the lobar boundaries were more distinct. With the exceptions noted above, hepatic veins seldom cross lobar boundaries and those that do are always small. Goldsmith and Woodburne found no anastomoses of significant size or number between radicles of the hepatic-venous system. Mall (1906), Gans and Elias and Petty frequently found anastomoses between ramifications at the level of small hepatic veins, especially in superficial areas, but apart from the instances noted above the anastomoses are apparently between radicles within a single lobe. Other anastomoses seem to be often the result of minor pathological conditions such as partial fibrosis, which is common particularly in superficial zones of the liver anteriorly. Immediately below the superficial level, the territories of each vein are distinct, and anastomoses

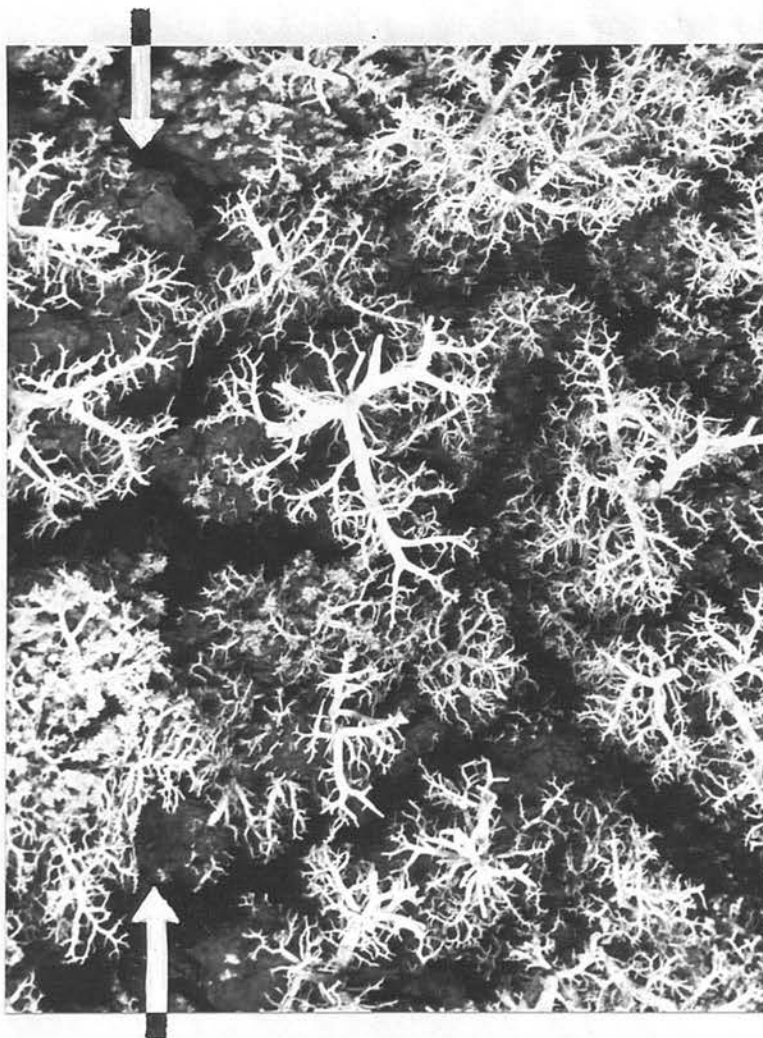


Fig. 17. Anterior surface of the left lobe of the liver, x 2.25. The hepatic vein has been injected with neoprene and the parenchyma digested down to a depth of about 3 cm.

The field is composed of about a dozen discrete clumps each about 1.5 cm., across. Each clump is separate and is related to a hepatic vein of about the 5th order. The radicles form a medusa-head pattern and do not anastomose. The arrows mark the line dividing the territory of HSI on the left from that of HSS on the right.

In one clump of veins, bottom left, the neoprene has entered sinusoids and the cast has a woolly outline. Elsewhere the finest vessels injected are central venules. Many of them are visible.

larger than sinusoids are very few and never large (Fig. 17), so that the venous system is really like a tree. Studies of livers in Chiari's Disease reported in Chapter V prove that anastomotic channels between the systems of each of the major hepatic veins are inadequate to maintain normal conditions if one of the major veins is occluded and, sinusoidal channels apart, the anastomotic vessels are usually abnormal.

GROSS STRUCTURE OF THE HEPATIC VEINS

The general outlines of the hepatic veins in man were studied by means of casts in which the natural angulation of the vessels was maintained. The larger radicles were found to enter the main hepatic veins at acute angles (Fig. 2) but the medium-sized and smaller hepatic veins in their turn often entered the larger radicles at blunt angles. Radiography of the hepatic veins during life also shows this characteristic (Fig. 18). Generally speaking the junction angles in this system are considerably less acute than those of the arteries shown in the casts of Gans and others and resemble those of the portal veins in the liver.

The diameter of the right hepatic ostium (15 mm. when dilated) is approximately $\frac{2}{3}$ that of the cava (22 mm.); the left ostium is somewhat smaller (13 mm.). The main hepatic veins (HS, HD and HM) are in turn roughly $\frac{2}{3}$ the diameter of the trunk. Where branching is dichotomous below this level, the smaller vessels are again roughly $\frac{2}{3}$ the diameter of the larger trunk (Fig. 18), as might be expected from a consideration of the cross-sectional areas. Although this Y type of ramification characterises the portal-venous system (Popper and

TABLE I. Measurements of Hepatic-venous channels in man and in the rat.
The figures given are diameters.

Species	Man - adult		White Rat, 200 gm. albino Wistar.		
Source of measurements	cadavers and casts.	paraffin sections x 1.2.		neoprene casts.	paraffin sections x 1.2.
Column	1.	2.		3.	4.
I.V.C.	22 mm.	21 mm.		4 mm	
<u>Ostia</u>					
right	15 mm	14 mm.		2 mm.	
left	13 mm.	12 mm.		3 mm.	
			caudate lobe	2 mm.	
			Right post. lobe.	1.3mm.	
<u>Hepatic veins</u>					
main.	10 mm.	10 mm.		2. mm.	
2nd order	7 mm.			1.3mm.	
3rd order	4.5mm.			0.8mm.	
4th order	3 mm.			0.6mm.	
5th order	2 mm.				600 μ
6th order	1.2mm.	1 mm.			400 μ
7th order	0.7mm.	0.6 mm.			250 μ
8th order	0.4mm.	0.4 mm. (often contracted)			
<u>Intercalated veins.</u>	100-350 μ	120-350 μ			100-200 μ
<u>Central venules</u>	40-100 μ	40-100 μ			40- 80 μ
<u>Sinusoids</u>	15 μ	12 μ			10 μ

Schaffner, 1957) it is only one of several types of confluence in the hepatic-venous tree, where multiple junctions of unequal veins and many other variations are common. The smaller hepatic veins also tend to increase proximally in calibre gradually, on account of the entrance of many tributaries of much smaller diameter (Popper and Schaffner) as may be seen in Figs. 18 & 19.

It is impossible to represent the complicated and variable ramifications of the hepatic-venous tree accurately in tabular form, but, since Y branching occurs often at all levels, a rough indication of the number of junctions existing between the smallest and largest can be arrived at by assuming that this is the only type of junction that occurs. Column 1 of Table I has been constructed on this assumption and is made up of representative direct measurements on casts taken at points of dichotomous branching, the vessels being measured, of course, in the dilated state. The upper and lower parts of column 2 are based on direct measurements on dilated veins in paraffin sections but these have been increased by $1/5$ to allow for shrinkage in preparing the sections and the figures in column 2 have thus been made to correspond roughly to those in column 1. Table I shows that if equal branching of the Y type were the rule, 7 divisions would be required to bring the diameter down from that of the main veins to that of the smallest or 8th order of hepatic veins (0.4 mm.). This arbitrary classification implies 12 divisions between the cava and the sinusoids in the large lobes, and examination of neoprene casts shows that this is often the case. In most instances, however, the number of divisions is less because small veins often join



Fig., 18. An intravital venogram of a terminal ramification of HD. Where small hepatic veins join large ones, the angles of junction are blunt, but where radicles of roughly equal size unite, the angles are more acute. The largest vessel is a hepatic vein of the 4th order and nearly all the vessels are small hepatic veins but a few intercalated veins can be made out.



Fig., 19. A portion of a neoprene latex cast of human hepatic veins. The largest vessel is a 5th order radicle of HSI. This receives hepatic veins of smaller size and numerous intercalated veins. The smallest of the vessels joining the large vein are central venules but they cannot be made out distinctly at their junctions in this photograph x 4.5.

large ones and short-circuit some of the divisions.

A feature of the ramification of the hepatic-venous system easily appreciated in casts is the fact that large veins receive many small tributaries - central venules and intercalated veins - at all levels along their courses (Figs. 18 & 19). In veins in livers fixed in the ordinary way, that is when the veins are in a state of slight contraction, longitudinal ridges can easily be seen running along the inner surfaces. The same thing is visible in the hepatic cava (Fig. 11) and the ridges are caused by the underlying longitudinal muscle bundles of the adventitia. Elias & Feller illustrated transverse ridges at regular intervals in the large hepatic veins fixed by hot formalin but these cannot be seen by the ordinary methods of fixation.

MICROSCOPICAL STRUCTURE

The hepatic veins in their various orders in man differ from veins of similar calibre in the limbs. Miyake showed their microscopical structure was similar to that of the hepatic portion of the cava and my observations confirm this. The structural similarity may be related to the close association in development of this part of the cava with the hepatic veins, for it is derived from an anastomosis between the right vena revehens and the right subcardinal vein (Fig. 36). Husten (1927) stated that the structure of the cava was not fully differentiated at birth and that it did not reach its full complexity till several years later; after 40 years of age elastosis of the intima was found with great frequency. The hepatic veins of neonates show a similar immaturity in the

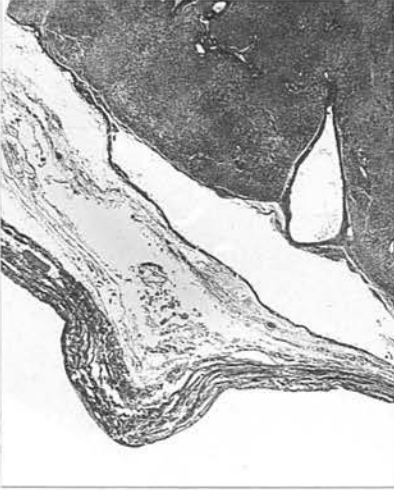


Fig., 20. Upper lip of right hepatic ostium (cf. Fig., 11). A low fold is formed by the muscle of the caval (left) and ostial walls. The dense external collagenous layer of the vessel wall provided by the liver capsule, normally firmly adherent to the liver, is separated by artefact. Picro-Mallory stain x 8.

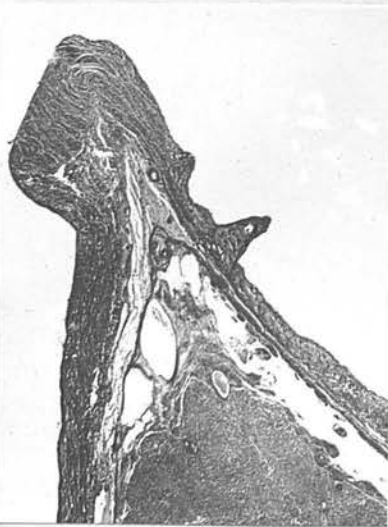


Fig., 21. The distal fold at the mouth of the right hepatic ostium. The gross appearance is shown in figure 11. This fold is similar to the upper one (figure 20) in structure, but is larger, more muscular and more loosely attached to the liver substance.

Picro-Mallory stain
x 8.

details of their structure but the main elements of their walls are well formed. Variations in the walls of the hepatic veins in adults have seemed to me to be related rather to the pathological histories of the subjects from which they were taken than to their ages. The various elements of the intima, for instance, are particularly prominent and apparently hyperplastic in subjects in whom an elevated venous pressure during life may be assumed.

In histological sections of fresh tissue, the hepatic veins are often contracted and reduced to $1/2$ or even $1/3$ of their diameters in the dilated state, either because contraction is maintained after death or because the veins are compressed during fixation or dehydration of the tissues. Intercalated veins are rarely contracted and may appear in sections wider than contracted veins of the 8th order into which they may drain.

Ostia: The similarity in structure to the cava is greatest in the ostia. Their walls are about 0.7 mm. thick. The muscle coat in the adventitia is arranged in longitudinal bundles about 0.3 mm. thick, that is about half the thickness of the corresponding bundles in the cava (Figs. 20 & 21). The muscle is surrounded by loose connective tissue continuous with that round the cava, an arrangement that permits some movement of the vessels unfixed in the cadavar and could permit contraction during life. At the ostial rim the muscle coat projects inwards in a fold which is better formed at the lower edge (Fig. 21) than elsewhere (Fig. 20) and which in cross sections resembles an inverted V. One arm of the V is formed

by the caval and the other by the ostial wall, and loose connective tissue, lymphatics, blood vessels, nerves and sometimes fat lie between. Some of the longitudinal fibres loop round the ostial lips and these can be seen as a thicker band at the apex of the V in Fig. 21. Apart from this there are no particularised elements of muscle. The arrangement provides a considerable amount of smooth muscle at the sites of ostial narrowing and could readily act in the fashion shown in Fig. 13. It was described as a "spur" (spore) by Popper (1931) and is the form taken in man by what Tischendorf termed the "extrahepatic (ostial) sphincter", although his illustration is somewhat misleading. The physiological action of this throttle mechanism is discussed in Chapter III.

Similar but less developed structures are present where the major radicles join the ostia. There is an abrupt reduction in thickness of the muscle below these junctions. The loose connective tissue zone is about 1 mm. thick round the ostia where they are buried in the liver and is rich in lymphatics, nerve bundles and small blood vessels. It separates the ostial muscle from the external collagenous zone of the vessel wall which is really the liver capsule and which may contain a few small bile ducts here and there. The loose zone and its contents are less prominent round the hepatic veins. In other respects the ostia resemble the hepatic veins in structure.

Hepatic veins: The hepatic veins are uniform in design but progressively simplified in their diminishing orders. They are free of valves.

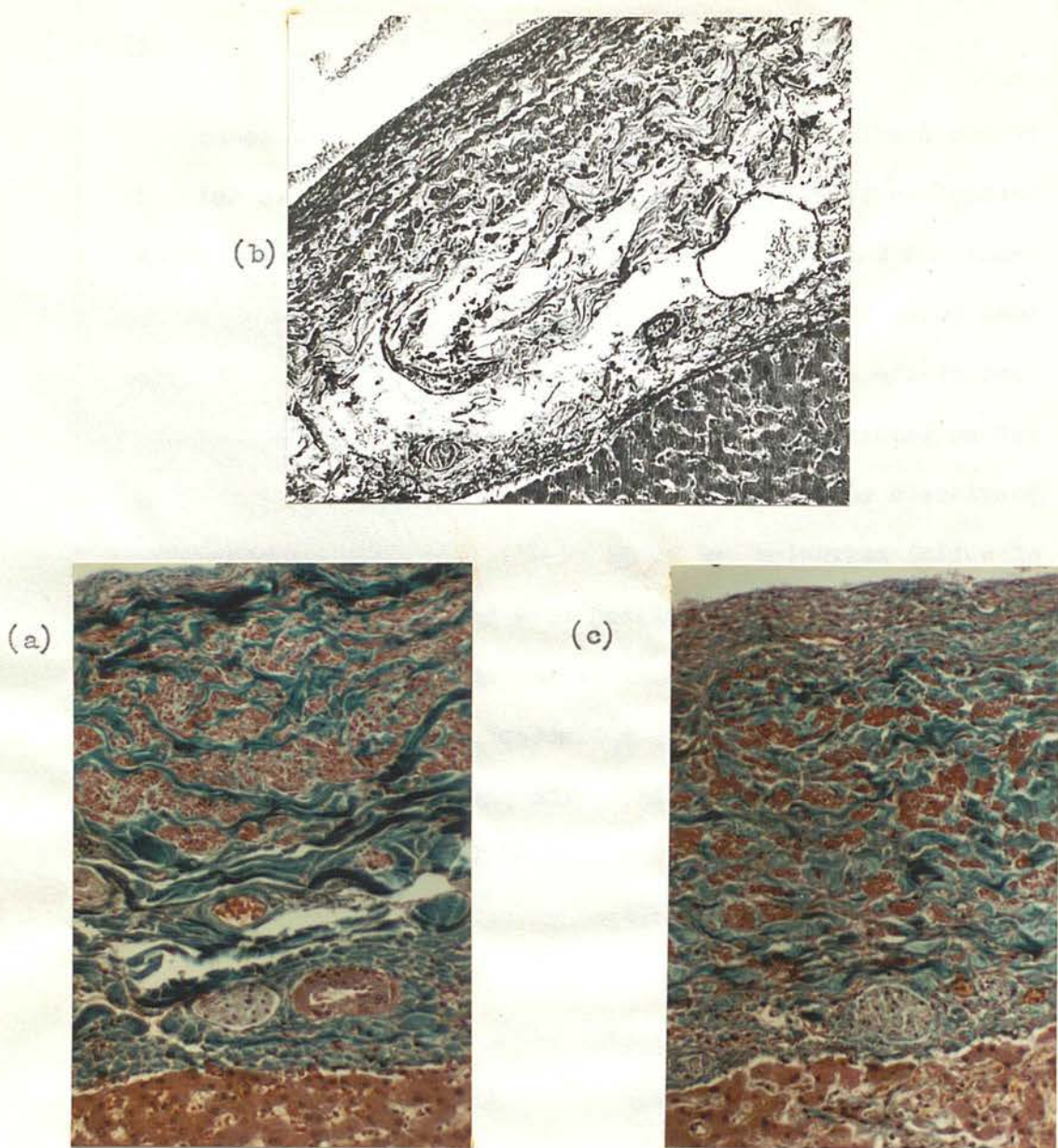


Fig., 22. Sections of hepatic veins, (a) 8 mm., diameter, 2nd. order & (b) & (c) 6 mm., diameter, 3rd order. The intima (b) & (c) contains fine circumferential smooth-muscle and elastic fibres. The main bulk of the wall consists of adventitia in which there are longitudinal muscle bundles surrounded by elastica and collagen. The bundles are larger in (a). External to this is loose connective tissue seen best in (b) from an oedematous subject, in which nerves, arteries and lymphatics are present.

The most peripheral layer - the external collagenous layer - which is rich in elastica is closely applied to the liver and is really an extension of the liver capsule.

(a) & (c) Picro-Mallory, x 150.

(b) Haemalum, Weigert's elastica, eosin-phloxine and tartrazine, x 110.

The intima is moderately developed (Fig. 22). It contains elastic fibres and fine, relatively numerous and circularly arranged smooth-muscle fibres which lie singly among a little collagenous fibrous tissue. The latter is about equal in amount to the muscle and not arranged in bundles either. At the points of junction of major tributaries the intimal muscle is generally a little increased in thickness. Intimal muscle is found at all levels in the hepatic veins, though in the smallest (8th order veins, with a diameter of 400 μ in dilatation) the fibres are scanty. Fine elastic fibres are numerous in the intima and run parallel to the muscle fibres. They are partly condensed to form an internal elastic lamina on the outer aspect of the intima. Although this lamina is ill-defined it can be made out in veins as small as those of the 3rd order.

A media is absent from the hepatic veins, as it is from the cava at the level of the ostia.

The adventitia forms the main muscular and collagenous coat of the hepatic veins as in the cava. There is an even reduction in the amount of adventitial muscle from the large to the small veins. The muscularis in the larger orders is composed chiefly of longitudinally arranged bundles (Fig. 22) which are evenly distributed and individually inconspicuous when the vessels are dilated. In a state of contraction the bundles stand out distinctly like straw packing round a water pipe; the lumina are then polygonal or oval. In the smaller orders the fascicular arrangement is indistinct. The muscle fibres may be asymmetrical in their grouping round the periphery of the vein and, like the intimal muscle, may appear

slightly increased where tributaries enter (Figs. 27 & 28). Large eccentric masses of muscle like those in the large renal and adrenal veins are absent from the hepatic veins.

As in the cava the muscle bundles in the larger veins are surrounded by elastic fibres and intermingled with fibrous tissue and are bound together by the inner collagenous layer of the adventitia (Fig. 22). The latter is composed of transversely arranged fibrous tissue and varies in thickness with the calibre of the vessel. Below the 6th order of veins, the adventitia is made up of longitudinal and transverse fibrous tissue and very few muscle fibres can be seen. In picro-Mallory-stained sections adventitial muscle was rarely found in 7th order veins (600 μ) where intimal muscle fibres are often visible. Miyake and Tischendorf found smooth muscle in veins of 300 μ but they do not state whether the vessels they measured were contracted or not. Tischendorf's findings clearly disagree with those in this thesis only in that he observed longitudinal muscle in smaller veins than circular muscle.

The external collagenous layer of the adventitia may be thought of as an extension of the liver capsule along the hepatic veins. It is firmly adherent to the liver and is reinforced by relatively coarse elastic fibres which are present down to the lowest level of the hepatic veins. This outer layer is separated by a zone of loose connective tissue from the muscular and internal collagenous layers of the adventitia (Fig. 22). In the loose zone there are a few collagenous and elastic fibres and a variable number of lymphatics, arterioles and nerves. The lymphatics are nowhere

as well developed as those in this site in the dog. Those round the hepatic veins are smaller than those round the ostia and they are most easily seen in neonatal and in oedematous livers. In the latter they can easily be found in ordinary histological sections of veins of the 5th order. Small arteries are present in the loose zones of the adventitiae of the larger and medium-sized hepatic veins along with nerves. While there are many small nerves round the ostia, the number diminishes rapidly in the hepatic veins; minute branches can be observed regularly in the walls of 3rd order veins (Fig.22) at points well removed from the external liver capsule. They are composed of single bundles of fine non-myelinated fibres of autonomic type and are fewer in number and individually smaller than those round the portal veins. The terminations of the nerves of the hepatic veins and the courses of individual fibres were not studied in this work and an adequate account of them does not exist.

In general the hepatic veins of man may be said to be well muscularised but not unusually so in comparison with, for instance, the veins of the leg, which are also usually subject to gravitational effects in man. The main peculiarity of the musculature lies in the arrangement of the fibres. Miyake considered that the hepatic veins of man contained a little more muscle in their walls than the intrahepatic portal branches of similar size. My own occasional observations confirm this. The portal trunk and sinus, on the other hand, in man as in other species, are well muscularised particularly in the medial coat.

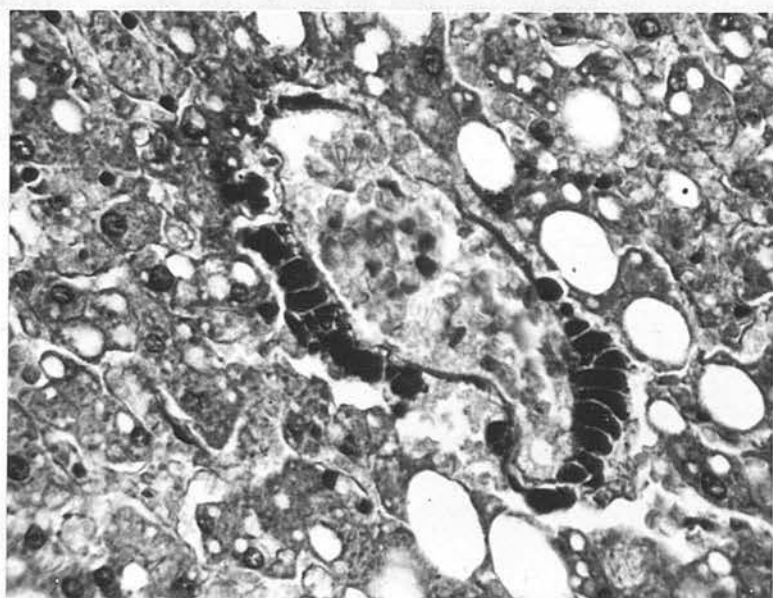


Fig., 23. Intercalated vein in a collapsed state. Collagenous fibres are scattered irregularly round the circumference of the vein. Pfuhl (1922) noted a similar appearance in central venules. Picro-Mallory stain x 450.

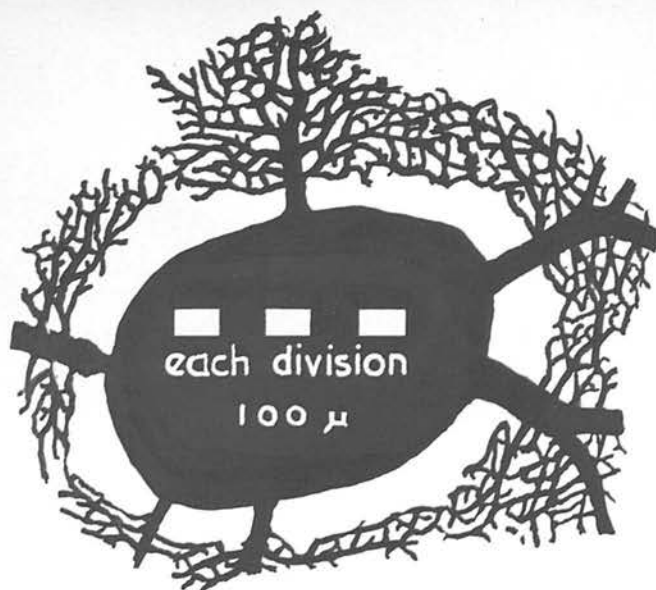


Fig., 24. Camera-lucida drawing of part of a thick section of a neoprene-latex cast from an adult-human liver. Central venules join an hepatic vein of the 7th order at approximately right angles. The sinusoids anastomose freely but do not enter the hepatic vein. The central venule on the left is constricted where it enters the large vessel. The other venules are not affected. The central venules vary in size and drain lobules of differing sizes and shapes.

The small veins: Of the small veins two larger types are usually mentioned, the collecting and the intercalated (sublobular) veins. For reasons discussed later, this distinction does not seem worth making. Popper and Schaffner mention scattered muscle fibres with no definite arrangement in the smallest veins or central venules, but like Tischendorf I have not found muscle in any of the small veins (Fig. 23). Elastica is present in relatively small amounts; the fibres are scanty in the intercalated veins and are seen only infrequently in the walls of central venules in normal livers. Central venules are thin partitions in the dilated state, only a little more substantial than the walls of the sinusoids which empty into them at frequent intervals. The endothelial linings of all the small veins are however backed by collagenous fibres which constitute the main part of the wall. The fibres are arranged in a longitudinal or wide spiral (Tischendorf) direction and are often bunched together round part of the outside to give an irregular outline (Fig. 23). This may be due to pressure by the liver tissue or may represent a state of active contraction produced by elements other than muscle, but the existence of such elements is dubious. Zweifach (1957) points out that both anatomical and physiological studies are needed to work out the distribution of smooth muscle in the finest vessels and notes its presence in collecting venules of the peripheral circulation as small as 40 - 50 μ . At any rate the absence of any clearly visible muscle distinguishes the small veins having a diameter of 400 μ or less from the true hepatic veins of the liver above them. The diameters of the terminal veins and of the sinusoids

EACH DIVISION 100 μ

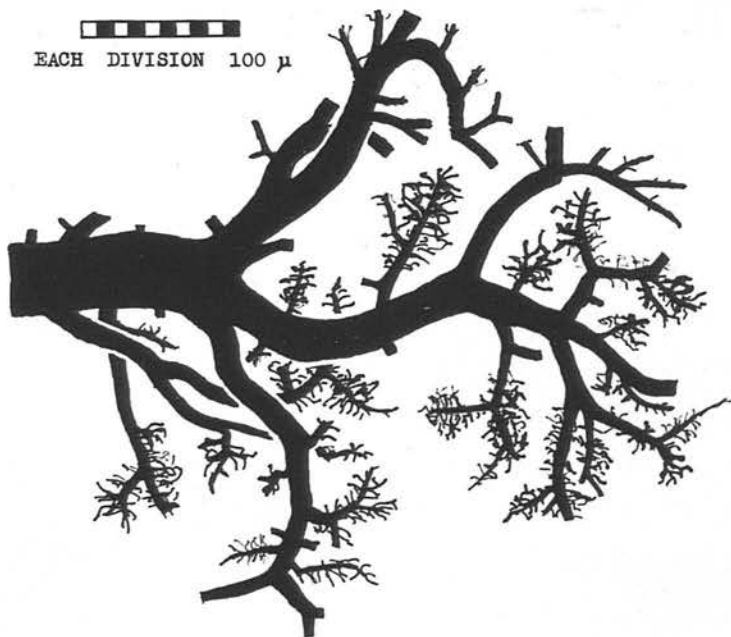


Fig., 25. Tease preparation of a central portion of a neoprene cast of the hepatic veins of an adult. An hepatic vein of the 8th order (left) is made up chiefly of intercalated veins of different sizes. Central venules join both types of vein. In some instances sinusoids round the venules have been drawn.

each division 100 μ



Fig., 26. A tease preparation from the periphery of the neoprene cast as that shown in figure 24. Two large intercalated veins unite to form hepatic vein of the 8th order which in turn joins a large vein. The intercalated veins are made up by smaller intercalated veins and by central venules. The intercalated veins tend to be longer than those in the central areas. Some of the sinusoids joining the central venules are shown.

listed in Table I are based on direct measurements. The figures are in good general agreement with those given by other workers where these are available, but differences in terminology make detailed comparisons too lengthy for inclusion here.

Composition and terminations of the small veins: Although the small veins have been listed in Table I in a regular order of decreasing size, all the blood from the sinusoids does not pass through each class of vessel to reach the hepatic veins, as one would gather from the work of Pfuhl. The true arrangement is difficult to make out in gelatine preparations but thick sections (Figs. 24, 32 & 33) and tease preparations (Figs. 25, 26 & 34) of cleaned neoprene casts show that many of the central venules in man enter hepatic veins without intermediate vessels. Most of the central venules join hepatic veins of the 8th - 6th orders but central venules not infrequently enter even in the largest veins (Fig. 19). Most of the junctions take place at an angle of approximately 90° (Figs. 24, 25 & 26).

Towards the edge of the liver, where the lobules are partly subcapsular and not surrounded by other lobules on all sides, the central venules empty more often into intercalated veins (Figs. 17 & 26) than is the case in the central parts of the liver (Fig. 25). In these peripheral veins, each segment tends to be longer, and intercalated veins as long as 5 mm. may be found. Wakim & Mann (1942) observed similar long small veins in the subcapsular areas of the rats' livers which they transilluminated. It is well-known to pathologists that the vascular anatomy and other features of a peripheral

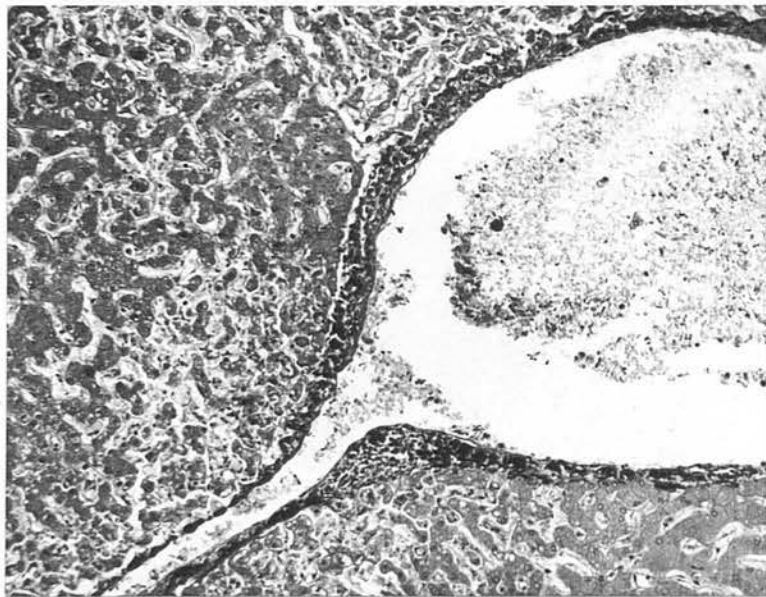


Fig., 27. Dilated 6th order hepatic vein (800 μ) and a central venule of 50 μ . The junction is widely patent. Picro-Mallory x 110.

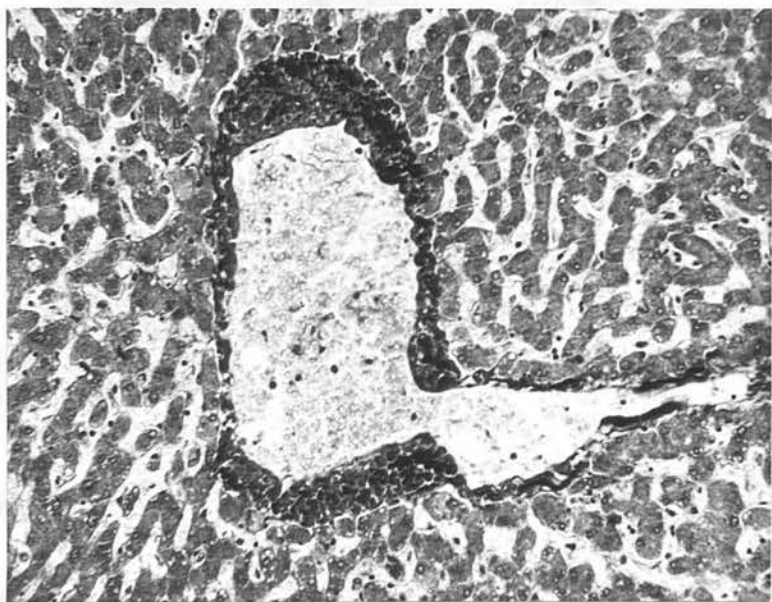


Fig., 28. Contracted 8th order hepatic vein (diameter 300 μ in this state). It is joined by a large central venule which is constricted at its mouth. This is a funnel-like junctional constriction. The muscle is irregularly distributed round the wall of this contracted hepatic vein. Picro-Mallory x 110.

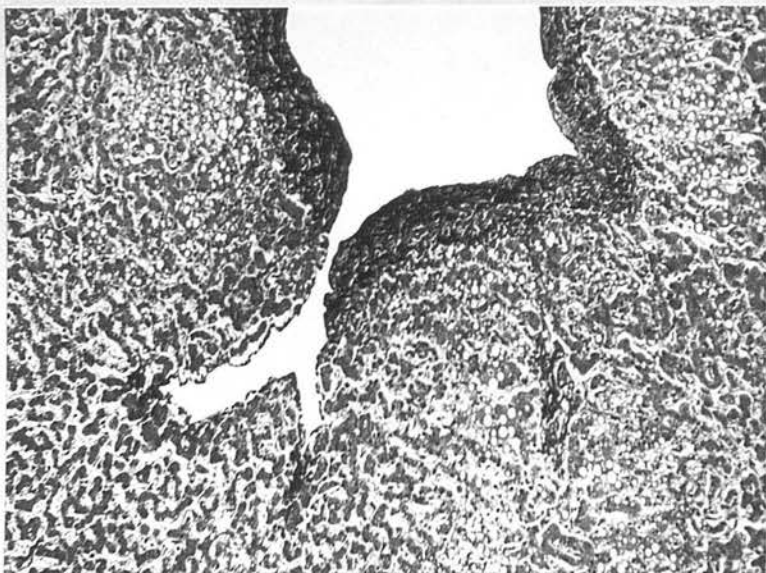


Fig., 29. Contracted hepatic vein of the 5th order, (approximately 1 mm., in diameter in this state) which is joined by a dilated central venule of about 60 μ diameter. The latter is constricted at its junction. Picro-Mallory x 80.

portion of the liver may be unrepresentative of the organ as a whole and it is clear from the present studies that the hepatic-venous ramifications are not uniform. There are apparently considerable differences in length between the various channels normally open to blood for its flow through the liver and the equalisation of pressure seems therefore to be carried out by vascular reactions and not to depend on constant anatomical structures. The presence of free anastomoses throughout the sinusoidal system in man casts doubts on the functional applicability of the view propounded by Mall (1906), Pfuhl and others that all channels from the periphery to the centre of any lobule are equal in length. In any case changing views on the fundamental structural unit of the liver, such as those of Rappaport et al. (1954), make it difficult to discuss this satisfactorily.

At the junctions of thin-walled central venules with the relatively thick-walled small hepatic veins, and less frequently with larger hepatic veins (Fig. 19), the former can be constricted by the contraction of the latter (Figs. 27-29). Intercalated veins are less affected in this way when they join hepatic veins, than central veins are. The contraction of the larger vessel is often not symmetrical so that only some of the tributaries are narrowed (Fig. 24). Popper refers to these junctions as "funnel-like" (Trichterformige) on account of the configuration of the entering vessel (Fig. 28). In my experience junctional constrictions of the present sort are common in man and it seems likely that a considerable throttle action can be exerted overall by the contraction of hepatic-vein muscle, even though it is feeble in the smaller

vessels. It is perhaps worth noting that Elias & Popper (1955) refer to these constrictions as being "central-sublobular" (intercalated) junctions but the size of the larger veins they illustrate clearly indicates that they are small hepatic and not intercalated veins. Because intercalated veins are thin-walled and devoid of muscle (Fig. 23) there are no regular constrictions of central venules where they join them. Since these junctional constrictions are absent also at points where two or three intercalated veins come together to make up a hepatic vein, not all areas of the liver are equally influenced by them and circulation through the peripheral parts of the liver in particular is probably the least affected. Free sinusoidal anastomoses will however tend to diffuse the action from one lobule to another.

Termination of the sinusoids: Transillumination studies on frogs and rats, referred to in Chapter II, have shown narrowings of the sinusoids at their points of entry into central venules in these animals. The nature of the preparations examined for this thesis i.e. post-mortem casts, does not permit one to say whether this applies to human sinusoids. At any rate no muscular or other specialised elements were observed at this level in casts or sections that could be considered to work in this way.

Elias & Popper state that there are no inlet venules or other specialised channels intervening between the sinusoids and the central venules; certainly the terminal ramifications of the hepatic-venous system cannot be classified in the same orderly way as those of the portal system, but there does

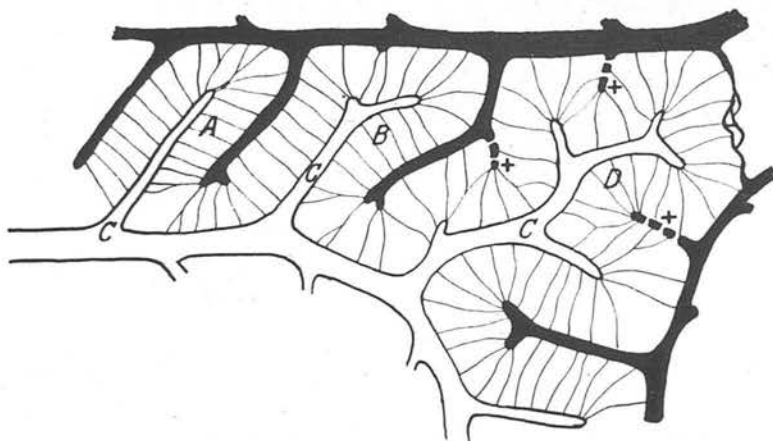


Abb. 6. Schema der Läppchenformen.

A = schlauchförmiges, B = keulenförmiges, D = massiges Läppchen. Pfortadersystem und Gefäßscheiden schwarz, + = intralobuläre Pfortaderäste. Lebervenen weiß. C = Zentralvenen.

Fig., 30, copied from Pfuhl (1922). The central venules C emptying into an intercalated vein are shown in white. The central venules vary in form according to the type of lobule drained; A, tubular; B, "dog-leg"; D, massive lobule.

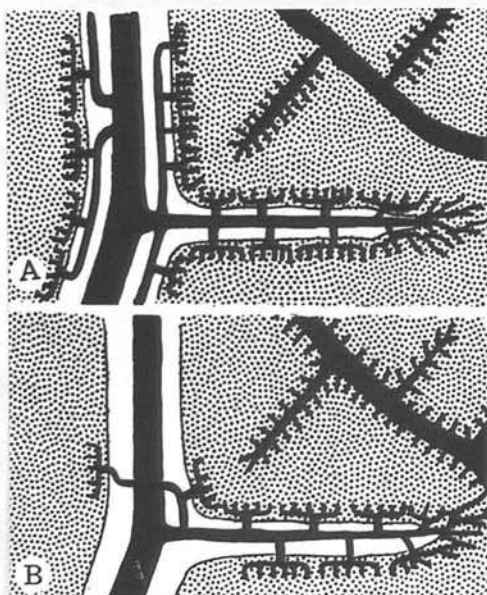


Fig., 31 a schematic diagram from the paper of Elias and Popper (1955). A, in man, sinusoids enter only central venules (top right) and not the intercalated and larger veins, as they do in the rat, B. Thus the drainage of the liver is better in the latter species.

appear to be a wide variation in the make-up of individual central venules. Central venules in the present material varied in diameter from 40 to 100 μ , the largest ones being made up by the confluence of smaller ones. The united venules continued to receive sinusoids till close to their terminations in hepatic or intercalated veins and so could be distinguished from the smallest intercalated veins of about the same size. Pfuhl noted this variation in size of central venules and showed that the largest ones drained particularly large lobules (massiges Läppchen). He also illustrated tube-like (schlauchformiges) and club-like or "dog-leg" (keulenformiges) lobules, each with a different type of central venule (Fig. 30). My casts although they represent lobules incompletely, show various lobular outlines (Figs. 32-34) which can best be interpreted in the light of Pfuhl's findings. His account of variation in lobular size and shape has been too often neglected in favour of less satisfactory schemes which attempt to depict the liver as a collection of entirely uniform lobules. In parallel with these variations in the size and form of central venules, the terminations of the sinusoids are also irregular, for they enter the venules sometimes singly and sometimes in small groups. Keeping this variety of structure in mind I have not encountered any vessels at this level which could not be classified as sinusoids or as central venules.

In casts in which the neoprene had entered the sinusoids (Figs. 24, 32 & 33) a clear space without sinusoids and about 100 μ wide surrounds the intercalated and hepatic veins. These veins lie relatively free amid the anastomosing network

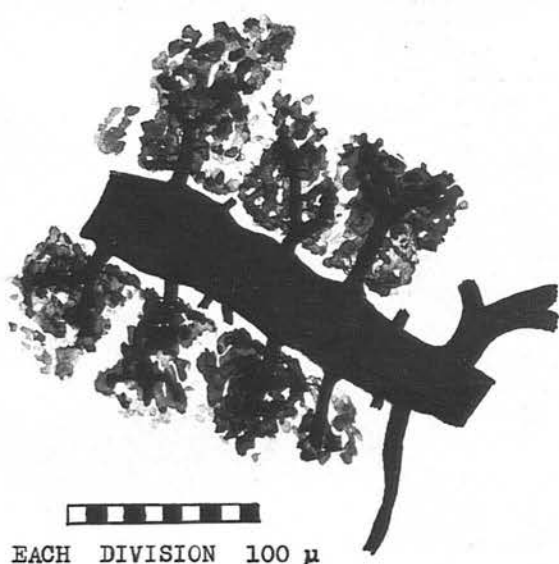


Fig., 32. An hepatic vein of the 8th order made up by the junction of two intercalated veins (right) receives central venules directly and at approximately right angles. Sinusoids do not enter the hepatic vein. From a central area of a neoprene cast of the hepatic veins of a three-day-old infant.

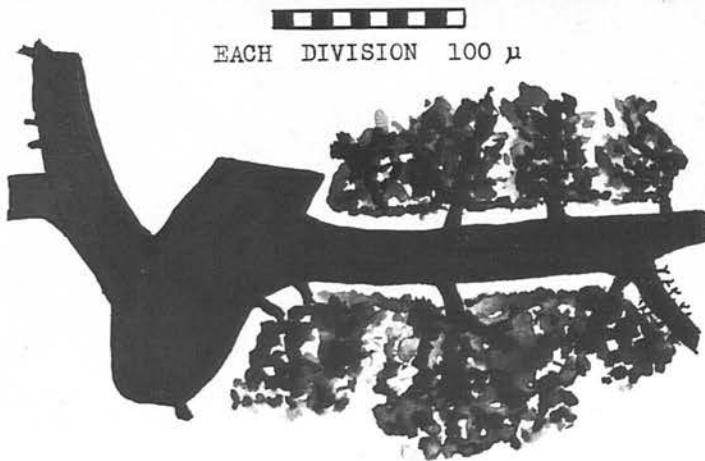


Fig., 33. Central venules draining lobules of various sizes directly into an intercalated vein which does not receive any sinusoids. Two central venules join the hepatic vein of the 7th order. From a central area of the same cast as Fig., 32.

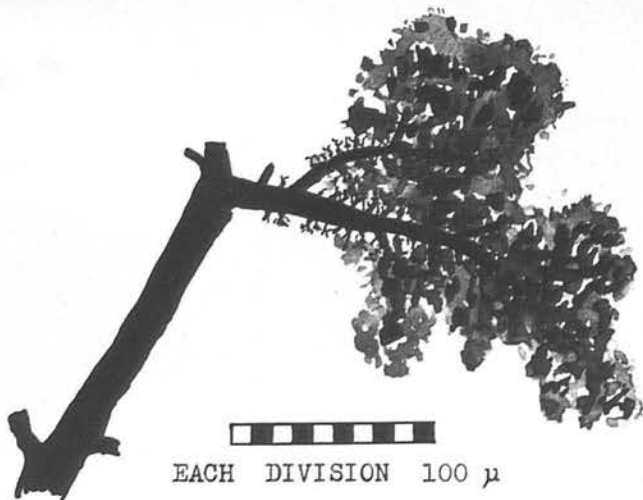


Fig., 34. A "massive lobule" of Pfuhl and its central venule joining a long intercalated vein. Sinusoids do not enter the latter. From a peripheral area of the same cast as Fig., 32.

of injected sinusoids connected to it only at intervals by hair-like central venules. The veins can thus be separated fairly easily from the main mass of the casts, but it is only by breaking many sinusoids and largely destroying the cast that central venules can be pulled out. It has thus been possible to confirm on the casts the statement of Elias & Popper that sinusoids terminate only in central venules in man (Fig. 31) - a statement that ran counter to some earlier work (e.g. Tischendorf). Elias & Popper point out that the human liver differs in this respect from that of the rat in which sinusoids enter veins of all types (Fig. 31). The effect of this anatomical variation is that the central venules in man are bottlenecks in the liver drainage and the tissue round them is congested in venous obstruction, while areas round hepatic veins may escape (Fig. 27). The numerous direct connections of sinusoids to intercalated and hepatic veins in the rat, on the other hand, tend to equalise the flow. Centrilobular congestion is thus produced more easily in man and assumes a more easily recognized pattern than in the rat.

Terminology: There is a sharp distinction from partially muscular to non-muscular walls at the 400 μ level in dilated veins in the hepatic-venous system. Above this level are the hepatic veins with a relatively complex structure and below the 400 μ level extend what have been termed in this thesis the small veins. This distinction seems to have escaped the attention of other authors, probably because of the chaotic state of the terminology in this field. For example, the term "Sammelvene" i.e. collecting vein was used by Pfuhl to

include apparently all veins above the level of intercalated veins (Schaltvenen) but Tischendorf who described small venules as "Sammelvenen", clearly meant something different to Pfuhl by the term. Since I have found few non-muscular veins big enough to be called collecting veins in my preparations and no structural difference between them and the intercalated veins, the equivocal term "collecting vein" has been abandoned in this thesis.

The term "intercalated vein" (the Schaltvene of Pfuhl) has been adopted in this work and also by Maximow & Bloom (1952). The observations reported here confirm that these veins are surrounded, as Pfuhl described them, by a complex of lobules and are not strung out below the lobules which they drain. Accordingly the term seems more appropriate than the alternative "sublobular vein". In any case the latter term has been applied in different senses in the past. Deysach (1941) denominated as "sublobulars" veins 1 - 2 mm. wide which had well developed muscular walls in his animals. In the French literature the hepatic veins in general are termed "veines sushépatiques". It is worth insisting on the difference between intercalated veins and central venules in man because of the mode of termination of the sinusoids.

The variations found in the hepatic system among mammals are so numerous that criteria suitable for man are not universally valid. It is only, however, when a classification is made that the rôles of vessels of different calibres in disease processes can be understood and comparisons made between different species and the works of different writers on the subject.

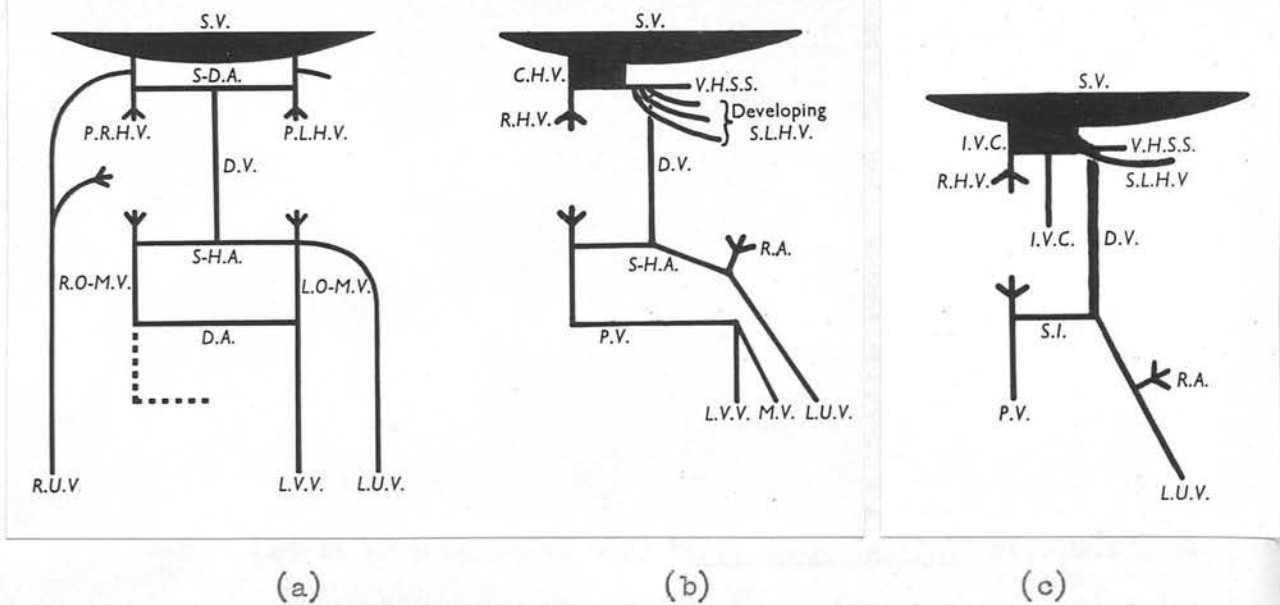


Fig. 35. Diagram copied from Dickson (1957) to show the liver vessels at various stages of their development in the embryo, (a) at the 5 mm., stage, (b) 7.75 mm., stage and (c) about 10 mm.

Key to the labels.

CHV - common hepatic vein.	RA - ramus angularis.
DA - dorsal anastomosis.	RCCV - right common cardinal vein.
DV - ductus venosus.	RHV - right hepatic vein.
IVC - inferior vena cava.	RO-MV - right omphalomesenteric vein.
LCCV - left common cardinal vein.	RUV - right umbilical vein.
LO-MV - left omphalomesenteric vein.	S-DA - subdiaphragmatic anastomosis.
LUV - left umbilical vein.	S-HA - subhepatic anastomosis.
LVV - left vitelline vein.	SI - sinus intermedius.
MV - mesenteric vein.	SLHV - secondary left hepatic vein.
PLHV - primary left hepatic vein.	SV - sinus venosus.
PRHV - primary right hepatic vein.	VHSS - venum hepatica cranialis aut superior sinistra.
PV - portal vein.	

CONGENITAL ANOMALIES

The development of the hepatic veins has been restudied recently by Dickson (1957) and is adequately summarised in Fig. 35. In the development of the portal vein and of the cava, complex rearrangements of blood flow occur in response to alterations in different parts of the body. In the hepatic veins on the other hand the only major alteration is the replacement of the primary left by secondary left hepatic veins; their development is generally simple and dependent only on proper formation of the liver, diaphragm and heart. The published reports of congenital venous anomalies confirm the stability of the hepatic venous system. The upper part of the inferior cava occasionally develops along a subcardinal-medial sympathetic (or azygos line) anastomosis instead of through the normal subcardinal-hepatic plexus anastomosis (Fig. 36). The hepatic portion of the cava then fails to form and the blood from the lower part of the body passes to the heart via the azygos vein. Huseby and Boyden (1941) discuss the embryological aspects of a case and list some published examples. Absence of the hepatic vena cava has also been reported, generally in association with partial or complete transposition of the viscera, in man by Abernethy (1793), Griffith (1892), Miller (1925) and by Effler et al. (1951) and in the dog by Hickman et al. (1949). In all of these instances the venous blood from the liver drained to the heart in an approximately normal fashion, by a common hepatic vein. Griffith's case was particularly interesting because the liver consisted of four separate lobes, which the author named right, left, spigelian and quadrate. In Abernethy's case, blood

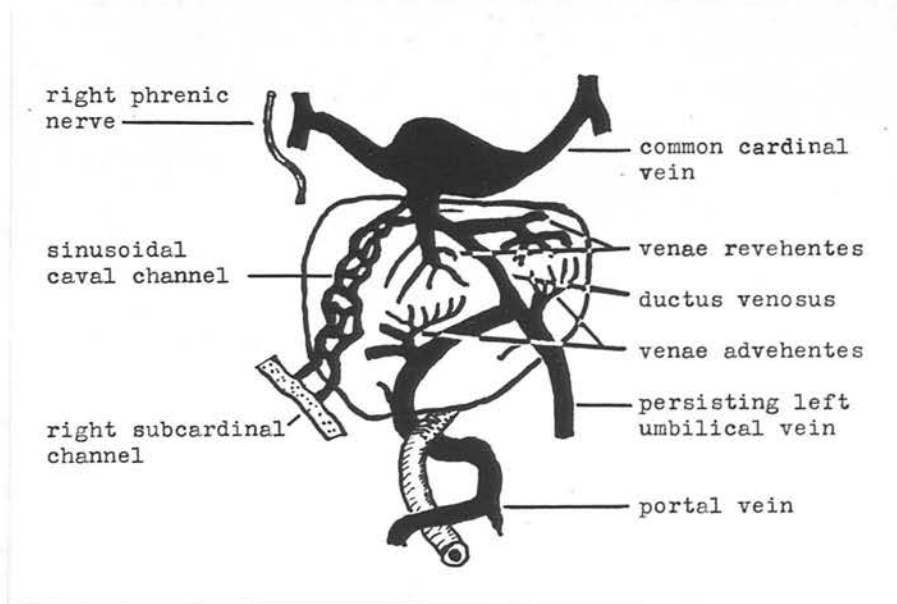


Fig., 36. Semi-diagrammatic picture of the veins of the liver about the 10 mm., (36 day) stage of embryonic life in man.

from the portal bed joined the inferior cava. In Hickman's it went to the azygos vein. Hellweg (1954) described an infant in which the portal blood bypassed the liver posteriorly to join a common hepatic vein below the right atrium. There were no intrahepatic portal branches and the hepatic arterioles in the portal tracts were coiled and abnormal. Despite this portal-vein anomaly the hepatic venous drainage was approximately normal.

A single instance of a true hepatic-vein anomaly has been collected from the literature and as one might expect, this involves the left veins. Nabarro (case 2, 1902-03) reported a persistent left superior vena cava which was joined by a left hepatic vein in a 3-month-old child. The left hepatic vein, apparently a persistent primary left hepatic vein, was of considerable size and did not communicate with the other hepatic veins. It received a left diaphragmatic vein before entering the left superior cava. The latter vessel was then joined by the coronary sinus of the heart (which is derived from the left duct of Cuvier) and entered the right atrium where the coronary sinus is usually found. In this case, as in other examples of persistent left superior vena cava, the common cardinal vein and all of the left duct of Cuvier remained open, but the persistence of the left hepato-cardiac channel in conjunction with it, resulting in the anomalous termination of the left hepatic vein is, as far as I know, unique.

NERVE SUPPLY

Small non-myelinated nerves are easily seen in the adventitia of the ostia and of the large hepatic veins at some

distance from the external capsule of the liver. Popper & Schaffner refer to occasional sympathetic and parasympathetic fibres round central veins. The source of their information is not clear and it may be questioned if there is any parasympathetic innervation of this system. The absence of nerve bundles from the thin hepatic veins of the rat suggests that those present in man are related to the action of the muscle which is much greater in the human species. Andrews et al. (1954) brought forward evidence that autonomic relays exist in the liver of the dog and considered they were related to the hepatic veins.

The routes by which the hepatic veins are innervated are not adequately known. Dickson (1954) noted fibres from anterior gastric and right phrenic nerves passing to them in foetal livers. The right phrenic nerve moreover supplies part of the liver capsule (Lewis, 1951) and together with the right phrenic-artery plexus innervates the hepatic cava (Mitchell, 1956). On anatomical and developmental grounds it is likely that these nerves supply sympathetic fibres to the veins. A parasympathetic supply from the coeliac plexus might also reach the veins via the right phrenic-artery plexus with postganglionic fibres originating at the right phrenic ganglion. The caval sphincter of the seal (*phoca vitulina*) reacts to phrenic nerve stimulation (Harrison et al. 1954). It is suggested in Chapter III that the action of the hepatic veins may be related to the variations in venous pressure brought about by respiration and this may entail coordination with diaphragmatic movement which may be reflected in some sharing of nerve supply.

LYMPHATIC DRAINAGE

Lymphatics are found in the portal tracts of the liver, in its capsule proper and in the walls of the hepatic veins, and connections exist between all three systems. The lymphatics of the portal tracts are the largest and drain through the hepato-duodenal ligament in trunks which end in the biliary and left gastric lymph nodes (Brash & Jamieson, 1943). Many of the capsular lymphatics drain through the falciform ligament to the retrosternal (anterior diaphragmatic) nodes. They have been particularly studied by Hass (1936). The lymphatics of the hepatic veins and ostia (Figs. 20-22) unite with similar vessels round the cava and drain to posterior and right mediastinal lymph nodes. They can be seen in the walls of veins as small as the 5th order and are most easily identified in oedematous or in neonatal livers, but they are not so large as those of the portal tracts. The lymphatics of the portal tracts tend to lie close to the arterial branches.

The beautiful illustrations by Didusch of hepatic lymphatics of a cat injected by Lee (1923) show an arrangement which is very close to the human one and they have been used by several subsequent authors to depict the latter. Lee reviewed the earlier literature on the lymphatics of the liver and came to the conclusion that they extended down to the smallest portal tracts but not into the liver lobules. Hale (1951) draws the same conclusion from his more recent review. Disse's (1890) contention that lymphatics extend into the lobules between the endothelium of the sinusoids and the liver cords (space of Disse) has not stood the test of time. Similarly Mall's (1901) concept of another space at the

periphery of the lobule between the liver cells and the connective tissue of the portal tracts has now been generally abandoned. Yoffey and Courtice (1956) state that "one must consider that fluid and solutes leave the liver sinusoids in the lobule and are for a time tissue fluid between the liver cells and the walls of the sinusoids. This fluid, in so far as it is removed as lymph, remains extravascular until it reaches lymph capillaries at the periphery of the lobule."

The circulation in the liver is sinusoidal, that is the small vessels, unlike capillaries, have no connective tissue in their walls and their arrangement is dictated by the parenchymal tissue. The hepatic cells are thus in a particularly intimate relationship to the blood and the completeness of the structures separating them is still in doubt. The electron-microscope studies of Fawcett (1955) indicate that a certain space exists between the endothelial lining of the sinusoids and the liver cells. The two elements are kept apart by small feet (microvilli) of the liver cells supporting the sinusoids. That author was not certain whether this comprised the space of Disse nor was he able to resolve the old question of whether the sinusoidal pattern is complete or partial. The importance of obtaining an answer to this question may be less if others confirm the contention of Bloch (1955), based on transillumination studies that sinusoidal permeability varies in normal physiological activity.

SUMMARY

1. Retrograde injections and corrosion casts of the hepatic veins have been used to demonstrate the courses and composition of the vessels. These can be partly related to schemes of lobation based on the portal-venous system, particularly to that of Gans, but there are important differences.

2. The structure of the hepatic ostia is described. The ostia are notable because of their loose attachment to surrounding tissues especially at their lips and because of the arrangement of the muscle there. In distinction to the hepatic veins, the ostia are capable of contracting greatly at their terminations in the cava. A significant degree of narrowing can also take place at the junctions of the main hepatic veins and the ostia.

3. Descriptive terms have been applied to the hepatic veins by other authors frequently in a hap-hazard fashion and reappraisal is necessary. The efferent vessels of the liver are described and classified according to measurements and other data obtained from study of histological sections and corrosion casts. Excluding the ostia at one end of the scale and the sinusoids at the other, there are two classes of vessels, (i) small veins (central venules and intercalated veins) and (ii) hepatic veins. Smooth muscle is present in the latter but it cannot be made out by ordinary histological methods in the former; a sharp transition occurs at the 400 μ level. The larger of the small veins is an intercalated vein and the use of the term "collecting vein" is unnecessary and misleading.

4. Many central venules terminate in intercalated veins but probably a considerably greater number end in small hepatic veins in man. The former termination is more common at the periphery of the liver. There is considerable variation in the number of junctions intervening between central venules and the ostia. The hepatic-venous ramifications are not rigidly systematised and control of the circulation through different parts of the liver would seem to depend more on the reactions of the hepatic vessels than on fixed structural arrangements.

5. A study of the literature reveals disagreement regarding the existence of venous barriers affecting small veins within the liver and regarding the termination of the sinusoids. Central venules may be constricted where they enter hepatic veins. The structural basis for these junctional constrictions is described. The present studies confirm that sinusoids terminate exclusively in central venules in man.

6. Congenital anomalies of the hepatic veins are reviewed in the light of recent work on the development of the liver.

7. The nerve supply of the hepatic veins and the lymphatic drainage of the liver in man are briefly reviewed.

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CHAPTER II

COMPARATIVE ANATOMY OF THE HEPATIC VEINS

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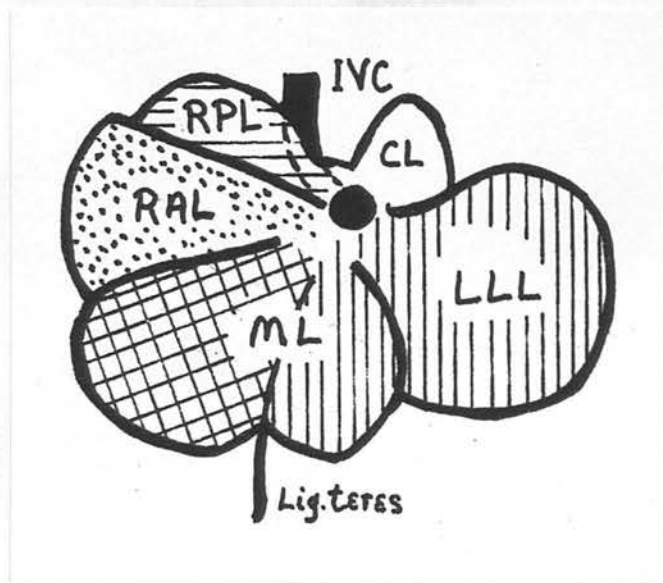


Fig., 37.

The rat's liver seen from above.

CL - caudate lobe.

LLL - left lateral lobe.

ML - median lobe.

RAL - right anterior lobe.

RPL - right posterior lobe.

COMPARATIVE ANATOMY OF THE HEPATIC VEINS
in certain mammals

HEPATIC VEINS OF THE RAT

A number of authors have dealt briefly with some of the characters of the hepatic veins in the rat. Gershbein and Elias (1954) have made the only systematic study of the courses and composition of the hepatic veins, which they examined in 5 rats together with the portal veins by corrosion preparations. The present investigation of the distribution of the hepatic veins was made independently. Its conclusions at a few points are at variance with those of Gershbein and Elias. The study is supplemented by a description of the histological structure of the veins, since the published accounts are inadequate.

Method of investigation: Neoprene-latex casts were made in 6 normal albino Wistar rats (Rattus norvegicus: albinus) of about 200 gm., both sexes being included. The latex was injected into the inferior vena cava above the liver, after preliminary washing through of the vessels with water, and ligation of the cava where it emerges below the liver. The casts were cleaned by immersion in concentrated hydrochloric acid and by washing in water. Hepatic-vein casts were also made from several of the rats used in the experiments recorded in Chapter VI, but with less success, on account of the narrowing which had been produced in the cava. The small liver of the rat is usually better suited to the making of neoprene casts than is the adult human liver. Examination of casts

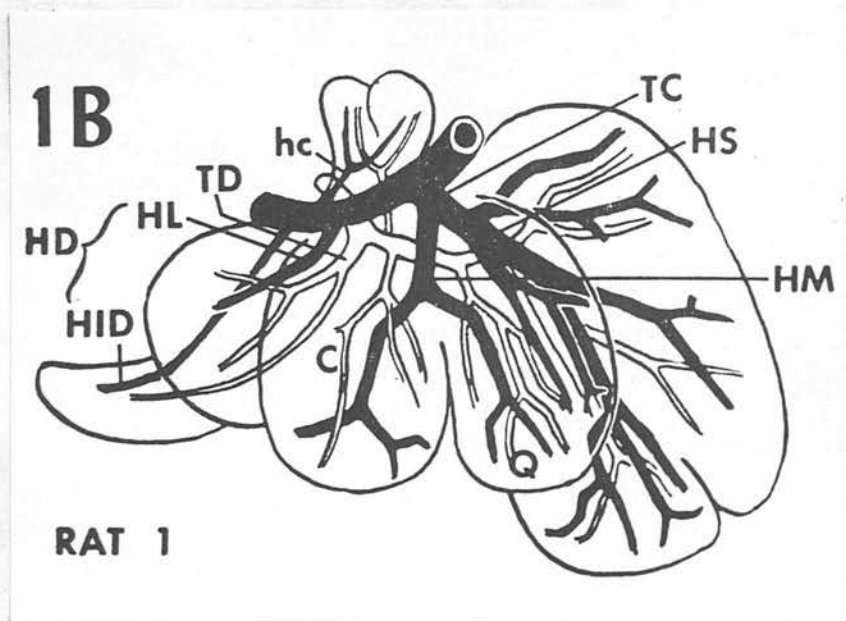


Fig., 38. The rat's liver seen from above, copied from Gershbein & Elias (1954). Hepatic veins are black and portal veins white.

- TC - truncus communis venarum hepaticarum sinistrae mediaeque.
- HS - vena hepatica sinistra.
- HM - vena hepatica media.
- HD - vena hepatica dextra.
- HID - right caudal division of HD.
- HL - right lateral division of HD.
- TD - truncus dexter venae portae
- hc - vemula hepatica caudata.
- Q - quadrate part of median lobe and branches supplying it.
- c - ramulus centralis.

was supplemented by ordinary methods of dissection in other rats from time to time.

Ordinary histological methods and particularly the picro-Mallory stain (Lendrum and McFarlane, 1940) were used to work out the fine structure, special attention being paid to the ostia. For this part of the work, 4 male and 6 female albino rats weighing 150 gm. or over were used. The histological findings were confirmed incidentally in the examination of many other rat livers.

The terminology applied to the lobes (Fig. 37 and Tables II and IV) is that used by Farris and Griffith (1949). The veins have been denominated by letters. Gershbein and Elias introduced a terminology for the hepatic veins which they claimed corresponds to that of the human veins and this is shown in Fig. 38 and in Table II. These authors used the portal veins as the basis of their comparisons between the human and the rat liver and their conclusions are unsatisfactory at several points regarding the hepatic veins. Since, too, they do not list all the hepatic veins, their terminology has not been used here.

Gross description of the veins: In a 200 gm. rat the inferior vena cava in the thorax is 3 cm. long and measures 3 mm. in diameter. It is readily collapsible. At the diaphragm where the left hepatic ostium (TC, Fig. 38) joins it, the vessel is at its widest (lacus venae cavae) and is irregular in outline (Fig. 39). The hepatic portion of the cava (4 mm. in diameter) is buried in liver tissue between the caudate and the right anterior and posterior lobes of the liver. This part of the

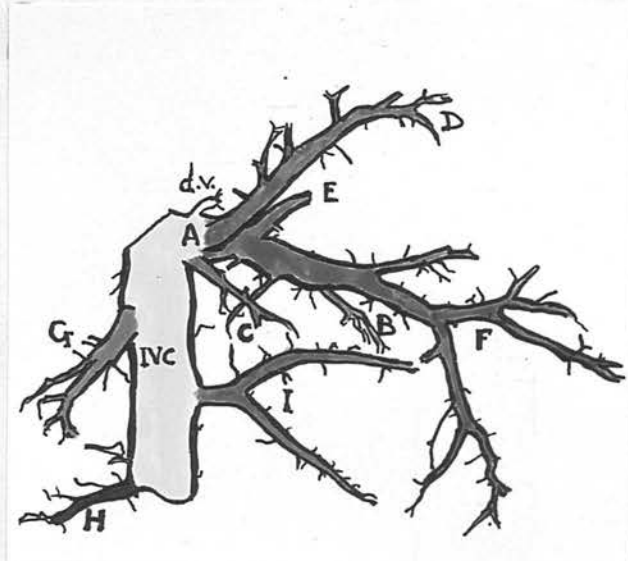


Fig., 39. Hepatic veins of rat. Neoprene-latex cast viewed from the right side x 2.

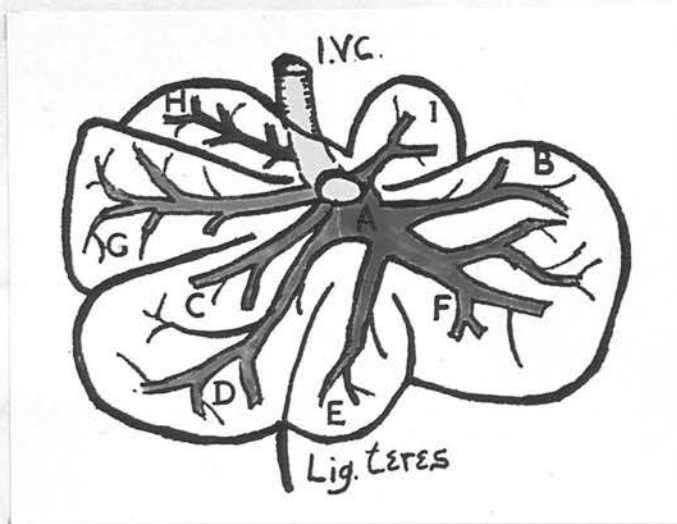


Fig., 40. Diagram of hepatic veins of rat viewed from above.

Letter	Vein	Colour.	Lobe	Terms used by Gershbein & Elias, 1954.	Human Homologue.
IVC	hepatic cava	yellow	...	IVC	IVC.
A	l. ostium	blue & green.	...	TC	l. ostium.
B	...	green	LLL	...	hss.
C	...	blue	ML	HMd	part of HM.
D	...	"	"	"	HM.
E	...	green	"	Hmv	HSI.
F	...	"	LLL.	HS	HSS.
G	...	red	RAL.	HL	HD
H	ostia	black	RPL	HID	HDL, HR, HCD
I	access- oria.	purple	caudate omental	hc	hcs, hci, hc.

Table II. Key to lettering and colouring of Figs., 39 & 40.
The terminology of Gershbein & Elias (1954) is shown for comparison
(see also Fig., 38), but the human homologues worked out here
are not in full agreement with those given by these authors.

cava may be considered almost as a hepatic vein. In addition to the hepatic ostia it receives many small veins from the liver tissue around it, and casts of this part of the cava look like bushes till they are stripped. The hepatic ostia enter the cava more or less at right angles and not at the acute angles seen in man. The portal vein enters the liver close to the front of the cava.

The lobation of the rat liver is shown in Figs. 37 & 52 and the comparative anatomy is indicated in Table IV. The weight of the liver was calculated as a percentage of body weight in 43 normal rats of the same stock. The mean was found to be 3.53% (S.D. 0.41) in 14 males and 3.99% (S.D. 0.99) in 29 females. The left lateral and median lobes make up between them more than half the weight of the rat liver. They are drained by a single ostium (Figs. 39 & 40). This left ostium (A, Fig. 39) or truncus communis (Rex, 1888) is much the largest ostium. It is 3 mm. wide (Table I) in a 200 gm. rat and is thus nearly as big as the cava which it joins. It is subperitoneal and only partly embedded in liver tissue. Where it joins the cava, one or two diaphragmatic veins (dv, Fig. 39) enter its free superior surface. The tributaries of the ostium are shown in Figs. 39 & 40 and their human homologues are indicated in Table II. The relationship of the vein E to the other radicles of the ostium and to the falciform ligament shows it is the homologue of HSI in man and not of part of HM as Gershbein & Elias state.

The right ostium is relatively much smaller in the rat than in man, being 2 mm. in diameter. It is composed largely of one vein (G, Figs. 39 & 40) draining blood from the right

SMALL RADICLES AND
HEPATIC VEINS, NORMAL
RAT

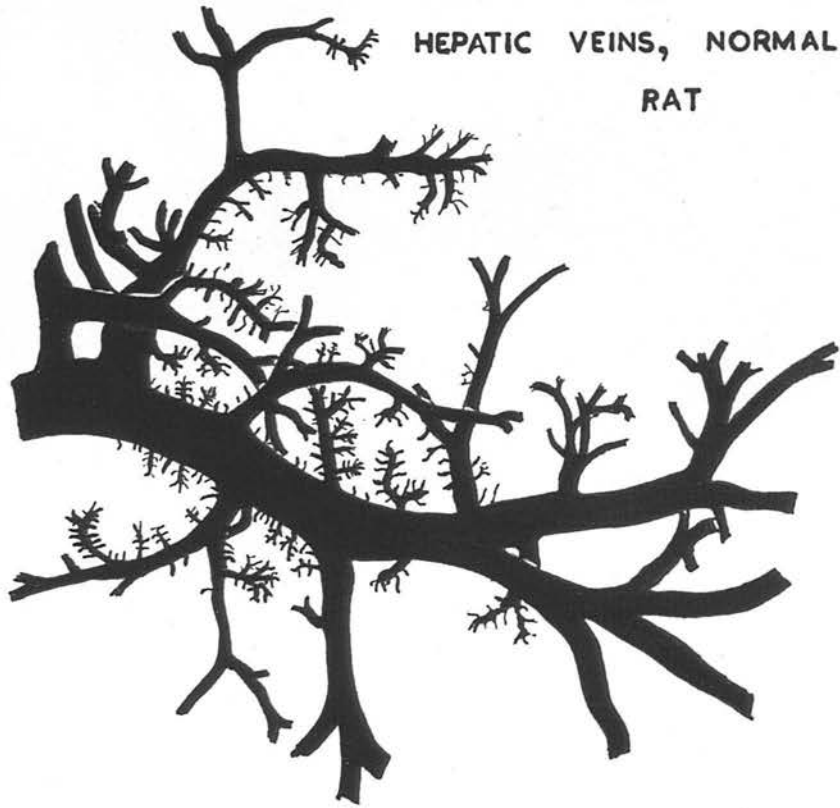


Fig., 41. Camera-lucida drawing of part of a neoprene-latex cast. The largest vessel is a hepatic vein of the 6th order and it is joined by intercalated veins, central venules and sinusoids. Some of the latter are shown here; they do not end exclusively in central venules, x 27.

anterior lobe which corresponds to the right lobe in man. Immediately below the right ostium in the cava lies the ostium of the right posterior lobe continuous with its vein (H, Figs. 39 & 40). This vessel, and perhaps some of the smaller veins entering the cava nearby, corresponds to HDL, HR & HCD in man (Fig. 15) and does not appear to be homologous with "part of HD" as Gershbein and Elias state. The right posterior lobe of the rat would thus seem to be, to a large extent, the homologue of the paracaval portion of the human right lobe.

The true caudate lobe in the rat consists of 2 portions which are largely separate and lie one on top of the other. The superior part is usually called the caudate lobe and is homologous with the main portion of the caudate lobe in man. The inferior part, the papillary or omental lobe, corresponds to the caudate process and its tuber omentale (see Fig. 10c) and not to the papillary process of the human liver. The veins from these 2 lobes in the rat (I, Figs. 39 & 40) unite in a vertical plane to form an ostium 2 mm. in diameter in the left side of the caval wall 1 cm. below the main left ostium.

Major deviations from the pattern described above were encountered in only one rat, killed for another purpose; the left lateral lobe and its vessels were completely absent.

The branching of the hepatic veins of the rat (Fig. 41) is similar to that in man in many ways and it is possible to define 6 orders of hepatic veins (Table I) to correspond to the 8 orders in man. There are no anastomoses of any importance between the hepatic-venous radicles in the liver normally and few veins exist in relation to the thin capsule. Fig. 41 shows an important difference between the species; many sinusoids in

the rat terminate in hepatic and intercalated veins, and they do not lead exclusively into central venules as in man. This was first shown by Gershbein and Elias. The demonstration by Wakim & Mann (1942) of long small veins in the subcapsular region indicates that there are differences in the venous drainage of peripheral and central areas of the rat liver similar to those in man (Figs. 17, 25 and 26).

Histological structure: The hepatic veins of the rat are relatively thinner than those of man and poorer in collagen, elastica and muscle. Starck (1933) who investigated these vessels in a small number of rats reported that muscle was entirely absent and Tischendorf (1939) stated that they have in general no muscle. The present observations show however that a small amount is present. Starck considered that absence of muscle from the hepatic veins in small animals was related to the thinness of their liver capsules and to the correspondingly firm fixation of the hepatic veins to the liver parenchyma. The possibilities for constriction of the hepatic veins are certainly less in the rat than in man and the paucity of connective tissue is particularly striking round the hepatic cava buried in the liver.

In the hepatic ostia an adventitial and an intimal coat are present but they are less defined than in man. Broad slanting longitudinal muscle fibres are present in moderate numbers in the adventitia. They are gathered together in large and prominent spiral bands (Fig. 42) in certain fields at the mouths of the ostia, chiefly but not exclusively at points where the vessel wall is free of a parenchymatous investment.

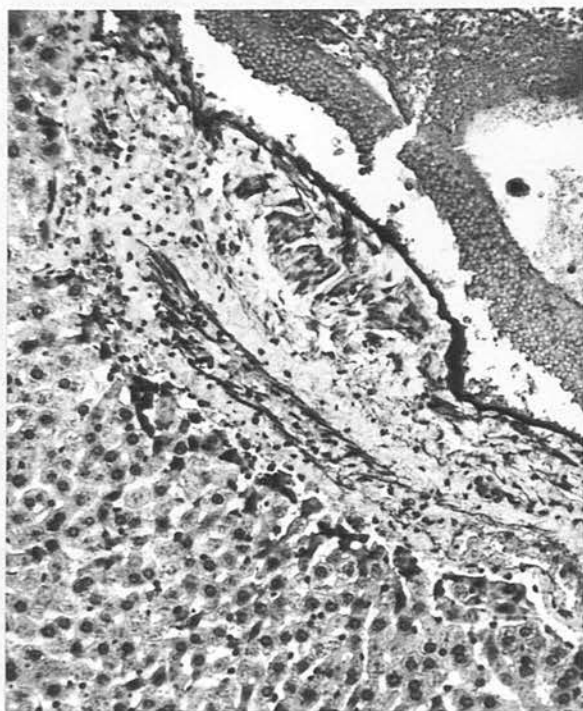


Fig., 42. Left ostium of normal rat. The intima is thin here and sharply demarcated by an internal elastic lamina from the adventitia. A group of smooth muscle fibres is present in the adventitia. Some loose connective tissue divides this from the external elastica (reduplicated on account of a tributary) and from the liver beyond it. Haemalum, eosin-phloxine, tartrazine and Weigert's elastica x 165.

The left ostium is the best supplied with muscle. This does not extend into the cava. Sling-like arrangements of muscle like those at the mouths of human ostia are not seen. Where muscle is present there is a zone of loose tissue in the adventitia, which probably allows movement of the ostia. Lymphatics and occasional arterioles are present there as in man, but nerve bundles definitely related to the vessels cannot be seen. The intima is thin and consists of tenuous collagen fibres under the endothelium, together with a few fine smooth-muscle fibres, probably arranged in a circular direction, and a moderate number of delicate elastic fibres. The latter are loosely aggregated in some places and in others form a clearly defined internal elastic lamina (Fig. 42).

The bands of adventitial muscle seen in the ostia continue into the hepatic veins at only one place, that is where vein E joins vein F (Figs. 39 & 40) below the left ostium. The veins at this point lie directly under the peritoneum. Elsewhere the muscle in the hepatic veins is in the form of individual thin fibres and is scanty. It can be seen in the adventitial coats of 2nd order veins (Table I) and only rarely below that level; the adventitia then consists of elastic fibres and collagenous connective tissue. An internal elastic lamina and intimal muscle fibres are often recognizable in veins of the 2nd order though they are scanty. Intimal muscle can be seen occasionally in veins of the 4th order. Just as in human hepatic veins, the intimal muscle in the veins of the rat extends further down the hepatic venous tree than does the adventitial muscle.

The smallest orders of the hepatic veins (Fig. 43) are

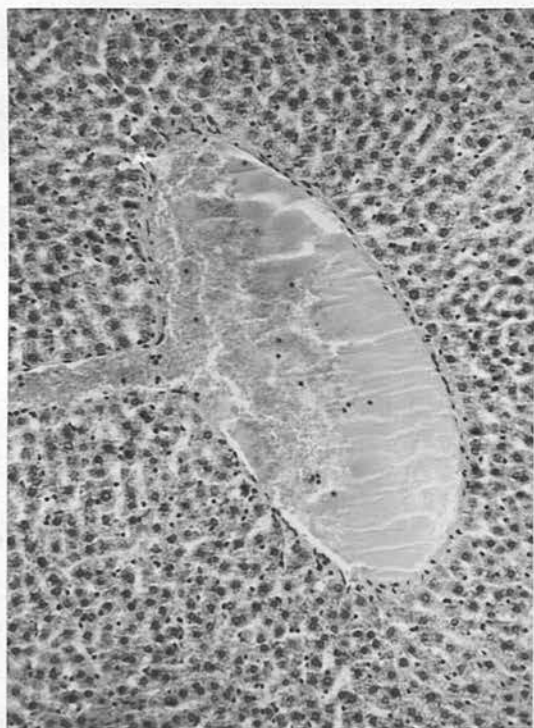


Fig., 43. Rat hepatic vein of 5th order joined by a central venule (36 μ diameter). The vein wall is thin and not muscular and there is no constriction of the central venule at the junction. A sinusoid joins the vein directly (bottom left). H. & E x 150.

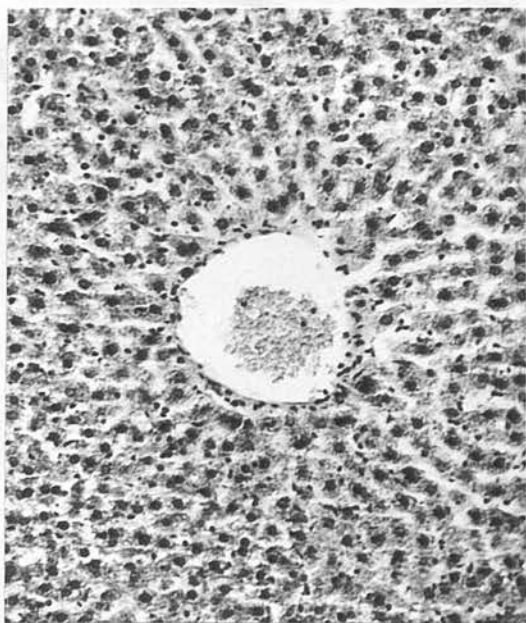


Fig., 44. Intercalated vein of rat (150 μ diameter). It has a very thin non-muscular wall and sinusoids join it (right) without any obstruction. H. & E x 165.

little more than fibrous tubes with endothelial linings. The walls are 5 - 15 μ thick. The vessels are firmly embedded in the liver tissue and fine fibrous strands pass from them into the liver parenchyma (Tischendorf). They have relatively more elastica than their human counterparts. Most of the elastic fibres are arranged in a roughly longitudinal or spiral direction and, in transverse sections of the smaller hepatic veins, the fibres appear radial rather than circular in orientation. This may be related to the fact that sinusoids drain directly into hepatic veins (Figs. 41 & 43). Sinusoidal junctions are common in the smaller hepatic veins but uncommon in 4th order and larger veins. Wakim and Mann in their transillumination studies noted long ramifications of hepatic veins, parallel and close to the liver edge and receiving sinusoids from the tissue there.

The small veins of the rat liver are similar to the small hepatic veins but thinner (Figs. 43 & 44). They have been observed in vivo by others in transillumination studies. These studies, which are referred to in more detail later, suggest that the small veins can contract actively. In histological sections, sinusoids often appear narrowed where they pass through the walls of hepatic veins, but this is not generally so when they enter intercalated veins (Fig. 44) and no anatomical basis for an active contractile power in the small veins was found in the present studies. In the casts both central venules and intercalated veins received sinusoids and the veins increased in calibre more gradually in the rat (Fig. 41) than is the case in man (Fig. 25). The composition of the small veins is otherwise similar to that of the corresponding veins



in man. The small veins are not sharply distinct in any respect from one another or from the hepatic veins above them and the terminology applied above in man has been adopted and the veins divided into two types only, viz. central venules and intercalated veins, omitting the term "collecting vein".

The diameters of the various components of the hepatic venous system are shown in Table I. The figures for the small veins have been calculated by increasing direct measurements made on paraffin sections by 1/5 to allow for shrinkage.

Friedman et al. (1953) measured the sinusoids and central venules in their transillumination preparations of living rats and reported them to be 6 - 10 μ and 30 - 80 μ respectively, figures that are close to those in Table I.

Venous barriers: On account of their poor contractility and firm fixation to the surrounding liver, the hepatic veins in the rat are usually seen to have widely patent, round or oval lumina in histological sections (Fig. 43) and they rarely take up the polygonal cross section that is assumed by human veins in contraction (Fig. 29). DuMais (1944) noted contractions in casts of the hepatic veins of rats made in a condition of spasm but they were not seen in the present material.

Tischendorf did not find any "intrahepatic ostial" sphincters in this species. In histological sections and neoprene casts, one rarely encounters in the rat any constrictions of the mouths of venules where they enter hepatic veins (Fig. 43).

The scarcity of these junctional constrictions, which apparently represent functional barriers in constricted hepatic veins in man, is in keeping with the paucity of muscle and thinness of

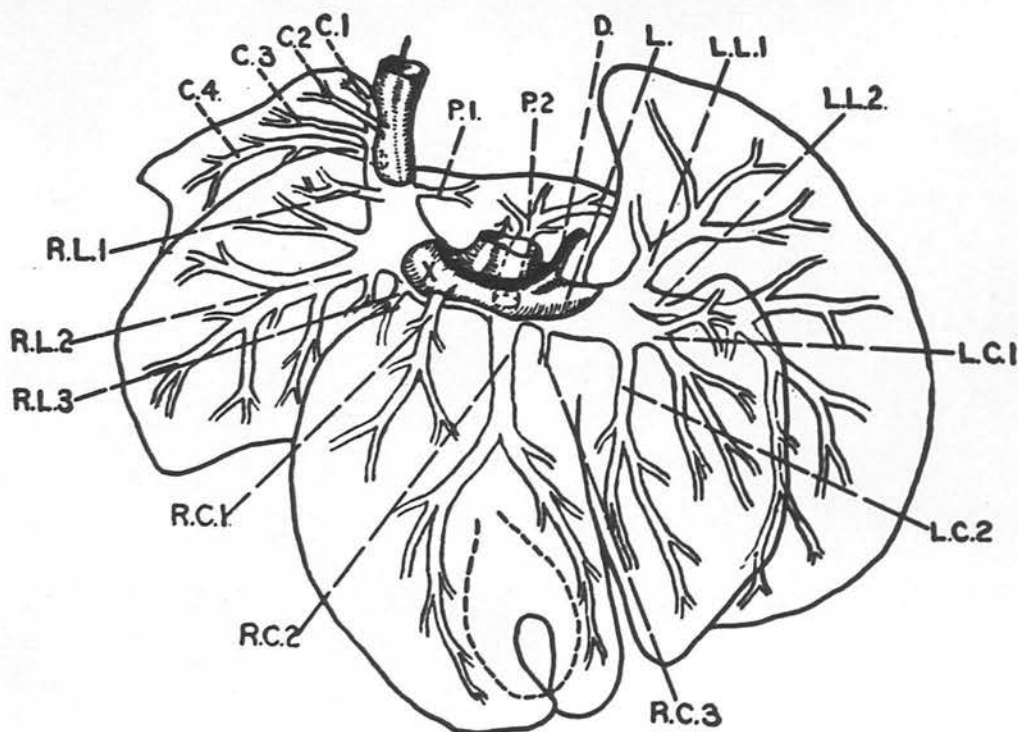


Fig., 45. The hepatic veins, hepatic cava and liver in the domestic dog. Copied from Kershner et al., (1946). The veins are lettered according to the lobes they drain:

L - Left ostium.

D - ductus venosus.

X - portion of hepatic cava lying directly under the peritoneum.

the hepatic veins observed in the rat and with the firm fixation of the veins to the hepatic parenchyma. There appears to be very little impediment to the outflow of blood from the rat's liver at this level. Free venous drainage is also favoured in the animal by the gradual increase in the size of the veins and by the direct entry of sinusoids into hepatic veins (Figs. 41 & 43), an arrangement which eliminates differential stasis round central venules (Elias and Popper, 1955). Although muscle bands are present at the left ostium arranged like those described in the rabbit by Starck (1934a), this structural arrangement is probably capable of at best a modest physiological action.

Lymph drainage: The lymph drainage of the rat's liver is mainly to the coeliac nodes via the hepato-duodenal ligament and the general arrangement of the lymphatics is similar to that in man and in other animals. Few, if any, lymphatics run in the thin capsule of the rat's liver, but the hepatic veins down to the 2nd order are supplied with lymphatics on a scale similar to that in man. The main lymphatics in the portal tracts are often related closely to the hepatic-arterial branches (Fig. 171).

Portal system: Although a detailed study of this system was not undertaken, certain features of the anatomy of the portal vein in the rat deserve attention here. The intrahepatic branches of the vein are more muscular than their hepatic counterparts of the same size, and they have a distinct medial coat. The portal trunk is similar in plan but, as in other

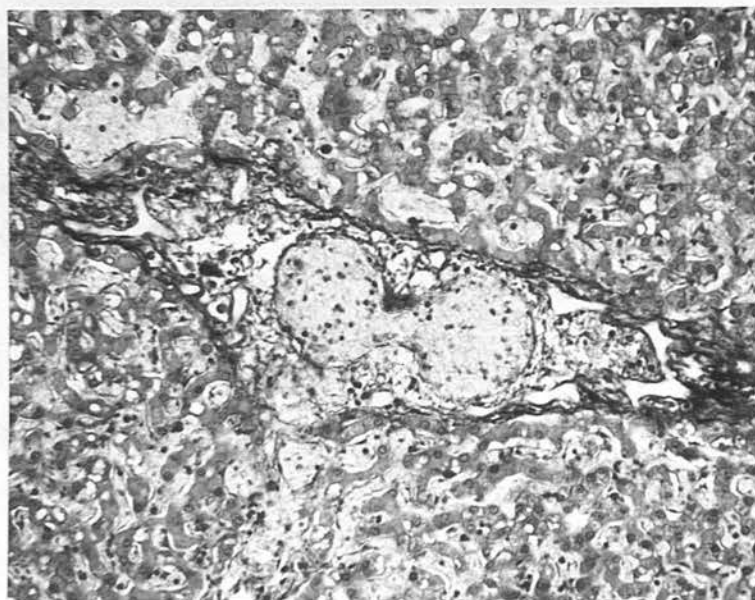


Fig., 46. A small (100 μ) intercalated vein of a normal dog. It is separated from the liver by a sheath composed of fine fibrous tissue, which contains lymphatics. The vein is markedly constricted by a band of intimal smooth muscle. Picro-Mallory x 155.

animals, it is relatively more muscular than its intrahepatic branches. There is a special arrangement of the intima and media in the portal stem in the form of a narrow band running round it in a low-pitched spiral (Baker, 1958). A similar structure is present in other rodents (Hyrtl, 1870; Rex; Baker, 1956). Possibly the function of this structure is to distribute portal blood from its various sources in a random fashion to the different liver lobes and so to counteract any streamline effect. It may be associated with the relatively large size of the omental and left lobes in rodents.

Another peculiarity of the portal system in rats is the direct communication that exists between it and the pulmonary veins via the perivagal veins (Butler, 1952). The homologous veins in man are mere vasa nervorum, but abnormal termination of the pulmonary veins in the portal has been reported as a congenital anomaly (Young, 1947; Weinberg and Kolson, 1949). Reynell (1952) describes the portasystemic anastomoses that are visible in experimental hypertension in the rat.

HEPATIC VEINS OF SOME OTHER ANIMALS

The hepatic venous system of the domestic dog (*canis familiaris*) has been outlined by Kershner et al. (1946), from whose paper Figs. 45 & 53b have been taken, and by Elias and Petty (1952). The lobes of the liver are listed in Table IV. The structure of the canine hepatic veins has been described by several authors (e.g. Tischendorf) and Arey (1941) points out that it differs from that of other mammals including closely related species. The central venules and intercalated veins lie in loose connective-tissue septa surrounded by small

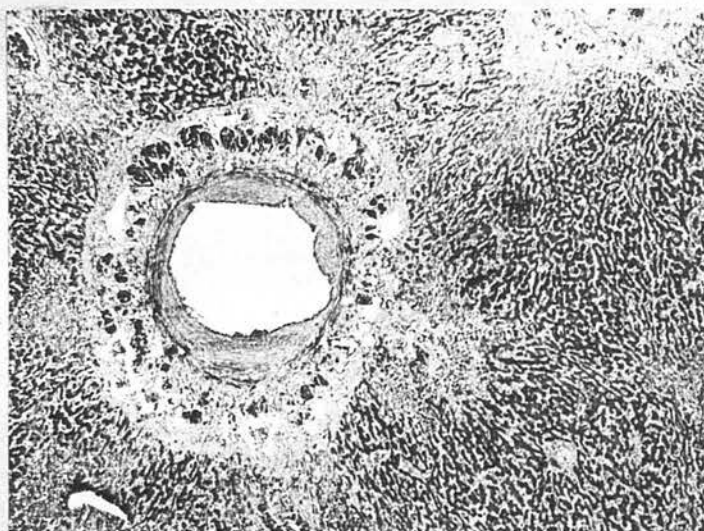


Fig., 47. Medium-sized hepatic vein of dog. This transverse section shows the circular intimal muscle and prominent longitudinal bands of muscle in the adventitia. Lymphatics are present in the loose tissue of the adventitia. The muscle is somewhat hypertrophied in this specimen which is from a dog (no. 49 - chapter VI) in which the inferior cava had been ligated in the thorax some months before. Picro-Mallory x 30.

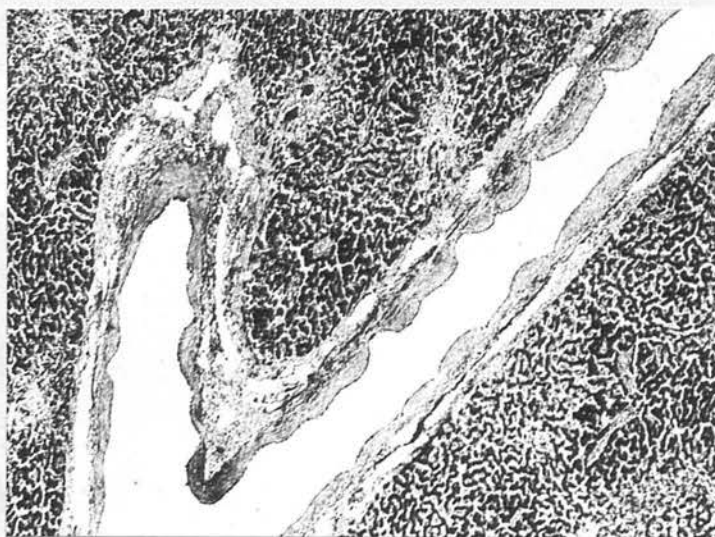


Fig., 48. Dog 49, the same animal as in Fig., 47. Two small hepatic veins are joining. Note the elevations of the intima and the enlarged lymphatics and muscle in the adventitia. Picro-Mallory x 30.

lymphatics and they are narrowed at frequent intervals by incomplete spirals and rings of muscle (Fig. 46), so that casts of them have a beaded appearance (Mall, 1906). In the hepatic veins, muscle is exceptionally profuse; there are circular fibres in the intima and large longitudinal bands of fibres in the adventitia (Figs. 47 & 48). Contraction of the muscle is facilitated by the loose attachment of the vein walls to the liver substance and by the presence of large lymphatics in the loose tissue. Dilatation of the lymphatics reciprocally with contraction of the hepatic veins probably helps to minimise hepatic congestion caused by the latter. The lymphatics anastomose with the usual portal and capsular systems. The capsule of the dog's liver is thick in comparison with the rat's. It is more like the capsule of the human liver and it is well supplied with lymphatics (Fig. 49).

The intrahepatic branches of the portal vein are poorer in muscle than the radicles of the hepatic veins of the same size.

Certain peculiarities of the venous system are found in aquatic mammals which probably act to increase the pressure in the veins of the abdomen and of other compressible parts in submersion. The structures and mechanisms have been reviewed by Franklin (1937). In the walrus and seal, a large subdiaphragmatic venous reservoir is formed by the expansion of the cava below the diaphragm at the level of the lacus venae cavae (Fig. 55) and this is further increased by massive enlargement of the hepatic ostia which have thick muscular coats. The central venules and intercalated veins of the seal are narrowed at frequent intervals by intimal muscle (Lacoste & Gouelmino, 1925; Arey,), but in the liver of a "cape seal"

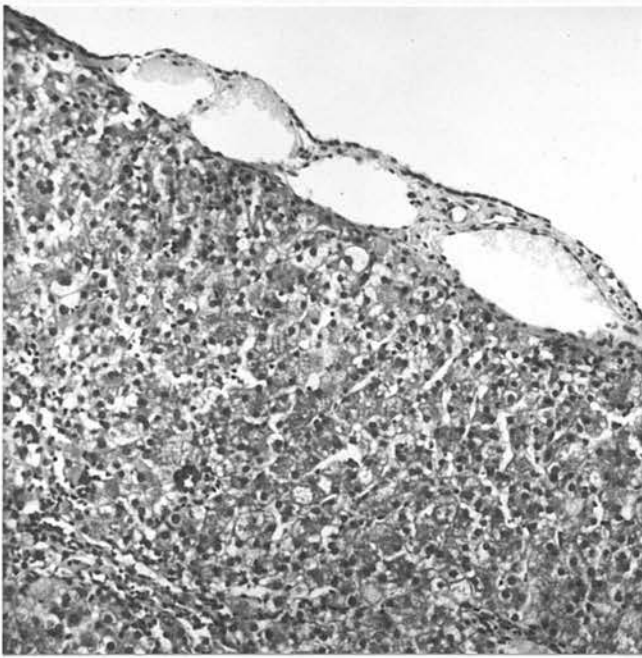


Fig., 49. Large lymphatics in the liver capsule of a dog with ascites after 21 weeks of carbon tetrachloride administration (dog CPC3 of McCredie et al., 1957). H. & E. x 120.

(arctocephalus pusillus) which I have examined the constrictions were less than in the dog (Fig. 51) and the veins adhered directly to the liver parenchyma and did not lie in specialised septa. The hepatic veins of seals are much less muscular than those of dogs.

Andrews et al. (1956b) state on the basis of unpublished observations that "Despite popular acceptance to the contrary the hepatic venous tree of monkey, cat and rabbit as well as other mammals including man contain considerable amounts of smooth muscle." Livers of single representatives of a number of species of monkey, kindly given me by Dr. W.R. McC. Morton, have been examined to determine the degree of muscularity of the hepatic veins in this order. The results are shown in Table III together with comparable estimates in some other species. The hepatic veins of monkeys contain relatively as much muscle as those of man and often more (Fig. 50). Perivenous lymphatics are often large. No definite attempt was made to discover whether muscle was present in the small veins of the monkey livers. In general they appear to resemble those of man.

The structure of the hepatic ostia in the cat is partly muscular but not markedly so. Tischendorf did not find any sphincter-like arrangement there. The hepatic veins are less muscular than the portal branches in the liver according to Popper (1931) who described them as largely fibro-elastic tubes, though capable of slight contraction in various physiological and pathological circumstances (Popper; Deysach, 1941; Thomas & Essex, 1949). Tischendorf and Arey point out that Mall was wrong in describing spiral valves in the small veins of the cat.

In the rodents the smooth muscle in the hepatic-venous system tends to be concentrated at the ostia near where the vessels emerge from the liver into loose tissue. It has been shown that in the rat it is not entirely confined to this. Ostial muscle is well developed in the amphibious hydrochoerus capybara (Starck, 1934, b) in which it is probably modified to control the circulation when the animal is in the water. The hepatic veins of the guinea-pig (*cavia porcellus*) and of the rabbit have been described by Starck (1934, a). In the lagomorpha, Mautner (1923-24) on pharmacological grounds denied the existence of ostial sphincters in rabbits (*oryctolagus cuniculus*) but Tischendorf noted them in his histological studies. In addition to ostial muscle, the rabbit has specialised bands of muscle in the intimal coats of hepatic veins at the points of junction of tributaries. Tischendorf who described this "intrahepatic ostial type" of sphincter found them with certainty only in the rabbit. They are not identical with the junctional constrictions found in other animals although they occur at the same sites. Deysach described his sluice channels in the rabbit as well as in the cat, and their operation in the rabbit may be due to this special arrangement. My own observations indicate that the hepatic veins of the rabbit are well supplied with smooth muscle throughout.

Naftalin and Howie (1949) reported a considerable amount of muscle in the hepatic veins of the pig and illustrate a junctional constriction in this animal like those in man.

Rex noted the termination of the left diaphragmatic vein in the left hepatic ostium in some mammals and my observations confirm that this is the case in rats and dogs. There are no

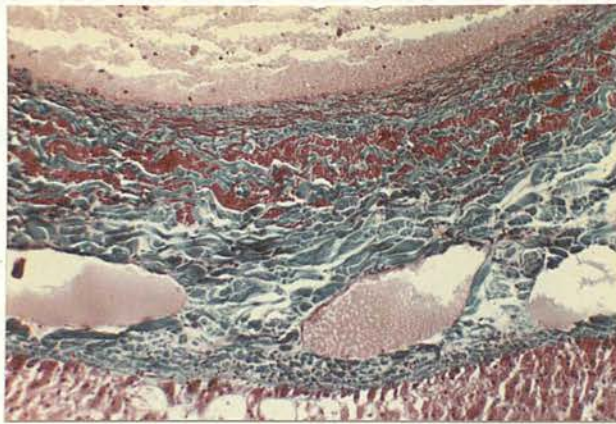


Fig., 50. Large hepatic vein of chimpanzee. The structure closely resembles that of the hepatic veins of man. Fine smooth-muscle fibres are arranged circumferentially in the intima and thick longitudinal bands of smooth muscle are present in the inner layer of the adventitia. Lymphatics are dilated in the more loosely textured connective tissue below and the external collagenous layer is densely adherent to the liver. Picro-Mallory x 80.

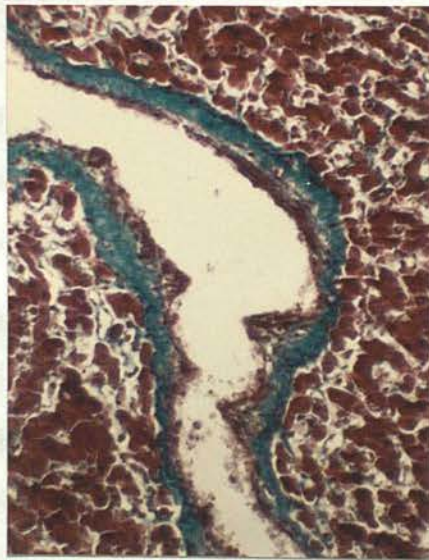
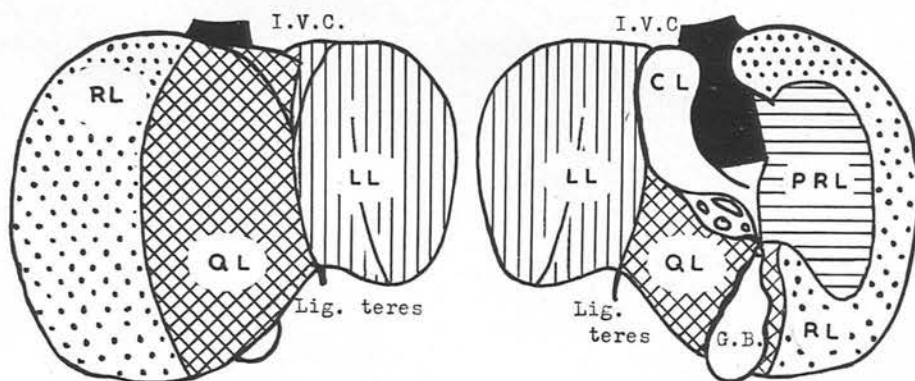


Fig., 51. Liver of cape fur seal. Central venule (below) joining an intercalated vein. The lumen is narrowed at intervals by little muscular elevations in the intima. Picro-Mallory x 150.

TABLE III. The amount of smooth muscle observed in the hepatic veins of different species.

<u>Species.</u>	<u>Order.</u>	<u>Ostia</u>	<u>Larger</u> <u>H.V.</u>	<u>Smaller</u> <u>Veins</u>	<u>Outline</u> <u>drawing and</u> <u>comment.</u>
White Rat. <u>Rattus Norvegicus</u>	Rodentia	+	+	-	Fig., 52.
Rabbit. <u>Oryctolagus Cuniculus</u>	Lagomorpha	++	++	...	
Wallaby. <u>Macropus Ualabatus</u>	Marsupialia	+++	+	...	56.
Cape Seal. <u>Arctocephalus Pusillus</u>	Pinnipedia	+++	+	+	55. much collagen in sinusoid walls.
Kitten. <u>Felis catus.</u>	Carnivora	++	+	...	56.
Domestic dog. <u>Canis Familiaris</u>	Carnivora	++	+++	++	52.
Rhesus Monkey. <u>Macaca Mulatta.</u>	Primates	+++	+	...	56.
Capuchin Monkey. <u>Cebus Capucinus</u>	"	++	+	...	57.
Squirrel Monkey <u>Chrysoteryx Sciurea</u>	"	+++	++	...	57.
Sooty Mangaby <u>Cercocebus Fulginosus</u>	"	+++	++	...	57.
Kra. <u>Macaca Irus.</u>	"	++	+++	...	58.
Mandrill <u>Mandrillus sphinx</u>	"	+++	+++	...	58.
Chimpanzee <u>Pan Troglodytes</u>	"	+++	++	...	58. large lymphatics.
Man. <u>Homo Sapiens.</u>	"	++	++	-	52.

... = no observation.



BELOW - COMPARABLE LOBES IN ANIMALS:

LEFT - DOG,

RIGHT - RAT.

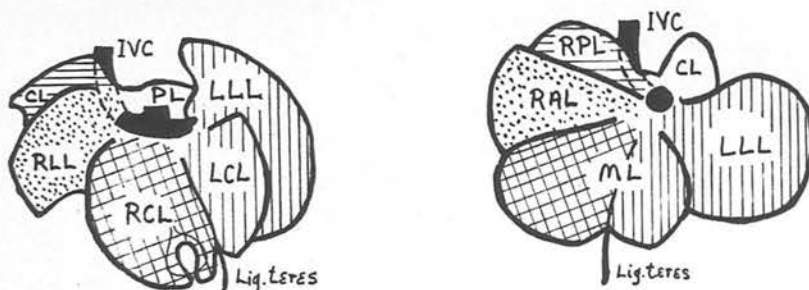


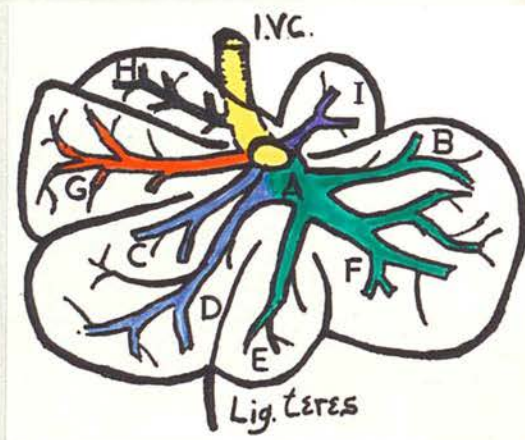
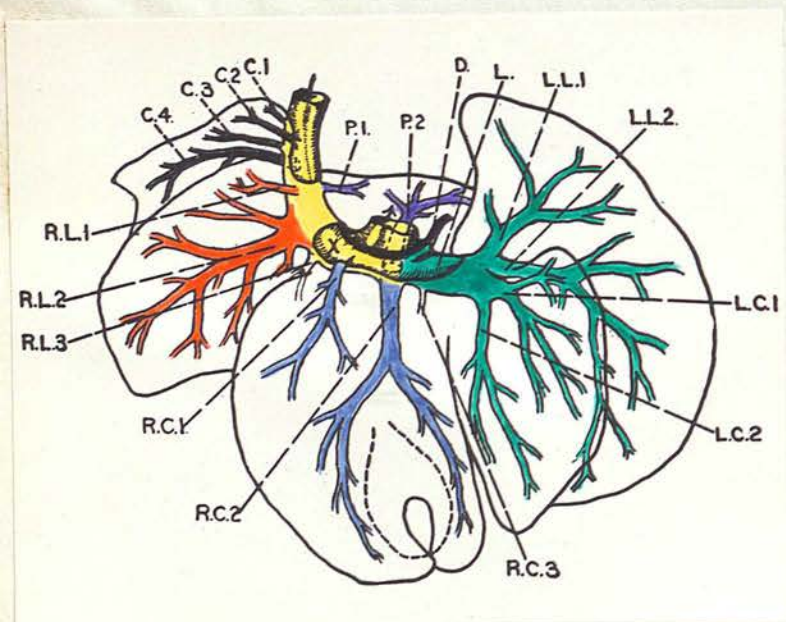
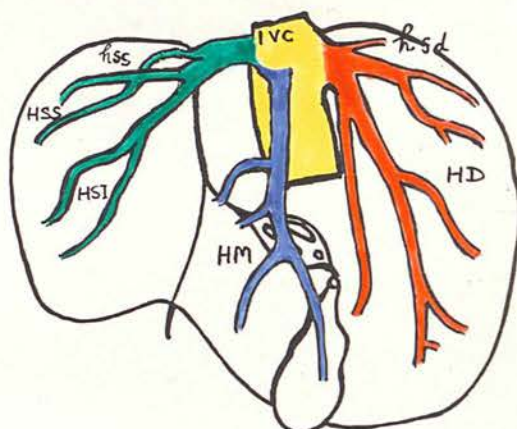
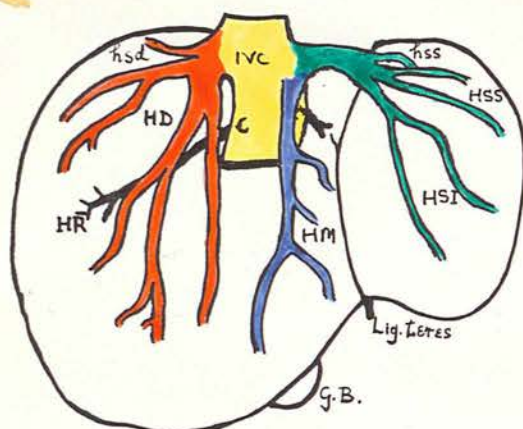
Fig., 52. Comparative lobation of the liver in man, the dog and the rat on the basis of venous drainage, the corresponding territories being shaded in the same way. The human liver, above, is divided according to the data presented in chapter I. The dog liver is shown below on the left and the rat liver on the right; they are seen from above - labelling as in Table IV.

The attachment of the falciform ligament and the ligamentum teres mark the right boundary of the left lobe proper in each species. A line drawn on the left lobe of the human liver corresponds to the external division of this lobe in the animals in which the homologue is compound. On the human liver the line marks the limits of the territories of the veins HSS and HSI.

TABLE IV, COMPARATIVE LOBATION OF THE LIVER
OF MAN, OF THE DOG AND OF THE RAT.

Main Lobes in Human Liver	Corresponding Lobes in Animals.	
	Dog. (Kershner et al., 1946).	Rat. (Farriss & Griffith, 1949).
Caudate lobe & process CL.	Papillary PL.	Caudate CL. Papillary (omental) lobe.
Left lobe. LL.	(Left lateral LLL. Left central LCL.	(Left lateral LLL. Left part of median lobe ML.
Quadrate lobe. QL.	Right central RCL.	Right part of median lobe ML.
Right lobe. RL.	Right lateral RLL.	Right anterior RAL.
Paracaval part of right lobe. PRL.	Caudate CL.	Right posterior RPL.

(a)
man.



(b) left, dog.

(c) above, rat.

Fig., 53. The comparative anatomy of the hepatic veins in (a) man, (b) the dog and (c) the rat. The homologues are shown in the same colours. In (b), X marks a subperitoneal portion of the cava.

other examples of systemic tributaries entering the hepatic venous system in mammals. In birds, however, an epigastric vein joins the hepatic veins before their termination (Child, 1954).

COMPARATIVE LOBATION OF THE LIVER

Most of the mammals have externally lobated livers which differ in outline from the human organ. Gershbein and Elias base their comparative studies in the rat on the portal-venous supply of the liver lobes, stating that the portal veins are the most stable identifiable elements. It is possible, however, to use the hepatic veins as guides to the homologues of the different parts of the liver in different species. This system is easier to apply, for the terminations of the hepatic veins can be found easily in the cava without the necessity of making casts. The territories of the main veins in man, in the dog and in the rat are compared in Fig. 52 and the homologues are listed in Table IV. The veins themselves are compared in Fig. 53. The details of this comparison are too lengthy to discuss here but it may be stated that the scheme can be applied readily to other species (Figs. 55-58). The comparative status of the central mass of the liver (ML in the rat - Fig. 52) and the position of the falciform ligament, to mention two features, can be understood better with reference to the hepatic than to the portal veins.

Effects of lobation: In multilobed livers, the portal-venous branches, as they enter the lobes through small pedicles, run parallel to the hepatic-venous radicles, and this relationship

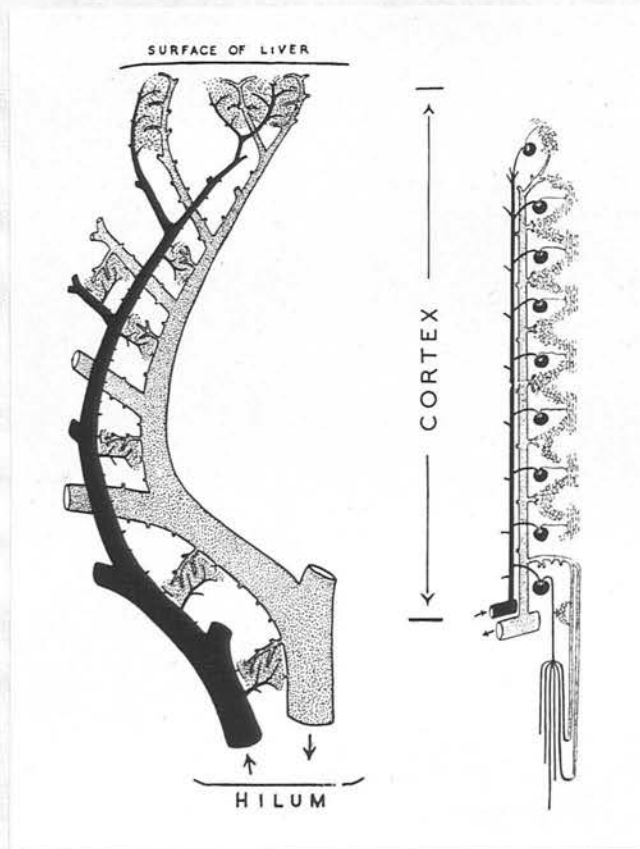
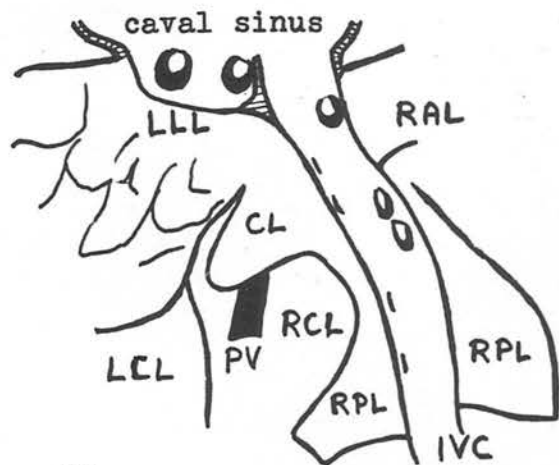
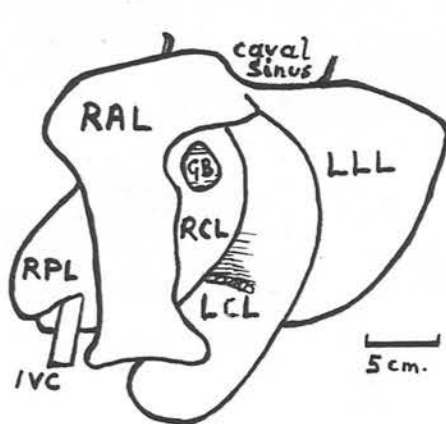


Fig., 54. Short-circuit routes in liver and kidney. This is figs., 12 and 13 of Pritchard and Daniel (1952). In the animal liver on the left, blood from the portal vein (black) can pass to the hepatic vein (stippled) at all levels from hilum to periphery because the two veins run parallel and have small branches or feeders. A similar state of affairs exists in the kidney (right). The anatomical arrangement of the human liver does not permit of this type of short circuit.

is maintained throughout most of the courses of the vessels. In unified livers like that of man on the other hand, the portal and hepatic vessels interdigitate, each group crossing the line of the other at an angle which is variable but often approaches 90° . This was appreciated by Glisson (1654). Although large portal and hepatic veins are closely related throughout their courses in many animals, this is not the case in man where the hepatic veins join the cava at a distance of 5 - 6 cm. from the porta.

(i) Short circuits: The short-circuit route for blood flow through the liver described by Daniel and Pritchard (1951) depends not on the existence of previously undescribed vessels but on the close spatial relationship of large portal to large hepatic veins throughout their courses and on their intercommunication through small branches and radicles of the large vessels (Fig. 54). In the experiments of these workers on anaesthetised rabbits, cats and rats, blood flow was noted to switch from one path to the other and it has been accepted too readily that such changes occur in man. Since in man the hepatic veins follow courses that are very different from those of the portal veins in the liver, it is clear that the anatomical requirements of this route are not fulfilled in the human liver, although routes of variable length are open. Pathological data also indicate that this type of short circuit is unimportant in man for there are no morbid anatomical conditions which can be explained by its operation such as are seen in the kidney, in which a suitable anatomical arrangement does exist (Fig. 54). Sherlock and Bradley (1952) have not obtained from bromsulphthalein tests any evidence of the



cape seal
arctocephalus pusillus

Fig., 55. On the anterior surface of the liver of the cape fur seal (*arctocephalus pusillus*) the ligamentum teres and falciform ligament enter between the medial portion of the left central lobe (LCL) and the right central lobe (RCL). The right posterior lobe (RPL) envelopes the lower part of the cava (IVC) which opens up above into the large caval sinus.

In the posterior view (right) the cava has been opened from behind to display the hepatic veins draining each lobe. This drawing, which is on a larger scale, shows the irregular posterior surface of LLL and the portal vein (PV) entering the liver in front of the caudate lobe (CL).

operation of a short circuit in the human liver.

Andrews and his colleagues (1953 and 1956 a) deduced from perfusion and other experiments in the dog the existence in the dog of direct communications between hepatic arteries and veins. Prinzmetal et al. (1948) demonstrated with glass beads the existence of shunts 50 - 180 μ in diameter between portal and hepatic veins in the rabbit. Although the vessels they postulated are as large as intercalated veins, they have not been recognized in normal animals. The anatomical basis of the arterio-venous shunts in the dog is also unknown. Certainly it does not seem that either type of communication exists in man, except possibly in conditions of disease.

(ii) Liver parenchyma: As regards the liver parenchyma, the most obvious effect of lobation of the liver is to increase its flexibility. Owen (1868) put forward the view that a body structure and habit of life involving considerable movement of the trunk at this level was associated with a multilobed liver. Lobation is particularly marked in the seal (Fig. 55). The effect of increasing the surface area of the organ is probably incidental, for although considerable quantities of fluid can be transferred by this route to the peritoneal cavity in disease, it is improbable that this takes place in health.

SUMMARY

1. Observations on neoprene-latex casts and on dissections of livers of albino Wistar rats are recorded in detail in a study of the courses of the hepatic veins of the rat. A full histological description of the system is given. The veins are poorly endowed with muscle but are not completely deficient in it, as some others have reported. Muscle bands are present at and near the ostia and are best developed around the left ostium. These bands form the only noteworthy anatomical structure that might act as a sphincter in the hepatic-venous system of this animal and there are no junctional constrictions. It is confirmed that in this species sinusoids end in intercalated veins and frequently in the smaller hepatic veins, as well as in the central venules. Thus venous drainage is freer from the rat liver than from the human organ. The intrahepatic portal veins are unusual in the rat in being more muscular than the hepatic veins.

2. The structure of the hepatic veins of several species of mammal is reviewed chiefly on the basis of accounts published by others. Anatomical differences are important in interpreting results of experiments on animals and must be considered before applying such results to human conditions.

3. The courses of the hepatic veins in the dog and rat are used as a basis for comparing the lobation of the livers of those species with that of the human liver and may be used in comparisons with other species. The short-circuit route for blood flow through the liver described in the multilobed livers of animals by Daniel and Pritchard is of little importance in

the unified liver of man and the existence of other routes is unproved in the human species.

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CHAPTER III

COMPARATIVE
PHYSIOLOGY OF THE HEPATIC VEINS

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COMPARATIVE PHYSIOLOGY OF THE HEPATIC VEINS

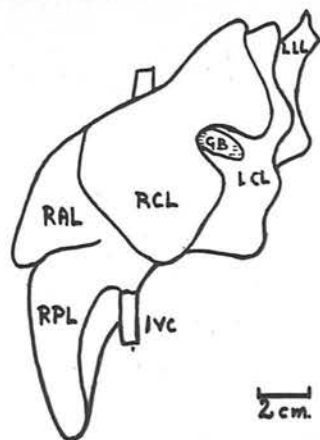
HEPATIC VENOUS BARRIERS

Sphincters of the ostia and large hepatic veins: The muscular folds in these situations in man have already been described and their possible mode of action discussed (Figs. 11, 13, 20 & 21). Bradley et al. (1945) refer to spasm occurring at this level of the hepatic-venous tree, presumably as a result of minor trauma, during a few of their intravital catheterisations. There is little doubt that constrictions sufficient to reduce the hepatic venous outflow can take place at these sites under certain circumstances, but it has not yet been shown that they occur under physiological conditions. The low pressure in the portal vein in health (about 10 mm. Hg) and the large volume of the hepatic blood flow indicate that the liver normally offers little resistance to the blood flow through it. Feeble barriers might thus exert a significant effect. The amount of muscle present at the ostia seems adequate for an effective partial throttling action at this site. The muscle is, however, relatively less, at any single site, than that found in any of the multiple renal or adrenal venous sphincters. An indication of the existence of an effective sphincter here might be expected from observations in hepatic catheterisations, but the available data is not yet adequate for a final analysis. The mean figure for F.H.V.P. (free hepatic-venous pressure) of 6 mm. Hg. given by Paton et al. (1953) is midway between the portal-venous pressure (10 mm. Hg.) and the inferior caval pressure which is 3 mm. Hg. (Bell, Davidson and Scarborough, 1956). Normally then there appears to be a small amount of obstruction to outflow between the medium-sized veins

and the cava. Probably there is some sphincteric action at the ostia in man under normal conditions, but it is not likely that it plays any part in controlling the general circulation. The ostial sphincters may act in conjunction with other mechanisms in the hepatic vasculature to influence blood flow through the liver, but they are not the sole or even the most powerful of the venous barriers. Their possible rôle in disease and in experimental conditions in animals will be discussed later.

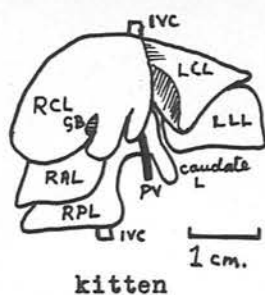
Junctional constrictions: Venous outflow can be altered at the level of small hepatic veins in several species (Deysach, 1941; Maegraith et al., 1949; Thomas and Essex, 1949). This is due to special muscular arrangements in the dog and possibly in the rabbit (the "intrahepatic ostial sphincters" of Tischendorf, 1939). The most common mechanism seems to be that of junctional constrictions (the "funnel junctions" of Popper, 1931) which are found in man. They have been discussed in Chapter I and are illustrated in Figs. 24 and 27 - 29.

Deysach reported the histological features of animal livers following perfusion with drugs and other procedures. He described in several species a new channel of drainage for the sinusoids, simple endothelial tubes, which he called "small sluice channels" emptying into what he termed the "sublobular" veins. These channels were widely opened by adrenalin and closed by acetyl-beta-methylcholine chloride and drugs of similar action. The drugs acted on the walls of the "artery-like sublobular veins" which closed the small sluice



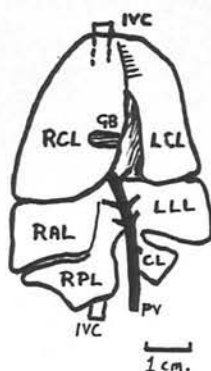
wallaby
macropus ualabatus

(a)



kitten

(b)



rhesus
monkey

(c)

Fig. 56. The lobation of the liver in (a) the wallaby-*macropus ualabatus*; (b) the cat - *felis catus* and (c) the rhesus monkey - *macaca mulatta*. In (a) and (c) the terminations of the hepatic veins are shown in the cava opened from behind.

The falciform ligament is indicated by horizontal shading. The key to the lettering is given in Table IV.

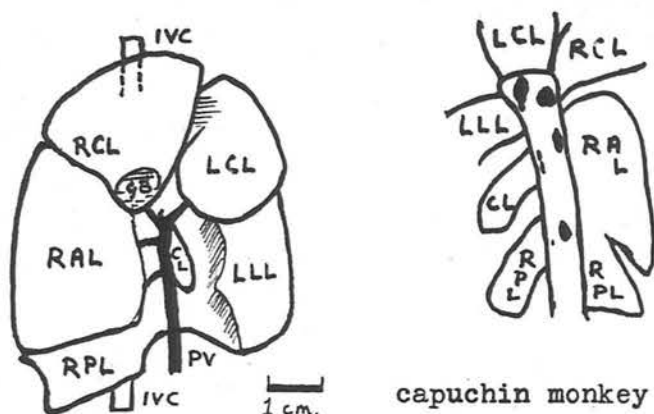
channels when they contracted. Deysach referred to "central veins" as large sluice channels. These histological findings are not in keeping with the older descriptions of Pfuhl (1922) and Popper and the structures mentioned have been assigned to various different levels by subsequent authors. It may be pointed out, however, that if Deysach's nomenclature is altered, his descriptions of the structure and composition of the vessels coincide with those given above in man. Direct measurements taken from his illustrations (which may be compared to Fig. 29) confirm that his "sublobular" veins, which measure 1 - 2 mm. in diameter, are hepatic veins with muscular walls, his "large sluice channels", which were never completely closed, are intercalated veins and not central venules and his "small sluice channels" (simple endothelial tubes) are central venules. Andrews (1957) apparently came to similar conclusions. The identification by Knisely et al. (1948) of the sluice channels with their own "outlet sphincters" is incompatible with the illustrations in Deysach's paper.

Deysach's experiments were carried out chiefly in cats, rabbits and vervet monkeys but he reported similar venous arrangements in several other mammals. In most mammals junctional constrictions are probably an important means of controlling the venous outflow from the liver, but not in the rat. The experiments of Maegraith et al. (1949) and of Thomas and Essex yielded doubtful results in this species and the histological evidence reported above is against the existence of effective barriers to the hepatic-venous outflow at this level in the rat's liver.

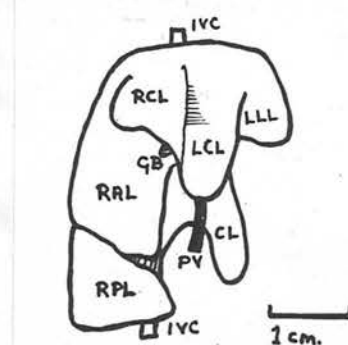
Casts of post-mortem human material (Fig. 23) indicate that

one central venule may be constricted where it enters a hepatic vein while others remain open, and the muscular coat of the hepatic veins when seen contracted in histological sections is often asymmetrical (Fig. 28). It seems likely, though it has not been proved, that similar selective closure can occur during life. Wakim and Mann (1942) and Seneviratne (1949-50) observed alternation of blood flow and stagnation affecting relatively large areas of liver under basal conditions of their transillumination experiments on anaesthetised rats. Torrance (1957) using internal calorimetry came to the conclusion that segmental alternations of this sort do not occur in the human liver, and in view of the free anastomoses existing within the sinusoidal system, the effects of closure of a central venule would be diffused entirely, just as in the case of impaction of a venous catheter in a small hepatic vein. On physical grounds it is likely that any individual sphincter as weak as a junctional constriction would have an "all or none" rather than a graduated action. It seems likely that fine regulation of the hepatic outflow is achieved in the case of this type of venous barrier by variation in the number of units in operation throughout the liver rather than by a gradual narrowing of each. Perivenous connective tissue is sufficient in man to allow minor realignments of the vein walls, and any tendency on the part of the contracting vessel to draw away from its close investment of liver tissue would be compensated by the congestion produced in the latter.

The volume of the hepatic blood flow is so great and the pressures involved so low that an effective sphincter action might be expected from the action of weak structures if



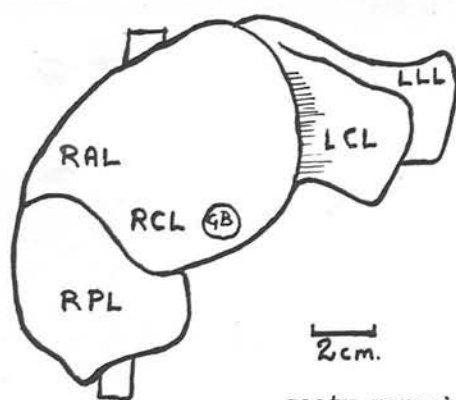
(a)



(b)

Fig. 57. Hepatic lobation and venous drainage of three monkeys. In (a) and (c) the lobes RCL and LCL are distinct as in the dog. In (b) they are united as in the rat.

- (a) capuchin monkey - *cebas capucinus*.
- (b) squirrel monkey - *chrysoteryx sciurea*.
- (c) sooty mangaby - *cercocebus fuliginosus*.



sooty mangaby
cercocebus fuliginosus

(c)

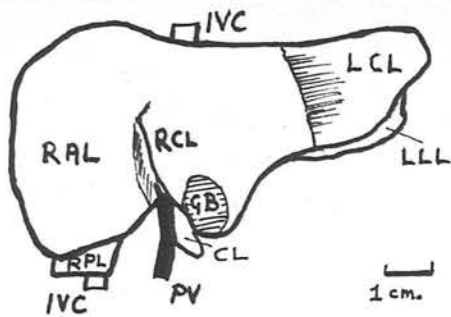
sufficiently numerous. Junctional constrictions are not present at all venous confluences but central venule-hepatic vein unions are so common that the system appears to provide man, and probably most mammals, with the main hepatic sphincter mechanism of a purely venous character.

Vasomotor action of central venules and sinusoids: Transillumination studies on frogs (Knisely et al.) and rats (Wakim and Mann; Senevirātne; Bloch, 1955) have suggested that the sinusoids can constrict actively in these animals. A structural basis for contraction has not been shown. Contractile elements are probably absent from the walls of capillaries (Zweifach, 1957) and are certainly absent from the walls of sinusoids. It seems unlikely that swelling of littoral or of Kupffer cells (if the two are distinct) would be able to occlude the sinusoids by their unaided action. It is uncertain whether endothelial cells can effect occlusion even in peripheral capillaries (Burton, 1954; Zweifach) where they are more numerous and where the vessels are narrower. Maegraith et al. (1947) rejected the possibility that swelling of the lining cells could cause sinusoidal obstruction even when the cells are enlarged in malaria. The sinusoidal circulation of the liver, however, operates at pressures below 40 mm. Hg. so that the critical opening pressure of the vessels is probably above the critical closing pressure and this factor will tend to maintain any closure of the sinusoids that follows a reduction in blood flow. A reduction in the amount of blood entering the sinusoid is probably the primary factor in causing narrowing (Andrews), though subsequent changes in the

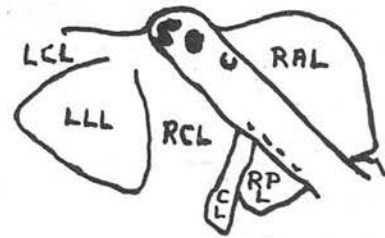
lining cells may complete the effect. It is not possible to exclude the possibility that changes in the shape or alignment of the liver cells themselves can occur in such a way as to alter the diameter of the sinusoids under physiological conditions. The sinusoidal character of the circulation implies a more intimate association of the parenchyma with the blood stream than that prevailing in organs with capillary circulations.

Knisely et al. noted sphincters at the junctions of sinusoids with central venules - outlet sphincters - in frogs, and related them to smooth muscle in the walls of the latter vessels. They observed these outlet sphincters also in the rhesus monkey and in the guinea-pig. The sphincters have been illustrated in rats by Bloch. Friedman et al. (1953) and Wakim and Mann recorded confirmatory evidence. Although smooth muscle is generally present in peripheral venules of similar size, it cannot be seen in histological sections of the central venules of man or of the rat. This does not exclude the possibility that some muscle cells are present and function (Zweifach), but it casts doubt on the active role of the narrowings observed at these outlet sphincters in the rat and it would be unwise to postulate that such sphincters operate in man. The evidence for sphincters at this level rests at present on transillumination studies alone.

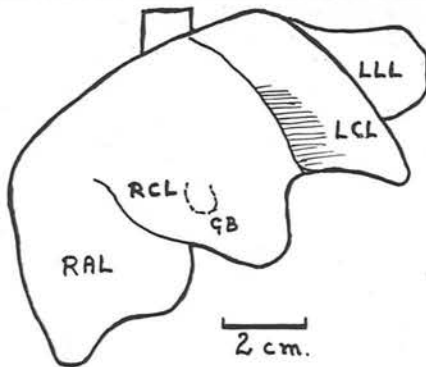
Species variations in venous barriers: The sphincters are developed to different degrees in different species and the explanation of this disparity is not clear. Tischendorf reviewed the German literature and discussed the question. He



kra monkey

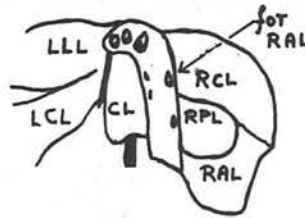


(a)



mandrill

mandrillus sphinx

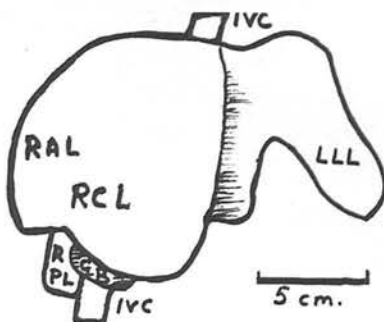


(b)

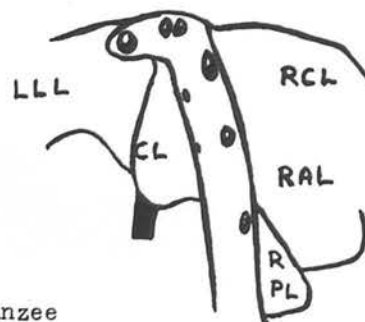
Fig., 58. Hepatic lobation and venous drainage in three monkeys

- (a) kra monkey - macaca irus.
- (b) mandrill - mandrillus sphinx.
- (c) chimpanzee - pan troglodytes.

In (c) LLL and LCL form a single lobe and are not separate as in most other species. Though indented at the site of the inter-lobar fissure in other species, the left lobe resembles that of man.



chimpanzee
pan troglodytes



(c)

concluded that the habits of life of the various species were important in this regard and the finding of equivalent amounts of smooth muscle in the hepatic veins of species of monkey of different sizes (Table III) supports this view. Erect posture may also play some part. Like man, monkeys and the wallaby have relatively well developed hepatic venous muscle. Bradley (1949) noted a drop in hepatic blood flow in men when they stood up. The marked difference between the hepatic veins of the dog and those of closely related species (Arey, 1941) is however difficult to explain.

For physical reasons, a single throttle arrangement on a large vessel is unstable and tends to act in an "all or none" fashion (Burton). The most economical method of achieving graduated control is the employment of many points of constriction in small vessels. This consideration presumably becomes more important the greater the volume of blood concerned. Thus we should expect that multiple small venous barriers such as junctional constrictions would be more important in large than in small animals and this is certainly exemplified in a comparison of the human and the rat liver.

The weakness of hepatic-outflow control in the rat suggests that control of the inflow is better, and experiments recorded in Chapter VI tend to confirm that this is so. In most species including man and the rat, intrahepatic portal veins are more muscular than hepatic veins at corresponding levels. In the dog with its massive hepatic venous musculature the ratio is reversed. Where the hepatic-venous control of portal outflow is weak, there would appear to be more control on the part of the portal vein itself. For instance

the muscular valves in the portal vein of the dolphin - *delphinus delphis* - (Lacoste and Gouelmino, 1926) probably compensate for the absence in the species (Rex, 1888) of the special hepatic-venous and caval arrangements found in other aquatic mammals.

EVIDENCE FOR A PHYSIOLOGICAL ACTION ON THE PART OF THE HEPATIC VEINS

Franklin (1937) has reviewed the older physiological work on the hepatic and portal veins in detail. Other reviews of the many experiments on the hepatic vasculature have been published by Seneviratne, by Child (1954) and by Andrews. Some of the actions recognizable under pathological conditions may play no part in the normal functioning of the body; spasm, for instance, is probably a non-specific reaction to any of a number of pathological insults. Elevation of pressure at the venous end of the sinusoids increases the amount of tissue fluid in the liver under pathological conditions. Lamson and Roca (1921) drew attention to this method of removing fluid from the general circulation but it is uncertain how important a rôle it plays in the normal control of the water content of the human body. Similar doubts may be expressed regarding the function of the liver as a depot influencing the distribution of blood in the body.

Blood flow through the liver is relatively free and the hepatic circuit offers little obstruction. By brisk suction with a syringe on a catheter impacted in a hepatic vein, it is possible to obtain oxygenated or arterial blood in place of the usual venous sample (Taylor and Myers, 1956). The venous

pressure falls from about 10 mm. Hg. to 3 mm. Hg. between the portal vein and the cava (Bell et al.). Under such conditions it appears that hepatic-venous barriers are normally in a state of tonic rather than of positive contraction. Taylor and Myers reported evidence of venous tone on releasing their catheters after impaction in small hepatic veins about 2 - 4 cm. from the edge of the liver in man. Bradley et al. refer to what was apparently spasm at a higher level in a few such catheterisations but the procedure has not yet yielded convincing evidence of a normal hepatic-venous barrier in man.

Action of an apparently physiological character is most easily seen in experiments on the dog, as might be expected from the complex structure of the veins in that species. The literature concerning the actions of adrenalin and acetylcholine and the effects of sympathetic and parasympathetic stimulation has been reviewed by Bauer et al. (1932) and by Andrews et al. (1955). The latter authors reported different responses to adrenalin in their own experiments according to whether the liver preparations were congested (blue) or well-oxygenated (red) and concluded that the responses of the canine liver vessels to this drug were complex. Acetyl-choline led to constriction of the hepatic vein which was greater when the injections were made into the hepatic artery instead of into the portal vein. Blood flow through the liver can be impeded in the dog by a number of procedures, but there is no convincing evidence that it can be facilitated beyond what normally prevails.

Experiments on rats by transillumination and other methods are reviewed by Seneviratne. These have generally

failed to show any notable action on the part of the hepatic veins and this is in keeping with the thinness and other structural features of these vessels which apparently suit them for limited contraction only. Those who have used transillumination have generally assigned to the sinusoids a more important function in controlling the outflow of blood from the liver than to the hepatic veins.

The hepatic-venous muscle in monkeys, cats and rabbits is comparable in amount, and to a large extent in arrangement, to that in man, and experimental results in these species probably give more indication of human reactions than do observations on dogs or on rats. Andrews et al. (1956) obtained a little constriction of the hepatic veins in these species with acetylcholine. Similar experiments by others (Mautner, 1923-24; Bauer et al., Griffith and Emery, 1930) have given varied results. There is little doubt that adrenalin and noradrenalin lead to constriction of the hepatic veins (Andrews et al.). One may conclude that the hepatic-venous muscle of these animals is capable of a physiological action which could be governed by autonomic innervation. In man, nerves are present which might initiate such action and Torrance has shown that some at least of the vascular responses of the human liver can be eliminated by coeliac-nerve block.

These physiological experiments on animals go some way to compensate for the paucity of direct physiological evidence in man. They strongly suggest that the hepatic-venous barriers described in Chapter I are able to operate physiologically in man, possibly under nervous control. In view of the small drop in blood pressure between the portal vein and the cava,

it would seem more accurate to think of the venous barriers in the liver as normally being relaxed or rather in a state of tone and not in a contracted condition.

THE PHYSIOLOGICAL ACTION OF THE HEPATIC VEINS

The existence of a sinusoidal circulation between the portal-venous system and the heart cannot be without effect on normal haemodynamics, but the normal disposition is not essential for life. The shunting of portal blood from this sinusoidal bed through an Eck fistula is not generally a fatal procedure in man; it was sometimes followed by cardiac failure in the hands of older workers on the dog (Franklin). More recent experience with these animals is varied, but in several series the health of the dogs has been poorly maintained afterwards (McCredie et al., 1957). The operation is apparently better tolerated in human beings. Although the conditions under which the operation is done in the two species are not identical, it may be suggested that the dog responds badly to the short circuit because its liver, and particularly its muscular hepatic veins, normally play a more important part in regulating the circulation than is the case in man. Despite considerable species variations in structure, it is probably more valuable to think of the control of outflow from the portal system under most circumstances as a concerted action on the part of all the liver blood vessels and not to attempt, at present, to unravel the interactions that produce the total result. In the effect of vascular changes on the liver itself, one can distinguish more readily the results of isolated action on the part of the hepatic veins.

The greater part of the muscle in the hepatic veins of most mammals is found in longitudinal formations in the adventitia, and the absence of a medial coat and of valves are other striking differences from most other veins. The structure of the hepatic veins in man seems to suit them for a more or less automatic action in protecting the liver from the variations in venous pressure to which, because of its nearness to the heart and thorax, the organ is particularly exposed. Unlike other large veins close to the heart, the hepatic veins are unable to collapse, although considerable narrowing is possible at the ostia. Brecher et al. (1952) have pointed out that in their experimental animals (dogs) collapse of extrathoracic veins such as the axillary and jugular veins converts the continuous venous flow to the heart into a discontinuous one and protects the peripheral circulation from the sucking effect that inspiration exerts on the cava. Though fixation to liver tissue prevents the hepatic veins from collapsing, a certain reduction in lumen is possible throughout the system by muscular contraction of their walls, as already shown. When blood is sucked out of the veins, contraction will naturally occur in their muscle to maintain tone and in this way the central venules will be narrowed at their junctions with hepatic veins. Junctional constrictions then inhibit the quick transmission of the sucking effect of inspiration to the liver. Tissue round small radicles of large veins, which would be the most exposed to this effect is the best protected and the negative pressure is damped down before it reaches the sinusoidal circulation of the liver or possibly even the portal system.

The portal venous pressure is not however maintained steady

by this means. Paton et al. found a rise in "occluded hepatic venous pressure" (equivalent to portal venous pressure) in human subjects with venous catheters impacted in hepatic veins during forced inspiration, and Brecher (1956) notes that the portal-venous pressure rises in dogs during inspiration. McMichael's (1932) observation of the same rise in cats with open thorax indicates that the rise is not dependent on the existence of a negative pressure in the thorax. In man the liver is compressed by the diaphragm at the time when the junctional constrictions probably close. This co-ordination may be incidental, as suggested above, or else may be the result of a common nerve supply of the diaphragm and hepatic veins. It is probably due to both occurrences that the intra-hepatic and portal pressures rise.

In the rat, junctional constrictions are not found, and the hepatic veins cannot act to damp down caval pressure changes. Normally during the rapid inspirations of the animal, diaphragmatic compression apparently flushes the hepatic veins sufficiently to offset the sucking effect of the intrathoracic negative pressure, but when respiration is deep and laboured the liver becomes pale with inspiration. Seneviratne reported that the sinusoids narrowed with inspiration and widened with expiration under the latter circumstances, and this is most probably due to the direct transmission of a negative caval pressure to the sinusoids.

The association of the hepatic-venous muscle with respiration is exemplified in the modification of this muscle in evolution so as to help to control the circulation in diving mammals during immersion when respiration is in abeyance.

The main function of the muscle of the hepatic veins in man would appear to be that of protecting the sinusoidal circulation of the liver and possibly to some extent the portal circulation from the greatest fluctuations in the caval pressure. These fluctuations are not wide when the subject is at rest, and the amount and the arrangement of the smooth muscle in the veins would appear adequate for the task. While tonic contraction of the hepatic veins is probably of real value in man under physiological conditions, it is more difficult to make a case for the occurrence of positive contractions of the vessels except in circulatory adjustments to unusual conditions outside the body's daily experience. Since these are, properly speaking, of a pathological nature, they are considered below.

SUMMARY

1. Arrangements of smooth muscle capable of narrowing the veins are present in the hepatic ostia of man and of animals, but they are less powerful and less important than other special arrangements deeper in the liver.

2. The muscular structure of the hepatic veins of most mammals, with the exception of the rat, is such that slight contractions of the veins lead to narrowing of the mouths of small tributaries. These junctional constrictions have been named variously by different authors and comprise Deysach's sluice mechanism. They are apparently the most important venous-barrier structure in the human liver.

3. Transillumination studies have suggested that central venules and sinusoids are capable of an active vasomotor action. There is no evidence that any such action takes place in man and a possible anatomical basis for it has not been demonstrated. In view of the nature of sinusoidal circulation, it is possible that what is made visible under certain circumstances may be an alteration in the liver cells themselves.

4. Some possible reasons for species variation in venous barriers are considered, including the habit of life of the animal, the size of the liver and the volume of its circulation, and the method employed in regulating outflow from the portal system.

5. Evidence from various observations on man and from physiological experiments on animals indicates that the hepatic-venous system is probably capable of a physiological action. Normally the flow of blood through the liver is impeded very

little and the main action reported in experiments has been that of increasing and not of decreasing the hepatic resistance to flow. Physiological contractions of the venous sphincters are probably not, in most instances, isolated occurrences but are part of a total action in which all the liver blood vessels take part.

6. It is suggested that the clearest instance of a physiological action on the part of the hepatic-venous muscle concerns respiration. The peculiar structure of the hepatic veins, including their inability to collapse, suits them for an action in protecting the sinusoidal circulation of the liver from the effects of intrathoracic negative pressure which is transmitted to the cava. This action is co-ordinated with compression of the liver by the diaphragm occurring at the same time and both may be initiated by the same nervous stimuli. Alternatively a more or less automatic increase in tone in the veins following reduction in their contents may be the means by which the junctional constrictions at the terminations of central venules are produced. Thus the hepatic-venous muscle may be thought of as one of the structures safeguarding intra-hepatic and to a less degree portal circulatory autonomy.

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CHAPTER IV

PATHOLOGY OF THE HEPATIC VEINS

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THE PATHOLOGY OF THE HEPATIC VEINS

The participation of the hepatic veins in pathological mechanisms is better attested than their participation in physiological responses. It is also easier in pathological circumstances to distinguish the rôle of the hepatic veins from those of the other vessels of the liver and to observe the results of species variations in structure. Some of the pathological conditions which may be modified by the action of the hepatic veins are briefly mentioned in the earlier part of this chapter. Fuller consideration is given to certain states and diseases in which the venous changes are of unquestioned importance. The effects of malignant disease are not considered.

SOME NATURAL AND EXPERIMENTAL CONDITIONS

Hepatic venous contraction may be an important factor in haemorrhagic shock (Wiggers et al., 1946; Friedman et al., 1953) and in the production of the vasodepressor V.D.M. (Shorr et al., 1951). Naftalin and Howie (1949) considered that hepatic venous constriction was the probable cause of liver lesions and ascites in piglets reared in cold and damp surroundings. Maeraith et al. (1947) suggested that centrilobular necrosis in malaria and in other human diseases might be influenced by hepatic-venous constriction. In the dog in which the hepatic-venous musculature is strikingly developed, constriction of these vessels probably dictates the severe congestion that dominates the centrilobular lesions of hepatitis contagiosa canis. The histological features in material from 2 cases of this condition personally examined closely resemble those

brought on by severe experimental constriction of the intrathoracic vena cava in this animal (Figs. 47-48), although inclusion bodies are of course lacking in the latter material. Centrizonal "necrosis" due to other causes produces a similar lesion in this animal (Rubarth, 1947). Digitalis causes the hepatic veins of the dog to constrict (Katz et al., 1938 and others) but the reduction in systemic-venous pressure that occurs in the treatment of congestive cardiac failure in man is probably not brought about in this way (McMichael and Sharpey-Schafer, 1944).

Histamine, anaphylactic shock, &c. ("Shockgifte"): Histamine causes constriction of the hepatic veins in dogs (Mautner and Pick, 1915; Tainter and Dock, 1930; Bauer et al., 1932; Andrews et al., 1955) and in most monkeys (Child, 1954; Andrews et al., 1956) but only occasionally in rabbits, cats and goats (Bauer et al., 1932; Andrews et al., 1956). In the experiments of Bradley et al. (1952) histamine did not diminish hepatic venous outflow in man.

Mautner and Pick (1915) were the first to put forward the idea of a venous barrier in the liver and considered then and in subsequent work (1929 and 1931) that the barrier section was the hepatic veins. This view was also held by Simonds (1923), but Bauer et al. focussed attention on the ostia, and sphincters at this level are often held to be responsible for the anaphylactic reaction in the dog. Although it is likely that there is some degree of constriction of the large veins and of the ostia of the dog in anaphylaxis, more recent work (Arey, 1941; Thomas and Essex, 1949) has shown that contraction of

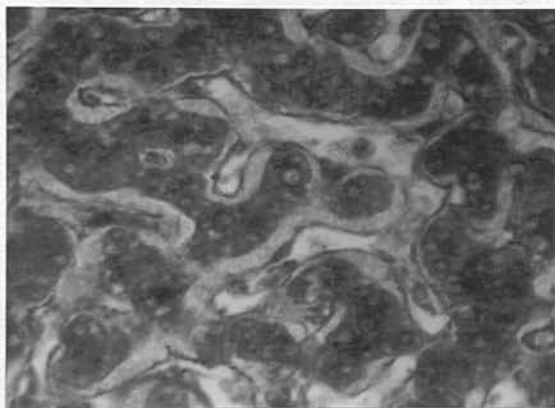


Fig., 59. The spaces of Disse in a case of terminal uraemia in the nephrotic syndrome. The sinusoidal wall is separated from the liver cells by a space containing albuminous fluid. Carbadid-fuchsin stain, x 370.

the intercalated veins throughout the liver is the main element.

The massive musculature of the hepatic veins of the dog accounts for the special characteristics of anaphylaxis in this animal and for the similar occurrences in peptone shock (Simonds, 1923 and others) and after injection of extracts of ascaris suum (Thomas and Essex). When the same procedures are carried out in other animals comparable results may occur, but they are less severe and do not always take place. They have been observed in cats (Mautner and Pick, 1915 and 1929; Thomas and Essex) and in rats and guinea-pigs (Maeagraith et al., 1949). Similar experiments in rabbits give negative (Maeagraith et al., 1949), occasional positive (Appendix B, rabbit HS2) or equivocal results (Thomas and Essex), possibly on account of species variation in susceptibility, rather than because the anatomical basis is lacking. Spasm of the hepatic veins may be the cause of shock in man following spillage of hydatid-cyst fluid into the peritoneal cavity, but the main pathological interest in this mechanism centres round the possibility of less transient effects on the liver being produced in allergic or hyperergic reactions.

Serous hepatitis: A considerable literature exists in German on this subject with which the names of Rössle and Eppinger are particularly linked. Some aspects have been reviewed by Kettler (1954). An essential feature of serous hepatitis is the distention of the spaces of Disse by albuminous exudate. There is no question that these spaces form in certain conditions (Keschner and Klemperer, 1936) such as the nephrotic syndrome (Fig. 59) but Popper (1948) has shown that they are

most often opened up by agonal changes. Allyl formate was originally thought to have a similar action to serous hepatitis and to act primarily as a mesenchymal poison increasing sinusoidal permeability and so causing exudation into the spaces of Disse (Popper, 1937). More recent work reviewed by Kettler and Stoner (1956) has shown, however, that the effect of allyl formate is primarily on the parenchymal cells of the liver. The action of urethane is interesting, since Doljanski and Rosin (1944) found from their experiments that its primary action on the rat liver was to increase the permeability of the sinusoids and since Meacham et al. (1952) ascribed to long-term urethane treatment fibrous narrowings of the central venules of the liver in a human case of multiple myeloma. In preliminary tests of chronic poisoning of rats by urethane, which are reported in Appendix A, the present author found no lesions of the central venules, the chief effects being on the hepatic parenchymal cells. A comparison may be drawn with pyrrolizidine poisoning. In view of these results further experiments with urethane were not undertaken.

Although the phase of serous hepatitis is transient in these drug poisonings and perhaps of little importance, it is possible that a similar effect in anaphylactic shock may lead to liver damage. Dean and Webb (1924) and Weatherford (1935) considered that anaphylactic shock affected chiefly the sinusoidal endothelium and the hepatic cells in the dog. Doljanski and Rosin compared the action of urethane on the rat liver with anaphylactic shock and reviewed some of the older evidence for the assumption that there was a breakdown in the integrity of the sinusoids in certain conditions such as in

Weatherford's experiments. A temporary failure of the "blood-tissue barrier" was termed "Dysorie" by Schürmann and MacMahon (1933) who considered that the lesions of malignant hypertension were brought about in this way. Kettler traces the application of the "Dysorie" theory to serous hepatitis and it has been widely held by writers in German that the lesions of "endophlebitis hepatica obliterans" originate in a temporary failure of the blood-tissue barrier of the venules and sinusoids of the liver and that the disease resembles acute rheumatism in its pathogenesis. This is discussed in Chapter V.

Hepatic lesions following anaphylaxis: The hepatic lesions in rabbits surviving anaphylactic shock have been studied by several workers. Thus McKeown (1947) reported arterial lesions similar to those of polyarteritis nodosa. ~~Arteritis~~ was the most common hepatic lesion described by Apitz (1933) but he also noted necroses of the parenchymal cells. Large areas of necrosis were observed by Hartley and Lushbaugh (1942) who used the mesenteric vein, spleen and other routes of intravenous injection and employed albumin instead of horse serum as the antigen. Hepatic-venous lesions were not recorded in any of these reports. Since venules are frequently affected in antigen-antibody reactions (Zweifach, 1957), it was thought worthwhile to try the effect of repeated injection of horse-serum into the portal system of rabbits using the dosages and schedule of Rich and Gregory (1943). The spleen was used for the injection site because of severe haemorrhage from the portal vein in the slow infusion of large quantities of serum, and it

(a)



(b)

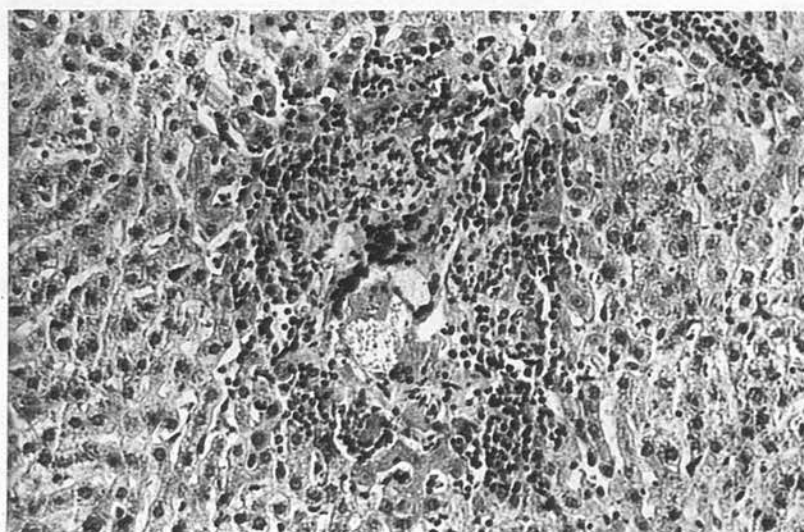


Fig., 60. Liver damage in rabbits following anaphylaxis in the experiments reported in Appendix B - 2 injections of horse serum into the spleen.

(a) Inflammation of a portal tract due to severe arteritis, the most common lesion, rabbit HS 5, H. & E. x 150.

(b) A small focus of necrosis with lymphocytic infiltration and giant-cell formation round a central venule, rabbit HS 3, H. & E. x 280.

was found that the injected serum was rapidly discharged from the organ and did not accumulate there. These experiments are recorded in Appendix B.

Four rabbits survived to receive the second large dose into the spleen. In the liver of one which died shortly after this injection, dilatation of central venules and of the central portions of sinusoids was seen. There were no arterial lesions in this animal. In the 3 animals surviving the full period of the experiment, arterial lesions were found in the liver and elsewhere (Fig. 60a). In one of these 3, arterial lesions were scanty in the liver, but a few focal and sometimes centrilobular parenchymal-cell necroses were found (Fig. 60b).

Hepatic-venous lesions were not present.

The lesions produced in these experiments were similar to those reported by other workers who injected the antigen into systemic veins and it was not thought profitable to carry out further experiments on these lines.

Veno-occlusive disease of the liver: This is a condition occurring mainly in young and undernourished children in Jamaica. The major signs in the acute phase are hepatomegaly and ascites and the mortality from hepatic failure is considerable. Fig. 61 copied from the comprehensive article by Stuart and Bras (1957) shows the clinical course. Veno-occlusive disease appears to be the commonest condition leading to the hepatic fibrosis and cirrhosis which are frequent in Jamaica (Bras et al., 1954). The term veno-occlusive disease was introduced by Bras et al. to indicate the main histological lesion. The histopathology is described by Bras and Hill

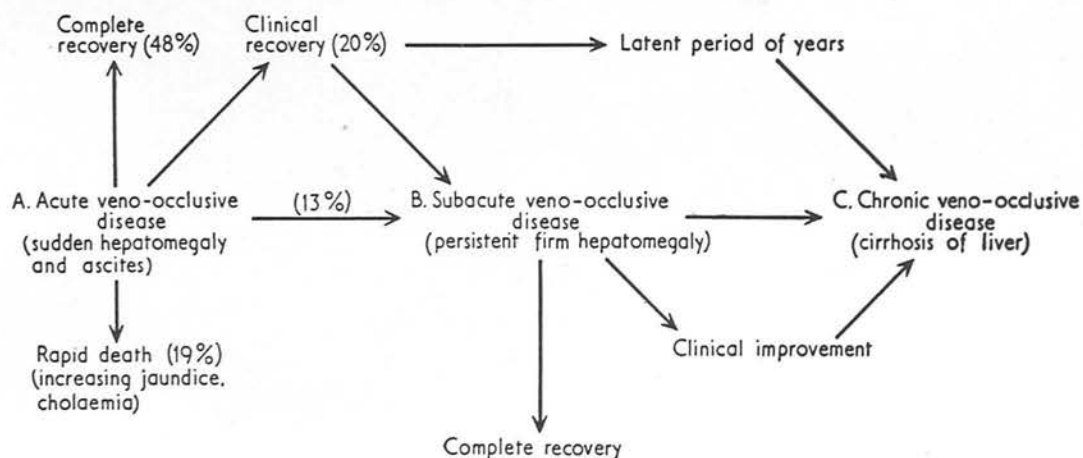


FIG. 1. Clinical natural history of veno-occlusive disease of the liver. B and C may be present with no clinical history of preceding illness.

Fig., 61. Clinical natural history of veno-occlusive disease of the liver (copied from Stuart & Bras, 1957).

(1956). In the acute phase the liver has a nutmeg appearance. The small hepatic and intercalated veins and the central venules are narrowed by subendothelial swelling, which is at first oedematous and then fibrous. The authors did not find primary hepatic-parenchymal-cell damage or concurrent necrosis and state that "the centro-lobular cells seemingly perish as a result of the congestion" leaving central blood lagoons. Persistent cases tend to go on to a non-portal cirrhosis which is indistinguishable clinically from other forms of cirrhosis.

There are several points of distinction from Chiari's Disease, which is described in detail in Chapter V. These are summarised in Table V. On the other hand there are many similarities not only in the clinical manifestations but also in the effects of the venous obstructions on the liver parenchyma and its lymphatic drainage. Of the liver-function tests reported in the earlier phases of both conditions, flocculations and biliary-retention tests show small deviations from normal and B.S.P. is markedly retained. Stuart and Bras consider that serum-cholinesterase estimations taken in conjunction with serum albumin are of the greatest value in assessing the degree of liver damage in veno-occlusive disease. The disease might be said to represent a special form of the Budd-Chiari syndrome (chapter V). A localised outbreak in Germany reported by Wurm (1939) as endophlebitis hepatica obliterans in 8 infants bears many similarities to veno-occlusive disease, but few, if any, of the other European and American cases could be classified satisfactorily in this way.

The aetiology of veno-occlusive disease lies partly in the low-protein, high-carbohydrate diet on which many Jamaican

Table V.

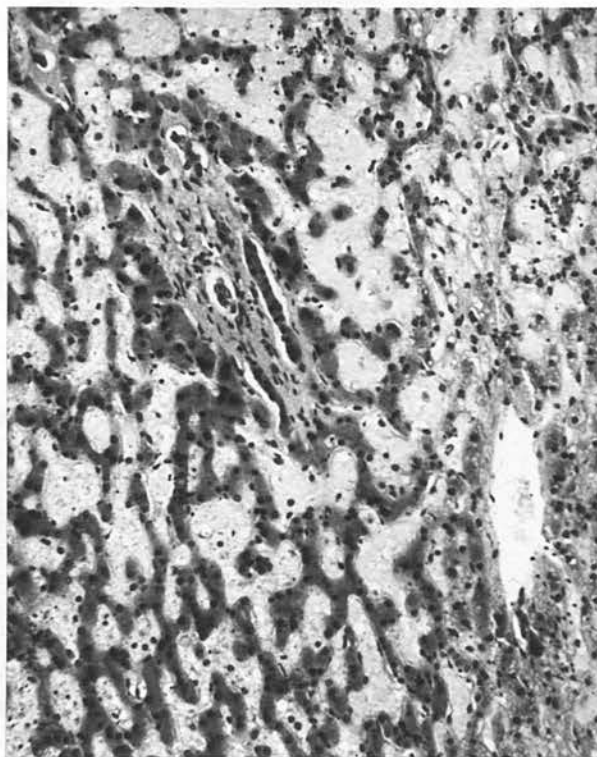
Points of Distinction between

Chiari's Disease and Veno-occlusive Disease of the Liver.

Chiari's Disease.		V. O. D.
Chief age-incidence.	young adults.	young children.
Distribution of cases.	sporadic.	endemic.
Ostia.	involved.	not involved.
Large hepatic veins.	usually spared at first.	usually spared.
Small veins.	involved secondarily (according to most authors).	primarily involved.
Course of lesions.	complete resolution not recorded.	complete resolution often occurs.
mortality	100% eventually.	27% in acute phase 57% in chronic phase



(a)



(b)

Fig., 62. Chronic venous congestion of the liver with a recent exacerbation in a woman of 36 years with a history of acute rheumatism 10 years before death. At death - mitral stenosis; liver, 1,400 gm., portal lymphatics dilated, no ascites.

In Fig., 62 (a) the hepatic veins are dilated and their walls are thick and porcelain-like on account of increased fibrous tissue in intima and adventitia. The photomicrograph (b) shows gross dilatation of sinusoids and marked centrilobular atrophy with "watery" vacuolation of the cells. The distance between central venule (bottom right) and portal tract is greatly reduced because of atrophy. H. & E. x 130.

children are reared (Rhodes, 1957) and the cirrhosis which occurs in Indian children receiving a similar diet resembles veno-occlusive disease (Jelliffe et al, 1957). On the other hand it is likely that poisoning with pyrrolizidine alkaloids may play a part. The lesions in the liver are similar to those found in cattle suffering from ragwort (senecio) poisoning and it has often been maintained that "bush teas", which are herbal infusions widely taken as medicines and beverages by Jamaicans may play an important role. It remains to be shown which herbs are usually responsible; the recipes for bush teas are varied. The present author (1957) has suggested that, in outbreaks such as that reported by Wurm, pyrrolizidine alkaloids may have been ingested by the infants in milk from cows which had eaten ragwort or other plants containing them. In cattle there is often a latent period between the ingestion of ragwort and the development of symptoms (Forsyth, 1954). Schoental (1958) has demonstrated that pyrrolizidine alkaloids may be transmitted in the milk of poisoned female rats to the young which they are suckling. It is not impossible that König's case (1943), which undoubtedly began in utero, might be due to poisoning of the mother.

An objection to the view that pyrrolizidine alkaloids cause the veno-occlusive disease of Jamaica lies in the fact that the hepatic lesions caused by these substances in rats - the chief test animal - do not generally resemble those in larger animals. The toxic effects of the alkaloids on the rat liver are described in Chapter VI. Fibrous occlusions similar to those in cattle have, however, been recorded with the alkaloid retrorsine by Davidson (1935). In addition Hill

Fig.,
63.

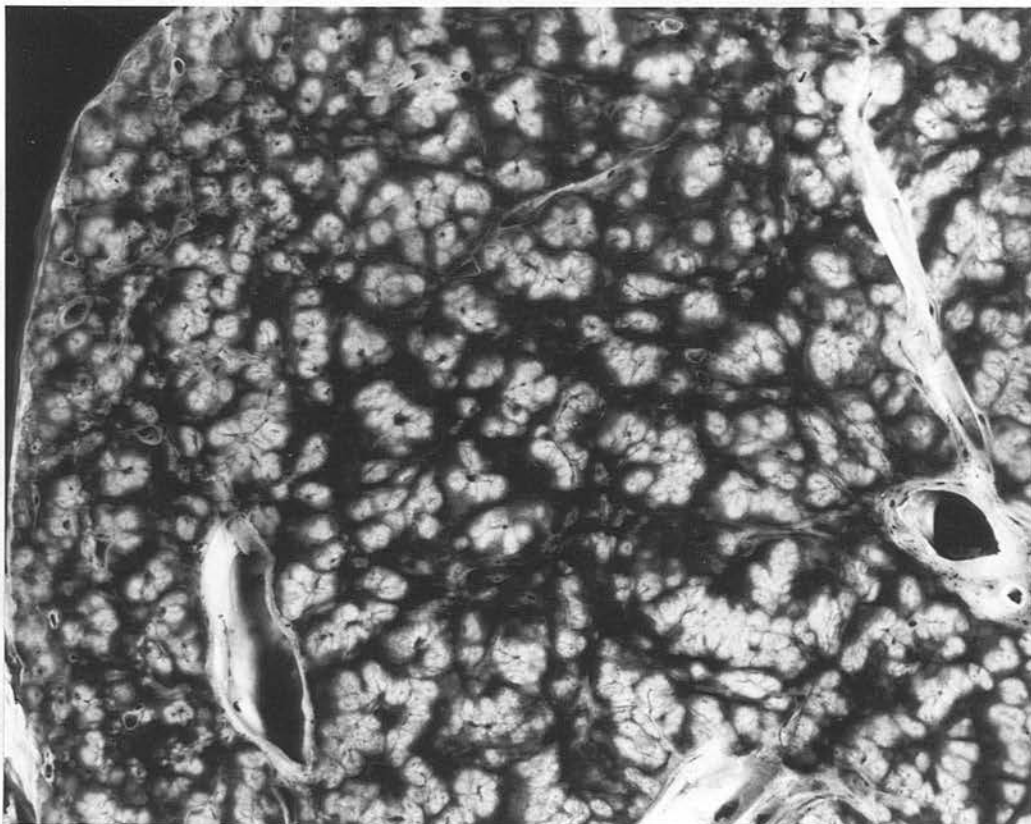
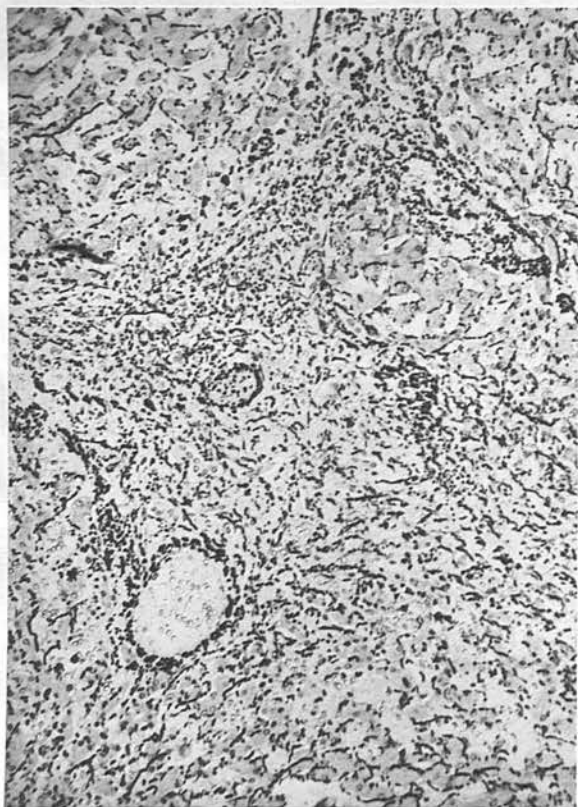


Fig.,
64.



These two figures illustrate an early case of cardiac cirrhosis in a woman of 49 with a large interatrial septal defect and aortic and mitral stenosis. She complained of abdominal swelling and dyspnoea for five weeks before death. Ascites was present.

Fig., 63 shows the predominantly regular pattern with preservation of lobular architecture in most parts. Pale tissue is garlanded round the portal venules x 3.

In Fig., 64 a central venule is completely closed with loss of the corresponding lobule. The reticulin pattern of the lobule is irregular and condensed.
— Laidlaw's reticulin stain x 130.

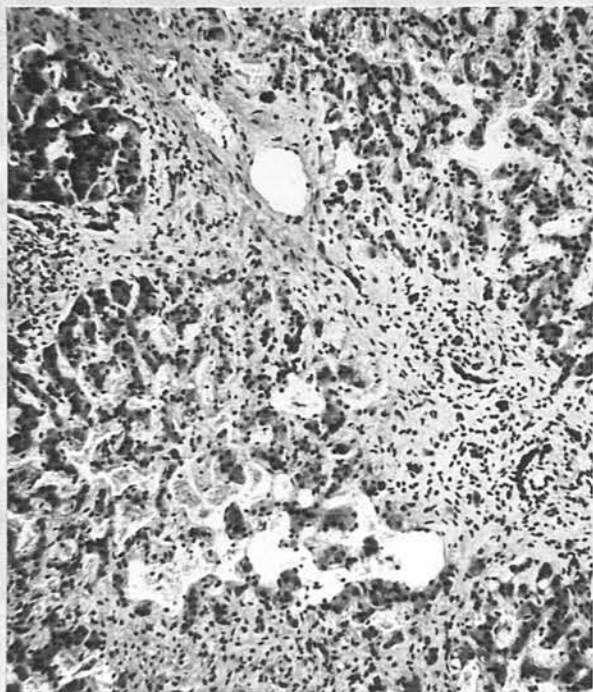


Fig., 65.

In this case of cardiac cirrhosis, the lobular architecture has been completely lost and the liver has been divided into nodules with a distorted vascular supply. A grossly narrowed intercalated vein, above, is joined by a septum to a portal tract. Some irregular venous channels (blood lagoons) have developed on the basis of dilated sinusoids. H. & E. x 100.

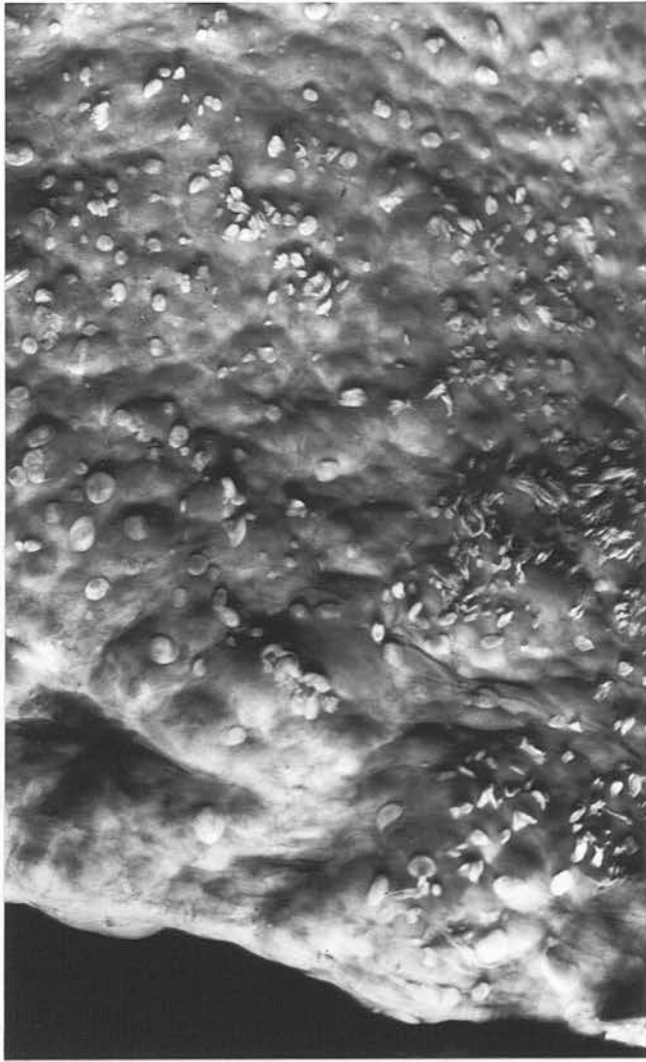
illustrate an
cardiac cirrhosis
with a large
portal defect and
portal stenosis. The
portal swelling
was diagnosed for five weeks
before death. Ascites was
present.

Fig. 63 shows the predominantly
regular pattern with preservation
of the lobular architecture in most
of the liver. The portal tracts are
small and the interlobular
spaces are narrow. The
reticular pattern of the lobule
is irregular and condensed.
- Exfoliate's reticular stain x 130.

et al. (1958) have recently reproduced veno-occlusive disease in rats by the administration of monocrotaline, a pyrrolizidine alkaloid isolated from several species of crotalaria (leguminosae) which occur in Jamaica. The pathological findings in the cases of pyrrolizidine (senecio) poisoning in man reported by Selzer and Parker (1951) are in fact the same as those of the endemic Jamaican disease although the clinical presentation was different.

Chronic venous congestion of the liver: This subject has been investigated by many authors among whom Sherlock (1951) and Popper and Schaffner (1957) may be mentioned. Belli and Sprovieri (1956) have made casts of the vessels and Boland and Willius (1938) and Moschcowitz (1952) have traced the progress of the histological lesions from the stage of simple congestion to cardiac cirrhosis. A similar pathological process is demonstrable in Chiari's Disease and is discussed at length in Chapter V where reference is made to parallel changes in chronic venous congestion. Accordingly only a few features of the condition will be reviewed and illustrated here.

The lesions of the hepatic veins in severe congestion have been described by Castberg (1952) and by Moschcowitz as predominantly fibrous, both intimal and adventitial sheaths being involved (Figs. 62a and 63), sometimes to a considerable degree. Castberg noted occasional instances of fibrinoid change in the walls of veins, particularly those under the capsule. Moschcowitz found a zone of fibrosis of the liver parenchyma round the veins, remarking that a significant amount of the fibrous tissue in a severely congested liver is formed



(a)



(b)

Fig., 66. Fibrous tags on the surface of the liver in chronic venous congestion. This is the same case as Figs., 63 and 64. The naked-eye appearance of the anterior fringe of the liver x 1.9 is seen in (a). The microphotograph (b) shows the fibrous character of the tag which has developed from the thickened liver capsule. H. & E x 150.

in this way. He believed that perivenous fibrosis is the result of pressure. Reference to the finer structure of the veins as described in Chapter I suggests why these portions of the liver should be particularly susceptible to damage from an increased venous pressure. Brecher et al. (1952) have shown that in congestive heart failure, the normal intermittent return of blood is replaced by a continuous flow. One may presume that the hepatic veins are thus continuously dilated and if this is so there can be no contraction of the junctional constrictions at the many points of entry of small radicles (Fig. 19). In this way central venules and their lobules round the larger hepatic veins are continuously exposed to the elevated systemic venous pressure of heart failure.

While it is common to ascribe the disappearance of centrilobular cells to necrosis (e.g. Sherlock), persisting necrotic cells are not found in the absence of toxic factors (Popper and Schaffner) or possibly terminal anoxaemia. The process by which cells are lost from the central areas is one of atrophy (Fig. 62b) often with "watery" vacuolation. Analogies are seen in other types of venous obstruction in the liver. The older views on the occurrence of necrosis in chronic venous congestion are discussed by Boland and Willius.

The slowly progressive increase in fibrous tissue in the liver, which may be seen at all stages of chronic venous congestion does not itself constitute cirrhosis. When there is added a nodular alteration in the lobular structure of the liver (Fig. 65) the condition is then clinically and pathologically comparable to other forms of cirrhosis (though it is usually less severe) and the term cardiac cirrhosis is

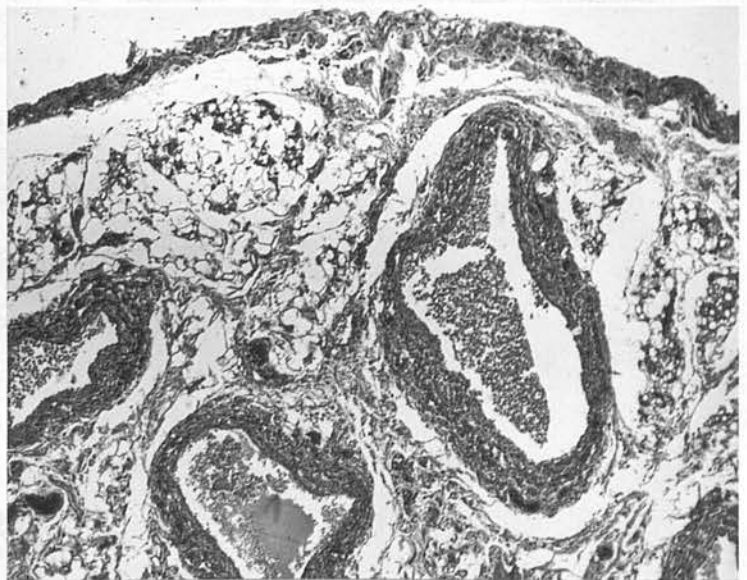
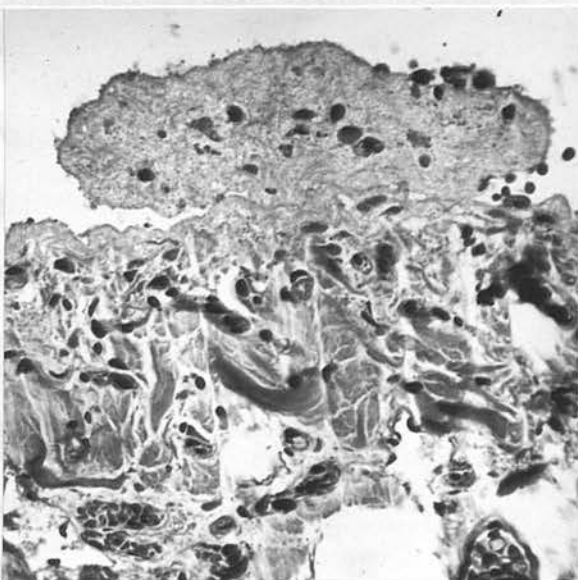
Figs., 67 - 69. The microphotographs are from a case of cardiac cirrhosis in a woman who died aged 31 of rheumatic heart disease with constrictive pericarditis. Oedema of ankles and ascites had been present for three years before death.



Fig., 67 (left) shows a fibrous tag on the peritoneal surface of the liver. H. & E x 155.

Fig., 68 (below left) is an oedematous tag on the surface of the hepato-duodenal ligament. It is smaller and less developed than that on the liver. H. & E x 310.

Fig., 69 (below right) dilated lymphatics in the hepato-duodenal ligament. H & E x 40.



justifiable. The cirrhotic architecture apparently develops in cardiac disease in the same way as in Chiari's Disease (Chapter V), that is to say by the formation of septa and occasionally by the complete disintegration of a lobule when its central venule is occluded (Fig. 64). Other features of cardiac cirrhosis include the formation of irregular venous channels on the basis of dilated sinusoids or previous blood lagoons (Fig. 65).

Much emphasis is placed in Chapter V on the effects of congestion of the liver in the Budd-Chiari syndrome in producing an increased lymph flow with exudation of lymph or tissue fluid from the surface of the liver. It is suggested that the fibrous tags which may be found on the surface of the liver and hepato-duodenal ligament in these cases indicate the site of this transudation. A search was made for superficial fibrous tags in cases of chronic hepatic venous congestion with ascites of cardiac origin because they have not apparently been recorded in the literature. Lesions similar to those in the Budd-Chiari syndrome were readily found on the surface of the liver in cases of sufficient duration (Fig. 66). On the liver the fibrous tags were usually smaller in heart failure than in hepatic-venous occlusions and they were frequently small (Fig. 68) or absent from the hepato-duodenal ligament in the former cases, although the lymphatics of the ligament were enlarged (Fig. 69).

In chronic venous congestion the spaces of Disse are not usually visible and oedema fluid is not demonstrable in sections of the hepato-duodenal ligament. In the more acute forms of heart failure as, for instance, in infants with congenital heart

Fig., 70.

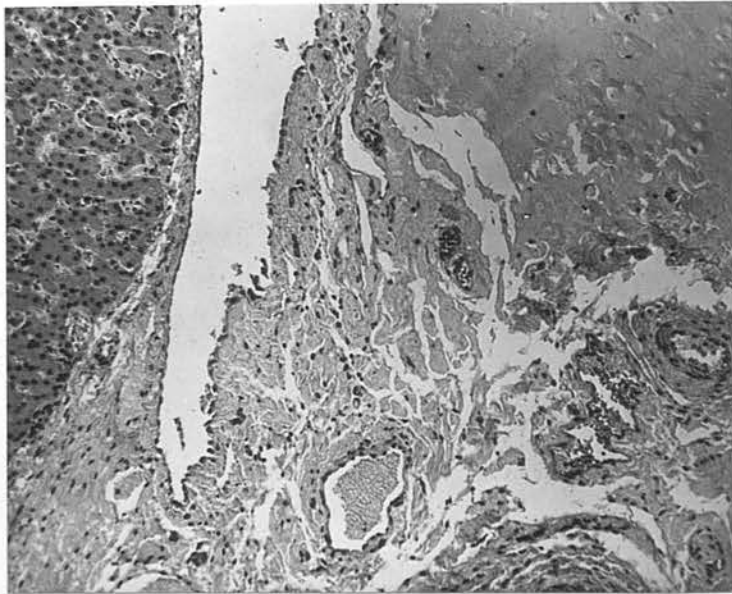


Fig., 70. Oedema fluid in the interstitial tissues of the porta hepatis in an infant of 40 days who died of congenital heart disease. H. & E x 100.

Fig., 71.

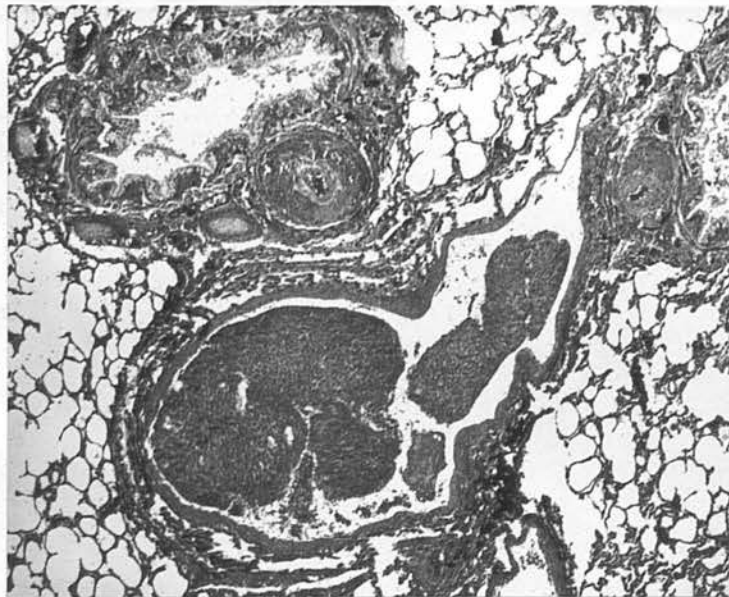


Fig., 71. Pulmonary embolism by liver tissue in severe hepatic trauma. Liver tissue is recognizable in a pulmonary artery. The largest fragment shown here is over 2 mm., in diameter. H. & E x 12.

disease, however, oedema fluid is present in the interstices of the portal tracts and hepato-duodenal ligament (Fig. 70) and can often be seen there and round the gall-bladder with the naked eye. Apparently the lymphatics require to hypertrophy to deal with the increased transudation of severe venous congestion.

Embolism from the liver: The relative fixity of the walls of the hepatic veins to the surrounding liver tissue in man prevents their collapse, and so there is a particular danger of air embolism in surgery on this field. In cases of lacerating trauma to the liver, particles of liver are on occasion carried into the blood stream and form pulmonary emboli. Straus (1942) found only one instance of this in 40 cases of severe lacerating injuries of the liver. A new example is shown in Fig. 71. Several masses of liver tissue up to about 2 mm. in diameter were found on histological examination of the lungs of a child of $4\frac{1}{2}$ years who died 20 minutes after being run over by a lorry. The lateral third of the right lobe was severed from the rest of the liver. The subject of liver embolism is reviewed by Straus who refers to its occasional occurrence in hepatic necrosis.

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