

THE HEPATIC VEINS IN HEALTH AND DISEASE

A Thesis by James Blackburn Gibson

V O L U M E 2

Chapters V and VI.



CHAPTER V

CHIARI'S DISEASE AND THE BUDD-CHIARI SYNDROME

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I.

Ueber die selbständige Phlebitis obliterans der Hauptstämme der Venae hepaticae als Todesursache.¹⁾

Von

Dr. H. Chiari,

Professor der pathologischen Anatomie an der deutschen Universität in Prag.

Hierzu Tafel I.

Die zur Obliteration tendirende chronische Entzündung der grossen Stämme der Venae hepaticae hat bisher nur wenig Beachtung gefunden, obwohl diese Phlebitis sehr bedeutungsvoll werden und das Centrum eines unter Umständen geradezu zum letalen Ausgange führenden Krankheitsprocesses im menschlichen Körper darstellen kann.

Die Literatur über die Phlebitis obliterans der grossen Stämme der Venae hepaticae ist eine sehr kleine und konnte ich nur sieben publicirte Fälle ausfindig machen.

Den ersten Fall erwähnt BUDD²⁾. Bei einem 52jährigen Manne zeigten sich sämtliche Venae hepaticae verdickt und auf ihrer Innenfläche mit einer dünnen „Pseudomembran“ überzogen, welche sich in den grösseren Zweigen leicht abziehen liess. Ausserdem fand sich in allen grösseren und auch in einigen kleineren Pfortaderkanälen reichliches „fibrinöses Exsudat“, welches der Leber zwar eine grössere Consistenz aber nicht das gewöhnliche granulirte Aussehen verlieh. Die Leber und die Milz waren mit den angrenzenden Organen fest verwachsen und auch

¹⁾ Besprochen auf der 70. Versammlung deutscher Naturforscher und Aerzte in Düsseldorf Sept. 1898.

²⁾ BUDD, Krankheiten der Leber, Deutsch von HENOCH, Berlin 1846.

Fig. 72. The title page of Chiari's paper in Ziegler's Beitr. f. path. Anat., 1899, 26. He refers to Budd's earlier work.

CHIARI'S DISEASE AND THE
BUDD-CHIARI SYNDROME

INTRODUCTION

In 1899 H. Chiari published his paper "Über die selbständige Phlebitis obliterans der Hauptstämme der Venae hepaticae als Todesursache" (Fig. 72) and the name Chiari's Disease is properly applied to occlusion or severe constriction of the hepatic-venous system at the level of the ostia when it occurs as a primary condition and not as a complication of liver disease, tumour or other primary conditions. The ostial occlusions cause congestion and enlargement of the liver and lead after a time to secondary thromboses in the small hepatic veins although the larger ones are often spared. The main symptom of massive ascites develops at what is apparently a variable interval after the closure of the ostia. From several reports antedating Chiari's publication, particularly those of Reynaud (1829) and Budd (1845), and from many observations since, it is clear that a state, which is indistinguishable clinically, may be caused by occlusions of the hepatic veins distal to the ostia or by a spread of a caval thrombosis to occlude the ostia, provided that a sufficient amount of liver is affected. The term "Budd-Chiari Syndrome" which is in common use is best applied unless the lesions are known to be ostial.

Single hepatic veins of medium size may be occluded by thrombus as a terminal event in a number of conditions. This leads to congestion of the affected part of the liver (Fig. 73) but does not usually cause symptoms. Except possibly in relation to the aetiology, little is gained by considering

(a)

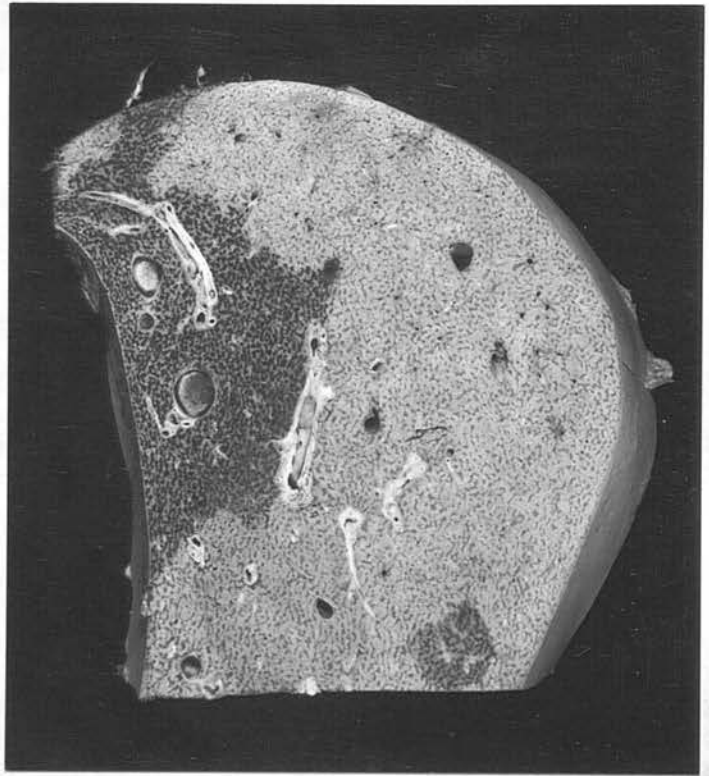
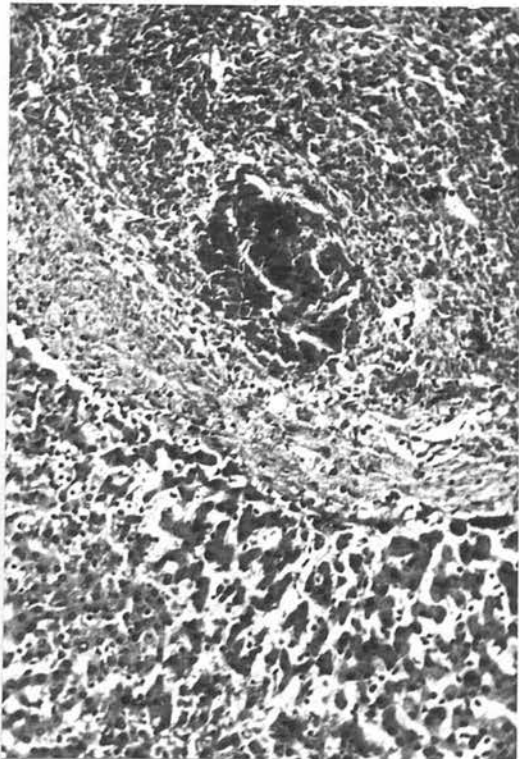


Fig. 73. Focal hepatic-vein thromboses occurring towards the end of an illness due to adenocarcinoma of the pancreas in a 62-year-old man who died of empyema following excision of the primary tumour. There were a few secondary deposits in the liver. There was no ascites. The gross photograph (a) x 0.8 shows that the paracaval portion of the right lobe is sharply demarcated from the rest because it is congested. The thrombosed veins HDL and HR are clearly seen. In the photomicrograph (b) of the wall of a small radicle there is early organisation of the clot. H. & E. x 125.



(b)

these cases along with overt examples of the Budd-Chiari syndrome and they will not be dealt with further here.

Sixteen of the 20 cases of hepatic-vein occlusions reported by Kelsey and Comfort (1945) from the autopsy records of the Mayo Clinic over 29 years were of this type. In only 4 of them was the venous occlusion a major factor in the illness. In 2 of these the Budd-Chiari syndrome was caused by carcinoma, as also in 7 cases published by Palmer (1954). The possibility of blockage of hepatic veins by tumour directly or indirectly as a result of an induced tendency to thrombosis must be recalled in the diagnosis of the syndrome (Fig. 73) but this aetiological factor is beyond the scope of the present work.

Little and Montgomery (1952) calculated that intra-abdominal malignancy, inflammatory conditions and blood dyscrasias were the commonest known factors in the aetiology of approximately 115 cases of the syndrome published up to that date. Cases of this type are classified as secondary Chiari's syndrome by Fruhling et al. (1951). Since these conditions predispose to thrombosis, it might be thought that the Budd-Chiari syndrome is generally the result of thrombosis, even when it is apparently primary and a predisposing factor cannot be demonstrated. Although thrombi in the hepatic veins may organise so that they resemble endophlebitic lesions, they have generally been recognized for what they are. In Chiari's Disease on the other hand, the ostia are affected often in a strictly localised fashion without occlusion of the major hepatic veins below them, and the aetiology of this condition remains unsettled. The current theories have been listed by Hirsh and Manchester (1946) and Palmer and some of them discussed critically by Thompson and

Turnbull (1911-12), Hutchison and Simpson (1930) Fruhling et al. and Rosso (1953). Most of the modern German authors have adopted Rössle's view (1933) that the disease is an allergic-hyperergic (rheumatic) manifestation. The aetiology and pathogenesis are discussed in this chapter in the light of the anatomical and physiological facts presented in the earlier ones and in relation to 12 new cases of the Budd-Chiari syndrome. The recent demonstration by Hill and his co-workers of the occurrence of the veno-occlusive disease of the liver in Jamaica, discussed in Chapter IV, makes it desirable to define once again the Budd-Chiari syndrome as it presents in this country and in view of other recent reports in the British literature to re-emphasise its occurrence in the absence of caval lesions.

The reviews in English by Hess (1905) and by Thompson and Turnbull are invaluable in classifying the older cases because of their detailed references to the naked-eye lesions. Nishikawa's excellent critical treatise in German (1918) is the most exhaustive work in the older literature. It is based on 10 cases, in some of which carcinoma of the liver was also present. Unfortunately less attention has been paid to the gross findings in later accounts. Coronini and Oberson (1937) examined material from 11 cases dealing chiefly with the microscopical findings and the aetiology. Thompson (1947) published a useful review of 97 cases and dealt with the incidence of signs and symptoms. Most of the recent articles have dealt with single cases of Chiari's Disease or the Budd-Chiari syndrome. In the present series of 12 cases it has been possible to trace the development of the lesions and

relate their progress to the clinical course and so to follow the natural history of the conditions and point some applications to the commoner states of cirrhosis and chronic venous congestion of the liver.

In view of the improvements in the investigation of liver disease and the advent of surgical and other new methods of treatment, and because other reviews have dealt with the older literature, reference is made in the present work chiefly to about 30 recent cases not included in Thompson's (1947) review. Many reports have undoubtedly been omitted; some do not contain any new facts and others are not readily accessible or are printed in little known languages. Recent reviews in French, German and Italian have however been drawn upon and the main facts or views that they express incorporated along with those taken from a more thorough cover of the reports in English.

DESCRIPTION OF CASES

Nature of the Material: For the present study 12 fatal cases of the Budd-Chiari syndrome have been examined. In 3 instances the autopsy was performed by the author. In 5 cases, specimens in the museums or other files of material in the Western Infirmary, Glasgow or in the Institute of Pathology, Belfast form the basis of the report. For the remaining 4 cases I am indebted to others who kindly submitted their autopsy material. In 11 cases, autopsy protocols, tissue sections and clinical details were available. In Case 12, the data were sufficient for diagnosis but inadequate for comparison clinically with other cases and histological sections only were available.

The cases have been arranged in 5 groups:-

- I. Cases in which the ostia are known to have been involved -
i.e. Chiari's Disease - 5.
- II. Cases in which the ostia were probably involved but in
which data on this point is lacking - presumptive examples
of Chiari's Disease - 3.
- III. A case in which hepatic-venous occlusion complicated a
previous caval thrombosis - the Budd-Chiari syndrome - 1.
- IV. Cases in which the ostia are known to have been patent at
death - the Budd-Chiari syndrome - 2.
- V. A case in which the data are scanty - 1.

Summaries of the clinical histories and autopsy findings are given seriatim below and each is followed by a short comment. Heart disease was not present in any of the cases.

Apart from the question of the involvement of the ostia, there are many similarities between the groups and most of their pathological and clinical features are discussed together.

Group I, known ostial cases (Chiari's Disease): Case 1 (7150)

A 25-year-old woman, a field worker, was admitted to the Western Infirmary, Glasgow (Prof. Anderson) on 12/8/1905 on account of swelling of the abdomen and legs of 2 weeks duration. She had been strong and healthy till 4 weeks before admission, when on the day following a long and exhausting journey in inclement weather a pain suddenly seized her left loin and continued for a week. Her urine was red at that time. A

few days later her legs became swollen and abdominal swelling started shortly afterwards; these swellings increased till her admission. Her last menstrual period was 2 months previously.

On her admission there was noted in addition, finger clubbing and hepatic enlargement. The liver edge was smooth and regular, not tender and 7 cm. below the costal margin. She was not jaundiced and lay comfortably in bed. The urine contained albumin but no blood. 5 days after her admission, 5 litres of albuminous fluid were tapped from her abdomen, but more quickly accumulated. She gradually became weaker and died on 20/8/05. The duration of her illness was 5 weeks.

At post-mortem the peritoneal cavity was full of serous fluid. The liver weighed 1,900 gm.; the left lobe was congested and sclerotic and microscopically showed a cirrhotic pattern; the right lobe was severely congested with foci of necrosis and preservation of the reticulin pattern microscopically; the caudate lobe was hypertrophied. Fine fibrous tags (Fig. 114, c.f. Fig. 80) were present over several parts of the surface of the liver. The left hepatic ostium was fibrosed and contracted (Fig. 97) so as to be almost unrecognizable. The adjacent portion of the cava, over 1 cm. of its length, was similarly contracted and occluded by fibrous tissue so that it formed an irregular fibrous cord 6 mm. in diameter where it passed through the diaphragm. Below this the cava was thick-walled and completely occupied by propagated laminated thrombus which had begun to organise and which was apparently of several weeks' standing. Propagated clot extended into the right hepatic ostium, which was only partly contracted; the large and medium-sized hepatic veins of the right lobe contained further

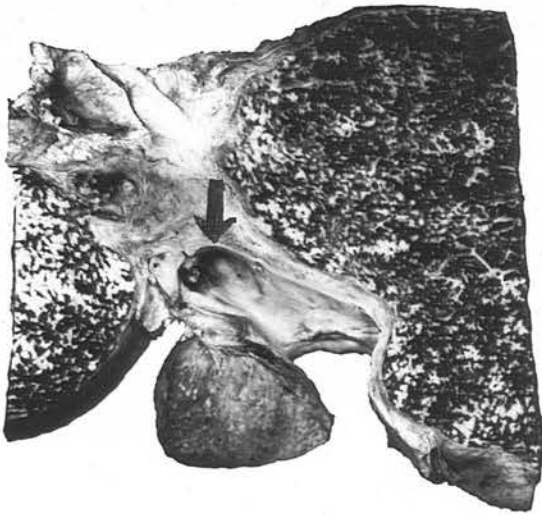
extensions of this clot. The caval thrombus had also spread into the renal veins. The azygos vein and veins of the abdominal wall were dilated and venules of the diaphragm and round the cava were also enlarged. The spleen (240 gm.) showed the features of fibro-congestive splenomegaly and oesophageal veins were dilated.

Death was due to the occlusions of the hepatic and renal veins.

Comment: The acute manifestations at the onset and the character of the caval and renal-vein thrombus is in keeping with an age of 5 weeks. The thrombi in the right hepatic veins were contemporaneous. On the other hand the contraction and fibrous occlusion of the left ostium and of the cava at the diaphragm were clearly of long standing. The parenchymatous changes in the liver are consistent with this dating. The old obstructions may have led to the finger clubbing but they did not cause any symptoms. Only when the right hepatic vein was blocked also did ascites develop.

Group I, known ostial cases (Chiari's Disease): Case 2 (B0175)

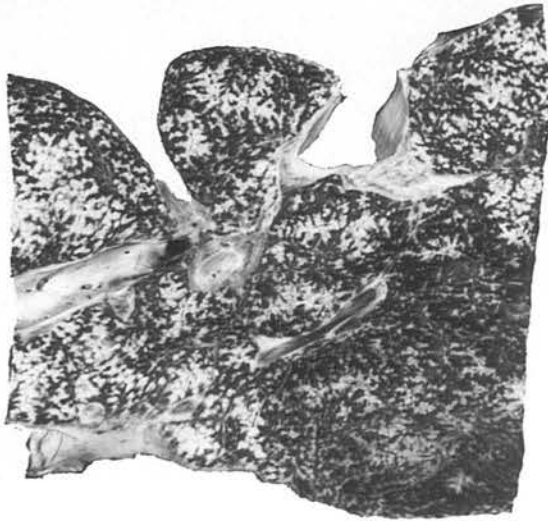
A 36-year-old Glasgow housewife was admitted to the Western Infirmary (Dr. McCluskie) on 24/1/56 complaining of lower abdominal swelling which had developed rapidly and become massive over a period of 6 weeks. The patient at first thought she was pregnant, but her periods continued with a longer interval. Despite the accumulation of fluid her weight had remained constant. During the week before admission, the ankles had become swollen and she had had pain in the right hypochondrium



(a)

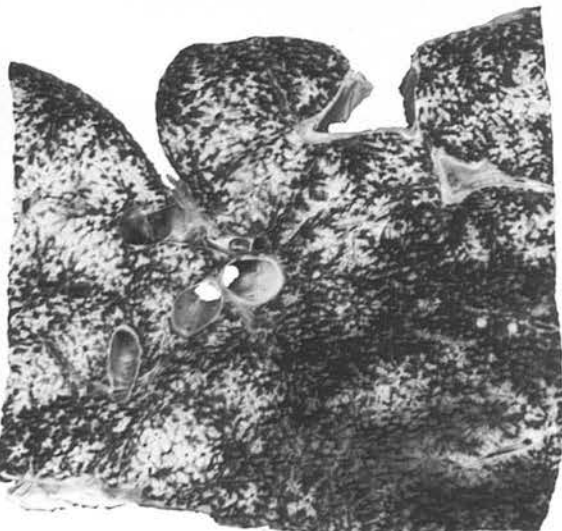
Fig., 74. Case 2. Horizontal sections of the congested liver at different levels x 9/10:

(a) shows the thick wall of the cava with the thimble-like depression at the left ostium anterior to the caudate lobe. The arrow marks the site of the blind dome-like termination of HM.



(b)

(b) is the lower surface of (a). The blind termination of HM (cut in T.S.) and the gross narrowing of HS (cut in L.S.) can be seen close to the lig. venosum. On the anterior surface of the cava the right ostium is seen as a fibrous scar.



(c)

(c) at 1 cm., below (b), HS & HM are dilated. HD upper right, is contracted and is occluded by glassy fibrous tissue.

on coughing. There was no disturbance of micturition. Her previous health had been excellent. She had had 4 pregnancies; the eldest child was 11 years old.

She was emaciated and her abdomen was grossly distended (umbilical girth 98 cm.). There was no cyanosis or jaundice. Paracentesis abdominis yielded clear fluid and the liver was enlarged. Examination gave no evidence of a gynaecological lesion. Her condition deteriorated and she died on 25/2/56. The duration of her illness was 10 weeks.

At post-mortem the peritoneal cavity contained 2.5 l. of straw-coloured fluid. The liver (1750 gm.) was moderately enlarged, firm and severely congested (Fig. 74) with atrophy peripherally. The tissue towards the porta was paler. Histological sections showed centrilobular sclerosis of congestive type. There were few fibrous septa and no nodules of regeneration. The large and medium-sized hepatic veins were thick-walled, widely patent and free of thrombi. The main ostia were occluded. The left ostium was marked by a thimble-like depression in the caval wall (Fig. 74a). The entrance of HS at the end of this depression was markedly obstructed by a largely fibrous nozzle-like obstruction, which was caused chiefly by a tight and localised indrawing of the vessel wall. A lumen of only 1 mm. diameter remained in the centre, and this was blocked by recent thrombus. Immediately distal to the obstruction, HS opened out again to its full size (Fig. 74b). HM was completely sealed off from the thimble-like vestige of the left ostium by a thin fibrous diaphragm which had apparently formed in the same way as that in HS. The domed, blind, upper end of this vessel is seen in Figs. 74b and 98. Some small

abnormal inter-communications had formed between the dilated terminations of HS and HM below the ostium and these had provided a minute drainage channel for the quadrate lobe, till terminal thrombosis supervened. The right ostium was also contracted down round a narrow fibrous plug (Fig. 74c) and its mouth in the cava was represented by a little puckering of the wall (Figs. 74a and b.). HCD was thick-walled and was blocked by recent thrombus.

The inferior vena cava was narrow and fibrous-walled at the ostial level (Fig. 74a), but not occluded. The part below the renal veins was occluded by recent thrombus which extended into the iliac vessels. Superficial abdominal veins were dilated. The portal vein was not remarkable. The spleen (200 gm.) was slightly enlarged and firm. Multiple softenings of the cortex and adjacent white matter of the left cerebral hemisphere, apparently due to venous thromboses, were the immediate cause of death.

Comment: This is a straightforward example of Chiari's Disease. The ostia were affected and the larger hepatic veins were not. The right ostium was occluded and the left ostium was grossly narrowed for a long time before death, probably before the onset of the symptoms, but no aetiological factor can be found in the history. HCD remained patent almost till death and together with the minute left ostium allowed a certain flow through the liver on account of the development of abnormal communications between the hepatic veins. The cava was puckered at the diaphragm, but the hepatic part was not occluded and the thrombus in the lower part formed only in the terminal

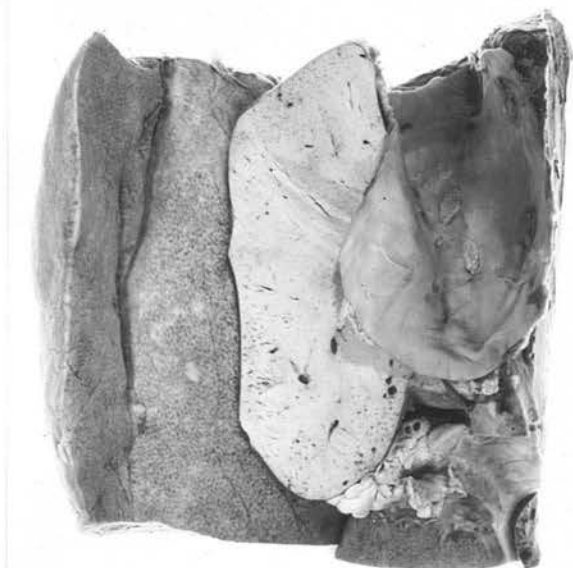


Fig., 75. Case 3. Posterior view of congested left lobe. The pale hypertrophied caudate lobe has been sectioned. x 3/5.



Fig., 76. Case 3. The cava opened from behind, to show the tiny venules at the site of the left ostium above the caudate lobe. The caudate-lobe ostium (hcs) is patent. There are some flat plaques of mural thrombus in the caval wall. x 2.



Fig., 77. Case 3. Dilated lymphatics and venules in bare area of the liver. H. & E. x 25.

stages. Portal hypertension was apparently less in this than in most other cases.

Group I, known ostial cases (Chiari's Disease): Case 3 (A3543)

A 50-year-old woman was admitted to the Western Infirmary, Glasgow (Dr. Morton) on 28/11/36 on account of progressive swelling of the abdomen. She had been well till 14 days previously when she began to feel breathless and tired; after that she noticed abdominal swelling.

On admission she did not appear dangerously ill and was not jaundiced. The limbs were not oedematous. The liver was markedly enlarged. T. 98.4°, P.R 106/min., B.P. 175/120; W.R. negative. The urine chlorides were diminished. The abdominal distension was great and 3 l. of fluid were removed, with transient relief. On 7/12/36 she became unconscious and died that day, having been ill for 3 weeks.

At post-mortem, the peritoneal cavity contained 3 l. of slightly turbid fluid. The liver (2,200 gm.) was deeply congested, except in the caudate lobe which was pale and hypertrophied (Fig. 75). The anterior margin of the liver was partly fibrosed; microscopical examination showed the sclerosis elsewhere to be confined to centrilobular areas. Diaphragmatic and portal lymphatics were enlarged (Figs. 77 and 137). Both main hepatic ostia were firmly closed and were represented by shallow depressions in the walls of the hepatic cava (Fig. 76). They were smoothly covered by an endothelial layer and were perforated by only one or two pin-hole venules. Of the accessory ostia, hcs was widely patent and HCD was narrowed. Recent but partially organised thrombi were found in many small

and medium-sized hepatic veins. Apart from a few pale mural flecks in the hepatic cava, no other thrombi were present. The spleen (800 gm.) showed the features of fibro-adenie. Oesophageal veins, the veins of Sappey and veins over the bare area of the liver and in the diaphragm (Fig. 77) were enlarged and prominent.

Death was apparently due to the effects of intrahepatic thrombosis.

Comment: This patient's illness lasted 3 weeks, but the closure of the hepatic ostia was so regular and smooth that it seems certain that the lesions were present for some time before symptoms occurred. The large size and freedom from involvement of the caudate lobe are notable. The development of many further thromboses in the small and medium-sized hepatic veins upset previous compensatory arrangements and precipitated the fatal illness.

Group I, known ostial cases (Chiari's Disease): Case 4 (P10419)

An 18-year-old male farm labourer was admitted to Tyrone County Hospital (Dr. Tattersall) on 11/9/56 on account of 7 small haematemeses in the previous 24 hours. He had not had any episodes of bleeding before and had not made any complaints till the day before his admission, although he was observed by others to be listless. He had no abdominal pain in hospital or previously; his appetite was poor and he admitted to slight indigestion recently. He had had a quinsy 1 year earlier but no other serious illness and he had never been jaundiced.

The patient was pale; P.R. 120/min., B.P. 116/50. He was not jaundiced. Heart and lungs were normal and there was no

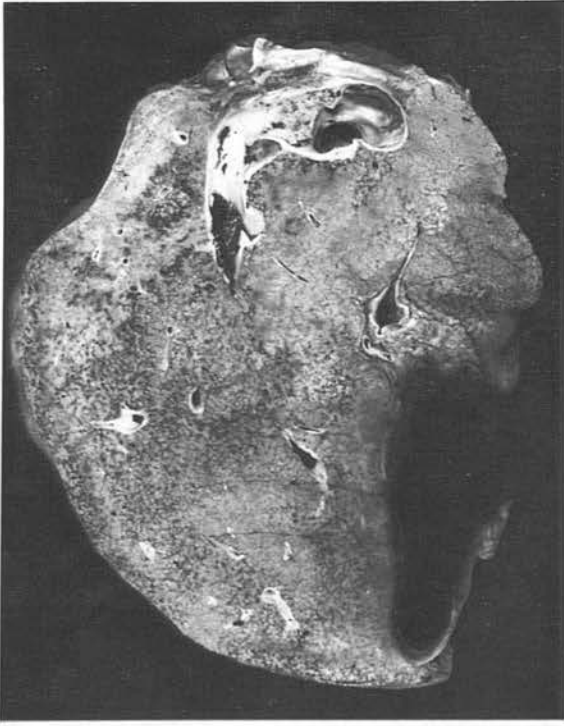


Fig., 78. Case 4. Oblique section through the liver showing the grossly dilated termination of HM above. Its wall is thick and porcelain-like. The liver is congested throughout. The antero-superior part is fibrous. The cava lies along the upper part of the specimen. x 3/5.

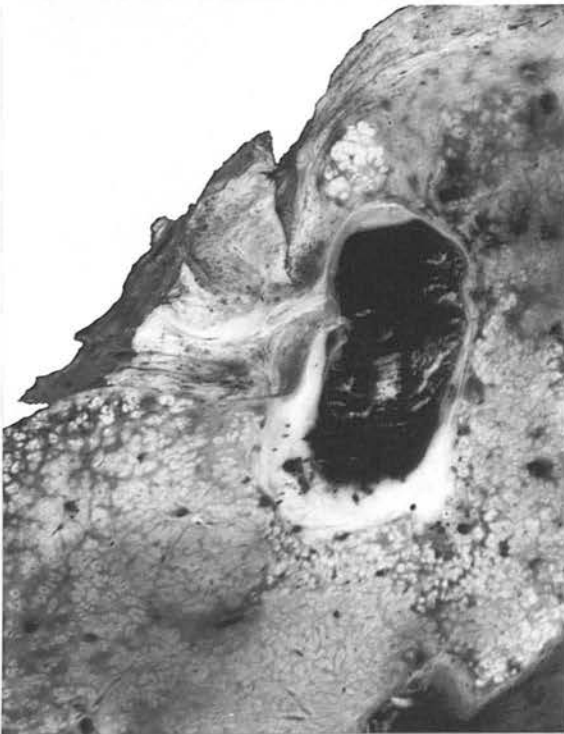


Fig., 79. Case 4. Longitudinal section through the left ostium. It is occluded, largely by contraction. The termination in the cava has been cut on the left. The dilated distal part of the ostium is seen on the right filled by postmortem thrombus. The liver tissue shows a nutmeg pattern. x 1.7.

evidence of a rise in peripheral-venous pressure. The left hypochondrium was tender. Liver and spleen were grossly enlarged. Ascites was not detected on admission. The urine was normal; blood urea 100 mgm./100 ml.; Hb. 8.4 gm./100 ml., p.c.v. 24 vols.%, m.c.h.c. 35%, r.b.c. 3.03 mil. and w.b.c. 15,400/c.mm. The day after admission the patient vomited blood again and a blood transfusion was given. His temperature began to rise and he became comatose. On 13/9/56 his temperature rose to 105° F., his pulse became weak and he died. The duration of his illness was 3 days.

At post-mortem, the cranial and thoracic cavities and their contents were normal. The peritoneal cavity contained 2 l. of straw-coloured fluid. The liver was enlarged (3,300 gm.), congested and fibrous with rounded borders and not jaundiced. Microscopical examination showed occasional foci of necrosis in addition to the congestion. The antero-superior surface was particularly firm and fibrous for a depth of about 3 cm. (Figs. 78 and 134). The central parts of the liver and the caudate lobe, though congested, were paler than the rest and somewhat granular. When post-mortem clot was removed, the larger hepatic veins were seen to be widely dilated especially towards their terminations (Figs. 78 and 79) and the walls were thick and fibrous (Figs. 100 and 101) with an appearance like porcelain (Fig. 78). The dilated veins formed large caverns close to the cava and communicated with it by occasional minute channels. Communications of medium size also connected the dilated portions of HM and HD. The terminal portion of HS and the left ostium, which is largely extrahepatic, was completely occluded and the block involved the mouth of HM

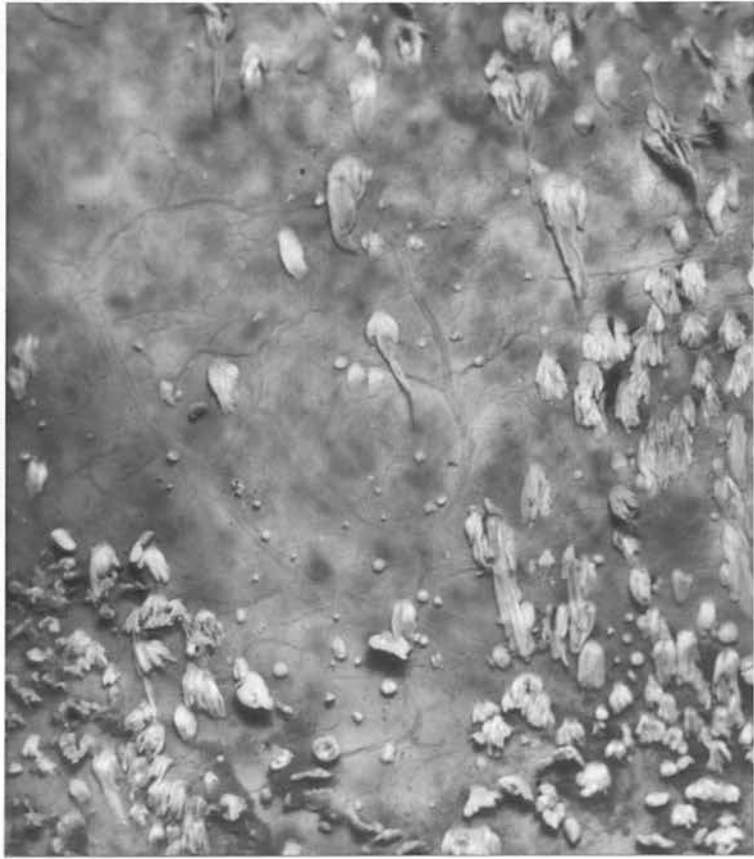


Fig., 80. Case 4. Anterior surface of the liver close to the gall-bladder, showing many small subperitoneal guttate tags on the surface. The largest are 3 mm., long and most of them about 1 mm. Dilated vessels, probably lymphatics, are seen under the peritoneum. x 4.

as well. The dilatation of HS ended abruptly at the point where the vessel ceased to be fully extrahepatic (Fig. 79). Longitudinal sections showed that the occlusion of the terminal segment was largely the result of contraction, and the central core of fibrous tissue was small and recanalised by only a few minute vessels. The proximal end of this segment was a shallow dimple in the caval wall and fully endothelialised. The right ostium was tightly closed in a similar fashion and the wall of the cava was puckered at this site round a few minute recanalising venules. The accessory ostia of the caudate lobe and of the paracaval portion of the right lobe were similarly grossly stenosed. There was no thrombosis of the inferior vena cava which was fully patent; its wall was slightly indurated. There were many small venules round the cava, especially at the diaphragmatic hiatus and also between the liver and the diaphragm in the bare area. On much of the anterior and posterior surfaces of the liver, particularly round the gall-bladder, there were many fibrous tags of guttate shape and about 1 mm. in diameter (Figs. 80, 115 & 116) which gave the surface a rough appearance. Similar tags were seen on the hepato-duodenal ligament (Fig. 138) which was oedematous.

The spleen (850 gm.) showed the naked-eye and microscopical appearances of fibro-congestive splenomegaly. Dilated veins were seen in the falciform ligament. Gross oesophageal varices were present and the intestine was filled with blood. The adrenals, kidneys and other abdominal organs were normal.

Death was due to haematemesis.

Comment: The overt illness in this case lasted 3 days, but the

hepatic-venous changes and some nodular regeneration of the liver parenchyma show that the ostia had been occluded for a long period. The occlusions may have been due to some unrecorded trauma or to the quinsy reported one year previously. It is clear that the patient was working at a time when the main ostia were completely occluded and the liver was extensively damaged. The absence of detectable ascites till late in the illness is proof of the high degree of compensation which can be achieved in young patients. The formation of minute communications between the dilated terminations of the veins and the cava indicates one of the ways in which this is brought about. The first complaints made by the patient himself were referable to secondary portal hypertension. The degree to which this had developed may be associated with the advanced type of liver change in this case comparable to cirrhosis. The foci of recent necrosis were probably caused by anaemic anoxaemia during the fatal illness. The absence of other evidence of hepatocellular failure may be due to the absence of secondary thrombi in the hepatic veins.

Group I, known ostial cases (Chiari's Disease): Case 5 (A6711)

A 22-year-old man was admitted to the Western Infirmary, Glasgow, (Dr. Snodgrass and Mr. Hutton) on 2/11/47. He had not felt well since his demobilisation 18 months previously, having had a poor appetite and lost 14 lbs. in weight, but he had remained at his work of machinist till 3 weeks before his admission. He had then a severe attack of tonsillitis which left him short of breath on exertion and suffering from recurrent bouts of sweating. Two days before admission, his abdomen began to swell and



Fig. 81. Case 5. Sagittal section through quadrate lobe. The caudate lobe has been sectioned obliquely. The liver is congested. Most of the hepatic veins are dilated and patent. HS (arrow) is completely occluded and small. A recent thrombus in the cava is seen above the diaphragm x $\frac{2}{3}$.

ache.

The abdomen was moderately distended on admission and the liver edge was 1 cm. above the umbilical plane. It was not tender. The ankles were moderately oedematous. He was not jaundiced. P.R. 100/min., B.P. 150/100; Hb, 100%, r.b.c. 4.18 mil., w.b.c. normal, W.R. weakly positive. Temperature at first elevated fell to normal after some days. B.S.R. also decreased from initial high figures. The urine at first contained considerable amounts of urobilin and urobilinogen, but this became normal later. Occult blood was present in the faeces from time to time; it was not found in a test meal. On 26/11 plasma proteins were 6.4 gm. / 100 ml., serum alkaline phosphatase 7.5 (K.A.) units, thymol turbidity and flocculation normal. The spleen, at first impalpable, was palpated later. Ascites and oedema of the legs became severe and laparotomy was performed on 22/12/47 (Mr. Wapshaw). The liver enlargement was greater on the right; it was smooth, congested and slatey in colour. A localised swelling was biopsied. This was reported to indicate thrombosis of the hepatic veins (Fig. 108).

The day after operation, plasma proteins were 6.3 gm./ 100 ml. Ascitic fluid continued to collect in large amounts. On 10/1/48 the patient became critically ill and he died on 13/1/48. The duration of his illness was 13 weeks.

At post-mortem, the peritoneal cavity contained about 4 l. of straw-coloured fluid. The liver weighed 2,000 gm.; the right and quadrate lobes were severely congested (Figs. 81, 109 & 110) and microscopically centrilobular sclerosis and condensation of reticulin were seen. In the left lobe there was an increase in fibrous tissue not only in the centres of the



Fig., 82. Case 5. The right ostium in the wall of the cava. It is scarred and contracted down to a diameter of 3 mm. A portion of caudate lobe is seen on the left. x 1.8.



Fig., 83. Case 5. Adrenal, showing infarct.
H. & E. x 25.

lobules but also in some broad fibrous septa, with destruction of lobular architecture (Fig. 133) and occasional early nodules of regeneration. A few medium-sized hepatic veins in the left lobe were occupied by thrombi showing early organisation and round some of these lay small areas of haemorrhagic infarction (Fig. 113). The caudate lobe and the paracaval portion of the right lobe were less congested than the other portions of the liver.

The right ostium (Fig. 82) was contracted down and scarred to leave an opening of 3 mm. diameter. At the opening, which was fully endothelialised, there was a thin collar of fibrous tissue in the intima. The vein HCD was thick-walled but patent, and fluid injected into some of the hepatic veins of the right lobe escaped through it as well as through the right ostium. The left ostium was closed by contraction and by fibrous tissue; a minute vessel traversed the scar (Fig. 99). The larger hepatic veins were patent and dilated (Fig. 81); their walls were moderately thickened by sclerosis. A hepatoma 3 cm. in diameter was present in the right lobe. There were small fibrous tags on the surface of the liver near the gall-bladder (c.f. Fig. 80).

Lying in the depression at the site of the left ostium in the caval wall was a cylindrical process of mixed thrombus 2 cm. long extending across the cava and partly blocking it (Fig. 81). A few flecks of thrombus were adherent to the caval wall below the left ostium. The vessel wall was a little indurated there (Fig. 82) and the surrounding tissues were more vascular than normal.

The spleen (390 gm.) was of the fibroadenic type and

contained several infarcts. Both adrenals contained small infarcts (Fig. 83). Oesophageal varices were present. Other porta-caval anastomoses were poorly developed. There were many small veins in the bare area running between liver and diaphragm.

Early meningitis was present and was apparently the immediate cause of death.

Comment: This man's illness lasted 13 weeks beginning with an attack of tonsillitis. It may be that his previous ill health was due to partially compensated blockage of the hepatic veins and that occlusions were present before the overt illness. The lesions found are such that they could all have developed within 13 weeks however and the progressive enlargement of the spleen during the illness tends to confirm this view. In this case the ostia were probably blocked about the time of the patient's sore throat; transient septicaemia at this time may have precipitated thrombosis. The presence of some normal liver-function tests six weeks after the onset of the illness is notable.

Group II, probable ostial cases:

Case 6 (A3417)

A 48-year-old woman, a clerk, was admitted to the Western Infirmary, Glasgow (Dr. Morton) on 10/4/36 on account of a swollen abdomen of 10 days' duration. She had no appetite and had lost a little weight recently.

The pulse was rapid. She was not jaundiced. The liver was hard and enlarged. The urinary output was low at first but improved later. Albumin was present in the urine. The



Fig., 84. Case 6. Sagittal section through the right lobe, showing intense congestion of most of the lobe and sparing of the posterior para-caval portion, which has its own venous drainage. The main radicles of HD are occluded by mixed and recently formed thrombus, x $\frac{1}{2}$.

abdomen was tapped twice and a total of 7 l. of fluid removed. After a few days the right leg became oedematous and later also the left. She died on 4/6/36, 9 weeks after becoming ill.

At post-mortem the abdomen contained 1.7 l. of serous fluid. The liver (1780 gm.) showed two different states. The caudate lobe and the posterior paracaval portion of the right lobe were pale and hypertrophied (Fig. 84). The rest of the liver was peculiarly mottled grey and dark red, being severely congested. Microscopically centrilobular sclerosis was seen. The large hepatic veins were filled with thrombus which had formed a few days before death and was not organised. The ostia were not described in the protocol. The spleen (110 gm.) was soft and contained several infarcts. Firm thrombus was present in the right femoral and external iliac veins and in the left femoral vein. The cava was free of thrombus except for a few small mural nodules in the hepatic part. The left pulmonary artery contained thrombus, probably a terminal embolus from the left iliac vein.

Comment: The nature of the changes in the liver and the small size of the spleen suggests that hepatic-venous obstructions were not present for long before the symptoms appeared 9 weeks before death. The sparing of the caudate lobe and of the paracaval portion of the right lobe shows that only the main veins were affected. The clot in the latter situation is clearly not as old as the symptoms and the pre-existence of ostial occlusions may be assumed.

Group II, probable ostial cases:

Case 7 (Cent. 54/3283)

This unmarried woman of 50, who had been living in poor circumstances, was admitted to South Tyrone Hospital (Mr. Loane and Dr. Milliken) on 22/11/54 complaining of crampy pain and swelling of the abdomen and breathlessness of one week's duration. She had had indigestion for many years.

The pulse rate was about 80/ min. during her illness; B.P. 135/80. She became increasingly dyspnoeic and basal collapse of the lungs was noted. By 10/12/54 ascites and oedema of the legs were severe. Hb 99%, w.b.c. 22,850/c.mm.; plasma proteins 6.7 (alb. 2.9, glob. 3.8) gm./100 ml.; serum alkaline phosphatase 30 (K.A.) units; thymol turbidity 2 units; blood cholesterol 128 mgm./100 ml. Paracentesis abdominis was performed with great relief to the patient, but fluid reaccumulated. She vomited several times on 14/12/54 and died the next day. Duration of illness 4 weeks.

At post-mortem in addition to ascites, enlargement and congestion of the liver were noted together with an increase in fibrous tissue. Microscopy showed the latter to be mainly centrilobular sclerosis; there was considerable loss of hepatic cells in that region. Nodules of regeneration were not seen. Organising thrombi were present in many small hepatic veins. The spleen was enlarged and had the characters of fibroadenie. The stomach was thick-walled, partly on account of oedema, but also due to a phlegmonous inflammation which had developed shortly before death and contributed to the fatal issue.

Comment: The reversal of the albumin-globulin ratio in this case and the elevation of the serum alkaline phosphatase

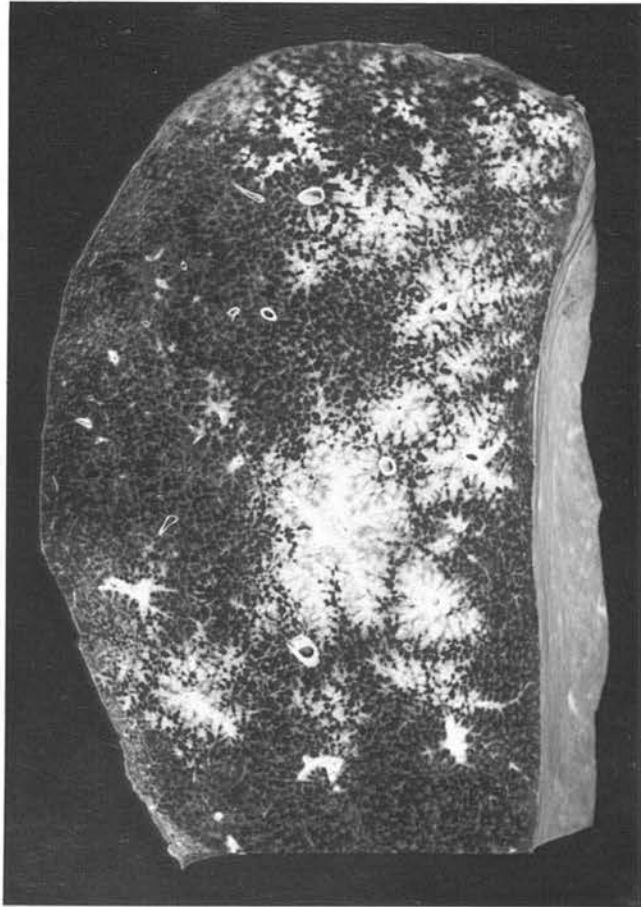


Fig., 85. Case 8. Sagittal section through the right lobe showing pallid areas in the postero-inferior half. The hepatic veins are dilated and their walls are thick and white x 3/5.

indicate chronic liver damage and suggest that the ostia had been occluded some time before symptoms appeared, but essential evidence is lacking. The diagnosis was made on histological grounds.

Group II, probable ostial cases:

Case 8 (A5913)

A 14-year-old boy, an orphan working on a farm, was first admitted to South Tyrone Hospital in February, 1946 on account of a haematemesis. A satisfactory cause for this was not found and he recovered and remained well till September of that year when he became weak and unfit for work and was readmitted to hospital. Two months later the abdomen was swollen and for some time paracentesis was required every 3 days. In June 1947, he was admitted to the Royal Victoria Hospital, Belfast (Dr. Boyd Campbell) when ankle oedema was noted as well as the abdominal swelling. The liver was enlarged, hard and, on most occasions, not tender. The spleen was palpable from time to time. There was no jaundice. Pulse rate was 100/min., B.P. 100/55, Hb. 57%, W.R. negative. Plasma proteins were 3.75 (alb. 1.2, glob. 2.55) g./100 ml. His condition did not improve and he passed through an episode of unconsciousness. He was transferred to Belfast City Hospital in August and died on the 25th., 78 weeks after the haematemesis and 49 weeks after the onset of ascites.

At post-mortem the peritoneal cavity contained large quantities of clear straw-coloured fluid. The liver (1300 gm.) was evenly enlarged, finely granular and severely congested (Fig. 85). On microscopical examination remarkably circumscribed centrilobular sclerosis was present largely dictated by

the formation of central blood lagoons where hepatic cells had disappeared (Fig. 127). Early formation of fibrous septa and of nodules of regeneration were seen. Organised thrombi occluded some of the medium-sized hepatic veins. Most of them were patent and had thick fibrous walls (Fig. 85). Recent thrombi were not seen. The ostia are not mentioned in the protocol. The inferior vena cava was not thrombosed. The heart was normal. Dilated veins were noted over the abdomen and thorax. The spleen (200 gm.) was of fibroadenoid type. Pulmonary oedema and early bronchopneumonia were present and contributed towards the fatal issue.

Comment: From the history of persistent ascites and the autopsy findings it is clear that comprehensive hepatic-venous occlusions were present, and since the major hepatic veins were dilated and thick-walled, it may be presumed that occlusions were present at the ostia although they are not mentioned in the protocol. Ascites developed during the patient's second hospital admission and hepatic-venous occlusions were probably responsible for the weakness that he complained of then, and doubtless too for the bout of haematemesis a year and a half before his death. If that is so occlusions were present for some time before that date.

The low plasma proteins recorded are an unusual finding in Chiari's Disease and are probably accountable to the frequent paracenteses as much as to the long duration of his illness.

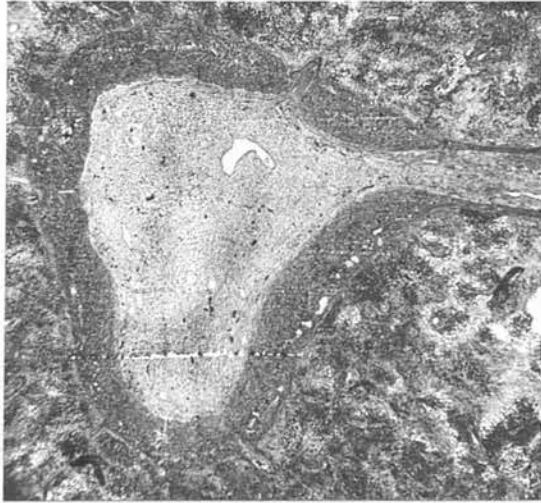


Fig., 86. Case 9. A section of the main hepatic vein of the right lobe HD occluded by organised thrombus. The vessel is only partly contracted and the occlusion is due more to plugging than to contraction. Picro-Mallory x 10.

Group III, a case secondary to caval thrombosis, the Budd-Chiari syndrome:

Case 9 (A1392)

A 28-year-old woman was admitted to the Western Infirmary, Glasgow, (Dr. Cameron) on 5/3/28, with the complaint of swelling of the abdomen of 10 days duration. She had been well till 1 year previously when she began to suffer from "septic ulcers" on the hips. 2 months later her legs became swollen and painful and walking was difficult. 3 months after that, psoriasis was noted and she was in bed for 2 months. On account of weakness and general ill health she did not return to work till shortly before the onset of the abdominal swelling. This was marked by a sudden pain in her right side on 24/2/28.

The abdominal distension was enormous on admission and paracentesis was performed. She was not jaundiced at any time. The urine contained albumin and later blood. At laparotomy on 8/3/28, distension of the bowel and liver enlargement were noted. The patient became weaker, then very drowsy and died on 25/3/28, 4 weeks after the onset of ascites.

At post-mortem the abdomen contained a considerable amount of transudate. The inferior vena cava was found to be occluded by long-standing and fully organised thrombus extending from the origin of the vessel to the hepatic ostia and including the renal and adrenal veins. Femoral, ovarian and perirenal venous anastomoses were well-developed. The liver (1560 gm.) was deeply congested with patches of pale fatty tissue interspersed. Microscopically, moderately advanced centrilobular sclerosis (Fig. 124) and the earlier stages in the formation of fibrous septa (Fig. 128) and of nodules of regeneration were seen. The right hepatic vein HD (Fig. 86) was occupied by

organised thrombus containing granules of iron pigment. This thrombus was similar to and apparently continuous with that in the cava; the ostia were not specifically mentioned in the protocol. The other hepatic veins contained recent thrombus. The spleen was normal. Pulmonary infarcts were present and, together with the liver damage, caused death.

Comment: The caval thrombosis, which was clearly of long duration, probably resulted from the septic ulcers of the hips. The occlusion of HD was apparently contemporaneous and had therefore been present for 10 months before death. This hepatic-venous obstruction caused no recognizable symptoms. Distortion of the liver architecture was just beginning and splenomegaly had not developed. The onset of ascites 4 weeks before death was marked by pain which probably coincided with the occlusion of the other hepatic veins.

Group IV, cases with patent ostia,
the Budd-Chiari syndrome:

Case 10 (A7455)

a 39-year-old countrywoman was admitted to the Western Infirmary, Glasgow (Dr. Snodgrass) on 14/1/50 complaining of abdominal swelling of 10 days duration. She had felt tired and listless since the birth of her 4th child, 2 months previously. Pregnancy and delivery had been uneventful.

On her admission there was no jaundice or finger clubbing. The liver edge was 7 cm. below the costal line and was smooth. The left lobe felt more enlarged than the right. The spleen was not palpable. Much free fluid was present in the distended abdomen. She had a procidentia uteri which corrected itself



Fig., 87. Case 10. Cava and hepatic ostia which are patent. The congested caudate lobe is also seen. x 1.



Fig., 88. Case 10. Looking down the right ostium. The radicles are narrow where they join the ostium. x 1.

later in the day. T. 99.6°F., P.R. 96/min., B.P. 130/110; Hb. 105%, r.b.c. 6 mil., w.b.c. 14,000/c.mm.; W.R. negative; there was urobilinogenuria. Three days later serum bilirubin was 3 mgm./100 ml., van den Berg indirect positive. Jaundice was marked by 23/1/50, when slight oedema in the legs and lumbar region was noted; the proclivita recurred. At open liver biopsy, Prof. Illingworth noted a grossly enlarged and congested liver with the left lobe more affected than the right. The portal radicles were dilated and the spleen was enlarged. The operative findings and the liver biopsy (Fig. 102) confirmed the diagnosis of thrombosis of hepatic veins.

During the beginning of February fluid continued to collect in the peritoneal cavity; urinary output was $\frac{1}{3}$ - $\frac{1}{2}$ of the fluid intake; urinary chlorides were low. The haematocrit P.C.V. was 61%, Hb. 105%; plasma protein 5.63 (alb. 3.64, glob. 1.74, fibrinogen 0.25) gm./100 ml. Cephalin-flocculation and colloidal-gold tests were negative; zinc turbidity 4 units; laevulose tolerance showed a delayed fall in the serum level. Bile was present in the urine and the temperature was generally slightly above normal.

On 18/2/50 Mr. W.A. Mackey performed a spleno-renal venous anastomosis. A large amount of ascitic fluid (2.2% alb.; 1.2% glob.) was encountered. The posterior wall of the abdomen and the stomach were markedly oedematous. The splenic-venous pressure was 280 mm. of water. The spleen, which was removed, weighed 520 gm. The histological features of fibroadenie were present but were less advanced than the size of the spleen would indicate.

After operation, the ascites and prolapse were completely

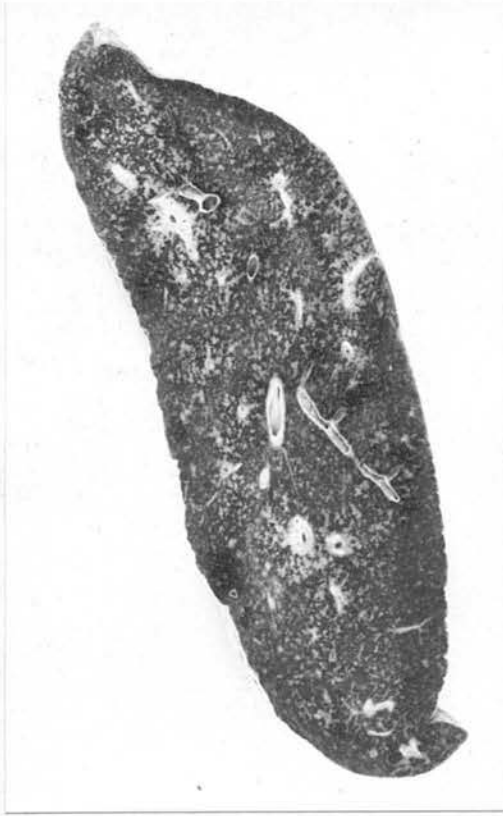


Fig., 89. Case 10. Sagittal section of left lobe which is dark and a little contracted. The hepatic veins are thick-walled. (See figs., 90 & 91). x 2/3.



Fig., 90. Case 10. HS at 2.5 cm., from the ostium extensively narrowed by organised mural thrombus but not fully contracted. Haematoxylin & van Gieson x 10.



Fig., 91. Case 10. HSS (visible in figure 89) with laminated fibrous intimal thickening. Laidlaw's reticulin stain x 7.5.

relieved. The plasma albumin was 3.9 and the globulin 2.5 gm./100 ml. Four days later the patient felt sick and looked pale and shocked but recovered after blood transfusion. Pyrexia developed and a moderate degree of jaundice was present at this time. Heparin treatment was started on 3/3/50 and continued till the patient's death. Jaundice cleared later and bile and urobilinogen disappeared from the urine. This improvement was not maintained; oedema of variable degree was present in the legs and arms; several pulmonary infarcts occurred. On 16/3/50 the patient's condition deteriorated; oliguria was present and thrombosis of the right external jugular vein was noted. She became comatose and died on 22/3/50. The illness lasted 11 weeks from the onset of ascites.

At post-mortem, ascites was not present. The liver (1900 gm.) was moderately congested. The left lobe was dark, shrunken and fibrous (Fig. 89). Microscopical examination showed moderately severe centrilobular sclerosis with considerable loss of liver cells. Fibrous septa which were not extensive were established in association with honeycomb blood lagoons (Fig. 111). The earlier stages of nodular regeneration were seen. The right lobe was mottled in a more complex pattern than that of the usual nutmeg liver (Fig. 92) and the posterior part of the quadrate lobe and the posterior paracaval portion of the right lobe were pale, somewhat granular and hypertrophied. Microscopically the main portion of the right lobe was more acutely congested than the left and sclerosis was less advanced. The caudate lobe was affected in a somewhat patchy fashion (Fig. 87). The major hepatic ostia were of normal diameter (Fig. 87) but short and funnel-shaped as they



Fig., 92. Case 10. Sagittal section of right lobe. The posterior paracaval part is less congested than the rest. HD is seen largely occluded in the upper half. Organising thrombus occupies portal veins. x 3/5.



Fig., 93. Case 10. HD is largely occluded by organised thrombus and partly contracted. Picro-Mallory x 7.5.

were followed into the liver, because the main radicles were narrowed by contraction and by thickening of the intima (Fig. 88). At the left ostium, HS had only a minute lumen while HM was 3 mm. wide. Fibrous pads smoothly covered by endothelium thickened the intima and narrowed the lumen of HS (Figs. 89 & 90). HD was also grossly contracted and largely plugged by organised thrombus so that only a slit-like lumen remained (Figs. 92 & 93). The medium-sized hepatic veins were thick-walled (Fig. 91) and some of them were plugged by organised thrombi of glassy appearance. Other veins contained recent clot and some were patent. The caudate-lobe ostium was slightly narrowed (Fig. 87). On the diaphragm and over the bare area of the liver, veins were increased in number and were prominent.

The porta hepatis was oedematous and the portal and the sub-capsular lymphatics were dilated. The left lumbar lymphatic was irregularly dilated to 3 mm. in diameter. The portal vein was occluded throughout its course by dry, brown, laminated clot adherent to the walls and organised in places. This continued into the hepatic branches (Fig. 92) and also into the splenic vein including the surgical spleno-renal anastomosis and the inferior mesenteric vein. Thrombi were present in some of the superior-mesenteric radicles but not in the main vessel. Much of the bowel was deeply congested. Oesophageal (Fig. 94) and haemorrhoidal veins were dilated and a prominent leash of veins coursed from the caecum and ascending colon over the right kidney.

The left kidney was congested and contained two infarcts. Its vein was thrombosed. Thrombi were present in both common iliac veins and in the innominate, subclavian and internal jugular veins and in an adrenal vein. Dural veins were thromb-



Fig., 94. Case 10. Oesophageal varices and antemortem digestion of the oesophageal lining. H. & E. x 6.

osed and an extensive, though superficial, area of the right frontal lobe was haemorrhagic and destroyed. Infarcts of varying ages were present in the lungs.

Comment: Although the mouths of the ostia were patent at the cava, occlusions and stenoses were found at the terminations of the major radicles and many of these had the characters of thrombi. The left lobe, originally the more congested, was shrunken. The cure of the ascites may have been due partly to the spleno-renal anastomosis, but the subsequent occlusion of the portal vein and its branches was most likely responsible for the continuation of this relief after the shunt thrombosed. The portal occlusion apparently took place on 22/2/50 when the patient became shocked. She was not receiving heparin at the time.

The lesions found at death could well have started about the time of onset of ascites, but the possibility exists that the hepatic-venous occlusions began early in the puerperium and gave rise to the tiredness the patient had felt before the onset of ascites. The hepatic lesions apparently began in the left lobe. The relatively low elevation of venous pressure measured in the splenic vein at operation suggests that the splenic enlargement may have been partly due to a persistence of the enlargement of pregnancy.

Group IV, cases with patent ostia,
the Budd-Chiari syndrome:

Case 11 (A6906)

A 29-year-old housewife was admitted to the Western Infirmary, Glasgow (Dr. Snodgrass) on 4/8/48 complaining of swelling of the legs and abdomen of 4 months duration. This had varied in degree. She had felt tired and she thought she had lost weight. The swellings had not incapacitated her till 5 days previously when the abdomen enlarged greatly.

On admission she was emaciated and not jaundiced. Oedema extended up the legs to the knees and there was considerable ascites. The liver was enlarged; the left lobe was palpated 8 cm. below the costal margin and the right lobe 3 cm. below; the edge was firm and irregular. The spleen was palpable. Temp. 98° F., P.R. 108/min., B.P. 90/50; urinary chlorides and other constituents normal. Paracentesis yielded 9 l. of straw-coloured fluid (alb. 1.5, glob. 1.1 gm./100 ml.). In the blood Hb. 120%, r.b.c. 5.6 mil. and w.b.c. 9,600/c.mm. Plasma proteins 4.37 (alb. 1.93, glob. 2.2, fibrinogen 0.24) gm./100 ml.; serum bilirubin less than 0.2 mgm./100 ml., colloidal-gold and cephalin-flocculation tests both 2 plus; laevulose tolerance normal; W.R. faint positive. During her hospital stay several large paracenteses were required. The spleen and liver diminished in size. She died on 16/9/48. Duration of the incapacitating illness 7 weeks.

At post-mortem about 2 l. of slightly blood-stained fluid were removed from the abdomen. The liver (1500 gm.) was distorted in shape. The right lobe was partly fibrous and about 2/3 of its expected size. The antero-superior and lateral portions were pale and fibrous with a condensed pattern



Fig., 95. Case 11. A small (5th order) hepatic vein in the fibrosed superficial area of the left lobe largely occluded by organised thrombus but not contracted. Picro-Mallory x 25.

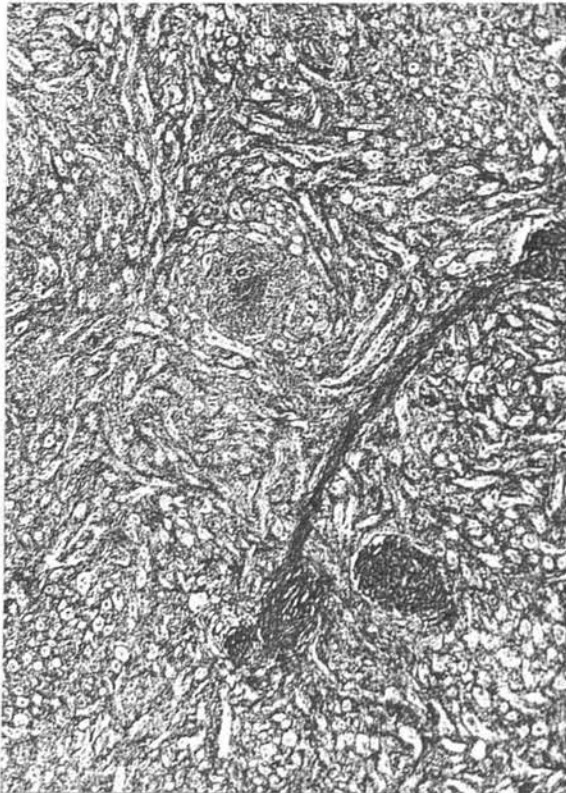


Fig., 96. Case 11. Fibro-congestive splenomegaly. Picro-Mallory x 50.

which was not recognizably lobular. Microscopical sections showed relatively dense fibrosis with broad septa, considerable distortion of liver structure and many small nodules of regeneration. This zone was divided from the more normal tissue in the posterior paracaval portion of the lobe by a congested zone in which centrilobular sclerosis was present. A small part of the anterior surface of the quadrate and of the left lobe were similarly fibrous but most of these lobes, together with the caudate, were increased in size and slightly congested. The hepatic ostia were fully patent. The radicles of the right hepatic vein of about the 4th order, which drained the fibrous area, were closed by plugs of slimy fibrous tissue (Fig. 95). There were no recent thrombi. The smaller hepatic veins in the affected portions of the liver were narrowed by concentric laminae of fibrous tissue (Fig. 119). Veins in other parts of the liver were normal.

A large leash of veins, covered by peritoneum, formed an extensive, abnormal anastomotic bypass to the hepatic veins. It ran from the antero-lateral surface of the right lobe to the right leaf of the diaphragm and to the upper pole of the right kidney. At the hepatic end, the veins were connected to irregular honeycombs of blood lagoons which were large and numerous immediately below the capsule. They became much smaller at a short distance below the surface and so must have failed to drain most of the fibrosed area. The portal vein was dilated and the spleen (300 gm.) showed the features of fibroadenie (Fig. 96) with Gandy-Gamna bodies and 2 healed infarcts. Oesophageal and abdominal-wall porta-systemic anastomoses were prominent. The venae cavae were normal.

Pneumonia was present and was the immediate cause of death.

Comment: The hepatic-venous and parenchymal changes indicate that the disease was of long standing and they may antedate the first symptoms possibly by some months. The low plasma proteins and the albumin/globulin reversal are notable and are probably partly responsible for the ascites. Death was not directly due to the liver disease, and since the liver and spleen were noted to be getting smaller during the illness, it is possible that compensation for the venous occlusions was improving through the abnormal superficial anastomosis. The high haemoglobin recorded during the formation of the ascites probably indicates haemoconcentration.

This is an example of the partial form of "endophlebitis hepatica obliterans" as defined by Meyer (1918).

Group V, a poorly documented case: Case 12 (SAIMR 383/50)

The patient, an adult African male of unknown age, was admitted to the Bagwaranath Hospital, Johannesburg on account of severe ascites of uncertain duration and died shortly thereafter. There was no indication as to whether or not his illness resulted from eating contaminated grain.

At post-mortem the liver was found to be severely and irregularly congested and partly fibrosed. Caval thrombosis was not present and there was no heart disease.

Histological sections included hepatic veins up to the 2nd order. There were partly recanalised organised thrombi in veins of all sizes and a few organising thrombi. The parenchyma of a large central part of each lobule was severely congested and

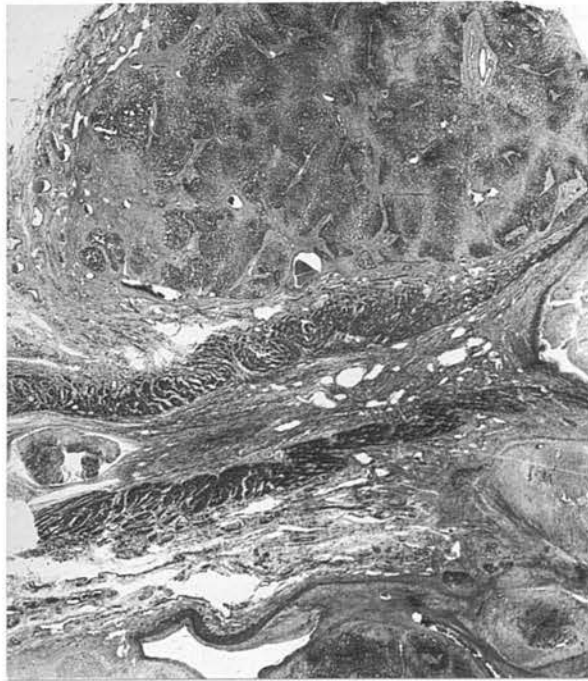


Fig., 97. Case 1. Lateral part of left ostium, contracted to a diameter of 2 mm., from its normal diameter of 12 mm., and filled with recanalised and organised thrombus. The distal portion opens out on the right into a dilated vein HS. The vein below is occluded only at its termination in the ostium. Note the vascular character of the liver capsule (above). M.P.A.H. x 6.

sclerosis was well established (Figs. 125 and 126). Early nodular regeneration was present peripherally.

HISTOLOGICAL DESCRIPTION OF THE CASES

The ostia: Longitudinal (Figs. 79 and 97) and transverse (Figs. 74, 81 and 98) sections of one or both ostia were made in 4 of the 5 cases in which they were known to be involved. Three types of ostial lesion were found, namely severe ring-like narrowing, complete closure and closure by a thin membrane. In all cases the muscle of the ostium was markedly contracted and most of the constriction or occlusion was achieved by indrawing of the wall, so that the lumen was reduced thereby from its normal diameter of 13-15 mm. down to 2-3 mm. Contraction of the muscle was made permanent by deposition of variable amounts of fibrous tissue in the walls of the vessels. The right ostium in Case 5 (Fig. 82) retained a lumen of 3 mm. and is an example of severe narrowing without occlusion, the first type of ostial lesion. In Case 2 the termination of HS preserved a central lumen of 1 mm. in the middle of a nozzle-like termination, but this was finally closed by a thrombus deposited shortly before death.

In most instances the lesions were of the second type and the ostia were closed completely by small occlusive plugs representing organised thrombi which blocked the narrow lumina of 1-3 mm. remaining after the contraction of the ostial muscle (Figs. 79 and 97). In Case 5 this type of occlusion involved the left ostium as a whole, including both its radicles together. In Case 2 only the radicle HS was affected in this way; the

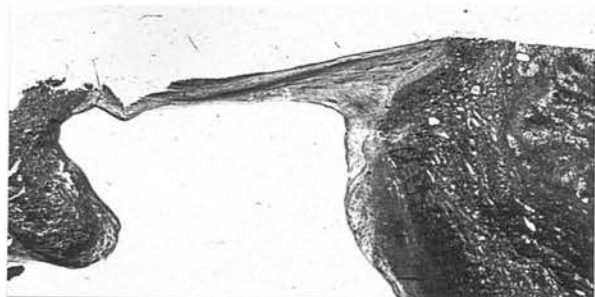


Fig., 98. Case 2. Membrane terminating vein HM at left ostium (c.f., fig. 74b). It is thin and is composed of fibrous tissue. Picro-Mallory x 4.

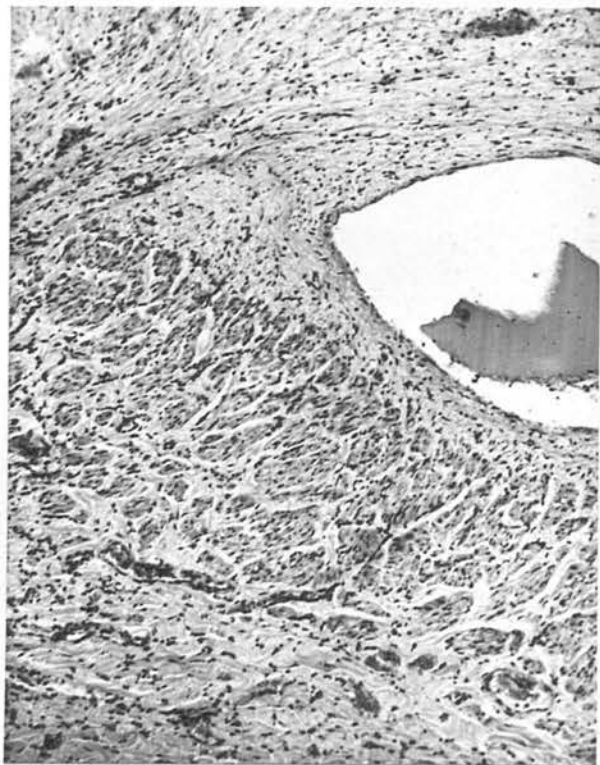


Fig., 99. Case 5. Contracted muscle and intimal fibrous tissue in the wall of the occluded left ostium. A recanalising vessel is seen. There are no inflammatory features.

H. & E. x 80.

termination of HM beside it was occluded by a lesion of the third type.

Third type. The vein HS is largely extrahepatic in the segment immediately distal to its junction with HM to form the left ostium, but HM is almost completely invested by liver tissue up to that point and so is much less able to contract. In Case 10, HM remained patent while HS was grossly narrowed. In Case 2, HM was also held patent by its parenchymatous attachment almost as far as its termination, but it was finally closed by a dome-like membrane (Figs. 74b and 98). This membrane was composed entirely of fibrous tissue spanning the gap between the muscle wall drawn in on either side round it. It was thin and almost avascular in the centre. A similar membrane closed the right ostium in Case 4.

In Case 5 the accessory ostia of the caudate lobe, which are closely invested by liver tissue, were narrowed not by contraction but by the building up of fibrous pads round their mouths apparently resulting from the organisation of mural thrombi in the hepatic cava.

The walls of the stenosed or occluded ostia contained more than normal amounts of fibrous tissue. In the intima this was usually well formed collagenous fibrous tissue of moderate cellularity (Fig. 99), often loose in texture and without any distinguishing features. There was no active inflammation in any of the cases and nothing to indicate that the fibrosis was due to previous inflammation rather than to organisation of thrombus. In some sections occasional granules of iron pigment were present but this was generally absent. Occasional flecks of fibrin were found within the fibrosed intima. In Case 4,



Fig., 100. Case 4. Fibrous tissue thickening the intima of a large hepatic vein near an occluded ostium. There is no active inflammation and the adventitial coat is largely unchanged.

H. & E. x 125.



Fig., 101. Case 4. A portion of the intima of an hepatic vein close to the occluded left ostium. The fibrous tissue is heavily collagenous and appeared porcelain-like to the naked eye, (c.f. figs., 78 and 79). It has been colonised by bile-duct structures. H. & E. x 125.

in which the lining of the hepatic veins distal to the occluded ostia was particularly thick and porcelain-like (Fig. 78), the intima was heavily collagenised in places and was penetrated in one field by bile-duct structures (Fig. 101). These are normally found only in the external collagenous layer of the hepatic veins and their presence in the intima is proof of considerable age in this occlusion.

In the cases of Chiari's Disease many of the small veins that normally enter the ostia were filled by organised thrombi, but a few remained patent and were continuous with recanalised channels in the occluded ostia. These venules received blood from a number of irregular and tortuous channels in the liver (blood lagoons) which had formed by the irregular enlargement of sinusoids and by loss of parenchymal cells. New entries into the cava had not been established and the effective collateral circulation was meagre and inadequate. There are no pre-existing collateral channels at this level. In contrast, the anastomoses round the occlusions at the distal ends of the ostia in Case 10 (Fig. 93) were formed entirely in liver. They were relatively large and discharged into veins terminating in the proximal and patent segments of the ostia and they were partially effective in circumventing the block.

Hepatic veins: Unlike the ostia, the hepatic veins were frequently patent in the cases of Chiari's Disease (Figs. 74, 81 and 85), even though flow through them must have been small. In case 10 the primary occlusions were close enough to the ostia to permit of some contraction of the vessel walls, but the veins were not completely closed (Figs. 89-91). In Case 11

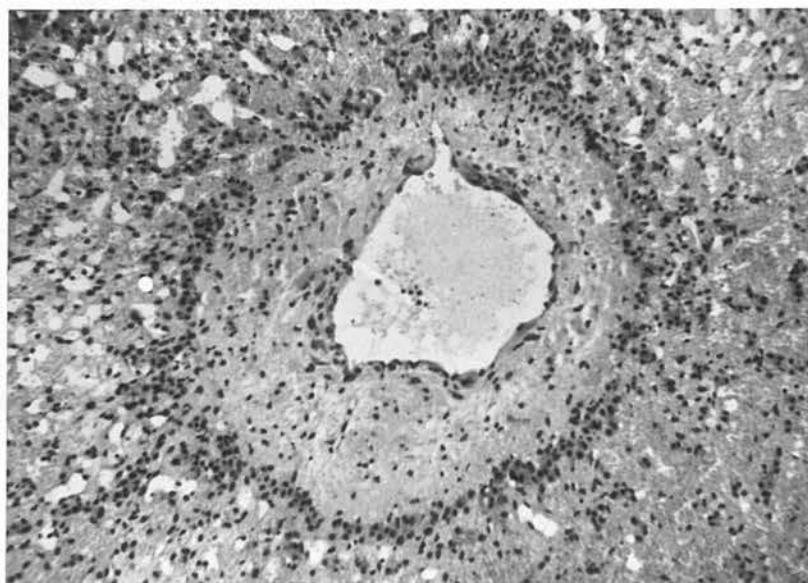


Fig., 102. Case 10. Biopsy; intercalated vein of 300 μ diameter with oedematous and fibrosed wall. H. & E x 120.

in which the ostia were unaffected the venous occlusions were restricted to vessels of the 4th order and below. These veins were filled with loose fibrous tissue containing granules of iron pigment, the result of organisation of previous occlusive clot; they were only minimally contracted (Fig. 95) and quite different from the ostial occlusions seen in other cases.

Similar organised or organising thrombi were found in most of the other cases, but in Cases 2, 4 and 8 there were few or no thrombi which could have formed during the fatal illnesses. There were no granulomata or other evidences of inflammation in any of the venous lesions. A common finding was thickening of the vein wall and narrowing of the lumen by a symmetrical inner lining of fibrous tissue sometimes relatively dense and collagenous (Fig. 119) like that seen at the ostia, sometimes looser-textured and more cellular (Figs. 120 and 121).

In addition to these venous changes, an interesting range of lesions were found in Cases 1, 3, 5, 6, 10, 11 and 12 in which thromboses were also found; these lesions are interpreted as the result of thrombosis too. Small mural thrombi were sometimes present in veins of all sizes and they were usually covered by endothelium (Figs. 105-107). In some larger veins, streaks of fibrinoid material lay a little below the surface undergoing organisation or absorption sometimes in proximity to granules of iron pigment. Fig. 104 shows a plaque of dense fibrinoid material under the endothelium with diffuse and partially absorbed fibrinoid remnants in the deeper part of the coat. In Case 1 loose festoons of platelets and fibrin with irregular coverings of endothelium were found in the veins of the right lobe. A somewhat similar portion of a mural thrombus from Case 3 is shown in Fig. 103 in which the zoning found in

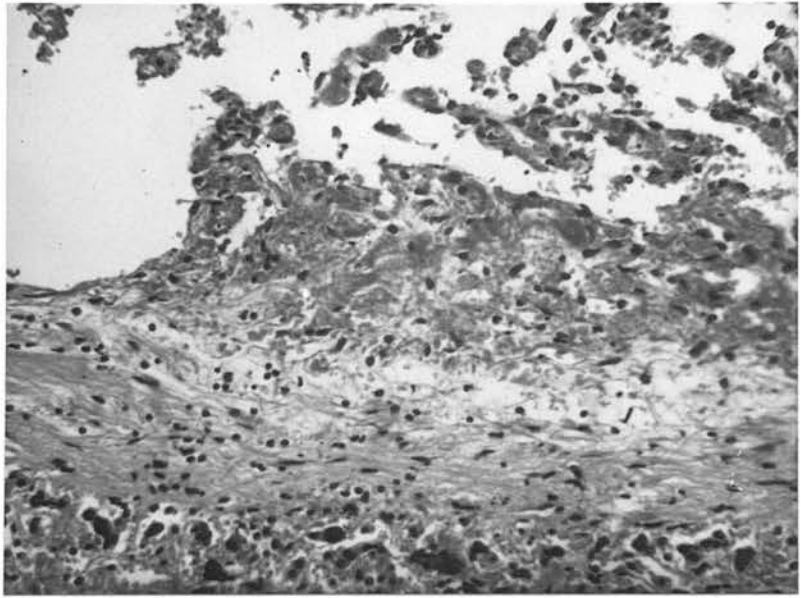


Fig., 103. Case 3. Non-occlusive thrombus being organised in the wall of an hepatic vein of the 6th order. Loose fibrous tissue characterises the organising zone. The free margin of the thrombus is polypoid. H. & E. x 175.



Fig., 104. Case 10. A dense plaque of fibrinoid material lies under the endothelium. More deeply in the fibrous intima there are diffuse and partially absorbed flecks of fibrinoid. The adventitial muscular coat of the vein is seen below. Mallory's phosphotungstic acid haematoxylin, x 65.

clots formed in a freely flowing stream of blood was absent. Fig. 106 shows a comparable lesion, a polyp with a fibrinoid core covered by endothelium.

Under the bare areas of most of the livers, and towards the abnormal superficial venous leash in Case 11, wide venous channels were present. They were partly derived from veins and partly from altered sinusoids. They penetrated only a short distance into the substance of the livers.

Liver parenchyma: The changes in the liver parenchyma were complex, and varied from one area to another.

First stage.

The earliest changes, seen in a biopsy specimen (Fig. 108, Case 5) and in similar areas in other cases, consisted of intense congestion of the greater part of the lobule with complete disappearance of most of the liver cells from the middle and central zones. Lakes or lagoons of blood occupied the centrilobular areas in which a few scattered liver cells survived. The walls of the central venules were oedematous and their outlines indistinct. In parts of the liver in Case 5 at post-mortem the areas of congestion were confluent and only collars of liver cells survived round the portal tracts (Fig. 109). In post-mortem tissues the debris of laked erythrocytes was sometimes difficult to distinguish from necrotic liver cells without special stains (Fig. 110), but unequivocal evidence of hepatic-cell necrosis was generally absent in the present series. A notable exception was Case 4 in which death followed severe haematemesis and in which necrotic liver cells were seen in some centrilobular fields. In the blood lagoons,

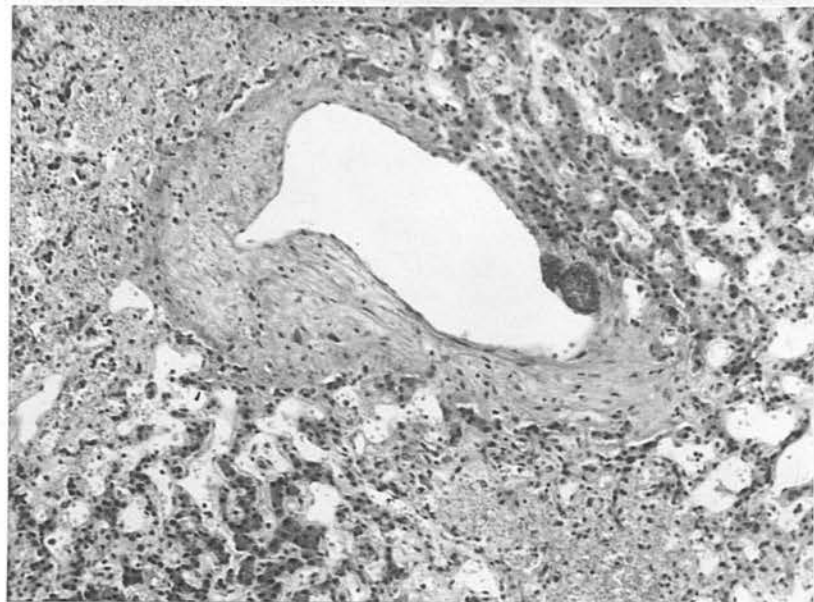


Fig., 105. Case 10. An hepatic vein of the 7th order narrowed by a loose fibrous-tissue lining. A small mural thrombus is present. Picro-Mallory x 100.

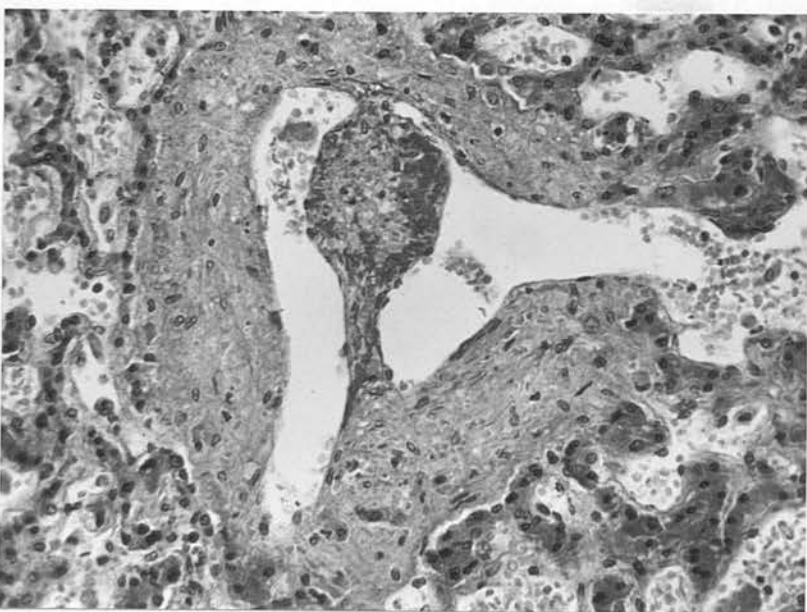


Fig., 106. Case 10. A polyp-like mural thrombus in an intercalated vein. The thrombus is being organised and is covered by endothelium. The vein wall is markedly fibrosed and thick. A central venule enters from the right. Liver cells are atrophied, sinusoids dilated and sinusoidal walls sclerosed. Picro-Mallory x 200.

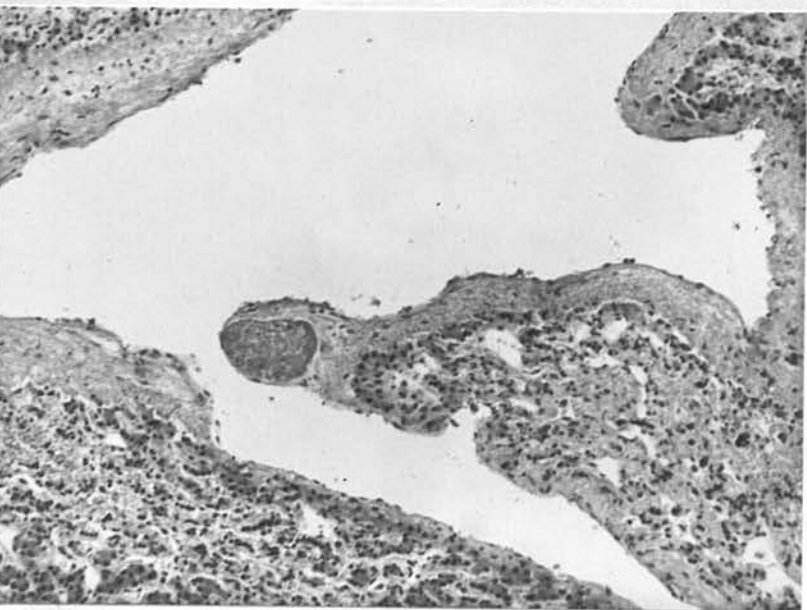


Fig., 107. Case 10. A small mural thrombus formed at the junction of a central venule with a medium-sized hepatic vein and endothelialised. H. & E. x 100.

macrophages containing brown pigment,^{*} negative to Perl's and to Turnbull's reactions for iron, were found in the damaged areas. In a few instances iron pigment was found in hepatic and Kupffer cells, particularly in Case 5 in which infarcts were present. Bile thrombi were not found. The sinusoidal walls could still be picked out by reticulin stains. The fibres were coarsened and irregular but the pattern was intact.

Second Stage.

At a later stage the reticulin round trabeculae of atrophied liver cells which had disappeared, was replaced by fine collagenous fibrils which outlined the sinusoids sharply - a condition of centrilobular sclerosis (Fig. 124). By the loss of liver cells, the central venules came to lie closer together and their lumina were narrowed by fibrous proliferation (Fig. 125). About the same time the reticulin pattern was gradually lost by compression, splitting and proliferation of the fibres (Fig. 126) and, as these were replaced by collagenous fibres, the structure of the central part of the lobule was eventually lost. Although the portal tracts gradually became fibrosed to a small degree, the peripheral portions of the lobule maintained their structure. The two zones of the lobule were sharply defined (Figs. 124-126) a feature which was particularly marked in Case 8 (Fig. 127). In Cases 2, 3, 6, 7 and 9 the lesions had not advanced beyond this stage.

* Foot Note: The pigment stains with basic fuchsin and is partially acid-fast. The more granular portions are P.A.S. positive, the more pigmented and homogeneous portions negative to this stain. It reduces silver and stains poorly with Sudan black in paraffin sections. These characters are in keeping with lipofuscin of ceroid type. A comparable pigment is found in chronic venous congestion of cardiac origin (Sherlock, 1951).



Fig., 108. Case 5, Biopsy: intense centrilobular congestion with loss of cells from most of the lobule. In the blood lagoon a few cells survive close to the central venule and the walls of that vessel are oedematous and blurred. Portal tract bottom left. H. & E. x 115.



Fig., 109. Case 5. Confluent congested areas with liver-cells surviving only as a narrow collar round portal tracts. H. & E. x 25.

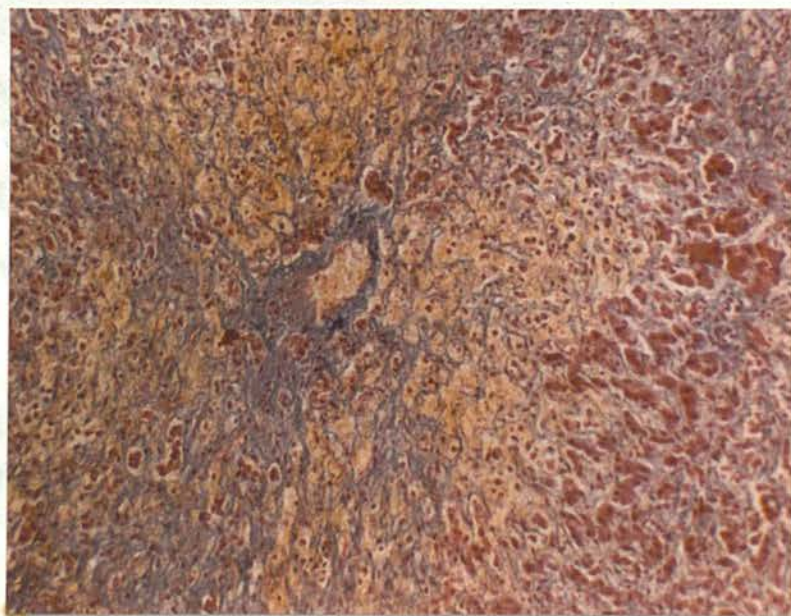


Fig., 110. Case 5. Centrilobular congestion with thickening of the wall of the central venule and collagenisation of the reticulin. Few liver cells survive in the central blood lagoon and necrotic cells are not seen. Picro-Mallory x 120.

Third stage.

Along certain lines, the collagenous fibres were sometimes laid down more densely (Fig. 128). In this way one central venule was linked to another, or with equal frequency to a portal tract. In Case 4 this formation of septa was marked (Fig. 129). At the same time nodules of regeneration began to form from hyperplasia of hepatic cells surviving in the peripheral zones. In some areas of Case 4 (Figs. 129 and 130) a structure indistinguishable from that of portal cirrhosis developed.

In other portions of the more fibrotic livers, a cirrhotic structure was brought about in other ways. Sometimes liver cells were isolated by a more diffuse fibrosis of intercellular type (Fig. 133) and this in turn led to small nodules of regeneration. Bile-duct structures proliferated to a varying degree (Fig. 134) as in other forms of cirrhosis. In Cases, 1, 4, 5, 10 and 11 dense scar tissue had formed in some parts of the livers in which no pattern was recognizable. In these scarred areas, connective tissue stains sometimes revealed the outlines of central venules almost completely occluded (Fig. 132) and it is probable that some of these scars were produced by the complete collapse of lobules brought about by the loss of their central veins.

Other changes.

Along fibrous septa and in other areas of fibrosis, irregular honeycomb vessels developed (Figs. 111 and 112). Most of these were clearly developments of the blood lagoons of the first stage, now made permanent by sclerosis of their walls.

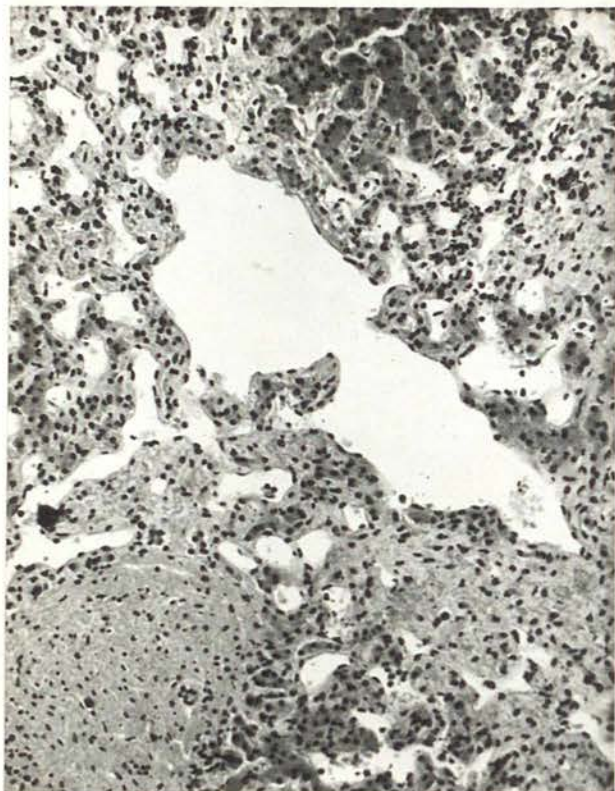


Fig., 111. Case 10. Blood lagoon with sclerosed walls close to an occluded intercalated vein, below. Many liver cells have atrophied. H. & E. x 130.

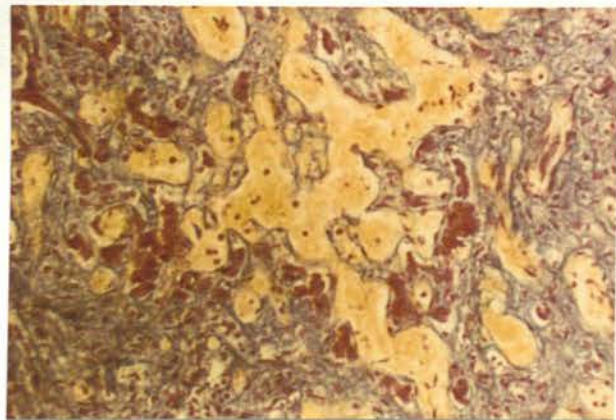


Fig., 112. Case 5. Dilated sinusoidal channels with sclerosed walls and some surviving but atrophied liver cells in the trabeculae. Picro-Mallory x 150.

Fig., 112.

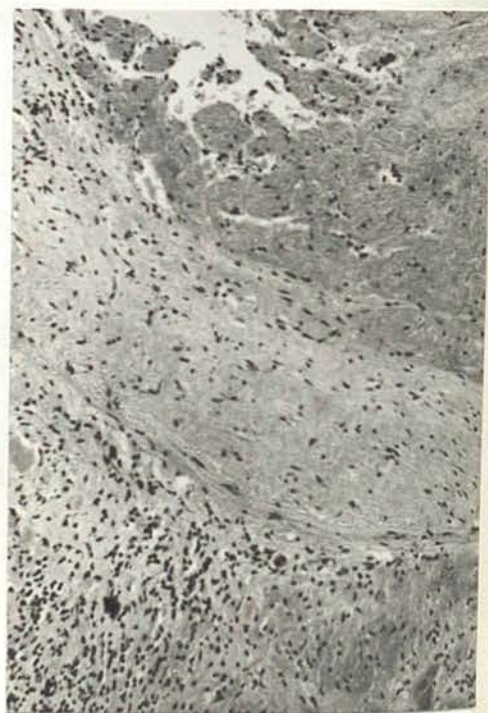


Fig., 113. Case 5. Organisation of occlusive clot in a medium-sized hepatic vein. Complete infarction of liver tissue below. H. & E. x 80.

In Case 5 there were numerous zones of genuine infarction of the liver tissue and these were related to thrombi in the medium-sized hepatic veins draining the part. (Fig. 113).

Extensive portal-venous thrombosis was present in Case 10. In Case 5 a few thromboses of small portal veins were seen, and occasional small hepatic arteries were occluded in this and in other cases. In several cases hepatic-artery branches appeared a little hypertrophied. In Case 10 a small simple angioma was present and in Case 5 a minute hepatoma.

Lymphatics: Sections of the hepatoduodenal ligament in Cases 3, 4 and 10 showed marked dilatation and an apparent increase in number of the main lymphatics of the liver there. The walls of the larger vessels were sometimes thicker than normal (Figs. 138 and 139). In Cases 4 and 10 in which the related lymph nodes were available for study, the sinuses were found to be dilated and the lymphoid tissue atrophied (Fig. 139). Sections of the hepatoduodenal ligament were not made in other cases. In Cases 1, 3, 4, 8 and 10 the lymphatics of the portal tracts were dilated (Figs. 135-137). In Cases 3, 5 and 10 grossly dilated capsular lymphatics were found. The lymphatics of the hepatic veins were also dilated in several of the cases but they were less affected than the other lymphatics. Spaces of Disse were not seen in any of the material, with certainty.

In Cases 1, 3, 4, and 10 curious fibrous tags were found under the peritoneal endothelium which had proliferated over them. They were papilliform and irregular in shape (Fig. 80), rather like wax gutterings and varied in size from a fraction of a millimeter to 3 millimetres in diameter. In most cases

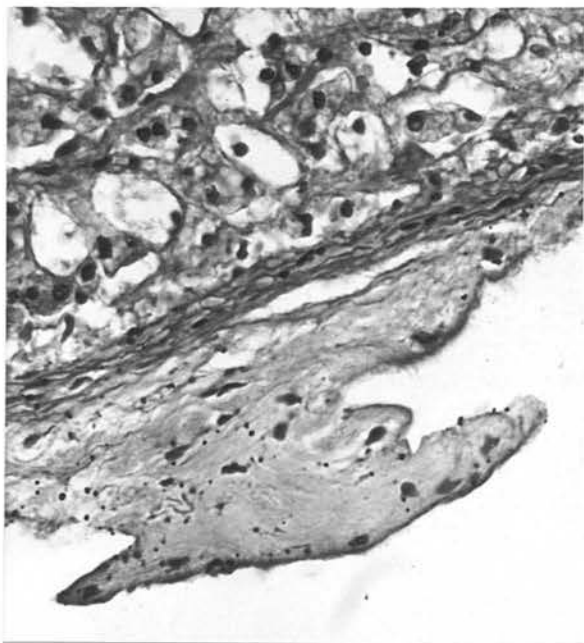


Fig., 114. Case 1.
Oedematous subperitoneal fibrous
tag. H. & E. x 350.

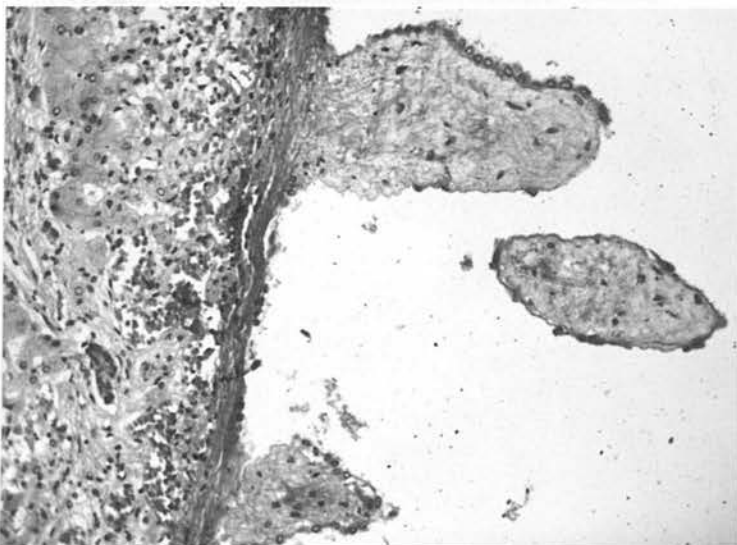


Fig., 115. Case 4. Oedematous
subperitoneal tags, right lobe.
H. & E. x 125.

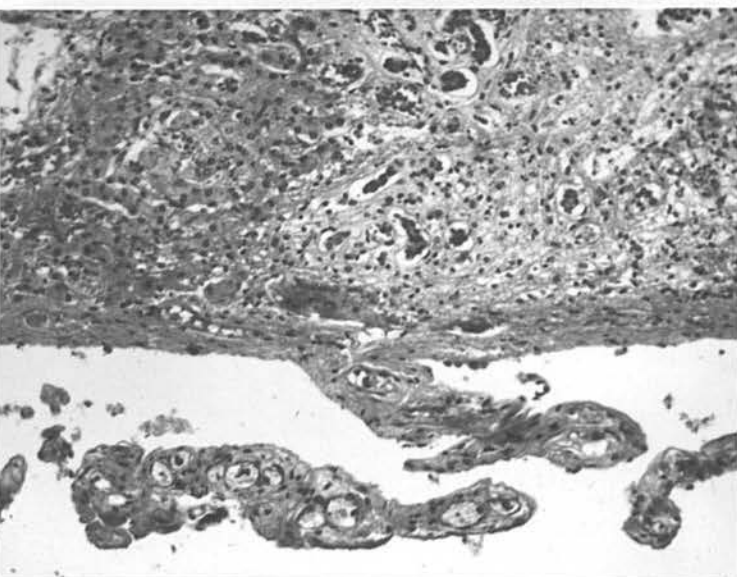


Fig., 116. Case 4. Vascular
fibrous tag on peritoneal
surface, right lobe.
H. & E. x 125.

the cores consisted of oedematous fine fibrous tissue (Figs. 114 and 115). Small blood vessels were present in some of them (Fig. 116). It was not possible to trace continuity between them and the capsular lymphatics, although the latter can be seen in neighbouring areas in Fig. 80. It is probable that similar lesions escaped notice in some at least of the other cases in this series. Identical fibrous tags were found on the surface of the hepato-duodenal ligament close to the dilated lymphatics in Case 4 (Fig. 138).

DISCUSSION OF THE PATHOLOGY

Localisation in the liver: The parenchymal damage caused by lesions of individual ostia or large veins in Chiari's Disease is determined in its extent by anatomical considerations and its severity by the degree of obstruction to the outflow from each individual territory and the ability of neighbouring territories to provide a bypass.

Where the left ostium was occluded, as in most of the cases reported here, both left and quadrate lobes were equally congested, but in Case 10 where the occlusions were restricted to the veins themselves the two lobes were differently affected (c.f. the case of Dodd et al, 1948). In Case 1 the left ostium seemed to have been closed for some time before the apparent onset of the patient's illness at a time when she was stated to be strong and healthy. Symptoms began when the right ostium was occluded in addition.

The disease was largely, though not entirely restricted to the right lobe in Case 11 and in the cases of Reynaud, Kelsey



Fig., 117. Hypertrophy of the Caudate Lobe in chronic
obliteration of the portal sinus in a girl of 15 x $\frac{1}{2}$.

Posterior to the left lobe in the horizontal section is an abnormal mass of liver tissue derived from hypertrophy of the caudate lobe and its process. It has enlarged leftwards from its normal position between the I.V.C. (in the middle of the lower surface) and the occluded portal sinus. See figure 10b for a comparable normal section.

and Comfort and Notter-Blum (1949). In Case 9 the occlusion of HD seems to have been tolerated without causing ascites for about 10 months, i.e. until the other hepatic veins were blocked. More commonly in the present series, partial involvement of the right lobe was seen. The posterior paracaval portion (Fig. 6b) largely escaped congestion in Cases 6 (Fig. 84) and 10 (Fig. 92), because the accessory ostia from the veins HDL, HR & HCD (Fig. 15) were not affected. In Cases 4 and 5, these ostia were partially closed and this portion of the liver was congested.

For similar reasons the caudate lobe may take part in the congestion, as in Cases 5 (Fig. 82) and 10 (Fig. 87) or it may be spared and hypertrophy. In Case 3, the vein hcs (Fig. 76) was widely dilated, and drainage through the caudate lobe and through minute recanalising vessels at the other ostia apparently sufficed for some time. Three weeks before the patient's death, however, compensation finally broke down, probably because thrombi formed below the occluded ostia and prevented the re-routing of blood. Enlargement of the caudate lobe, often in an irregular mass, has been reported by others (Hess; Thompson and Turnbull; Nishikawa; Baehr and Klemperer, 1930; Rigdon, 1933; Kelsey and Comfort; Murray and Kimmel, 1949 and Caroli et al., 1958). This portion of the liver hypertrophies when it is unaffected by the severe congestion that involves the rest. A similar massive enlargement may be encountered occasionally in intrahepatic occlusion of the portal vein in which the vein to the caudate lobe has been spared, as seen in a recent case (Fig. 117).

The fact that partial involvement of the liver can be related so accurately to the territories of the large veins

suggests that it is these vessels or the ostia that are primarily involved in Chiari's Disease and the Budd-Chiari syndrome as generally seen in Europe, and not the small hepatic veins as several German authors (e.g. Meyer, 1918; Kucsko and Portele, 1950) have suggested. The reverse is true of the Jamaican veno-occlusive disease.

Collaterals: The striking effects of ostial occlusion in Chiari's Disease are due to the fact that there are normally no collaterals for this portion of the venous system. There are indeed few organs with such an unsupported and vulnerable venous drainage. The new channels that form after occlusions at this level are small and ineffective. The condition in the porta hepatis is widely different, for the portal stem is surrounded by many small venules which proceed, after the occlusion of the portal stem, to carry the whole portal-venous supply to the liver, though at the cost of portal hypertension (Gibson and Richards, 1955).

The simplicity of the developmental pattern of the hepatic veins is in keeping with this paucity of collaterals, and contrasts with the complex development of the inferior vena cava and the many collaterals that form when it is obstructed (Pleasant, 1911). A comparison of the results of occlusions of the cava and portal stem on the one hand and of the ostia on the other shows that it is only when a venous collateral circulation is constructed on the basis of an extensive pre-existing normal network that it can be effective. The formation of new veins plays no significant part.

Fig. 77 shows the enlargement of veins in the bare area in

Case 3, and in Case 11 an abnormal venous leash developed (cf. Reynaud's case) but these anastomoses were ineffective chiefly because their feeders were only superficial and did not drain blood from a large enough area of the congested tissue. In Case 4, the dilated terminal portions of the hepatic veins approached the cava closely and a small abnormal communication opened up into the latter. It is surprising how unusual and how partial such natural processes of repair are in this condition. Probably this is due to the low venous pressure in the cava and hepatic veins. Case 2 (Figs. 74 and 98) provides an example of a feeble barrier which had persisted.

The formation of collaterals within the liver from one part of the organ to another is a little more successful. Although there are practically no anastomotic connections between hepatic veins in the normal liver (Fig. 17), the sinusoidal network is continuous throughout the organ. The smallness of the channels limits the value of collaterals developed on this basis and they are more effective the shorter the blocked segment they are circumventing. Blood lagoons (Figs. 111 and 112) which open up at an early stage of the disease as centrilobular cells disappear, serve to widen sinusoidal pathways. By these routes and through veins nearby, a blockage may be circumvented as in the instance of HD in Case 10, (Fig. 93). Abnormal anastomoses between large veins near the ostia were seen in Cases 2 and 4, and by this means a certain degree of compensation for the venous obstruction of one territory was possible so long as the neighbouring one was not affected. Another route of anastomosis was seen in Case 5 in which relatively large veins had developed under the capsule,

apparently permitting a moderate flow of blood from one part of the liver to another. Although only partially effective these anastomoses seem to have sufficed in some cases to prevent or minimise the symptoms till the vein into which they led was in turn occluded.

Caval lesions: Thompson noted inferior-caval lesions in 20 out of the 95 cases he reviewed, a figure in keeping with the findings in the present series, in which major caval lesions of significant duration were found in 2 out of the 11 cases (Cases 1 and 9). Minor changes were common, however, and the caval lesions in the Budd-Chiari syndrome deserve attention because they have been interpreted in different ways by a number of authors. In the paragraphs below, the caval lesions in the region of the ostia have been arranged in 6 groups to take cognizance of the more important lesions found in published cases, as well as those in the present series.

1. Trivial non-occlusive mural thrombi near the ostia were found in Cases 3 (Fig. 76) and 6. They are included here because they are clearly formed after the ostial lesions and yet suggest a way in which the second and third groups of lesions may form.
2. Narrowing and fibrosis of the cava in close association with ostial lesions were observed in Cases 2 and 5 (Figs. 74a and 82) and in both instances these were associated with the formation, shortly before death, of thrombi which finally occluded the ostia. The lesion in the cases of Hutchinson and Simpson and Rigdon was also of this type. In the case of Krass (1957) a bridge of thrombus crossed the cava between the

main ostia, and it seems likely that lesions of this group are simply the result of organisation of mural thrombus, first of all at the ostia and secondarily in the cava itself. The caval structure mentioned by Thompson (case 1) as a vestigial valve seems most likely to have been of this type.

3. Membranes or other complete but localised obstructions at ostial or diaphragmatic levels. Case 1 is an example. The left ostium and the cava at the diaphragm were occluded, probably by thrombosis, long before the overt attack. Secondary thrombosis of the cava and of the right hepatic-venous system apparently brought on the symptoms. Some structures comparable to those in Case 1 have been reported as congenital in origin; Nishikawa in particular thought that rudimentary valves might have induced thrombosis in some of his cases. The hepatic veins and the adjoining cava are never valved, however. They are formed relatively early in embryonic life (Figs. 35 and 36) and there is nothing in their development or in the congenital anomalies reported at this level (chapter I) to suggest how their development might be altered to produce stenosis. Organised thrombi at this level are described by Thompson (case 2) and by Jonas and Lawrence (1953-54) and the lesion noted by Bennett (1950) was probably an organised thrombus modified like the 3rd type of ostial lesion described above. In the case of Little and Montgomery a ring-like stenosis, similar to the first type of ostial lesion in Chiari's Disease, resulted from trauma.

4. Abnormal Eustachian valves undoubtedly occur but at a higher level and are really cardiac malformations. Rossall and Caldwell (1957) reported a case with the Budd-Chiari

syndrome in which the hepatic veins were patent but the liver was severely damaged as a result of venous congestion. In the case of Kibel and Marsden (1956) the valvular obstruction contained cardiac muscle. It was complicated by narrowing of the cava and hepatic veins below, in the way described in paragraph 3.

5. Primary tumour of the cava. A leiomyosarcoma has been reported as a cause of the Budd-Chiari syndrome by Hallock et al. (1940), who mention some similar tumours.

6. Extensive thrombi or organised thrombi of the hepatic vena cava involving the hepatic ostia secondarily. In Case 9 the caval thrombus, which was secondary to septic ulcers of the hips, had gone on to involve the right-hepatic-venous system. The Budd-Chiari syndrome did not develop, however, till the other hepatic veins were occluded 4 weeks before death. Cruickshank (1956) reported a case of the syndrome in which caval thrombosis followed lifting of a heavy weight and went on in 5 months' time to cause the Budd-Chiari syndrome. Reynaud's case was secondary to trauma. The cases of Osler (1879), Mann and Hall (1904), Lutembacher (1935) and Caputi and Warthin (1952) also originated in caval thrombosis.

Rigdon, noting that Chiari's Disease is often associated with caval lesions, concluded that the ostial lesions were generally an extension of a caval thrombophlebitis. The present analysis indicates, however, that the caval lesions are more often secondary to, or at least contemporaneous with, the ostial occlusions although some cases such as those mentioned in paragraphs 4 - 6 are the result of previous caval lesions.

The ostial lesions: The sharp restriction of occlusive and constrictive lesions to the ostial parts of the hepatic veins, during the primary stages of the illness at least, is the characteristic feature of Chiari's Disease in distinction to the Budd-Chiari syndrome. Since the greater part of the veins may be patent, even at death (Figs. 74, 78, 81 and 85) a careful study of the ostia is essential not only to distinguish the two conditions but also in any obscure case of liver disease. The lesions are often clearly of longer duration than the symptoms, and fibrosed and smoothly endothelialised ostial occlusions may be found in cases in which ascites has been present for only a few days or weeks (Thompson and Turnbull, case 2; Beattie and Hildebrand, 1950; Rosso; Thompson). Similar instances can be found in the present series in the left ostium in Case 1 and in both the main ostia in Cases 3 and 4 (Figs. 76 and 79). Discrepancy between the age of the ostial lesions and the duration of the fatal illness was less clear in Cases 2 and 5.

Three types of ostial lesion have been described above, namely severe ring-like narrowing, complete closure and closure by a thin membrane. Examples of similar lesions are given by Hess in his review of the older cases, but many published descriptions refer simply to fibrous closure or to closure by organised thrombi, or describe thrombi which may sometimes have been agonal. The common feature in all three types of lesion is gross contraction by the muscle ring.

In severe ring-like narrowing, contraction accounts for almost all of the reduction. Examples are found in the first case of Thompson and in Case 5 (Fig. 82) where the right ostium was $1/7$ of its normal diameter. Pads of fibrous tissue formed

at the ostia in the case of Burkhardt (1938) and this is probably the usual way in which the accessory ostia are closed (Fig. 76).

Thompson and Turnbull illustrated the second type of closure in their fig. 1. Figs. 79 and 97 show organised thrombus plugging the narrow contracted lumen at the portion of the left ostium formed by HS which can contract freely. Thin membranes, the third type of occlusion, were mentioned by Gee (1871). Thompson and Turnbull illustrated a membrane like that shown in Figs. 74b and 98 at the termination of HM which is relatively fixed. Beattie and Hildebrand describe a membrane at the right ostium. The characters of this third type of ostial lesion are not at first suggestive of an organised thrombus but it occurs in the same cases as the second type of obstruction which is undoubtedly thrombotic in origin. It seems probable that these membranes are organised thrombi which have been grossly modified on account of anatomical considerations and in which repair has proceeded almost to a successful outcome. Evidence for an inflammatory origin is completely lacking and there is no valid reason for supposing the membranes to be congenital.

Preferential involvement of the ostia in Chiari's Disease:

This is one of the controversial elements in the pathology. Several Italian authors have argued that the ostial lesions are congenital malformations and Rosso has summarised their evidence. Other literature favouring this theory was well reviewed by Hutchison and Simpson. The embryological facts, as we have seen, do not warrant the supposition that stenoses occur on a congen-

ital basis in the relatively simple development of the hepatic veins. The existence of fully developed though contracted ostia in the present series is also against a congenital malformation. Craven-Moore (1902) suggested that the occlusions were due to a spreading of the obliterative process from the ductus venosus, but since the ductus terminates in the left ostium, this theory would entail a greater incidence of the condition on the left than on the right and this is not so. In all cases of occlusion of the larger portions of the hepatic-venous system reported in young children, the ostia have been grossly stenosed, but this is probably due to the laxity of the tissues facilitating contraction of the vein wall and such cases, which are listed later, are rare. The peak incidence of Chiari's Disease or of the Budd-Chiari syndrome lies in the fourth decade in females and in the third decade in males and this does not accord with a congenital aetiology.

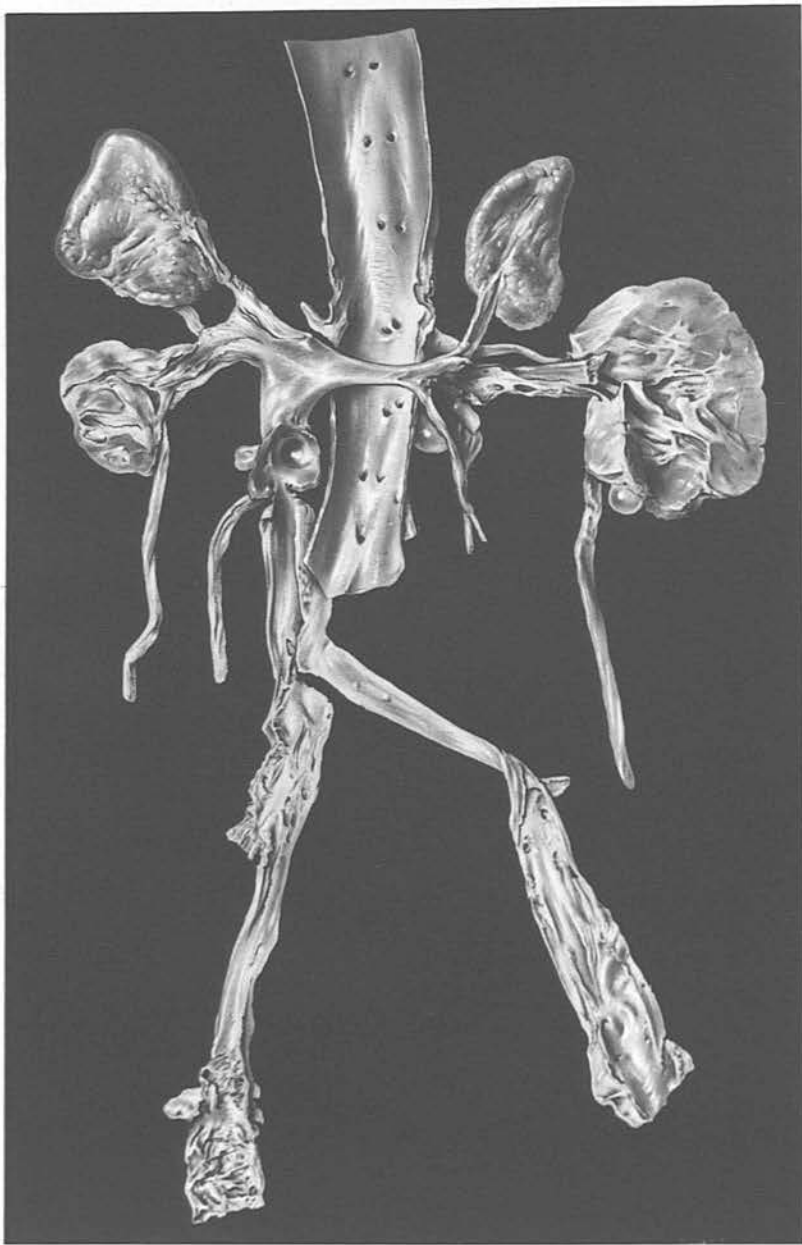
Reference is made later to the German theory of an inflammatory origin of Chiari's Disease. It is sufficient here to note that active inflammatory changes were not found at the ostia in the present cases and that the characters which the German authors refer to at this site and in other parts of the hepatic-venous system are equivocal evidence of inflammation of any sort. They have not been interpreted as inflammatory in the present work. Thompson and Turnbull and Hess refer to some of the older authors who ascribed the ostial location of the obstruction to inflammation of contiguous structures such as the liver capsule.

Kretz (1902) thought that the ostia were vulnerable to mechanical damage because of the gravitational pull of the liver

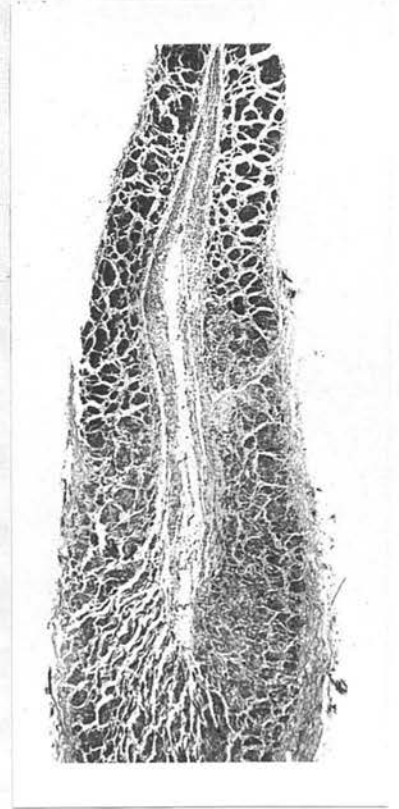
in coughing and so might be scarred. Several instances of a traumatic aetiology are cited later and Nishikawa, Hess and Baehr and Klemperer have given some support to Kretz's theory. It probably deserves fuller consideration, but it is difficult to establish.

In discussing thrombosis as a cause of the ostial lesions in Chiari's Disease a distinction must be made between the state of contraction described above and instances, such as the right ostium in Case 1, where the vessel was occluded by a propagated clot from the cava and was only partially contracted. A similar course of events apparently took place in Case 9, where thrombus, propagated from the cava into HD, was organised as a complete plug containing iron pigment (Fig. 86). Occlusions of this sort have universally been recognised for what they are, but the smoothly endothelialised surfaces of the ostial scars in the more typical instances and the shortness of the histories of symptoms in some of the patients have prevented many from accepting the view that the latter lesions are the results of an unnoticed episode or series of episodes of thrombosis in the past.

Thompson and Turnbull pointed out that the lesions of primary closure of the ostia contain little or no iron pigment and this was the case in the present series. It is only in the organisation of a laminated occluding clot or of a consecutive or propagated clot that large amounts of iron pigment are to be expected, for these forms, unlike primary thrombi, contain numerous erythrocytes. Thompson and Turnbull favoured a thrombotic aetiology ("thrombophlebitis") and considered that the confluence of vessels at this site was the main factor leading to the ostial localisation. An example of a single fresh



(a)



(b)

Left renal vein. Picro-Mallory x 16.

Fig., 118. Adhesive phlebitis. (a) is a drawing of the venous system with the aorta in a woman who died aged 21 of chronic pyelonephritis. The shrunken kidneys are little bigger than the adrenals beside them. The inferior vena cava was closed at the level of the renal veins. Below this it was thin and tape-like. A similar condition was found in most of the renal veins (b) and in the left iliac vein. Cavernous recanalized thrombus was found in the right iliac and femoral veins and at the termination of the hepatic vein HM at the left ostium.

This adhesive type of phlebitis is probably brought about by sustained spasm of the vessels and lack of flow through them.

thrombus formed in an ostium in septicaemia is given by Meyer (1947), and in the case illustrated in Fig. 118 an organised and recanalised thrombus was found at the termination of HM in the left ostium. Aschoff (1924) emphasised the importance of counter currents and zones of relative stagnation in the localisation of thrombosis, and Short (1954) and others have shown that one of the common sites of deposition of primary mural platelet thrombi in the leg veins is at the lines of venous junctions. Fig. 107 shows a small mural thrombus deposited at a venous junction within the liver in Case 10. Organisation of this type of deposit at the ostia may result in the formation of a fibrous intimal pad. The ostial junctions are sited at a place where venous flow is intermittent (Brecher et al., 1952; Kelsey and Comfort) and they are affected by diaphragmatic movement. Hess and Thompson and Turnbull considered these factors the usual reason for the location of the lesions at the ostia in Chiari's Disease and Thompson thinks they are the major reason. There is no doubt that the conformation of the veins and the character of the flow through them at this level is important in this respect but it does not explain why the ostia are affected more than other large junctions in the hepatic-venous system.

A comparison of the findings in Chiari's Disease - strict localisation of the primary lesions to the ostia and patency of the hepatic veins behind - with the normal anatomical characters of this region described in chapter I (Figs. 11, 13, 20 and 21) shows that the obstructions are located at the sites of the ostial sphincters. These segments of the hepatic veins are not invested by liver tissue entirely, but are to a varying

extent surrounded by loose connective tissue. Thus unlike other portions of the hepatic-venous tree which are held open by their attachment to liver tissue, the ostia are free to contract. The variation in the types of the ostial lesions, which depends to some extent on the exact site involved, can also be clarified in the light of the differing possibilities of contraction in each part.

Although the strict localisation of the occlusions in Chiari's Disease is a most unusual if not a unique finding in venous lesions, contraction is common in diseased veins. Frerichs (1861) described a case of the disease as "phlebitis hepatica adhesiva" and the term "adhesive phlebitis" was frequently used in the past in relation to other veins. A striking example affecting the cava and renal veins with a recanalised thrombus in the hepatic vein HM is illustrated in Fig. 118.

It has been shown in chapter III that the rôle of the ostial sphincters in normal physiology is only supplementary to that of other venous arrangements in the liver, but the strategic location of these barriers in the hepatic circulation and the virtual absence of collaterals accounts for their importance in Chiari's Disease. Only Eppinger (1937) and Rosso mention the element of muscular spasm in the lesions but it is the crucial one. Spasm converts trivial mural thrombi into occlusive lesions. It is even possible that, by altering the currents of flow over them, the ostial sphincters may be partly responsible for inducing thrombosis at this site.

The basic unity of Chiari's Disease, as opposed to other types of venous occlusion giving rise to similar manifestations,

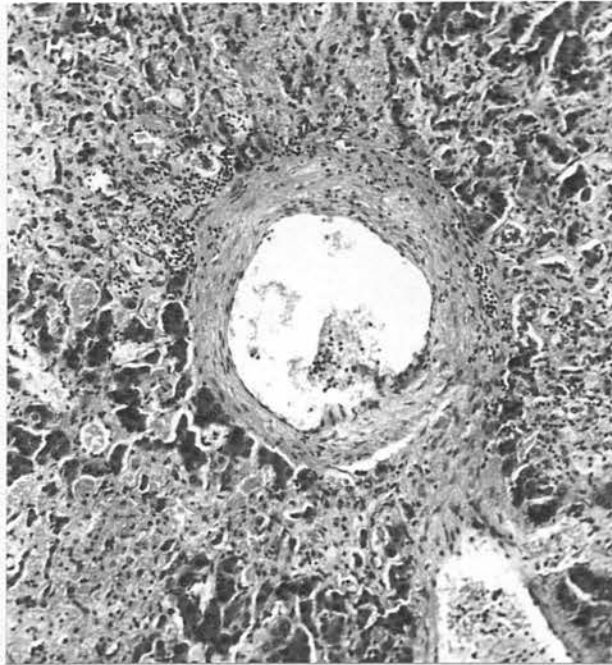


Fig., 119. Case 11. An hepatic vein of 8th order, with marked lamellar fibrosis of the wall. Slight irregularity of the endothelium at one point might be due to mural thrombosis nearby. Similar lesions have been put forward by German authors as important in the pathogenesis of allergic-hyperergic reactions in blood vessels (dysorie: chapter IV). H. & E. x 100.

lies not in aetiology but in an anatomical entity - the ostial sphincters.

The hepatic veins: In Chiari's Disease the hepatic veins often remain patent throughout most of the illness, as for instance in Cases 2, 4 and 8 and the disease does not seem to spread upwards from the smaller vessels. The abnormal state of the hepatic circulation encourages thrombosis however, and many organised and organising thrombi were found in several of the cases, particularly in Cases 3, 5, 10 and 12. Recent thrombi were particularly numerous in Case 3 and their development appears to have brought about the terminal illness, probably by causing an upset in previous compensatory arrangements. On the other hand death was due to cerebral-venous thrombosis and to haematemesis in Cases 2 and 4 respectively in which recent thrombi were not found.

Thromboses below the ostial level have been described in many published cases and constitute the venous occlusions in the Budd-Chiari syndrome, except in some tumour cases. In distinction to the ostia, where most of the occlusion is due to vascular contraction, the hepatic veins almost up to their terminations in the ostia are adherent to the hepatic parenchyma and when occlusive thrombi occur, they are organised into large loosely textured masses (Fig. 86). If the hepatic-venous occlusions had been observed alone, it is doubtful if any aetiology other than thrombosis would ever have been put forward. Nevertheless it is necessary to discuss the view that "endophlebitis hepatica obliterans" is an inflammatory lesion, if only because it has been held by most of the recent writers on the subject in German.

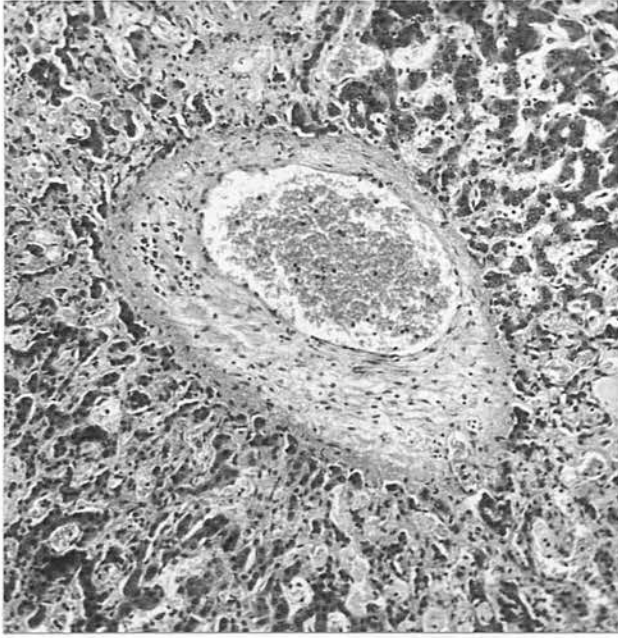


Fig., 120. Case 11. An asymmetrical narrowing of an 8th order-hepatic vein by formation of loose fibrous tissue. Lesions of this sort are common. They are probably formed by the organisation of mural thrombus or as a response to increased pressure and are not considered to be of inflammatory origin.

H. & E. x 100.

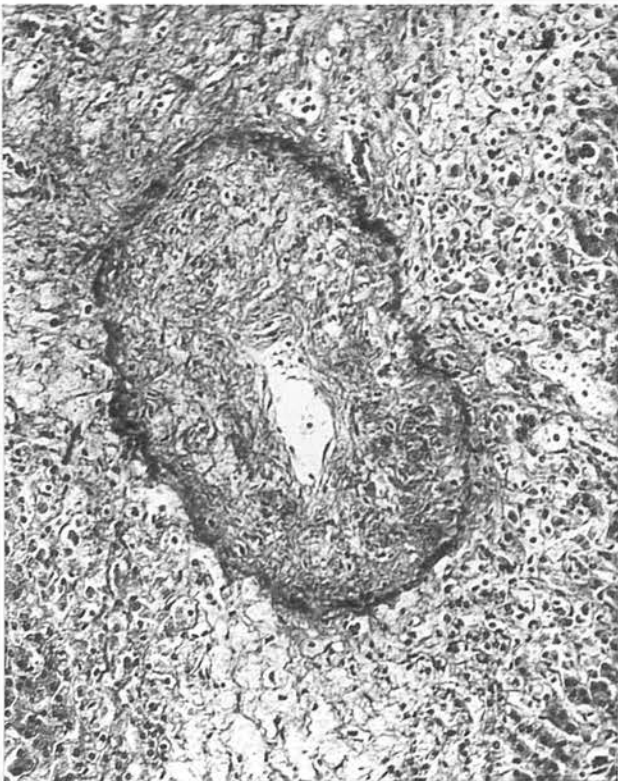


Fig., 121. Case 5. "Endophlebitic" lesion in an intercalated vein without any sign of an inflammatory origin. Picro-Mallory x 100.

Chiari's (1899) original and tentative suggestion that the aetiology was syphilitic has now been universally abandoned for typical cases. Rosso (1953) is the most recent author to deal with it at any length. The modern German view was first expressed by Rössle (1953) and is that the cause of the inflammation is a rheumatic or allergic-hyperergic reaction.

The argument for including Chiari's Disease among the rheumatic disorders is based mainly on the morphology of the venous lesions, the chief features being focal oedema of the vessel wall, (c.f. Fig. 108) the presence of fibrinoid material within the wall (c.f. Fig. 104), the formation of loosely textured fibrous tissue pads (sero-fibrillary change) in the intima (c.f. Figs. 119, 120 and 121) and the proliferation of endothelium, particularly in the form of polyps with fibrinoid cores and projecting into the lumen (c.f. Figs. 103 and 106). Kucsko and Portele refer to cobweb-like structures in the veins and Teilum (1949) and Notter-Blum illustrate these changes. Burkhardt and Coronini and Oberson noted granulomata.

All the morphological evidence in support of the German theory is probably susceptible of explanation on the basis of organisation of mural thrombi. Conventional signs of a rheumatic inflammation are almost invariably absent at the time of autopsy. Rheumatic infection in the sense used by the German authors is known to involve small arteries but these are usually spared in the present condition. Erythema nodosum which is probably allergic in aetiology causes a frankly inflammatory venous lesion (Fig. 148).

In Case 10 in which thrombosis was so persistently present, small mural thrombi were found in many hepatic and other veins

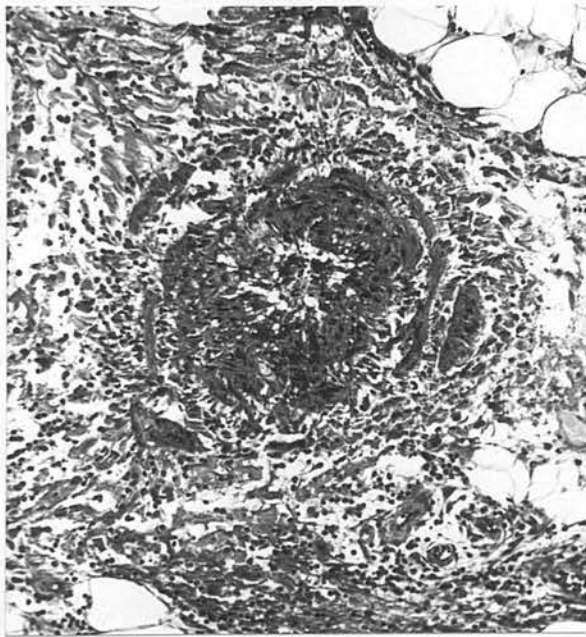


Fig., 122.

An inflamed venule in erythema nodosum.
H. & E. x 125.

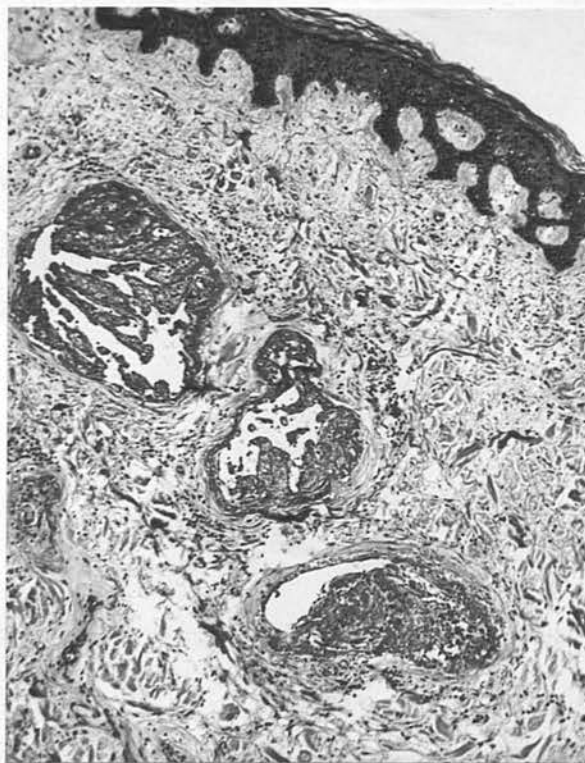


Fig., 123. "Endophlebitis proliferans" (Henschen, 1932) in a simple fibrous polyp of the abdominal wall in an otherwise healthy individual. H. & E. x 100.

(Figs. 105-107). These were often covered with endothelium so that fibrinoid material was incorporated and subsequently organised or absorbed in the venous walls (Fig. 104).

Asymmetrical pads of fibrous tissue such as those in Fig. 120 which were found in most of the cases, are probably the result of such lesions. The venous polyps probably also have a basis in thrombosis modified by the partial stagnation of the blood in the veins in which they form. Comparison of the edge of a non-occlusive thrombus in a large hepatic vein (Fig. 103) with a polypoid lesion (Fig. 106) suggests that each is a variant of the same process. These lesions, as Rössle pointed out closely resemble the "endophlebitis proliferans" described by Henschen (1932) and illustrated in Fig. 123. It occurs in grossly dilated venules of chronically inflamed lesions in which the flow is sluggish. It is well known that the flow through a vein greatly influences the arrangement of any thrombus that may form in it and this is exemplified in Case 1. Festoon-like lesions of endothelium and fibrinoid were found only in the right lobe in which the thrombi were recent. In the left lobe where the venous drainage had been occluded a long time previously, there were no recent thrombi, and the hepatic veins showed a densely collagenous intimal thickening.

Another common type of vascular lesion consisted of a symmetrical intimal thickening by fibrous tissue which was dense and collagenous in some veins (Figs. 78, 85 and 119) and fibrillary and cellular in others (Fig. 120). Similar and equally severe lesions have been recorded in simple chronic venous congestion of the liver (Castberg, 1952; Moschowitz, 1952). Proliferation of fibrous tissue in the walls of intercalated

veins (Fig. 121) and of central venules (Fig. 132) which was frequently found is similarly comparable to the phlebosclerosis at this level in chronic venous congestion (Sherlock, 1951). The indistinct staining of the walls of these small vessels in the acute stage (Fig. 108) is reminiscent of the findings of Selzer and Parker (1951) in senecio poisoning and would not appear to be a specific feature either of inflammation on the one hand or of any particular poison on the other. It is most improbable that any of the European cases apart from those of Wurm (1939) have been due to senecio poisoning.

The liver parenchyma: Published accounts of Chiari's Disease and the Budd-Chiari syndrome, which mostly refer to single cases, do not provide any synoptic description of the hepatic changes. Accordingly the findings in the parenchymal tissue of the liver in the present series have been described under several headings in a roughly sequential order to define the gradual progress of the disease. The stage at which the disease terminated was not the same in each case and changes of different ages were found in the same liver. The lesions were similar to those of chronic venous congestion and cardiac cirrhosis but they were more florid.

In the first stage (Figs. 108-110) the peripheral lobular tissue survived and maintained its vascular supply intact and probably on this account most of the hepatic functions were preserved. Necrotic debris, conspicuously absent in most of the present cases, may have been removed at an earlier period, but the silent clinical onset of the disease in several cases suggests that there were no large collections of necrotic

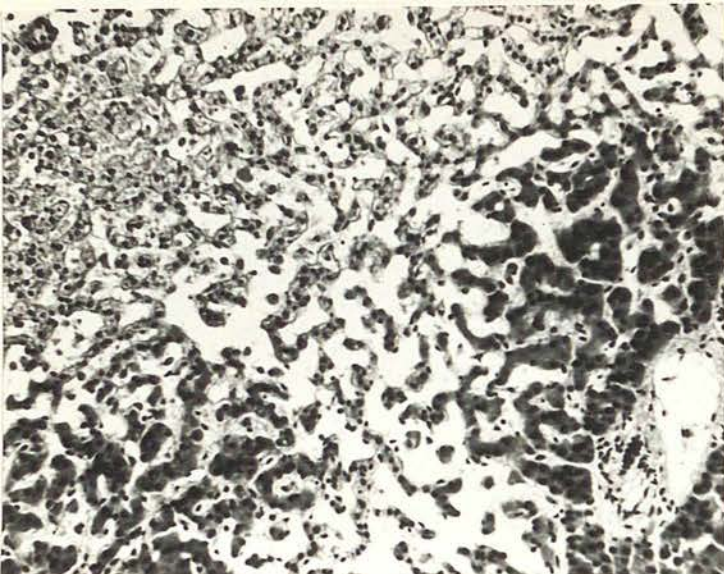


Fig., 124. Case 9. Centrilobular atrophy, top left, with fibrosis of sinusoidal walls. Picro-Mallory x 150.

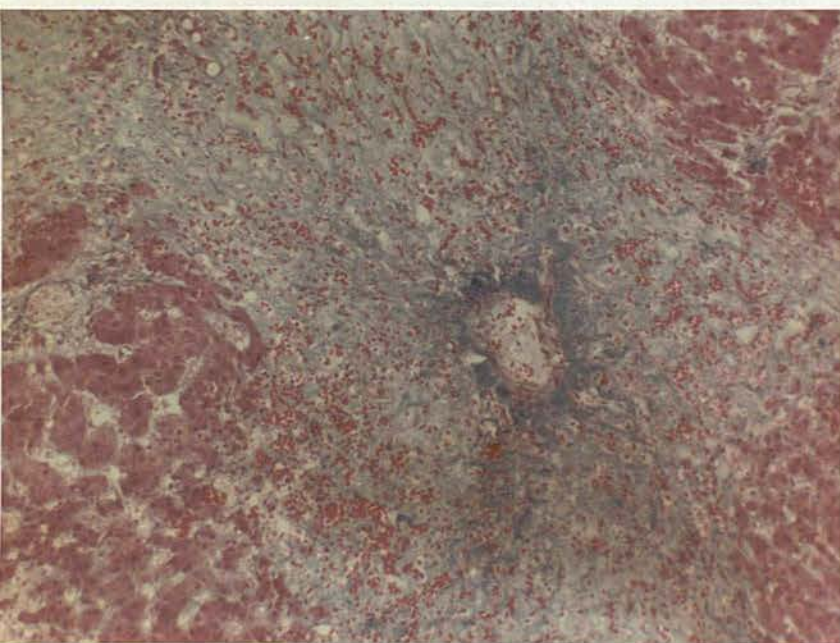


Fig., 125. Case 12. Fibrous thickening of intercalated vein, joined by central venules with early sclerosis of their centrilobular areas. Picro-Mallory x 120.

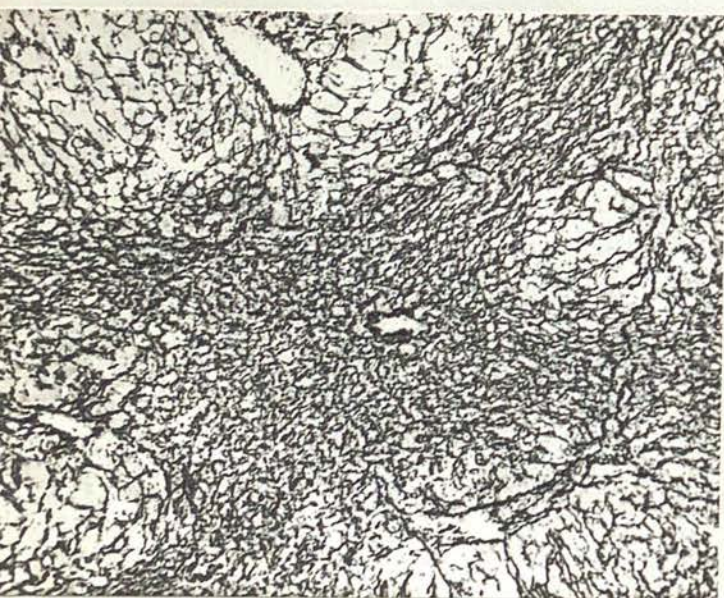


Fig., 126. Case 12. Condensation of centrilobular reticulin and junction of affected areas. Preservation of liver cells peripherally. Gordon & Sweet's reticulin stain x 80.

material at that time. Vámos (1938) described the centrilobular regions in his case as like an empty net and Brink and Botha (1955) refer to their angiomatoid appearance. Bras and Hill (1956) mention the absence of demonstrable hepatic-parenchymal-cell damage early in Jamaican veno-occlusive disease in which the liver cells seemingly perish to leave blood lagoons. In the causation of centrilobular necrosis in heart failure, anoxia due to the primary disease plays an important part (Moschcowitz) and this pathogenetic element is usually lacking in the present condition. Where necrosis was seen in the cases reported here it was associated with frank infarction (Case 5) and severe haematemesis (Case 4).

The centrilobular sclerosis of the second stage (Figs. 124-126) was similar to lesions that are well known in severe chronic venous congestion of the liver and have been studied by many workers. The older studies are reviewed by Boland and Willius (1938). The sclerosis has been ascribed to concurrent rheumatic disease (Coronini, 1939), to circulatory factors (Sherlock, 1951), to organisation of necrotic material (Moschcowitz) and to a more gradual collagenisation of coarsened and irregular reticulum (Koletsky and Barnebee, 1944).

From an analysis of the present material, the last-mentioned possibility appears the most probable in Chiari's Disease.

This view is shared by Rosso.

Examples of the second stage are seen in Cases 2, 3, 6, 7, 9 and 12. In 5 of these the condition of the spleen is known. One was fibrosed, another grossly enlarged (800 gm.) and showed the features of fibroadenie. A third was firm and two others were normal. Thus portal hypertension can, but does not always,

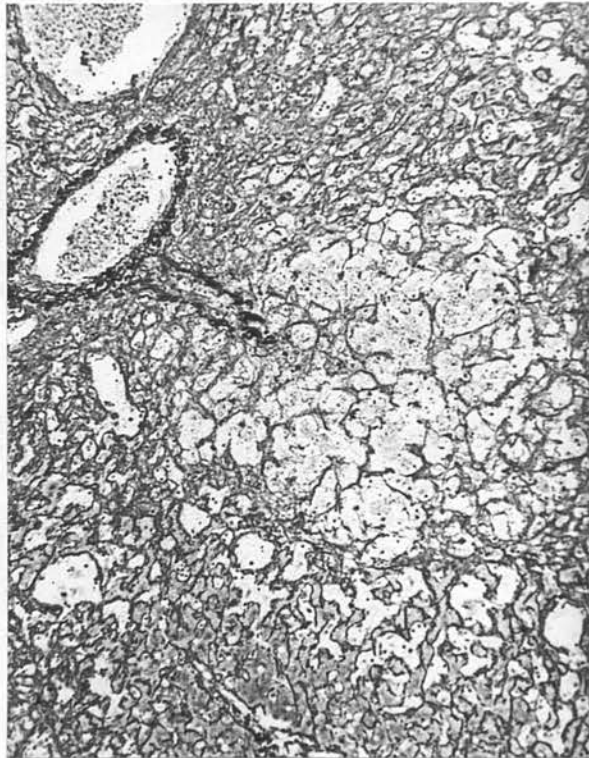


Fig., 127. Case 8. Severely narrowed central venule running out of central blood lagoon. The lagoon is divided up by several atrophied trabeculae and separated from the rest of the liver by a distinct zone which was collagenised in some fields. Foot's reticulin stain x 80.

occur in the Budd-Chiari syndrome before a cirrhotic type of liver change is present. When the latter develops, portal hypertension is apparently more severe. In distinction, Sherlock found that cardiac cirrhosis did not add portal hypertension to the clinical or post-mortem picture of heart failure.

The parenchymal liver damage of the third stage includes features with the hall-marks of cirrhosis. Moschowitz rejects the idea that congestion renders the liver more susceptible to Laennec's cirrhosis and it does not seem necessary in the present condition to invoke factors other than the venous occlusion to explain the cirrhotic appearances. Bennett considered that the cirrhosis was an extraneous factor added to the congestion in his case, but there is no doubt that a similar morphological end-result may follow different pathological insults to the liver (Dible, 1951; Popper and Schaffner, 1957). The definition of cirrhosis has been discussed by several writers (Baggenstoss, 1955; Popper and Schaffner; Popper and Zak, 1958) and it is now generally taken to imply the replacement of normal parenchyma to a greater or less extent by hyperplastic nodules of regeneration as well as the deposition of new fibrous tissue. The relentless progress of Laennec's cirrhosis is associated with the continued development of hyperplastic nodules at the expense of the normally arranged parenchyma. In Chiari's Disease and to a greater extent in cardiac cirrhosis, liver function is better maintained than in Laennec's cirrhosis and the stimuli to nodular regeneration are less imperative.

Fibrous septa and nodules of regeneration replacing normal

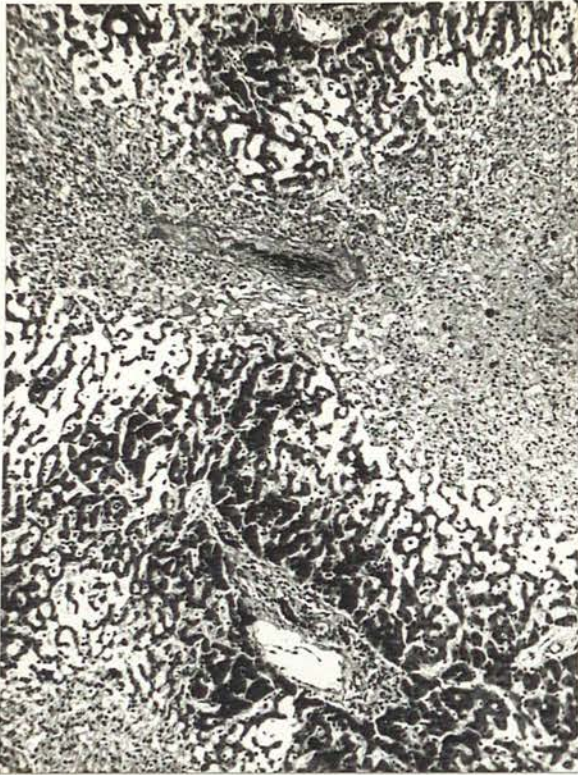


Fig., 128. Case 9. Early septum formation by extension of centrilobular sclerosis from one lobule to another. Picro-Mallory x 65.



Fig., 129. Case 4. Portal cirrhosis pattern. Picro-Mallory x 65.

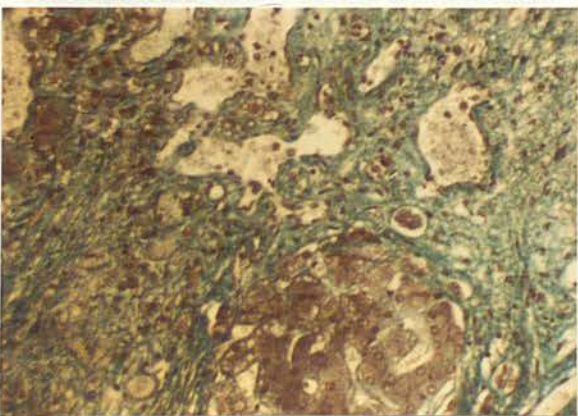


Fig., 130. Case 4. Nodule of regeneration amid fibrous tissue and irregular blood channels. Picro-Mallory x 150.

liver tissue were noted in Cases 1, 4, 5, 8, 10 and 11. The clinical data are not sufficient for a comparison of liver function to be made between these cases and those in which the hepatic damage was arrested at an earlier stage, but all the "cirrhotic" cases presented good evidence of portal hypertension, and haematemesis occurred in two of them. The clinical histories probably give little indication of the duration of the venous occlusions but it seems likely that compensatory arrangements were better developed in the cirrhotic group, so that the disease progressed more insidiously. Some of the lesions in some areas of Case 8 (Fig. 127) suggest a certain degree of stabilisation. The effectiveness of compensatory arrangements is probably due to individual anatomical variations and cannot be related closely to the character of the venous obstruction.

The tempo of the liver changes in Chiari's Disease allows one to analyse the formation of the cirrhotic structure. This seems to be brought about in two ways. Firstly there is a type developing on a background of a lobular structure which is still recognizable - c.f. the septal cirrhosis (Popper and Schaffner) or diffuse hepatic fibrosis (Himsworth, 1947) and secondly a type following total destruction of lobular integrity in some areas - c.f. post-necrotic cirrhosis (Karsner, 1943) or post-necrotic scarring (Himsworth).

Fig. 128 shows the linking up of contiguous areas of centrilobular sclerosis to form fibrous septa isolating the portal tracts, a process analogous to the formation of "pseudolobulation" in cardiac cirrhosis. The picture is not however usually as simple as this even in cardiac cirrhosis. Sherlock (1951) mentions connections between centrilobular plaques and portal



Fig. 131. Case 10. Junction of an occluded central venule with an intercalated vein and loss of lobular structure round about. Picro-Mallory x 100.

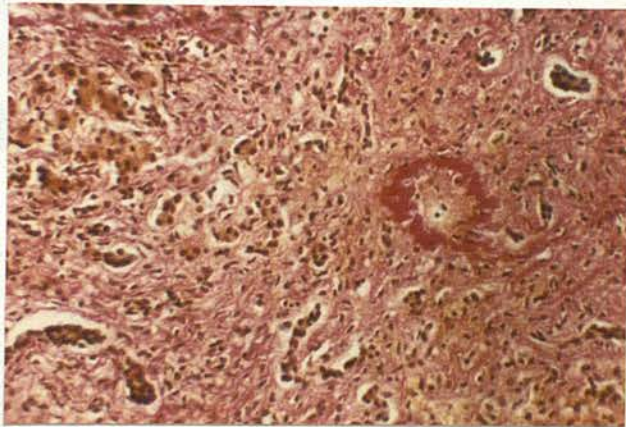


Fig. 132. Case 5. Loss of lobular architecture associated with almost complete occlusion of a central venule. The wall of the venule is thick and collagenous. Bile-duct structures are proliferating in the fibrous scar of the lobule and a few liver cells survive irregularly. Haematoxylin and van Gieson x 150.

tracts in the latter condition and Moschcowitz stresses the latter type of connection. In the present material the central-portal type of septum was found as often as those joining central areas, and typical pseudolobulation was rarely seen.

The lobule is totally destroyed when its central venule is completely occluded (Figs. 131 and 132) and this is the second way in which a cirrhotic architecture may be brought about. Careful examination of fibrotic areas by special staining techniques frequently showed the remnants of venules obliterated in this way (Fig. 132) or with a minute persisting lumen (c.f. Fig. 121), but a cirrhotic change was less often brought about in this way than by the formation of septa.

As a consequence of these changes, areas of dense intercellular fibrosis formed. Nodules of regeneration originated from groups of cells surviving at the periphery of the lobules or from individual cells isolated elsewhere. This development is less active in Chiari's Disease than in Laennec's cirrhosis but in some fields the processes may be indistinguishable (Figs. 129 and 130). Nodules of regeneration have been described by a number of authors in the Budd-Chiari syndrome (Jonas and Lawrence; Glaser and Smith, 1954; Brink and Botha; Norris, 1956; Rossall and Caldwell). Hutchinson and Simpson described fibrosis and nodular hyperplasia in their case, which survived 23 years. Hepatic carcinoma eventually developed. The authors reviewed 5 other cases of carcinoma complicating hepatic-venous occlusions; the more recent literature does not contain any further examples. In Case 5 of the present series a single small hepatic-cell adenoma was present.

Frank infarcts were found in Case 5 only. They were

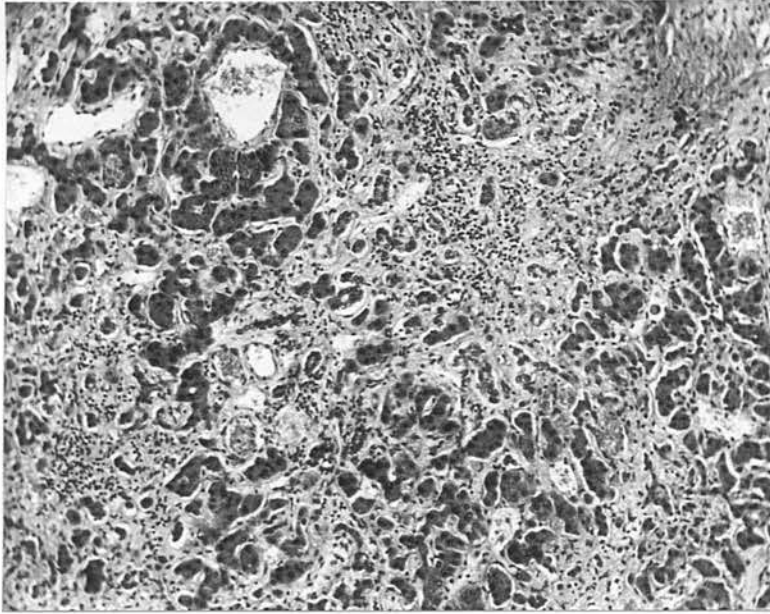


Fig., 133. Case 5. Area of dense intercellular fibrosis with loss of liver architecture. Some liver cells survive round a blood lagoon.
H. & E. x 100.

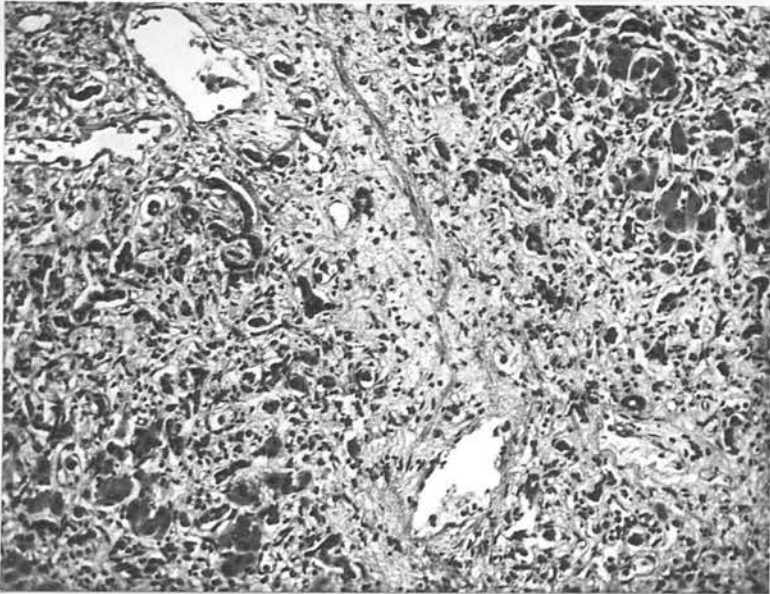


Fig., 134. Case 4. Intercellular fibrosis, with proliferation of bile-duct structures and loss of liver architecture. H. & E. x 125.

related to relatively large veins which were occluded by thrombi organising at the time of death (Fig. 113). Such infarcts may be an immediate cause of liver failure in the condition; dense scars which might have resulted from their occurrence in the past were infrequent in the present series.

There is a peculiar tendency for the superficial areas of the liver to be the most severely sclerosed portions in Chiari's Disease as for instance in Cases 4 (Fig. 78) and 11. The explanation probably lies in the difference between the normal venous drainage in the superficial and in the deeper portions of the liver which has been described in chapter I (Figs. 17, 25 and 26).

Lymphatics and ascites: Animal experiments, which are discussed in chapter VI, have drawn attention to the liver and its lymphatics as a source of ascitic fluid in chronic venous congestion. The polyps and buttons illustrated by Bolton and Barnard (1928) in cats in which the inferior vena cava had been obstructed in the thorax are similar to the curious fibrous tags found on the surfaces of livers in the present series (Figs. 80 and 114-116). These structures are also found in chronic venous congestion of the liver with ascites (chapter IV, Figs. 66 and 67). They have not been described previously in Chiari's Disease or in relation to human ascites, but since they are also found along the course of the chief lymphatics leaving the liver (Figs. 68 and 138) it seems very probable that they are connected with the transudation of fluid. Dilatation of lymphatics throughout the liver was common in the present series (Figs. 135-139) and in Cases 7 and 10 there was oedema of other

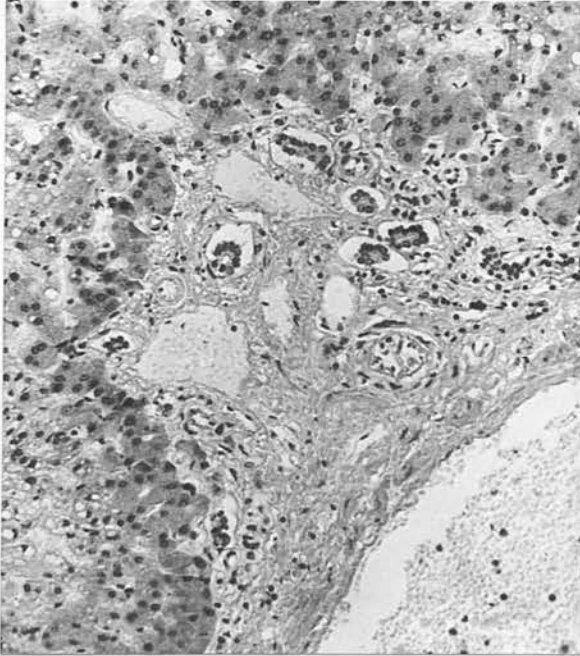


Fig., 135. Case 1. Dilated lymphatics at a division of portal tracts. H. & E. x 200.

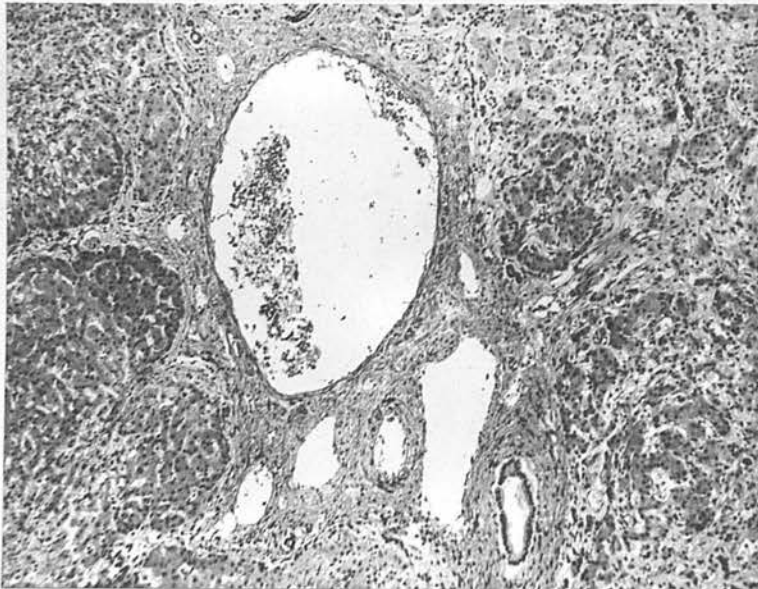


Fig., 136. Case 4. Dilated lymphatics in a medium-sized portal tract. H. & E x 60.

intra-abdominal structures. Meyer (1947) has studied the lymphatics in Chiari's Disease but otherwise the subject has been largely neglected. Recently Baggenstoss and Cain (1957) have drawn attention to dilatation of the efferent lymphatics of the liver in chronic venous congestion and in cirrhosis.

It is becoming generally accepted that portal hypertension by itself rarely leads to ascites. Surgical experience shows that operations which lower the portal-venous pressure are frequently ineffective in relieving ascites. When portal hypertension is produced experimentally in dogs by constriction of the portal vein, ascites rarely develops unless plasmapheresis is also carried out and the fluid is low in protein in comparison with that formed after experimental caval obstruction (Volwiler et al., 1950). In a series of cases of chronic obstruction of the portal vein published by Richards and the present author (1955), ascites was found only when the condition was complicated by acute thrombosis of the mesenteric veins, caval obstruction or hepatic anomalies. Baggenstoss and Wollaege (1956) largely confirmed these findings, but noted a few exceptional cases in which ascites was attributable to occlusion of the portal vein alone. The degree of portal hypertension as shown by splenomegaly and the dilatation of portasystemic anastomoses varies considerably in Chiari's Disease and it is often minor in cardiac cirrhosis (Sherlock, 1951). Probably hepatic congestion and the resultant increase in tissue fluid and lymph is the main element in the formation of ascites in both conditions.

The absence of effusions into serous cavities other than the peritoneal cavity in Chiari's Disease underlines the

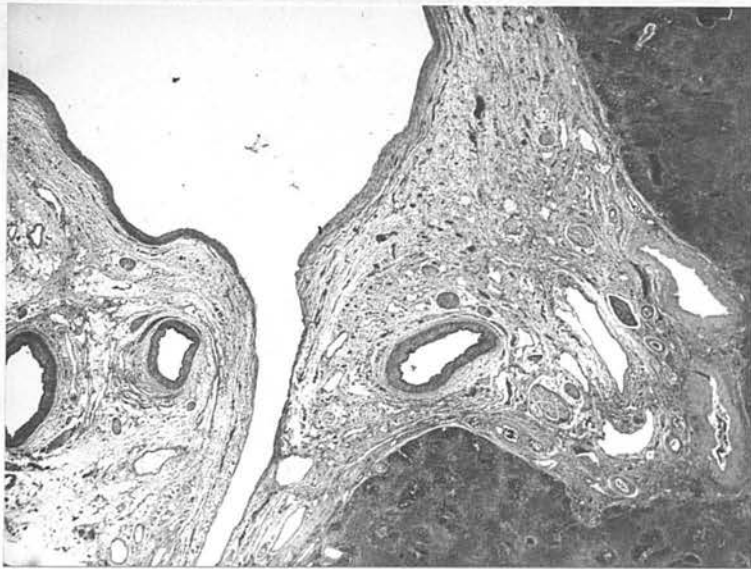


Fig., 137. Case 3. Dilated lymphatics in porta hepatis.
H. & E. x 7.

importance of local factors in causing the ascites. Certainly protein depletion seems to play little part in the initiation of ascites in this condition since plasma proteins are often normal at that time, but the level drops later, particularly if paracentesis is performed often (e.g. Case 8) and this together with sodium retention will hinder the reabsorption of fluid.

Liver lymph has a high protein content (Starling, 1894; Courtice and Yoffey, 1956). The total protein content of the ascites in Cases 10 and 11 was 3.4 and 2.6 gm./100 ml. respectively. The animal experiments quoted above would suggest that the ascites of hepatic congestion could be distinguished by its high protein content from that due to other causes. Caroli et al. (1958) state that this determination is used by French physicians to differentiate the ascites of heart failure (with a protein level of about 4 gm.) from that of liver disease (with a protein level of about 1 gm./100 ml.). They go on to propose that this difference should be utilised to establish at what level in the venous tree the occlusions are placed in the Budd-Chiari syndrome. A review of published cases shows that although high protein levels have been recorded in cases with caval occlusions (e.g. Cruickshank, 9.95 gm; Kibel and Marsden, 4 gm.) and low levels in some cases with hepatic-venous occlusions only (e.g. Casper et al. 1952, 0.7 gm; Thompson, 1 gm.) this finding is not sufficiently constant to be of real diagnostic aid.

Fibrous tags were particularly numerous in Case 4 (Fig. 80) in which ascites was not detected 2 days before death but the peritoneal membrane is capable of removing large amounts of fluid from the cavity (Prentice et al., 1952; Courtice and

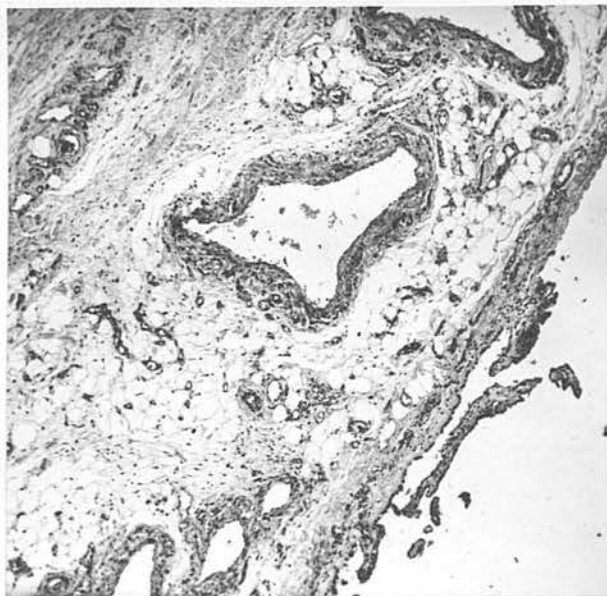


Fig., 138. Case 4. Dilated lymphatics in hepato-duodenal ligament with fibrous subperitoneal tag. H. & E. x 40.

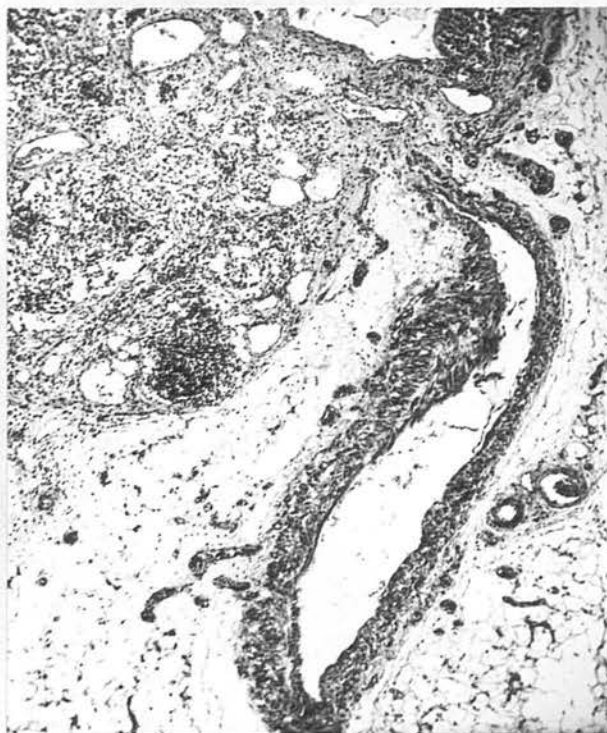


Fig., 139. Case 4. Dilated lymphatic entering portal lymph node with grossly dilated sinuses and atrophy of the lymphoid tissue. H. & E. x 40.

Simmonds, 1954) and it seems likely that enhanced absorption of the peritoneal fluid through diaphragmatic and pelvic lymphatics is an important factor in checking ascites. Small amounts of ascites cannot usually be detected clinically but in two cases (Bronte-Stewart and Goetz, 1952; Fitzgerald et al., 1956) ascites was absent at operation. During most of the long clinical course of the patient of Hutchison and Simpson there was no ascites and it was also absent in the early stages in Case 8. Slight ascites was noted at operation in the case of Rossall and Caldwell 4 years before death; the patient returned to work subsequently. Other examples of temporary relief are given by Rigdon, Armstrong and Carnes (1944), Plough and Bevans (1950) and Kløvstad (1953). It is unlikely that this can be achieved if the plasma proteins are low or if sodium is being retained.

The formation of ascites in cirrhosis has been the subject of several reviews including those of Hyatt and Smith (1954), Sherlock (1955), Lancet annotation (1955), Atkinson (1956) and Popper and Schaffner and it is generally accepted that several factors operate in most instances. Those factors which are the direct results of hepatic-parenchymal-cell damage such as the failure to produce albumin or to inactivate hormones are of more importance in cirrhosis than in the earlier stages of Chiari's Disease in which liver function is well maintained. On the other hand the antidiuretic action of ferritin or V.D.M. (Shorr et al., 1951) may be relatively more important in hepatic congestion, since hypoxia of the liver favours its production.

An increase in size of the hepatic lymphatics (Baggenstoss and Cain) and an increased flow of lymph from the liver (Theron and Allan, 1955) have been observed in cirrhosis and the work

of Madden et al. (1954) suggests that this may be due to an element of hepatic venous congestion in the condition. The latter authors demonstrated by latex-injection techniques supported by histological examinations that in the livers of patients with cirrhosis and irreversible ascites there was an absolute decrease in the hepatic-venous bed and an absolute and compensatory increase in portal and hepatic-arterial beds. This disproportion between outflow and inflow tracts was not found in livers from patients with cirrhosis and without ascites or with reversible ascites, in which there was a symmetrical loss of systemic-and portal-venous beds and an increase in the hepatic-arterial bed. Both Madden et al. and Walker (1952) consider that these 2 types of cirrhosis can be distinguished on histological grounds. It is hoped to examine at a later date a series of cirrhotic livers from this point of view to find out how clear cut this distinction is. The evidence in the meantime indicates that the territories of the portal-venous radicles are not the only possible site for the formation of ascites and that the liver itself must also seriously be considered. Sherlock (1955) holds that congestion of the liver "probably plays little part in the genesis of ascites" in human liver disease, noting in particular that the site of production of the fluid has not been demonstrated. The presence of fibrous tags on the peritoneal surface of the liver, however, probably supplies this missing link in the chain and a comparison of the frequency of this finding on the livers of cirrhotic patients with ascites and of those without would be of great value. Unfortunately the material available for review at present is not suitable for determining this point.

AETIOLOGY

Congenital causes: The incidence of the Budd-Chiari syndrome in children under 13 is low. Hutchison and Simpson described a case starting in a boy of 5 and summarised 4 other reported instances. More recent cases include those of Vámos, Thompson and Dodd et al. They are not essentially different from the adult cases. König (1943) described a unique case in which endophlebitic lesions with calcareous foci were found in an 8-day-old infant. He thought this was due to a maternal "intoxication". The possibility of congenital anomalies giving rise to the Budd-Chiari syndrome has been put forward only in relation to lesions at the ostia and in the cava and it has been discussed above under these headings.

Hepatitis: Most of the instances of the Budd-Chiari syndrome secondary to inflammations of the liver are found in the older literature and the forms of hepatitis now common in this country do not tend to cause the Budd-Chiari syndrome. The view has also been promulgated (Wurm; Notter-Blum; Rosso) that intestinal toxins might be responsible but there is no good evidence for this. The Budd-Chiari syndrome has been reported in ulcerative colitis (Kelsey and Comfort), and regional ileitis (Massachusetts General Hospital case, 1949) but this was apparently the result of thrombosis. Morison (1944) noted a small hepatic-venous thrombus in an infant with umbilical sepsis.

Endophlebitis: Chiari's Disease and the Budd-Chiari syndrome are described as "endophlebitis hepatica obliterans" in the

German literature. It can easily be understood that inflammatory lesions at the ostia, just as readily as thrombosis, might cause venospasm with indrawing of the walls there. Syphilis is now regarded as a rare cause and the weakly positive Wasserman reaction in Cases 3 and 10 is not thought to be important. Of the older cases mentioned by Nishikawa and by Thompson and Turnbull, some were certainly not syphilitic. The disease is now thought by most modern writers in German (e.g. Rössle; Coronini and Oberson; Burkhardt; Notter-Blum; Kucsko and Portele) to be an "allergic-hyperergic" manifestation. Like many instances of cardiac rheumatism "endophlebitis hepatica obliterans" often manifests itself in young persons as a late result of lesions acquired without any overt illness, but it is dissimilar in the occurrence of cases at the extremes of life. There are very few reports of coincident conventional rheumatic stigmata. Mitral lesions were described by Nishikawa and by Plough and Bevans. Erythema nodosum has been observed only in cases with caval obstruction. Coronini and Oberson, finding changes in the spleen, kidneys and heart in their 11 cases, put these forward as evidence of generalised disease of a rheumatic type. Most of their lesions are explicable as secondary phenomena; similar changes in the present series have been interpreted in that way. Gross rheumatic stigmata were not found at autopsy in any of the cases in the present series, and microscopical signs were absent in hearts so examined (Cases 2, 5, 8 and 10).

The blood sedimentation rate has been reported to have been normal in a number of cases (Salvesen and Torgersen, 1950; Casper et al.; Mandelbaum et al., 1953; Fitzgerald et al.).

In Kløvstad's case it was elevated during occasional bouts of fever and the elevation in Case 5 was probably similarly incidental.

The results of experiments on rabbits may have some bearing on this matter, for the muscle in the hepatic veins of these animals is approximately equivalent to that in man. Experimental anaphylaxis in rabbits (chapter IV and Appendix B) causes arterial and other lesions which are comparable to those found in rheumatic fever in man, but the liver lesions are quite dissimilar from those of "endophlebitis hepatica obliterans". It is chiefly on the nature of the hepatic-venous lesions that the German authors base their arguments for a rheumatic aetiology of Chiari's Disease and the Budd-Chiari syndrome. These lesions have already been discussed and it may be stated again here that, in the view of the present author, there is none of their characters that cannot be explained satisfactorily as part of the process of organisation of thrombi formed in stagnant vessels.

Thrombosis: In a few cases of the Budd-Chiari syndrome the venous occlusions are clearly extensions from caval thrombi and this need not be discussed further. An undue tendency to thrombosis is found in a number of conditions and in these Chiari's Disease and the Budd-Chiari syndrome occur with more than usual frequency.

Trauma may lead to thrombosis of deep-seated veins such as the portal vein (Falkenberg, 1928; Child, 1954). Shattock (1913) reported the reduction of the inferior vena cava to an empty tape-like band several years after an incident of severe

exertion and there are many other examples. Brink and Botha described the ostia as "completely sealed" in a case of Chiari's Disease following trauma 10 months previously. In other cases following trauma or severe exertion (Reynaud; Little and Montgomery; Cruickshank; Ekström and Hagberg, 1957) the ostia were not described in detail. In none of the present series was there any similar history but in young agricultural workers such as Cases 1, 4 and 8 such incidents might have been passed over.

The association is also clear in polycythaemia vera. Seven cases had been reported up to 1938 (Sohval). In some of these, such as Berk's case 2 (1932) the haematological diagnosis is in doubt, for great haemoconcentration may be caused by a rapid formation of ascites (Holmes and Melcher, 1949). In the present series, erythrocyte counts tended to be high or normal, possibly for this reason. In some recent cases of polycythaemia (Davis et al., 1949; Caroli and Soulier, 1956, and Fitzgerald et al.) symptomatic relief of the hepatic-venous occlusions has been achieved by treatment of the blood disease. Other cases have been reported by Mandelbaum et al. and by Caroli et al. (1958).

Thompson mentioned 4 cases in the literature in which the Budd-Chiari syndrome followed pregnancy. The occurrence of thromboses in the puerperium is well known. Case 10 did not become ill till 2 months after the birth of her child, so that the association might be questioned. Thran (1897) and Krass (1957) however reported cases in which Chiari's Disease developed 2 weeks after delivery of the patients. It is of interest that death was due in Cases 2 and 10 of the present

Idiopathic recurrent venous thrombosis.

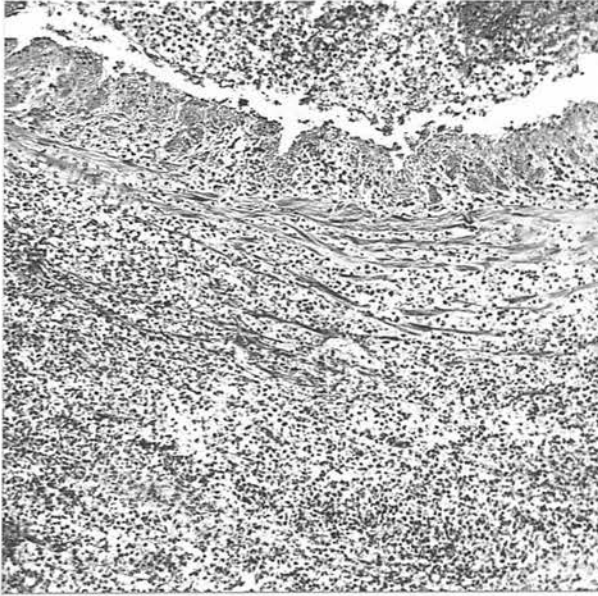


Fig., 140. Saphenous-vein biopsy from a man of 35 complaining of recurrent painful spots and pains in the legs, and rarely on the arms for two years. He developed a lower-caval thrombosis. Two-and-a-half years later he still complains of lesions on the legs but is otherwise well and works as a milk server.

H. & E. x 90.

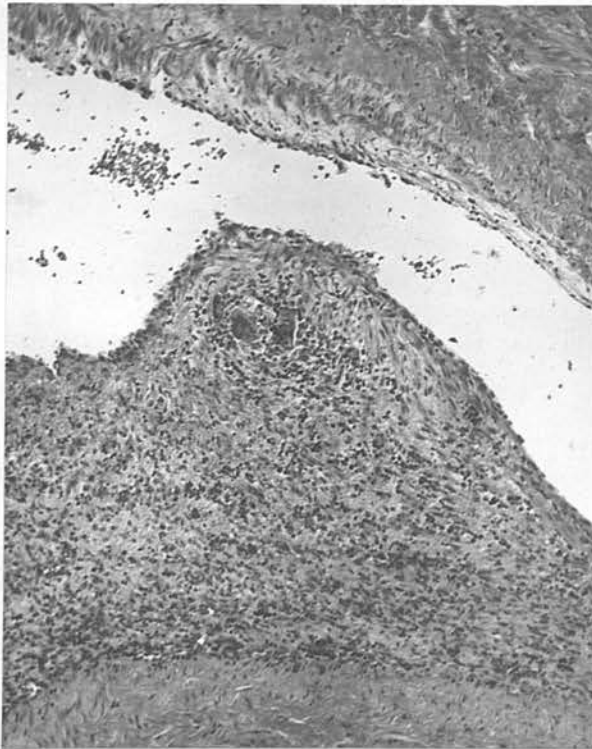


Fig., 141. Saphenous-vein biopsy from a man of 24 with fleeting superficial-venous thromboses in the legs for one year. In a venous-plethysmograph test (Prof. A. D. M. Greenfield) vascular responses to exercise showed no evidence of arterial disease.

H. & E. x 100.

series to dural-venous thrombosis, a lesion which occurs in the puerperium.

Apart from the conditions mentioned above and an association with visceral cancer, particularly carcinoma of the body and tail of pancreas (Thoenes, 1932; Sproul, 1938), the syndrome of disseminated venous thrombosis is a nebulous entity. Gerber and Mendlowitz (1949) linked together 6 cases including one of Chiari's Disease under the heading of "visceral thrombophlebitis migrans". Plough and Bevans ascribed their case to "recurrent idiopathic thrombophlebitis". Cruickshank published 3 cases of "venous thrombosis in internal organs associated with thrombosis of leg veins" in one of which the hepatic veins were involved. Kløvstad described a similar case and discussed the association of visceral thrombophlebitis migrans with thrombo-angitis obliterans. The evidence for such an association, which is also examined by Vinther-Paulsen (1952), is poor. Any resemblances between the lesions of Chiari's Disease and those of thromboangitis obliterans are superficial and there is no satisfactory record of their association in any patient. Barker (1936) found that idiopathic recurrent thrombophlebitis of the limbs, unlike recurrent venous thrombosis complicating cancer, was usually an inflammatory lesion. One recent case (Fig. 140) was of this type, while another was granulomatous (Fig. 141) like that described by O'Donnell and Kennedy (1955).

It has not generally been possible to relate the occurrence of thrombosis directly to simple elevation of the platelet count, and alterations in the adhesiveness of the platelets are probably more important. This subject has been reviewed by Wright (1942) and by Moolten et al. (1949) who draw attention to

increased agglutinability and adhesiveness of platelets as well as to an increase in their number after operations, after childbirth and in various other conditions. The increased level of platelet agglutination in these circumstances is probably due to an increased proportion of immature and unduly sticky platelets being put rapidly into circulation to compensate for those lost from the circulating blood in making good defects in the vascular bed. The best known example of a reactive thrombocythaemia, that following splenectomy, may be due to the loss of some regulating factor elaborated by the spleen. The most striking example of continued thrombosis in the present series is Case 10, in which it seems not unlikely that the splenectomy performed during the operation of lieno-renal anastomosis favoured the development of thrombosis subsequently.

A number of veins such as renal, adrenal and limb veins were thrombosed in Cases 2, 5, 6, 9 and 10. Pulmonary infarcts were present in Cases 9 and 10 and a large pulmonary embolus in Case 6. It was only in Case 9, however, that the liver or the ostia and adjacent portions of the cava were not the primary site of involvement. The high incidence of secondary thrombosis is probably not a specific effect of primary hepatic-venous occlusions since it is not mentioned in descriptions of Jamaican veno-occlusive disease and since it was not observed in rats in which severe venous congestion was produced experimentally, as reported in chapter VI. On the other hand there is some clinical evidence to suggest that one thrombus begets others at distant sites, possibly because of the release of fresh and unduly sticky platelets (Øllgaard, 1943) following consumption of mature platelets in the original clot. Nevertheless until



Fig. 142 Case 10. Massive ascites before operation.

a disseminated thrombosing condition is better defined as an entity, there seems little to be gained by describing under that title cases of Chiari's Disease or the Budd-Chiari syndrome.

In summary it may be said that in the great majority of cases there is no satisfactory evidence for the participation of inflammation in the pathogenesis. On the other hand thrombosis and the organisation of thrombi play a crucial part in the pathogenesis and the process is initiated by factors which are the same as in other instances of thrombosis.

SOME CLINICAL CONSIDERATIONS

Age and sex: Among the 9 proved and probable ostial cases in the present series, 6 were females and 3 were males. Both non-ostial cases were females. The average age of the males was 18, of the females 38. Thompson in a review of 86 published cases found the average age overall to be 33. Taking the present series together with 25 fatal cases not included by Thompson there are 17 males with an average age of 29, and 17 females with an average age of 35. The youngest patient was that of König, the oldest was that of Kløvstad, aged 81 at the time of his report.

Onset of symptoms: The rapid onset and progression of abdominal swelling in this group of adolescents and young adults forms a striking clinical presentation, but the onset does not always coincide with the formation of the occlusions. Massive ascites was the dominant feature (Fig. 142) of the overt illness in nearly all the cases. The extent, rapid progression and

persistence of the ascites contrasted with increasing emaciation as the disease ran its course. In most cases previous complaints were indefinite or slight. The onset may be very acute and oliguria may be present when ascites is forming rapidly (Holmes and Melcher). If pain is severe it may simulate an acute abdominal emergency (Dickinson, 1941).

Swelling (Case 9) or other symptoms in the legs (Kibel and Marsden; Rossall and Caldwell) may indicate a caval lesion, but crural oedema was found in cases without occlusions of the cava or its lower tributaries. Haematemesis was the presenting symptom in Cases 4 and 8. The latter patient, like those of Armstrong and Carnes and Jonas and Lawrence survived for a long period thereafter.

It is worth emphasising that the clinical onset need not follow closely on the actual occlusion of the ostia and there may be a latent period of considerable length. Experiments on rats reported in chapter VI show that these animals grow and remain healthy over long periods during which the hepatic venous outflow is grossly restricted.

Clinical evidence of liver damage: The liver was found to be enlarged in all cases. It was hard, smooth and rarely tender. As in published cases, jaundice was mild or absent in the present series. Liver-function tests were performed on only a few of the cases and the following account is prepared mainly from the results recorded in 34 cases in the literature.

The syndrome developed in the presence of normal plasma proteins in Case 5 and in 15 out of 27 cases in the literature; this includes some cases in which lesions had obviously been

present for some time. In the other 12 and in Case 10 the total was slightly reduced in most. The greatest recorded depression was in Case 8 (3.75 gm./100 ml.) after repeated paracenteses. Serial estimations over several years in the cases of Kløvstad and of Rossall and Caldwell show that the albumin levels gradually fall and the globulin rises with eventual reversal of the ratio. The ratio was reversed in Cases 7, 8 and 11.

Flocculations have generally given negative results and markedly positive results have not been recorded.

Alkaline phosphatase has frequently been reported to be between 20 and 30 K.A. units, but normal figures may be obtained as in Case 5.

Biliary tests. Serum bilirubin was normal or slightly raised in several cases, in keeping with the absence of clinical jaundice or the existence of only slight jaundice and the rarity of bile in the urine. Urobilinogenuria has been reported in several cases and it was transient in Cases 5 and 10. It is probably most useful in the early stages of the disease.

Depression of serum cholesterol with a relative reduction in the esterified fraction was mentioned by Sohval. Estimations in several subsequent cases confirm the value of this test but it is not an invariable finding.

Bromsulphthalein retention is frequently quoted to be of the greatest value in the Budd-Chiari syndrome. Some very high figures have been obtained e.g. 92.5% (Caroli et al.) and 80% (Armstrong and Carnes) at 45 minutes. In some cases much lower figures are given, including a normal reading (Hirsh and Manchester).

It is not surprising that these findings resemble those given by Popper and Schaffner in their review of liver-function tests in the chronic venous congestion of heart disease. In the veno-occlusive disease of Jamaica, the findings of Stuart and Bras (1957) are not dissimilar. The authors found that serum cholinesterase taken together with plasma-albumin levels gave a useful indication of hepato-cellular damage in this condition. The value of this indication in the forms of the Budd-Chiari syndrome seen in this country is untested.

Diagnosis: Tuberculosis and carcinomatosis of the peritoneum may be considered in the diagnosis but can usually be eliminated by suitable investigations. If portal hypertension is marked, occult blood may be present in the stools, as in Case 5. Superficial epigastric and other abdominal veins were not notably enlarged in the cases of the present series. When they are present in the Budd-Chiari syndrome they may result either from a concomitant occlusion of the vena cava, in which case the flow is upwards, or they may be due to porta-systemic anastomoses opening up along the falciform ligament. In the latter case the flow is often downwards and, further, the sugar content of the blood in such veins is higher than that of blood taken simultaneously from a peripheral vein (Sherlock and Walshe, 1946). When caval occlusions are present the development of collaterals (Pleasants, 1911) may be good enough to compensate almost entirely for the block. In Case 1 the cava was obliterated at the diaphragm for an unknown period without giving rise to symptoms; and albuminuria may be absent in cases with caval lesions (Thompson). Albuminuria was present in Case 9 in which the

renal veins were occluded and after this occurred in Case 1.

Among the special techniques of investigation, percutaneous splenic portal venography may be useful in excluding disease of the portal vein and in other respects, but a death has been reported (Caroli et al.) following its employment in this condition. Radiography after caval catheterisation displayed caval lesions in several cases (Kløvstad; Brink and Botha; Fitzgerald et al.) but a danger exists of dislodging clots (Caroli and Soulier). Needle biopsy of the liver has been practiced without ill effects (Davis et al.; Bronte-Stewart and Goetz). Open liver biopsy or inspection has been the method by which the diagnosis has been made during life in most of the cases up to date (Rigdon; Murray and Kimmel; Beattie and Hildebrand; Norris). Laparotomy enabled the diagnosis to be made in Cases 5 and 10 of the present series. While operation is undoubtedly the most satisfactory method of diagnosis, it places a considerable added strain on the liver function, and ascites may endanger healing of the incision. It is obviously advantageous to investigate cases fully beforehand along the lines indicated in this and in previous paragraphs so that any opportunity for remedial surgery may be taken at the same time.

Finally it is worthwhile restating that the syndrome may result from some underlying inflammatory, neoplastic or haematological disease. The extensive list of causes given by Palmer includes many rare and speculative ones and need not be reproduced here.

Course: In acute cases in which the clinical histories are of only a few days' illness (Burkhardt; Dickinson; Holmes and

Melcher; Case 4) chronic lesions of considerable duration have been found at autopsy. The latent period in 4 post-traumatic cases (Brink and Botha; Cruickshank; Little and Montgomery; Ekström and Hagberg) varied from 6 to 2 months. From the pathological point of view the distinction between acute and chronic forms, which was introduced by Thompson and Turnbull is not a sharp one, particularly if a rigid exclusion is made of the cases in which the hepatic-venous occlusions are terminal manifestations of some other disease.

Jonas and Lawrence stated, on the grounds of what was apparently a brief review of the literature, that chronic illness, in distinction to an acute form of the Budd-Chiari syndrome had most often been reported in cases with caval lesions. This is sometimes true. The cases of Bennett, Bronte-Stewart and Goetz and of Rossall and Caldwell with caval lesions survived 13, 9 and 4 years respectively after the diagnosis of liver disease or the appearance of ascites. On the other hand there were no significant lesions of the cava in the cases of Hutchison and Simpson, Baehr and Klemperer and of Armstrong and Carnes in which the equivalent periods were respectively 23, 13 and 8 years. There are many other examples. In some cases, such as Case 9, caval lesions may give rise to warning symptoms, but an extensive review of the literature contradicts the view expressed by Jonas and Lawrence.

It is probable that the clinical attack is often brought on by the occlusion of hepatic veins at a deeper level than the original occlusions (e.g. Case 3). Similarly the remissions of ascites that may occur (Rigdon; Plough and Bevans; Caputi and Warthin; Kløvstad) may be due to the establishment or re-estab-

TABLE VI.

Immediate Causes of Death in the Budd-Chiari Syndrome in 11 of the present series of cases and in 30 recently published cases.

Cause	Present series	Published cases.
Hepatic Failure alone	1	7
Septic Complications	4	7
Pulmonary emboli	2	3
Cerebral-venous thrombosis	2	0
Portal-vein thrombosis	0	3
Post-operative	0	4
Haematemesis	1	3
Uraemia	1	1
Heart failure	0	1
Intracerebral tumour	0	1
Total	11.	30.

ishment of collaterals. Terminal liver failure may be brought about by the development of fresh thrombi in small hepatic veins (e.g. Case 5). Hepatic failure alone was probably responsible for death in Case 7. Since liver failure has been stated in some reviews (e.g. Lancet, 1955) to be the chief cause of death, it is worth pointing out that the immediate cause of death is usually something else (Table VI). Portal-venous thrombosis is sometimes the cause of death (e.g. Chiari; Rössle; Holmes and Melcher), but some patients survive the occurrence for some weeks (Casper et al.; Case 10). Portal-venous thrombosis may precipitate a fatal haematemesis (Armstrong and Carnes) as in other types of portal hypertension (Gibson and Richards). Haematemesis is a rare cause of death but it was the fatal incident also in Case 4 and in the case of Kucsko and Portele.

Treatment: Medical measures, such as rest, restriction of fluids and salt and the use of diuretics have achieved temporary relief of ascites in some cases (Armstrong and Carnes; Plough and Bevans; Little and Montgomery). Paracentesis should be done as infrequently as possible. The term endophlebitis might suggest the use of cortisone to reduce exuberent granulation, but study of the pathogenesis has shown that an allergic-hyperergic reaction is probably not involved. Thrombosis on the other hand plays an important rôle at several stages in the condition and this contraindicates the use of cortisone. Anticoagulant drugs may be used with more reason, possibly over a long period. Reports of the use of coumarol drugs (Caputi and Warthin; Kløvstad; Caroli et al.) are encouraging but heparin

would appear preferable during an acute phase in view of the liver damage. Davis et al. successfully persisted in the use of dicoumarol despite a low prothrombin. At the same time any underlying condition such as polycythaemia must be treated promptly; some successful cases have been mentioned above, in the discussion of the aetiology.

Thompson and Jonas and Lawrence condemn surgical therapy in Chiari's Disease and in the Budd-Chiari syndrome but operations will usually offer a chance of better stabilisation than medical measures. Madden et al. favour the promotion of adhesions in the intractable ascites of cirrhosis, but the collaterals naturally formed in Case 11 effectively drained only superficial portions of the liver. One may also infer from the present cases that adequate connections with other parts of the liver would not form after such an operation. The establishment of a porta-systemic shunt might appear illogical in the present condition since such shunts have been shown to be of relatively little value in the ascites of cirrhosis and since the main indication for them in cirrhosis - haemorrhage from oesophageal varices - is rarely encountered in Chiari's Disease. In the present condition however the plasma-protein level is often maintained and the chief cause of the ascites is the delivery of more blood to the liver than can be drained from it. In Case 10 the ascites cleared after the lieno-renal shunt was performed and was absent at death. Better results have been reported by Kalk (1955) and Fitzgerald et al. The shunt thrombosed in Case 10 and in the case of Brink and Botha and this danger cannot be neglected in a condition in which there may be an underlying tendency to thrombosis. This tendency

may be favoured by splenectomy and for this and other reasons, a porta-caval anastomosis is probably preferable to a spleno-renal anastomosis. Blakemore (1948) reported a successful porta-caval anastomosis in the Budd-Chiari syndrome. Hepatic-artery ligation was practiced with limited success by Norris; the liver damage progressed. Theron and Allan have investigated more extensive arterial ligations in the treatment of ascites and Marson (1954) has tried adrenalectomy. Both operations are in the experimental stage.

Finally it is not beyond hope that some day it may be possible to perforate the contracted ostia in Chiari's Disease surgically. This must however await further refinements of diagnosis and surgical technique.

SUMMARY

1. Clinical and pathological data on 12 new cases of the Budd-Chiari Syndrome are given. The data are discussed in relation to published cases. Cases due directly or indirectly to carcinoma have been excluded. The ostia were involved in 5 of the cases and these are examples of Chiari's Disease or primary occlusion of the hepatic venous ostia.
2. Chiari's Disease is characterised by chronic localised obstructions at the ostia in which the vessel wall is contracted. The large veins distal to the obstructions tend to remain patent at first. This localisation may be explained on the basis of anatomical features permitting contraction of the vessels at the ostia and not within the liver. Occlusions at other levels in the hepatic-venous tree, if sufficiently extensive, may cause the same symptoms. Cases of the latter type should be classified as examples of the Budd-Chiari Syndrome.
3. The evidence in favour of an inflammatory aetiology particularly an allergic-hyperergic type of inflammation, as suggested by German authors, is discussed and found to be unsatisfactory.
4. The vascular lesions in the hepatic veins are such as might be expected to develop in veins held patent by their attachment to parenchyma and in which mural thrombosis occurs in varying conditions of flow and stagnation. The ostial lesions can also be explained best as manifestations of thrombosis. The nature of other morbid conditions sometimes associated with the Budd-Chiari Syndrome also favours the view that in this country the usual pathogenesis is thrombosis.

5. Most of the caval lesions which are sometimes found in Chiari's Disease are probably secondary to or concomitant with the ostial lesions and not the cause of the latter.
6. The absence of venous channels collateral to the hepatic veins accounts for the unusually severe effects of occlusions of this system. The varying localisations of the lesions within the liver can also be related to anatomical findings.
7. The changes in the hepatic parenchyma are similar to those in chronic venous congestion in heart failure but are more severe. There is extensive sclerosis of the central parts of the lobules. Centrilobular sclerosis tends to proceed to cirrhosis by the formation of fibrous septa linking central venules to each other and to portal tracts.
8. The degree to which the signs of portal hypertension are developed varies. It can be related to the degree of distortion of the liver architecture i.e. the degree of cirrhosis.
9. A latent period exists in many cases in which hepatic-venous occlusions are tolerated without the development of symptoms. Overt illness is probably often brought on by a break-down of previous compensatory mechanisms, for instance by the occurrence of fresh thromboses distal to the main occlusions.
10. Fibrous tags were found on the surface of the liver and of the hepato-duodenal ligament in several cases. This can be related to the chief symptom of the condition - massive ascites. The chief cause of the ascites is transudation from the surface of the liver. Plasma proteins are often normal at the outset of the disease and the occurrence of portal hypertension and its severity are variable.
11. Biochemical tests including plasma-protein determinations

show a remarkable maintenance of liver function in the initial stages. A review of these tests in the Budd-Chiari syndrome is given. The liver tends to fail gradually and this may bring about death by itself, but complications, particularly septic complications, are more commonly the immediate cause of death.

12. The clinical diagnosis, course and treatment are briefly reviewed.

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CHAPTER VI

EXPERIMENTS ON THE HEPATIC VEINS OF ANIMALS

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Fig., 143. *Senecio jacobea*, Lin. - the common ragwort.
The bright yellow colour of the flower is poorly reproduced here.

EXPERIMENTS ON THE HEPATIC VEINS
OF ANIMALS

PYRROLIZIDINE ALKALOIDS

Pyrrolizidine alkaloids are present in plants of the genus *senecio* including the common ragwort (*S. jacobea*; Lin.; Fig.143) and groundsel of this country. They cause liver lesions in grazing animals which ingest them (Forsyth, 1954). The diseases produced in animals in various parts of the world by plants containing pyrrolizidine alkaloids are mentioned by Smith and Jones (1957). Species of *senecio* are important in South Africa. Sapeika (1952) lists 29 different pyrrolizidine alkaloids derived from them and has reviewed their toxic action on experimental animals. Selzer and Parker (1951) reported 12 cases of human poisoning with *senecio* in which the clinical features were those of Chiari's Disease. Bull et al. (1958) have studied the acute toxic effects of heliotrine and lasiocarpine present in *heliotropum europeum* in Australia where it causes a chronic liver disease of sheep. Bras et al. (1957) mention the leguminous plant *crotalaria fulva* in Jamaica which contains the alkaloid monocrotaline and illustrate the fibrous narrowings of hepatic veins in domestic animals which, together with liver-cell damage, are a feature of the liver disease caused in man and in larger animals by pyrrolizidine alkaloids. Alkaloids of this group may be responsible for the veno-occlusive disease of Jamaica (see chapter IV).

The toxic action of the alkaloids is in general similar among the larger animals. Ascites is usually present. Davidson (1935) using retrorsine found a few fibrous narrowings of hepatic veins in rats and noted large cells which he took to

be endothelial, lining the hepatic veins in large numbers (Fig. 144).

Ascites was frequently present in his animals. Davidson concluded that the primary action of the toxin was vascular. In view of subsequent work reviewed by Schoental and Magee (1957), the damage to the hepatic cells themselves now appears more important, but recently, in experiments on rats with monocrotaline, Hill et al. (1958) have described fibrous narrowings of the hepatic veins similar to those in Jamaican veno-occlusive disease. It is possible that a difference in action in this respect may exist between different alkaloids. Relatively little work has been done on the pyrrolizidine alkaloids derived from British plants. Cook et al. (1950) and Schoental et al. (1954) reported tumour-like lesions in rats ingesting alkaloids from *S. jacobea* over long periods, but it was thought worthwhile to carry out a few experiments of shorter duration to see if alkaloids from the common British ragwort regularly produced a stenosis of the hepatic veins in rats.

Several rabbits have also been used, since there is relatively more muscle in the hepatic veins of this species than in the thin-walled hepatic veins of the rat. It seemed possible that an anatomical variation such as this might explain the frequency of fibrous occlusions of the hepatic veins in pyrrolizidine poisoning in larger animals in comparison with the scarcity of such lesions in chronic experiments on the rat. The toxicity of pyrrolizidine alkaloids for rabbits has been little studied. A disadvantage in their use lies in the larger doses necessary, but sufficient crystalline alkaloid was available to carry out experiments on 6 rabbits.

Preparation of the alkaloid: *Senecio jacobea* was collected from various parts of the City of Belfast and of County Down, chiefly during the month of July. The whole of the plant except the roots was taken. It was dried in a hot-air oven at 70°C. and milled to a powder. I am grateful to Professor Baskett and other members of the Faculty of Agriculture, Queen's University, Belfast for arranging most of the collection and the drying and milling. The powder was extracted by percolation with hot ethyl alcohol and the extract concentrated by distillation and purified by the method of Bradbury and Culvenor (1954). Dr. Michael Grundon of the Department of Chemistry, Queen's University, Belfast kindly undertook much of this work. He reported that the crystalline alkaloid in 2 separate batches had a melting point of 203-206°C. with decomposition, and concluded from this and other preliminary studies that it was probably a mixture of jacobine and seneciphylline. One Kgm. of dried plant yielded approximately 170 mgm. of crystalline alkaloid. A similar quantity of non-crystalline residue was also obtained.

A 6.6% solution for injection was prepared as follows:-
1 gm. of crystalline alkaloid was partly dissolved in 6 ml. of N. solution of HCl, and solution completed by the addition of 5 ml. of propylene glycol and 4 ml. of a 1% aqueous solution of chlorocresol.

Experiments on rats: 48 well nourished albino Wistar rats were given individually measured intraperitoneal injections of the alkaloidal solution. In 6 cases the livers were too autolysed, when the animals were picked up dead, for satisfactory examination, and only 42 animals will be considered.

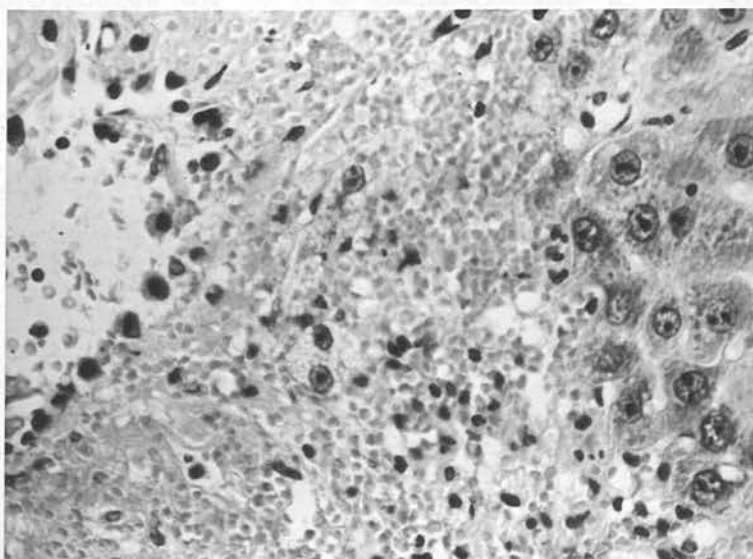


Fig., 144. Sen9. Female rat given single intraperitoneal dose of senecio alkaloids, 75 mgm./Kgm. The liver was dark and enlarged (5.8% of total body weight) and ascites (6 ml.) and pleural effusions were present at death 7 days after injection. An area of necrosis is seen round a small hepatic vein, left. The lumen of the vein is lined by large cells, probably macrophages. H. & E. x 300.

A. Acute experiment - To measure the toxicity of the solution, 14 female rats were given doses of 75-300 mgm./Kgm. 11 died within 2 days. The livers showed extensive foci of centrilobular and other non-portal haemorrhagic necrosis (cf. Fig. 144) with occasional fibrinoid droplets inside and outside liver cells. There was marked oedematous fibrillation of the walls of central venules and of intercalated veins simulating necrosis and a little swelling of the walls of hepatic veins. Collections of large cells, probably macrophages, lay within the lumina of the venules and of the hepatic veins (cf. Fig. 144). The endothelial cells of the veins were slightly swollen. Thrombosis was not seen. Ascites of a few ml. was present.

Three animals out of 7 given the lowest dose survived for 1 week. The histological features of their livers were similar to those of animals dying earlier (Fig. 144). Ascites was more marked.

B. Chronic experiment - To determine whether the venous changes of the acute phase persisted or healed, 28 rats including males and females were given intraperitoneal injections of 25 mgm./Kgm. of alkaloid using the schedule of Davidson (1935), i.e. injections on the 1st., 4th., 7th. and 14th. days. The results were as follows.

At all stages the males showed more liver damage than the females. Most but not all of the animals became ill, losing up to 25% of body weight. Illness was often due to intercurrent pulmonary infection in the females. Some rats became restless and mildly excited terminally; coma was not observed. In the later stages, the liver was small, brown and granular; a little ascites was occasionally present; the urine was often orange-

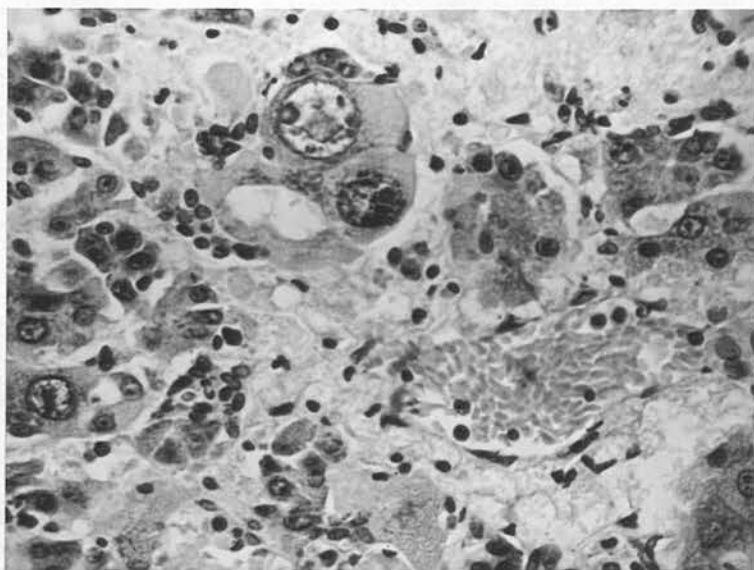


Fig., 145. Sen34. Male rat given 4 intraperitoneal doses of senecio alkaloids, each 25 mgm/Kgm. The animal died 8 weeks after the first injection. In this centrilobular region there has been a considerable loss of liver cells. Persisting liver cells show bizarre changes including vacuolation of the cytoplasm and the formation of globules within giant nuclei. There are no lesions of the central venule. H. & E. x 300.

coloured in male rats when they became ill. Microscopical findings in the livers of animals dead or killed at the times indicated were as follows:-

4 rats at 3 days; occasional necroses in one, with resorption of necrotic centrilobular cells in another. No venous thromboses. A few large macrophage cells in the lumina of the veins in cases with necrosis; a little oedema of the walls of the hepatic veins. No vascular changes in the livers without necrosis.

3 rats at 6 days; regenerative activity of liver cells in the immediate neighbourhood of central venules; no vascular changes.

4 rats at 13 days; irregularity of liver cells; slight fibrillary thickening of vein walls; no necrosis.

3 rats at 28 days; bizarre and irregular cells with grossly fibrosed hepatic-vein walls. In one male rat there was fibrous closure of occasional central venules.

5 rats at 34 days; similar to previous group.

5 rats at 42 days; similar to previous group.

3 rats at 60 days; very marked bizarre changes in liver cells with great reduction in the numbers of liver cells (Fig. 145) and increased prominence of Kupffer cells. Early fibrosis and nodular regeneration. Fibrosis of walls of intercalated and hepatic veins.

3 rats at 77-105 days; similar to previous group.

Lesions in other organs were similar to those reported by Schoental and Magee (1957) with lasiocarpine.

Comment on rat experiments: The crystalline alkaloids from *S. jacobea* had a melting point of 203-206°C. which differs from that reported by Schoental et al. (1954) in their crystalline product from this plant. Since both crystals were probably mixtures of alkaloids, the melting point variation may indicate merely varying proportions of alkaloids in the plants used for each batch and not a basic difference. Schoental et al. considered their product was possibly jacozone. The specimen used in the present experiments is thought to be a mixture of jacobine (m.p. 226°) and seneciphylline (m.p. 217°). In the acute experiments the level of toxicity found was similar to but higher than those given by Sapeika for either of these alkaloids - median lethal dose of jacobine 77 and seneciphylline 88 mgm./Kgm.

The marked susceptibility of the male animals over the females has been observed by other workers (Schoental and Magee, Bull et al.,) using other pyrrolizidine alkaloids and it is apparently due to a greater direct effect on the liver of the male. Schoental and Magee in a fully documented study have recently described the main features of the liver changes and the illness following single doses of lasiocarpine in the rat including the effects of diet and the formation of bizarre cells (Fig. 145) which is so striking and interesting a feature of the later liver lesions. Since the results in the present experiments were similar, it is necessary only to point out two minor differences. Restlessness was observed in the present series in contrast to coma in the rats of the other workers. This restlessness may be compared to that found in horses in Texas with pyrrolizidine poisoning - the condition being known as

"walk-about disease" (Smith and Jones). Schoental and Magee reported liver cells surviving round some of the central venules in their rats. In the present series the necroses were located at similar sites to those resulting from experimental obstruction of the thoracic vena cava and may be said to correspond as closely to human centrilobular necrosis as the micro-anatomy of the rat liver permits.

As regards the venous lesions, changes similar to those of Jamaican veno-occlusive disease were not produced and marked stenosis was rare. In the initial stages there was considerable oedema of the walls of the hepatic veins and of the small veins. A similar oedema and often an apparent necrosis of the walls of the small veins was reported in human senecio poisoning by Selzer and Parker but the vascular lesion is very like that found in Chiari's Disease (Fig. 108) and is most probably secondary to damage of the underlying liver parenchyma. In the later stages of the experiments a variable degree of fibrosis of the vein walls was found, without however much reduction in the vascular lumen, and fibrosis was considerably less than that following experimental obstruction of the cava above the liver as reported below.

In animals killed after 1 or 2 small doses of alkaloid, in which there was slight hepatocellular damage, vascular changes were not present and there is no evidence for a preferential involvement of the veins. Some doubt exists as to the nature of the large cells found lining the hepatic and small veins in the acute stages (Fig. 144). They were less prominent in the present series than in some published experiments with other pyrrolizidine alkaloids and were often mixed with polymorphs.

They could be distinguished also from swollen endothelial cells which were recognized from time to time in the small veins. The present observations support the view of Bull et al. that the cells are macrophages. It is concluded from this work that the mixture of jacobine and seneciophylline used does not have a primary vascular toxic action. This conclusion is in keeping with the findings of most other workers using pyrrolizidine alkaloids recently. On the other hand in their preliminary communication on monocrotaline poisoning, Hill et al. reported that the veins were narrowed by fibrous tissue in their rats after doses of 92 mgm./Kgm. and noted that the size of the dose did not appear to have any effect in this respect. In its action on the veins, monocrotaline would appear to be exceptional among the pyrrolizidine alkaloids. The thin character of the central venules of the rat means that they are almost as closely associated with the liver cells as are the sinusoids and any division of toxic action into vascular and hepatocellular components at this level may well depend more on the histological characters of the livers of the animals exposed than on individual differences between alkaloids. It is possible however that a greater degree of vascular involvement could be achieved by variation of the dose of jacobine and seneciophylline and of the nutritional state of the animals, and these possibilities have not been explored. Stoner and Magee (1957) note that after an intramuscular dose of lasiocarpine the liver temperature of the rat falls long before the hepatic blood flow alters and it seems likely that the primary action of pyrrolizidine alkaloids is on hepatic cells. In the experiments on rats with repeated doses of urethane reported in Appendix A, hepatic-

venous lesions were not found in any of the animals. In comparison with urethane the action of the pyrrolizidine alkaloids on the hepatic-venous system of the rat is clearly marked, but it may be concluded from the present experiments that the injection of alkaloids from the common British ragwort into rats in the manner used does not produce a lesion suitable for study as a primary venous phenomenon.

Experiments on rabbits: Six well nourished rabbits were given intraperitoneal injections of the crystalline alkaloids of *S. jacobea* according to the dosages shown in Table VII. Two were given divided doses; 2 tolerated doses of 80 mgm./Kgm.; 2, given larger doses, died within 36 hours. Necroses were found in one animal 35 hours after a massive dose and in another at laparotomy and liver biopsy 15 days after the last of 4 divided doses. Venous lesions of the acute type found in rats were not present. Ascites of moderate quantity was found at laparotomy in 2 animals, 4 and 6 days after single doses of 80 mgm./Kgm. and not in other animals. It was associated with a moderate fall in serum albumin from a normal of 4 (average of 4 normal rabbits) to 2.5 gm./100 ml. In the rabbits on which laparotomies were done at 4 weeks, when ascites was absent, the serum-albumin figures were 3.4 and 3.1 gm.

In the 4 animals surviving 12 weeks or more, the liver was reduced in size, yellow-brown and granular with occasional paler nodules about 1 mm. in diameter. Histological sections showed moderate irregularity of cellular and nuclear pattern similar to that seen in rats but not so marked. Hepatic veins at this stage showed slight fibrous thickening. All animals lost

TABLE VII.
 Intraperitoneal injections of crystalline pyrrolizidine alkaloid from Senecio jacobea into rabbits.

Rabbit Sex.	RS1. m.	RS2. f.	RS3. f.	RS4. f.	RS5. m.	RS6. f.	RS7. f.
No. of doses - four day intervals;	3.	4.	1.	1.	1.	1.	0.
amount of each dose in mgm/Kgm.	50.	20.	98.	156.	80.	80.	control.
Liver biopsy	normal.	necrosis.	cell irregularity; ascites.	cell irregularity; ascites.	...
time after first injection.	4 wks.	4 wks.	six days.	four days.	...
Fate	killed, 25wks.	died, 13 wks.	died, 35 hrs.	died, 2 hrs.	died, 12 wks.	killed, 12 wks.	killed 20 wks.
Gross appearance of liver.	small, brown & granular.	small, brown & granular	necroses.	congested.	small, brown & granular.	small, brown & granular.	normal.

weight within 6 weeks of the first injection, the losses being eventually up to 1/3. Terminally 2 rabbits became restless and drank large amounts of water.

It is concluded from this limited study, that rabbits are susceptible to poisoning with alkaloids of ragwort in doses similar to or slightly less than those affecting rats. The effects on the liver are severe and similar to those in female rats but less marked than those in male rats. Venous lesions are slight.

Comment on human toxicity: The experiments described above do not give any precise data regarding the minimum toxic dose for a well nourished rat or rabbit, but it would appear to be not less than 25-50 mgm/Kgm. If we suppose that the human infant is susceptible to a similar degree it will be seen that for an infant of about one year weighing 10 Kgm. the toxic dose lies between 0.25 and 0.5 gm. By the methods of extraction used, which are doubtless superior to those involved in the preparation of bush teas, this quantity could not be obtained from less than 0.7 - 1.5 Kgm. of dried senecio, or considerably greater quantities of the fresh plant. Higher yields of alkaloid have been obtained from ragwort by Barger and Blackie (1937) and it is possible that the yield from such plants as *crotalaria fulva* in Jamaica is still higher. It is true that large amounts of bush teas are said to be consumed on the island and the grounds may be ingested as well as the liquor, thus providing a higher dose, but this simple calculation should warn against accepting pyrrolizidine poisoning too readily as the sole cause of Jamaican veno-occlusive disease. Additional factors such as

malnutrition are probably essential for its production and cannot be neglected.

MECHANICAL OBSTRUCTION OF INDIVIDUAL HEPATIC VEINS IN THE RAT

It is possible in the rat to treat some of the hepatic veins directly in various ways because the left ostium and more especially its radicle from the left lateral lobe (Figs. 39 and 40) lie immediately under the peritoneum. Thrombosis is notoriously difficult to produce in the veins of the rat without temporarily occluding the blood flow, and occlusion of the accessible hepatic veins tends to cause serious shock (cf. Fig. 146), or the fragile liver may be torn. Local application of radon seeds or silver nitrate, cauterisation and intravascular injections of "calgitex" with or without concurrent courses of salmine sulphate (a neutraliser of heparin) were all unsuccessful or unreliable (rats R1 - 24 and RGS 1 - 23). The only result worth recording from these experiments was the extensive development of cholangio-fibrosis (cf. Fig. 175) found in the left lateral lobe of one animal killed several months after cauterisation of the related hepatic vein. The lobe was reduced to a quarter of its natural size; liver cells survived throughout, interspersed with many foci of cholangio-fibrosis; a cirrhotic architecture was not present. Gupta (1956) reported cholangio-fibrosis in chronic thioacetamide poisoning in rats and reviewed the literature on this lesion, which though not specific in origin has a high malignant potential in the rat. It was decided to follow up this observation by a study of the long-term effects of partial closure of the hepatic vein from the left lobe. Since cauterisation is uncertain in its effects, partial ligation was used.

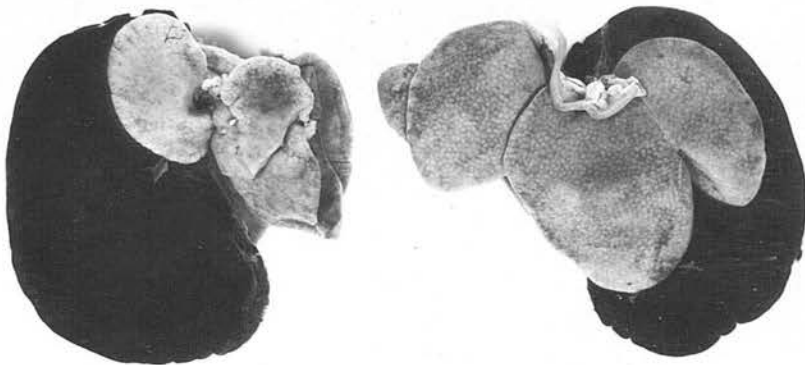


Fig., 146. Lower (left) and upper (right) surfaces of livers of rats RGS 52 & 53 dying one hour after ligation of the vein from the left lateral lobe. The lobe is deeply congested and grossly swollen, (cf. normal, Fig., 37). Nat. size.

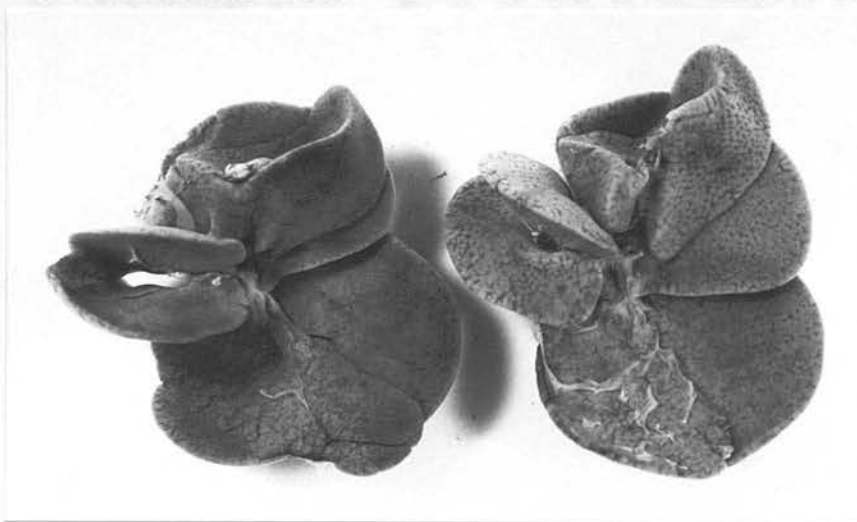


Fig., 147. Lower surfaces of livers of rats RGS 55 & 56, killed 59 weeks after ligation of the vein from the left lateral lobe. The lobe is atrophied and about a quarter normal size. It is adherent to the lower surface of the median lobe and has a granular surface. The other lobes are hypertrophied (cf. Fig., 146). Nat. size.

Experimental procedure: At abdominal operation on 38 young female rats of about 100 gm., a fine nylon or other suture on a small round-bodied eyeless needle was passed through the pedicle of the left lateral lobe and tied on the posterolateral aspect of the pedicle in such a way as to constrict the hepatic vein and leave the portal vein and bile duct intact medially. The rapid development of congestion in the lobe was taken to indicate a satisfactory result, but the degree of constriction by the ligature was difficult to control. The congestion soon became intense (Fig. 146) and 9 animals died in the immediate post-operative period from shock or haemorrhage. The remaining 29 rats were killed at varying times from 3-64 weeks after the operation. 12 additional animals were set aside and killed at the end of the period as controls.

Results: The livers and other major organs were normal in the 12 control animals. Examination of the site of ligature at death in the experimental rats showed complete closure at first with a varying degree of persistent narrowing. The reduction in diameter was always greater than half.

In animals dying in the first few days after operation, extensive necrosis was found, with preservation of liver cells only as narrow collars round the portal tracts, but in the livers of the experimental period (3-64 weeks), necrosis was not seen, the findings being those of restoration of liver tissue against a background of macrophage activity and small amounts of fibrosis. The left lateral lobe was reduced within a few weeks to a triangular yellow-brown plate-like structure measuring about 2 mm. thick and 1 cm. along the sides. It was adherent to the

under surface of the median lobe and often to the omentum, and a few venous collaterals of the size of intercalated veins penetrated the thin capsule at these sites. During this time there was hyperplasia of the unaffected lobes and their edges became rounded. The livers were weighed in 13 animals and the weights were approximately normal (3-4.5% of total body weight; chapter II).

The microscopical changes within the atrophied lobes could be divided into two types, one type with extensive restoration of the liver architecture and the other with survival of only a few irregular elements. By the 9th week the type was determined. In some livers of that period, the atrophied lobe consisted of parenchyma with a normal arrangement but with an increase in fibrous tissue within the portal tracts and many pigment-containing macrophages in the tracts. An advanced stage of this first type of change was seen in some animals killed at periods of 26-64 weeks in which the lobe had enlarged to about a quarter of its normal size and there were very few irregularities of structure except a superficial granularity (Fig. 147). In a few cases the lobe regenerated smoothly and up to about half of its original size. In the second type, in rats killed in the earlier stages, liver cells survived singly or in small groups amid large numbers of pigment-containing macrophages and structures of the portal tracts. In comparable animals killed later, hepatic parenchyma was completely absent from the minute structure persisting or remained only in small islands, and there was little fibrosis.

The degree of parenchymal-cell hyperplasia as judged by nuclear & cytoplasmic variation was similar in the atrophied

lobe to that in the rest of the liver at all stages. There was only a single instance of nodular regeneration, in RGS54 killed at 45 weeks in which one focus was found. Areas of cholangio-fibrosis were notably scanty and small. Only occasional hepatic veins in the affected portions of some of the livers showed fibrosis of their walls. Venous congestion was not present during the experimental period. The yellow-brown pigment, which stained many of the atrophied lobes deeply, was contained in macrophages. Pigmented macrophages made up much of the bulk of the more damaged lobes but they were present in the portal tracts in all cases. Microscopically, two kinds of pigment could be distinguished - granules of iron pigment giving Perl's reaction and a dust-like lipofuscin of ceroid type staining brightly with basic fuchsin and P.A.S.

Comment: A number of factors seemingly determined whether the microscopical structure of the atrophied lobe returned virtually to normal or whether atrophy continued. These factors included the tightness of the initial ligature, the degree to which the initial obstruction was overcome and the effectiveness of the development of collateral venous drainage through the median lobe and through the omentum. Because the lobes of the rat liver are thin, superficial adhesions provide more effective collaterals than they do in man. Since none of the factors determining the fate of the atrophied lobe can be controlled, the experimental procedure is an unsatisfactory one.

The changes produced were not progressive and the rarity of sclerosis of the hepatic veins suggested that the venous pressure was not elevated regularly in them and that the conditions were

not like those in chronic venous congestion. The left lateral lobes were not congested in the later stages of the experiment and a venous drainage adequate for the reduced amount of liver tissue was apparently present. Liver cells survived the initial congestion, and the damaged lobe was thus not comparable to a transplant of liver tissue, for instance a transplant to the anterior chamber of the eye, in which only biliary epithelium survives (Böck and Popper, 1937). The scarcity of foci of cholangio-fibrosis in this series was unexpected in view of the experiment referred to above and this emphasises the uncontrollable character of the process.

The degree of restoration of the microscopical structure of the liver to normal in some instances and the absence of nodular regeneration were notable. By the time that regeneration began in the damaged lobe, a considerable hyperplasia had taken place in the undamaged portions of the liver. It seems likely that factors promoting regeneration of liver tissue are most active when there is a deficiency of functional liver tissue. Because these stimuli were successful in causing hypertrophy of the undamaged lobes they acted with less intensity by the time the left lateral lobe was able to respond. The greater success of similar experiments in rabbits (vide infra) may have been due in part to the relatively larger amounts of tissue congested by the experimental procedure in that animal.

MECHANICAL OBSTRUCTION OF INDIVIDUAL HEPATIC VEINS IN THE RABBIT

In this animal it is possible to cause venous congestion of $\frac{2}{3}$ of the liver by partially occluding the hepatic veins from the median and right anterior lobes, using an abdominal approach.

This was done on 9 rabbits by means of cellophane or iodinated linen ligatures. Because of operative deaths or failure to narrow the veins adequately, only 6 of the experiments need be considered (Table VIII). The animals did not gain weight or show any other evidence of ascites. Cross et al. (1953) and Mallet-Guy et al. (1954) in contrast were able to produce ascites in dogs by causing partial obstruction of the left hepatic-venous ostium draining the left lateral and left central lobes (L in Fig. 45). Even when venous congestion of the whole liver of the rabbit is produced by constriction of the inferior cava above it, the amount of ascites is small (Milnes, 1951; Kawano, 1957) in comparison with that brought about by similar operations in the dog. By comparison with the work on rats reported below, one may conclude that this difference in the experimental results may be due to anatomical differences between the rabbit and the dog. The hepatic veins of the dog are more muscular than the portal-venous branches of the same size, whereas in most other mammals including the rabbit the ratio is reversed. Some of the control of the hepatic circulation exercised by the portal veins in the rabbit is probably exercised normally by the canine hepatic veins. Thus the effects of constricting the hepatic veins in the dog, and as it were paralysing them in dilatation, are greater than in the rabbit, for the canine portal veins are less able to compensate.

The tissue changes seen in the livers of the 6 rabbits are listed in Table VIII. The changes were more like those in human hepatic venous congestion than those in either of the two series of experiments on rats described in this chapter. This is possibly because the musculature of the hepatic veins and the

Table VIII. Experimental partial ligation of hepatic veins in the rabbit: tissue changes.

Rabbit no.	Fate	Time of death after ligation.	Tissue changes.
2 L	died (shock)	2 hours.	Centrilobular congestion, widening of sinusoids and oedema of portal tracts.
9 L	died (shock)	12 hours.	Extensive atrophy of mid- and centrilobular cells with vacuolation and early necrosis; dilatation of lymphatics, oedema of portal tracts and hepatic veins.
3 L	died (shock)	40 hours.	Parenchymal-cell necrosis in centrilobular masses sharply defined from rest of lobule; severe oedema and lymphatic dilatation.
7 L	died (abscess)	21 days.	Organisation and absorption of necroses; blood-lagoons containing pigment macrophages; centrilobular fatty change. Hepatic veins have thick fibrous walls and some contain organising thrombi. Capsule covered by thick fibrinous exudate.
5 L	killed	33 days.	Pigment macrophages and centrilobular sclerosis linking up by fine strands - early "pseudolobulation". Hepatic veins sclerosed and some intercalated veins closed. Thick capsule.
6 L	killed	80 days.	Fine patchy scarring of the liver with slight nodularity. Hepatic veins slightly sclerosed; no fibrous septa. Marked proliferation of bile-duct structures with cellular infiltration forming circumscribed foci in portal tracts.

terminations of the sinusoids in the rabbits are more like those in man than is the case in the dog. A curious proliferation of the bile ducts comparable to cholangio-fibrosis in rats (Fig. 175) was noted in one instance (6L, Table VIII). The necrosis was much greater in extent than that observed following anaphylaxis (Fig. 60b and Appendix B). Fibrosis of the hepatic veins was not seen in the latter experiments and one cannot conclude that hepatic necrosis following anaphylaxis is brought about by a primary venous reaction.

OBSTRUCTION OF THE INFERIOR VENA CAVA ABOVE THE LIVER

The experimental production of ascites by ligation of the inferior vena cava in dogs has a long history dating from Richard Lower (1728). Starling (1894) showed that the flow of lymph from the liver was increased following ligation. Bolton (1910 and 1914) was the first to observe the long-term effects of experimental ligation of the thoracic portion of the inferior vena cava in attempting to reproduce the features of human congestive heart failure. Working with cats, Bolton and later Barnard with him (1928 and 1931) studied the production of ascites and the changes in the liver.

Experiments on dogs: The inferior vena cava has often been partially obstructed in the thorax in dogs particularly by American workers (Zimmermann and Hillsman, 1930; Kershner et al., 1946; McKee et al., 1949; Volwiler et al., 1950; Berman and Hull, 1952; Davis et al., 1957 and others). Belli and Sprovieri (1956) studied casts of the hepatic veins and the histology of the liver after operation. The operation causes severe ascites

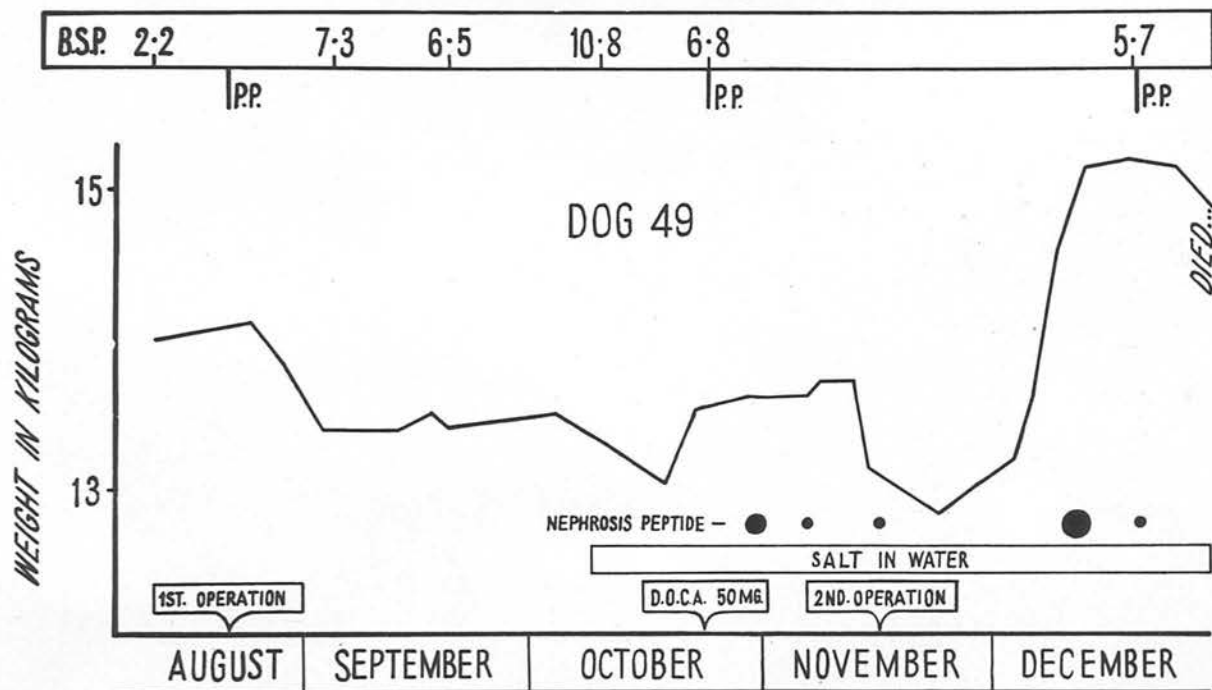


Fig. 148. Repeated intrathoracic ligation of the inferior vena cava in a dog, showing the weight curve in relation to times of operations and of administration of DOCA, estimations of nephrosis peptide in the urine and bromsulphthalein retention. Plasma proteins (P.P.) were estimated by electrophoresis on three occasions. The results of these and other protein estimations are given in Table IX below.

Table IX.

Proteins in 100 gm./ml.	Plasma			Serum	Ascitic fluid.	
	Dates	24/8	23/10	18/12	18/12	18/12
Albumin		3.73	2.33	1.82	1.76	1.22
Globulin α_1 α_2 β (includes — fibrinogen).	α_1	0.22	0.37	0.36	0.52	0.22
	α_2	0.26	0.30	0.62	0.60	0.43
	β	2.20	1.63	2.08	1.97	1.30
	γ	1.32	0.58	1.29	0.80	0.57
Totals.		7.73	5.21	6.17	5.65	3.74

in a few weeks which remits after many months. The ascitic fluid resembles liver lymph in composition (Volwiler et al., McKee et al.). Its formation is associated with a large increase in the lymph flow from the liver but not from the gut. The site of transudation of the ascites is the surface of the liver, for this may be observed at laparotomy. Further, Mallet-Guy et al. have shown that if the left lateral and left central lobes of the liver are congested, ascites forms when they are left in their normal position, but if the congested lobes are transposed into the thorax, a pleural effusion and not ascites results.

Record of a personal observation:* The effects of ligation with cellophane and linen thread of the inferior vena cava in the thorax of a dog are shown in Fig. 148. The procedure was carried out in 2 dogs of 14 Kgm., but the first animal died 2 hours later of post-operative shock brought on by too tight a ligation of the cava. The surviving animal (dog 49) recovered promptly and the postoperative course was smooth. Over the next 2 months, the bromsulphthalein retention rose from a normal of less than 4 by the method used (McCredie et al., 1957) to 10.8 - a moderate increase - and the total plasma protein fell from 7.7 to 5.2 gm./100 ml. At that stage, since there had been no gain in weight or other evidence of ascites, DOCA 50 mgm. was implanted subcutaneously and salt was added to the drinking water. These measures resulted in a return of the weight almost to the preoperative level.

* Mr. R.B. Welbourn, F.R.C.S. and other members of the staff of the Department of Surgery, Queen's University, Belfast kindly undertook the surgery and care of the 2 animals used.

Twelve weeks after the first operation, the thorax was again opened. The caval ligature was found to have reduced the vessel by a little less than half of its diameter but a moderate amount of ascites was present and the liver was a little congested. Collateral venous channels were found to be dilated and the cava was then further constricted by cellophane and braided silk. Thereafter the dog gained weight rapidly on account of massive ascites with a protein content about $\frac{2}{3}$ that of the plasma (Table IX). The plasma-protein level was maintained and the bromsulphthalein retention was less marked than previously. The excretion of nephrosis peptide (possibly equivalent to anti-diuretic hormone) was measured on several occasions by electrophoresis of the urine by Mr. J.R. Doggart. On 2 occasions it appeared greater than normal, but the significance of this is uncertain (cf. Volwiler et al.,).

The dog died suddenly 18 weeks after the first and 6 weeks after the second operation. The body was emaciated. The lungs were collapsed and oedematous. The peritoneal cavity contained 5 litres of dark, straw-coloured fluid i.e. $\frac{1}{3}$ of the total body weight, and a sticky fibrinous exudate was found on the surface of the liver. There were no fibrous tags. The lymphatics of the liver (Figs. 47 and 48) and of the hepato-duodenal ligament were dilated. The liver was deeply congested. Extensive blood lagoons occupied the centres of the lobules. The walls of the hepatic veins were thick (Fig. 47) on account of fibrosis and muscular hypertrophy. The general pattern of the liver lesion resembled that of Chiari's Disease in man.

Further experiments were not carried out in dogs because there is now a considerable literature on the subject. Since

ascites is so extensive in the dog after adequate constriction of the inferior vena cava above the liver, this animal is particularly valuable for use in studying possible methods of control of this symptom in man. The structure of the canine hepatic veins and their relationship to the lymphatics is unique, however, and it seemed desirable to examine the effects of similar procedures on a species with a simple venous-outflow tract. The results of experiments on dogs are in fact discordant in some respects with the findings in Chiari's Disease. Whereas marked ascites invariably follows severe constriction of the hepatic-venous outflow in dogs, almost complete obstruction of the hepatic-venous ostia can be present for a long time in man without overt ascites, as for instance in Cases 3 and 5 (Figs. 76 and 82, chapter V).

Experiments on rabbits and cats: In 3 rabbits a ligature was placed round the cava below the diaphragm. Adequate constriction was achieved in only one case and this animal died of shock 12 hours later. These experiments will not be discussed further.

Kawano however has perfected the technique and has described the histological changes from 1-600 days later in detail. The findings in Table VIII, i.e. following partial ligation of the veins from the median and right anterior lobes, are similar to Kawano's results but some of the tissue changes were later in their onset in the material of that author. In the later stages pseudolobulation occurred. Kawano mentions ascites of 20 ml. in animals surviving 3-4 weeks. Milnes also produced ascites of 20-40 ml. in rabbits by ligation of the inferior vena cava

above the diaphragm. The results of these experiments on rabbits by others resemble those on cats (Bolton and Barnard, 1928). In both species the ascites is less and remits spontaneously at an earlier date than in dogs. The tissue changes are more like those occurring in Chiari's Disease and in other examples of severe long-standing venous congestion in man than like those found in experimental venous congestion in the rat as reported below. This is probably associated with the fact that equivalent amounts of smooth muscle are present in the hepatic veins of man, of the cat and of the rabbit. Regarding the termination of the sinusoids also, the rabbit liver is closer in structure to the human liver than the rat liver is, for sinusoids join hepatic veins less frequently in the rabbit than they do in the rat (Elias and Popper, 1955). In their experimental cats Bolton and Barnard (1928) described the peritoneal tags that occur in man (Figs. 66, 67, 80 and 114-116.). These are rarely found in experimental venous congestion of the rat liver.

CONSTRICTION OF THE THORACIC INFERIOR VENA CAVA IN RATS

It was decided to examine the effects of venous congestion induced by this method because of the unsatisfactory results of the experiments described above in this species. When this work was begun no systematic study had been made of the effects of this procedure in the rat. The only relevant data discovered was the simple statement by Volwiler et al. that rats with congestion of the liver caused by caval cellophane ligatures placed just above the liver did not develop ascites. It was thought that because of the simpler structure of the hepatic veins in the rat, such experiments would provide a useful con-

trast to the extensive experience of others using dogs.

Intrathoracic ligation of the inferior vena cava was chosen in preference to an abdominal approach in order to avoid adhesions and other post-operative complications in the peritoneal cavity and because of the frequency of fatal tears of the diaphragm in trials of ligation of the cava between the diaphragm and the liver.

Plan of the experiments: Partial ligation of the cava was carried out with satisfactory survival in 73 albino Wistar rats. The immediate operative mortality was above 50% and animals dying during the operations have not been included in this total. Satisfactory constriction of the cava was achieved in 55 rats. On most operating days, 2 additional rats were subjected to thoracotomy and tracheotomy alone to act as controls in the subsequent weighings. This accounted for another 19 rats which need not be further identified.

Male and female rats of about 200-250 gm. were used and the operations were done under conditions of cleanliness but not of sterility. Intraperitoneal injections of 1000 units of benzyl penicillin were given on the day of operation and for 5 days thereafter. The animals were weighed before operation and frequently afterwards. Laparotomies were carried out in 8 rats between the 12th and the 20th postoperative days to detect possible ascites. 12 rats died within the first week and 2 others many weeks after operation and these have been included in the series. The rest were killed at various times from 5 days to 46 weeks after operation. The animals were then examined for the state of the ligature, the formation of collaterals (Fig.151)



(a)



(b)



(c)

Fig., 149. Trans-thoracic ligation of the inferior vena cava with tracheotomy. Three stages of the operation. The right phrenic nerve runs along the cava in this part of the thorax as shown in (c)

&c. and the livers weighed and submitted to histological examination. In addition to more common special staining techniques, the carbacid-fuchsin stain for basement membrane (Lendrum et al., 1945) was found to be a useful alternative (Figs. 59 and 164) to conventional techniques for reticulin. In 2 instances, neoprene-latex casts (Fig. 174) were made of the hepatic-venous tree but the injection was made incomplete by the caval obstructions in some others.

Operative procedure: The lines of the operative incisions for right thoracotomy and tracheotomy are shown on the shaved skin in Fig. 149a. The ribs were displayed by section and retraction of the serratus anterior and upper portions of the abdominal muscles from the lower costal margin up to the lower border of the pectoral muscle (Fig. 149b). Before opening the chest a tracheotomy was performed between the sternomastoids, care being taken to avoid cutting the jugular veins which lie close to these muscles inferiorly. The trachea was displayed by retracting the thyroid upwards, splitting the strap muscle round the trachea longitudinally and passing a thread behind it. The thread was useful in securing the trachea during section and subsequent manipulation. As small an incision as possible was made between the rings of the trachea but large enough to take a No.3 polythene tube (2.5 mm. outer diameter). While the animal was maintained by intra-tracheal oxygen, the chest was opened by an L-shaped incision through the 6th and 7th costal cartilages and the 7th inter-costal muscle (Fig. 149c) which avoided the diaphragm. The flap was retracted and the cava identified by the light of a head lamp and the clip or ligature was applied (Fig. 149c).

Two forms of constriction were used to close the cava partially. Originally Mackenzie's neurosurgical tantalum clips were applied partly closed. Later, to obtain gradual narrowing by scarring, the clips were applied over cellophane or talc. None of these methods was entirely satisfactory and in the later animals (RL31-73) bands of commercial cellophane film about 0.5 cm. broad were used as ligatures. They were passed round the cava with the aid of a suitably curved aneurysm needle which perforated the mediastinum (Fig. 149c). The ligatures were tied as tightly as the strength of the cellophane would permit round a smooth wire of 15 gauge (1.9 mm. diameter) which was then removed.

Oxygen or air delivered at about 100 ml./min. through a No. 1. polythene tube (0.5 mm. bore) passed down the trachea to the carina is sufficient to maintain life in the rat for an indefinite period with the chest open, but a tube of this diameter cannot transmit gas fast enough to reinflate the collapsed lungs. It is particularly necessary to reinflate effectively in the present operation in which the mediastinum is perforated. By experiment it was found that the smallest diameter of tube through which the lungs could be reinflated was a No. 3 polythene (1.5 mm. bore). This is too big to pass through the larynx and a tracheotomy must be established, although this is in other respects thoroughly undesirable. The tracheotomy was closed loosely after operation. Those left open became septic, and tight closure was usually fatal because of difficulty in breathing through the natural channels again after manipulation, when respiration was depressed by anaesthesia and shock. Basal anaesthesia by 5-10 mgm. of nembutal intraperitoneally, which

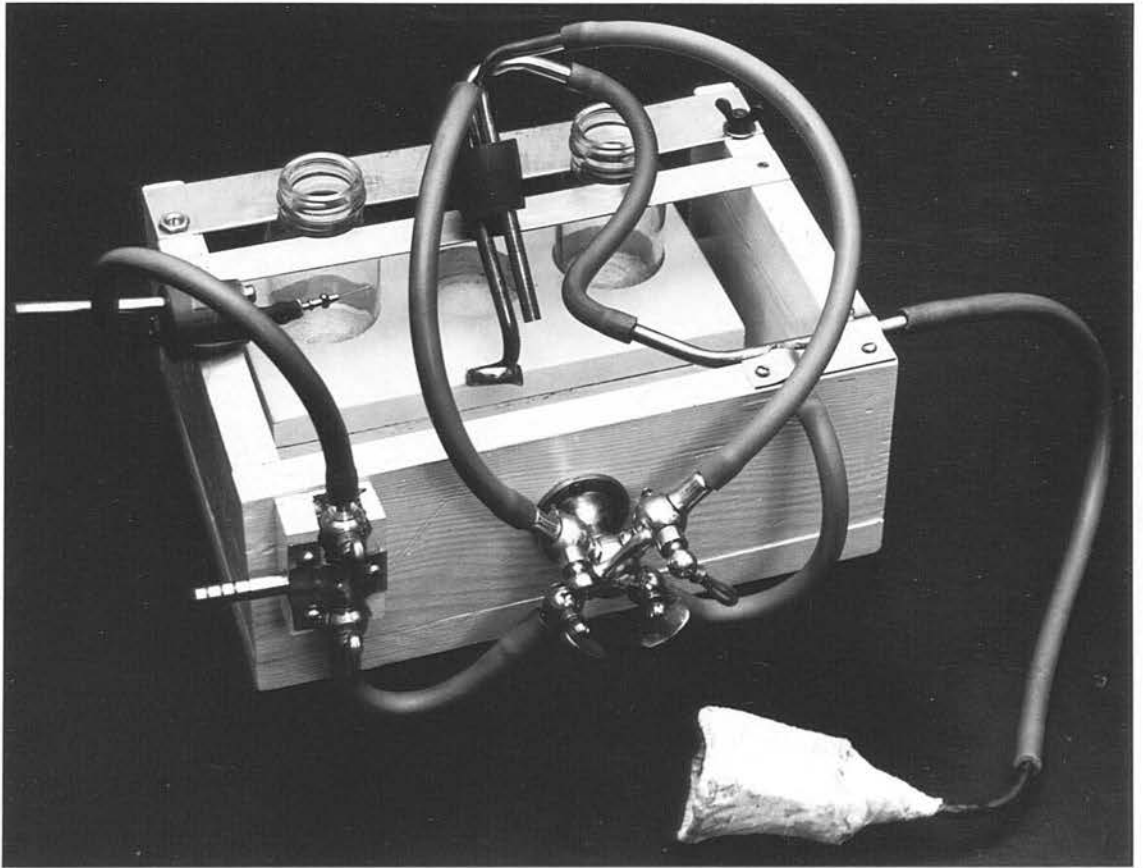


Fig. 150. Apparatus for anaesthesia of small animals, employing copper and rubber tubing and coal-gas taps. Air or oxygen from a cylinder enters in front on the left. A side tube may be opened to a simple flowmeter made from a hypodermic needle corked into a glass bottle containing water.

A multiple gas outlet has been modified to permit (i) direct flow of oxygen to the mask, (ii) bubbling of oxygen through ether in the right-hand bottle or (iii) passage of oxygen over the surface of the ether.

The mask is shown for a rat. It may be replaced by a suitably fitted no.1 polythene tube for endotracheal anaesthesia.

was otherwise of great help, delayed recovery at this crucial stage. Atropine 0.1 mgm. was given by intraperitoneal injection in many cases but had little effect. During the operation deep anaesthesia was maintained with ether supplied in oxygen or air through the endotracheal No. 1 polythene tube from a cylinder with a reducing valve. Anaesthesia was easily controlled when an apparatus was constructed suitable for delivering oxygen with or without varying concentrations of anaesthetic (Fig. 150). After ligation of the cava, oligoemic shock was such that very little more anaesthetic was required.

To reinflate the lungs a No. 3 polythene tube with a lug 1 cm. from its smoothly bevelled tip replaced the oxygen catheter in the tracheotomy just before the chest was closed. The lug was attached temporarily to the skin and a 20 ml. syringe two-thirds full of air or oxygen was connected to the other end of the tube and the lungs reinflated gradually by an assistant immediately prior to air-tight closure of the bony and muscular wall of the chest. Artificial respiration was continued in this fashion for another minute or so until the serratus and abdominal muscles were closed in a second layer. Over-inflation of the lung was the chief danger in this manoeuvre.

General effects of the operation: The mortality at operation and from shock and respiratory embarrassment immediately afterwards was high. Animals surviving this period had recovered from shock by the next day but remained weak for about 5 days, during which time there was often a little dyspnoea. Septic complications of the cervical and thoracic incisions were uncommon and eventually both sites healed well (Fig. 151). The

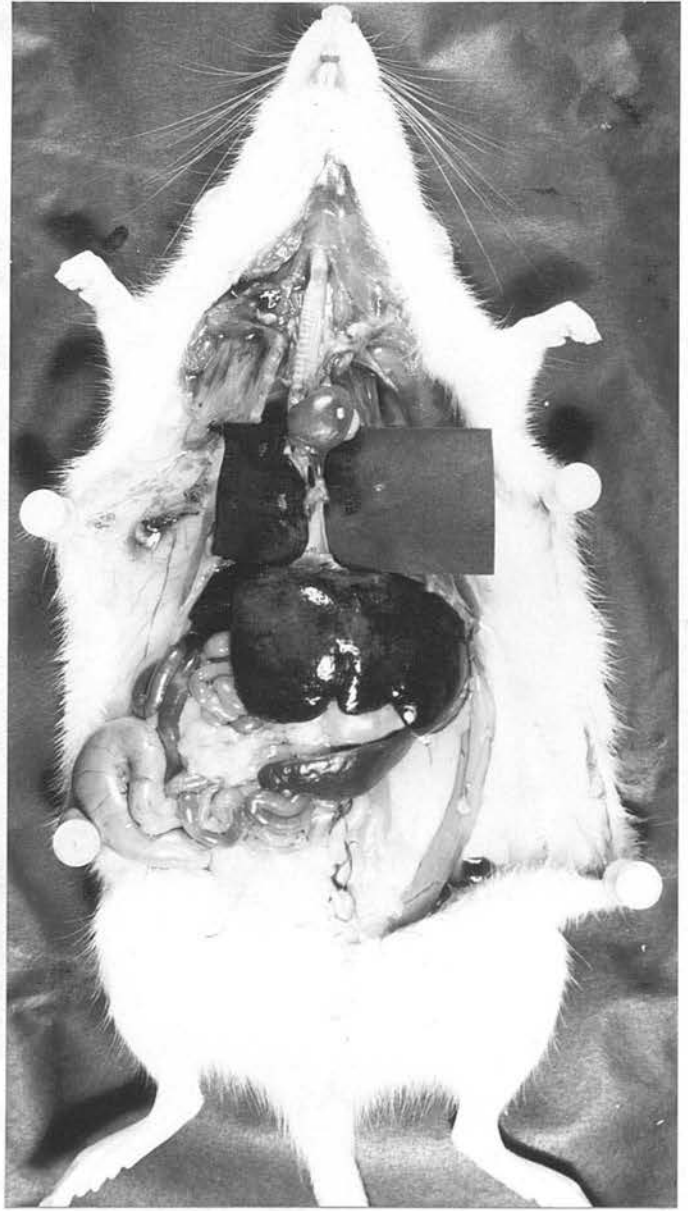
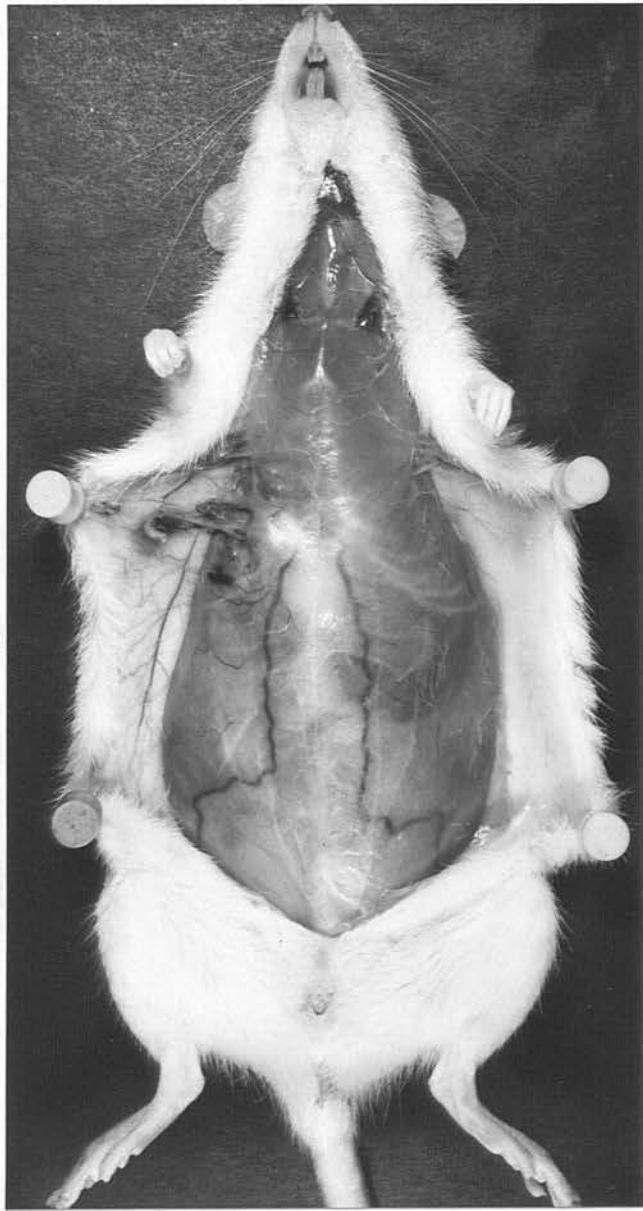


Fig., 151. Two stages of dissection of RL33 killed 42 days after tracheotomy and ligation of the inferior vena cava with cellophane. On reflection of the skin (left) superficial abdominal veins are prominent. The skin is adherent over the thoracotomy scar which is otherwise healthy. The tracheotomy site is satisfactory.

At a deeper level (right) the liver is dark and swollen. The ligature can be seen round the cava, which was completely closed at this level. The tracheotomy has healed, but the rings have receded from the site of the incision.

Histological sections from this animal are illustrated in figures 159, 162 & 172.

weights of the animals usually fell by about 10% from the preoperative level during the first week. Thereafter the rats appeared healthy and most of them regained their preoperative weights in 3 weeks. They remained healthy and continued to grow and gain weight normally in the ensuing period. The two deaths at that time were due to senile bronchiectasis and pneumonia which is common in mature animals such as those used.

There were no signs of damage to the hind limbs resulting from the caval occlusions. The urines of many animals were tested for albumin on several occasions with salicyl-sulphonic acid. A cloud indicating albumin often formed, but similar results were obtained in normal controls and the test is probably valueless in the rat. Histological sections were made of the kidneys of most of the animals killed and evidence was not found of any damage which could be ascribed to the operative procedure. Occasional assays of the urine for "nephrosis peptide" by Mr. J.R. Doggart did not show any noteworthy difference between the experimental animals and the controls. In routine histological examination of the major organs in many cases, lesions which could have been caused by the operation were not found in any organs other than those described below. In particular, venous thrombi were not found except in relation to the operative site.

It was not possible to trace any correlation between any parts of weight graphs of the animals and the degree of closure of the thoracic cava, the development of thromboses in the hepatic cava, the occurrence of ascites or the degree of chronic damage to the liver. Sex differences in the reactions of the animals to the experimental procedure were not observed.



(a)



(b)

Fig., 152. Cellophane ligatures of the cava.

(a) longitudinal section in RL 66 killed at 8 weeks. H. & E. x 12.

(b) transverse section in RL 44 killed at 18 weeks. H. & E. x 20.

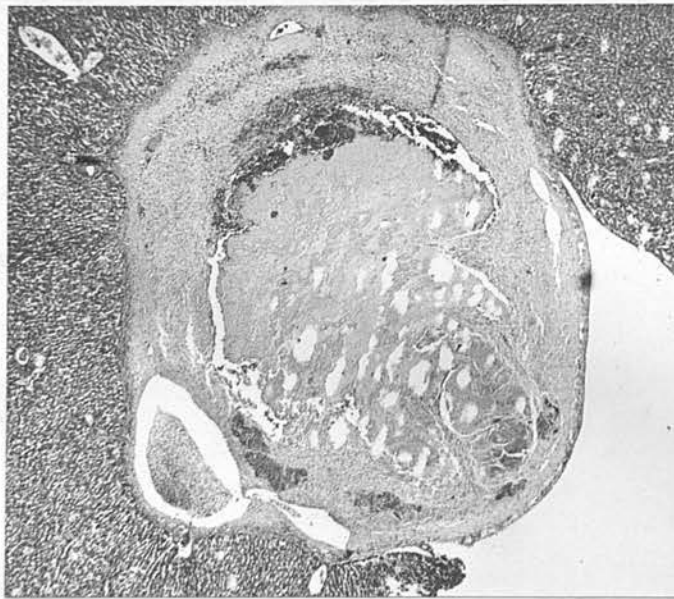


Fig., 153. Spontaneous thrombus in the hepatic cava in RL 32 killed at 31 days. x 15.

The caval ligature: Cellophane, and in a few cases talc, were used with the object of producing a gradual stenosis but the degree of fibrosis caused by the cellophane was not great and very little additional constriction was achieved by either agent beyond that originally imparted. The right phrenic nerve, which was included in the ligature did not show any signs of degeneration. There were no noteworthy differences in the hepatic lesions following cellophane ligation and those following the earlier use of neurosurgical clips. Reduction by half of the caval diameter (Fig. 152) was brought about by both and there were few failures once the clips were properly adjusted and once the right size of wire (15 gauge) was selected as a stop. The degree of caval constriction produced at operation was critical. Where the reduction was significantly less than half, hepatic lesions did not develop and where it was significantly greater, the rats died promptly. In rats surviving for several weeks, the thoracic constrictions were often further narrowed by mural thrombus (Fig. 152a) or completely closed (Fig. 151).

Collateral veins were noted to be enlarged in several animals at death or at laparotomy at 2-3 weeks. The prominence of collaterals varied unpredictably but tended to be greater the longer the animals survived. Channels between the superficial inferior epigastric and internal mammary veins were most often recognized (Fig. 151). The azygos arising from the left renal vein seemed the most important channel and was usually enlarged. In one case the right ascending lumbar vein was particularly large. In many cases which survived several weeks or more, occlusive or non-occlusive thrombi were found in the hepatic

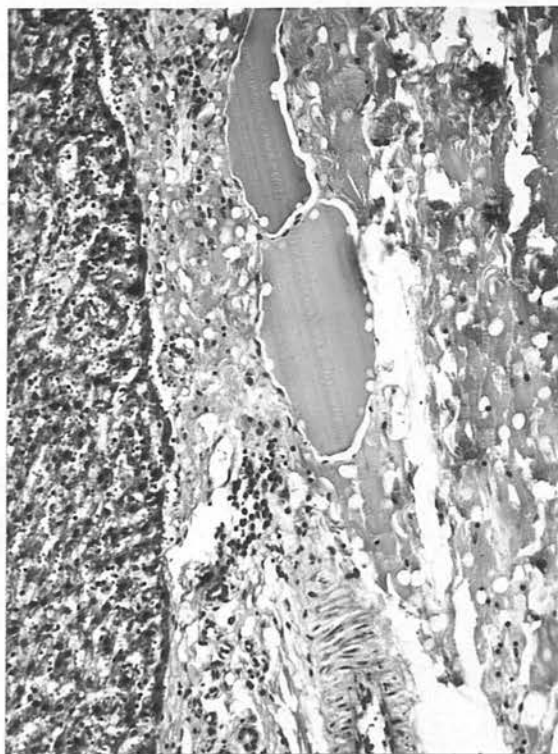


Fig., 154. The porta hepatis in RL 38 dying half an hour after operation. There is much fluid in tissue spaces and in a dilated lymphatic. H. & E. x 125.

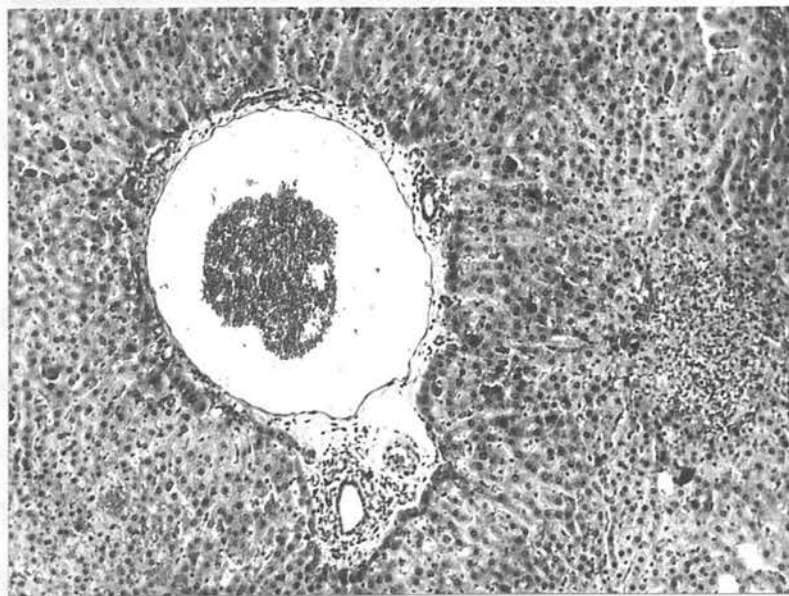


Fig., 155. RL 13 dying 60 hours after operation. Portal-tract lymphatics are dilated and a focus of liver-cell necrosis is present, right. H. & E. x 90.

portion of the cava (Fig. 153) which in several cases prevented hepatic-venous blood from reaching the renal and azygos veins, but this seemed to increase only slightly the degree of liver damage, probably because relatively large diaphragmatic veins join the left ostium close to the cava in the rat (Fig. 39 dv). When RL53 was killed at 18 weeks, the hepatic-venous outflow was found to be routed entirely through this vein.

Liver lesions: The animals have been divided into 4 groups according to the times of death.

Group 1 - 16 rats, 12 died and 4 killed at varying times up to 1 week after operation.

Immediately after operation the liver became moderately congested and the weight increased to about twice the normal of 3-4.5% of total body weight (see chapter II). Later the organ became paler, mottled by dark foci of necrosis and the weight was then about one-and-a-half times normal. At the end of the week, hepatic hilar lymphatics were readily visible and the lymph nodes in the hilum were swollen and red. Ascites was not observed during the first week.

Microscopically the earliest change was intense oedema of the liver generally, especially of the portal tracts and hepato-duodenal ligament with dilatation of lymphatics and fluid free in the tissue spaces (Fig. 154). After a few days the walls of the hepatic veins were thickened by oedema. As the necrosis was resorbed central venules were separated from the liver cells by an oedematous ring. Spaces of Disse were not observed regularly at any stage. Oedema of the tissues subsided after a few days and the portal-tract (Fig.155) and hilar lymphatics became enlarged.

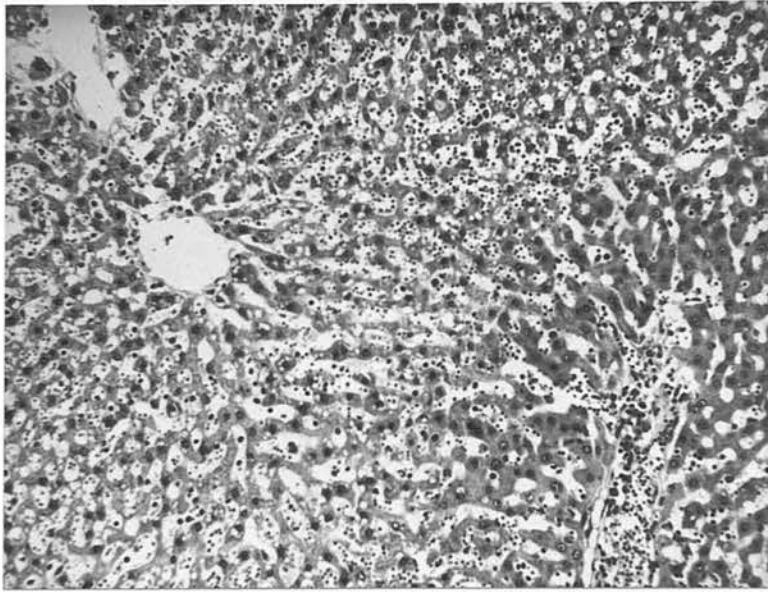


Fig., 156. RL 22 dying $3\frac{1}{2}$ hours after operation. There is "watery" vacuolation and atrophy of centrilobular cells (left). H. & E. x 125.

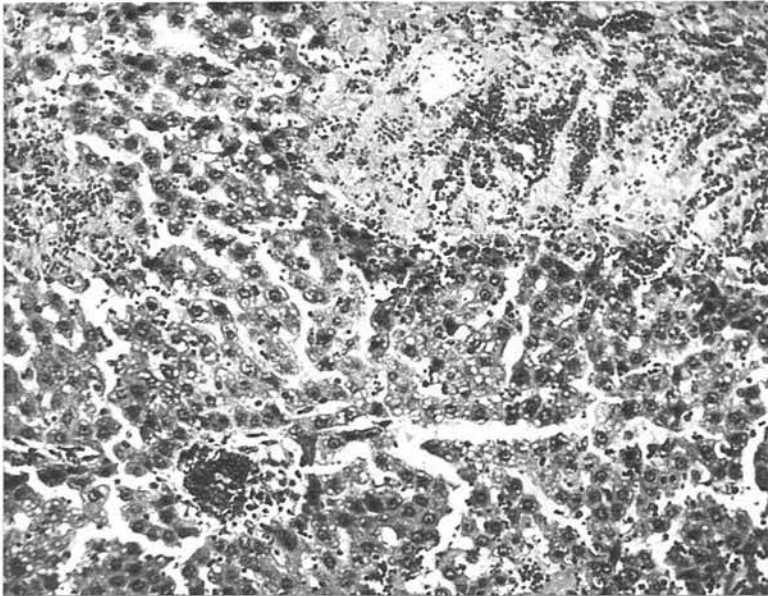


Fig., 157. RL 56 dying 48 hours after operation. The centrilobular area of necrosis, above, is sharply demarcated from the surviving periportal cells which are vacuolated. H. & E. x 150.

The overall congestion immediately following ligation gave way in 2-3 hours to a zonal lesion (Fig. 156) and by 4 hours the centrilobular areas were distinct from the rest of the parenchyma, the central sinusoids being dilated and the liver cells about them shrunken. Fine "watery" vacuoles appeared in the cytoplasm of the liver cells within a few hours (Fig. 156). In other cells, pyknosis of nuclei was associated with cellular shrinkage. At 12 hours there was coarse clumping of the cytoplasmic elements in one animal, and in another dying 24 hours after operation fibrinoid droplets were seen in the cytoplasm and foci of frank necrosis. In an animal dying at 48 hours, areas of hyaline necrosis were sharply defined from the rest of the lobule (Fig. 157) and polymorphs had begun to infiltrate round the edges. The outlines of the liver cords remained visible; reticulin impregnated poorly in the necrotic tissue but remained in continuity with that in the surviving peripheral zones.

The location of the necrotic areas was often clearly centrilobular and always non-portal. The pattern was, however, less clear-cut than in human disease because of incomplete involvement of some centrilobular zones and because foci of necrosis were present at junctions of intercalated veins (Fig. 158) as well as round central venules and because of more severe involvement of subcapsular areas particularly at the periphery of the thin lobes (cf. Fig. 169). The severe involvement of the periphery of the lobes was associated with cylindrical zones of necrosis round relatively long intercalated veins there.

By 72 hours there were irregularities in the nuclei of the surviving liver cells and a little lymphocytic and plasma-cell

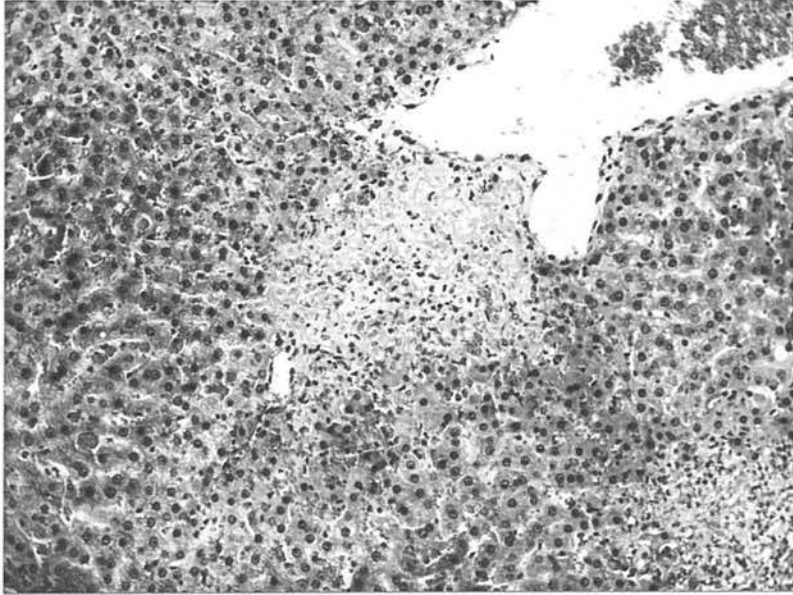


Fig., 158. RL 13 dying 60 hours after caval ligation. Necrosis is present between a central venule, left, and the junction of two intercalated veins, above, (cf. Fig., 166).

Note that the necrosis is asymmetrical round the central venule. H. & E. x 125.

infiltration of portal tracts. At this time the endothelial cells of the central venules became swollen and also many of the Kupffer cells. Kupffer cells proliferated in the necrotic zones. In rats killed at 120 hours, resorption of the necrotic material had begun, leaving areas of loose texture at the sites of previous necrosis partially occupied by necrotic debris and macrophages. A few fibroblasts were present in affected areas round small hepatic veins from which the cells were apparently derived.

Group II - 11 rats killed at varying times from 1-6 weeks after operation.

The livers were increased in weight by about one-and-a-half times; their surfaces were granular with dark patches of sub-capsular haemorrhage and lacked the normal sheen (Fig. 151). The hilar lymphatics and lymph nodes were enlarged (Fig. 159); 2-3 ml. of clear or blood-stained ascites was frequently but not invariably present. There were thrombi in the hepatic cava in 2 cases.

Microscopically the liver changes were characterised by repair of the process described in the previous group. At 10 days, necrotic material had been largely but not entirely removed from the centrilobular areas which now consisted of blood lagoons with occasional surviving liver cells; a little fine reticulin often preserved the outlines of the liver cords. In another animal killed at 12 days, deposition of collagen had begun in some of the areas close to large hepatic veins (cf. Fig. 166). In the peripheral portions of the lobules, the reticulin was coarsened and reduplicated. There was little cellular



Fig., 159. RL 33 killed 42 days after caval ligation, (see also Figs., 151 & 172). Dilated lymphatics at an hepatic hilar node. H. & E. x 20.

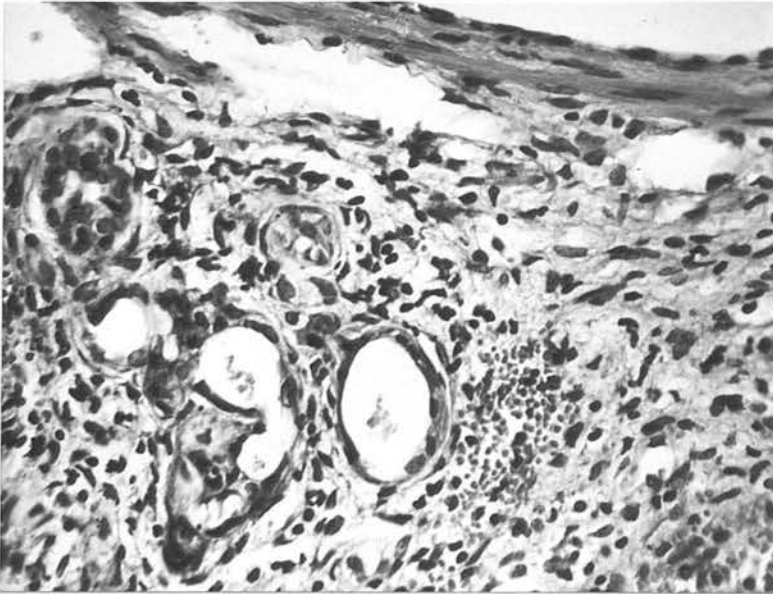


Fig., 160. RL 37 killed 28 days after operation. Dilated lymphatics and group of biliary cysts, (cholangio-fibrosis). H. & E. x 270.

infiltration of the portal tracts. Minor irregularities of the hepatic cells were present and liver cells showing the characters of regeneration were found, particularly round central venules, in animals killed at 18 days. The normal architecture was not, however, completely restored. Small foci of necrosis were seen at all stages in the period. These necroses seemed to have been newly produced and not simply to have persisted from the initial stages. Not all of the space previously taken up by blood lagoons was reoccupied in a normal way and the re-established sinusoids were often unduly wide and irregular in the centres of lobules (cf. Fig. 170). At a slightly later stage collagen was often visible in the walls of the central venules, and the intercalated and hepatic veins were often partly surrounded by collagenous areas (cf. Fig. 166). In one animal killed at 28 days a few irregular microcysts of biliary epithelium (cholangio-fibrosis) were found in these scars (Fig. 160).

Throughout this period the repair of damage to the sub-capsular areas was retarded in comparison with the rest. These zones consisted of little more than areas of interstitial haemorrhage (Fig. 172) containing a little irregular reticulin and a few surviving liver cells. Fig. 173 from an animal killed at 31 days shows the irregular pattern of coarse reticulin; the central venule draining the area is occluded. In other portions of the liver similar occlusions were sometimes found associated with necrosis (Fig. 164). In larger hepatic veins there were occasionally mural thrombi (Fig. 161). Occlusive or stenosing thrombi were found in the cava (Fig. 153) in 2 animals with marked degrees of liver damage but the liver lesions were similar in other animals without such thrombi.

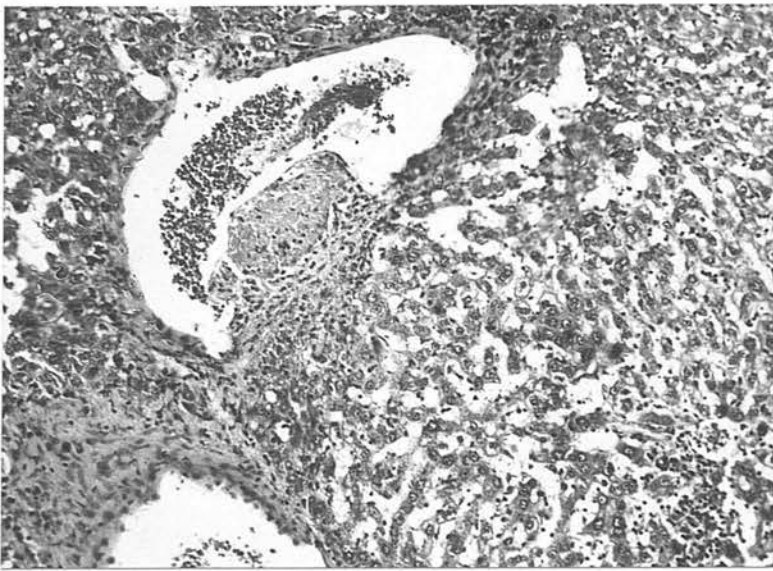


Fig., 161. RL 32 killed at 42 days. A small mural thrombus in a thickened hepatic vein. H. & E. x 100.

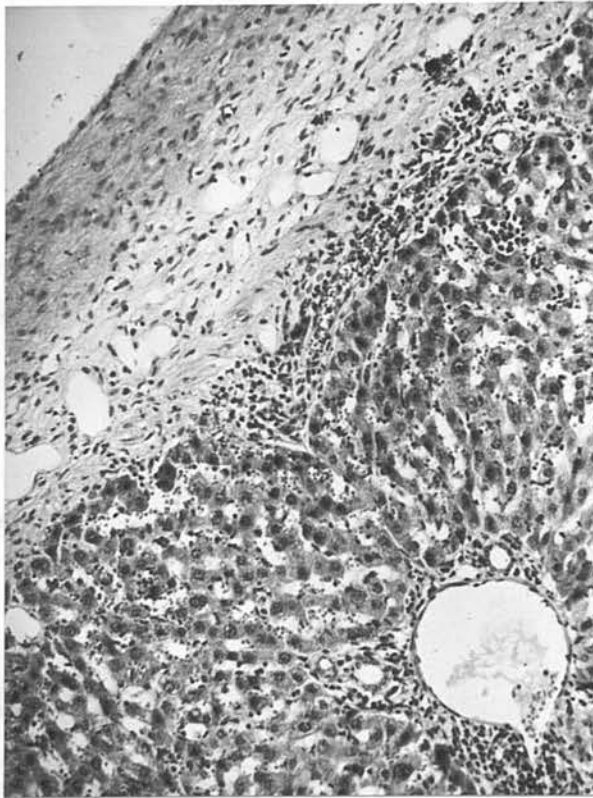


Fig., 162. RL 33 killed at 42 days. The wall of a large hepatic vein is grossly thickened. Tributaries and lymphatics are seen in the wall. H. & E. x 125.

In animals killed at the end of the period, the hepatic veins were generally much thickened by collagenous fibrous tissue which increased their thickness about 3 times (Figs. 161 and 162) and tributaries entered by tortuous courses. Lymphatics were numerous even in hepatic veins smaller than those in which they are normally visible (2nd order, see chapter II and Table I). The lymphatics were widely dilated in the portal tracts, in the hilum and round the hilar lymph nodes (Fig. 159). Lymphatics were not found in the capsule and only in one animal, in which there was a serosanguineous effusion of 4 ml. in the peritoneal cavity, were peritoneal tags present (Fig. 163). They were scanty.

Group III - 15 rats killed at varying times from 6-14 weeks after operation.

The livers were a little less enlarged than in the previous group and showed variable degrees of congestion and superficial haemorrhage. The surface was granular. The hepatic veins could be recognized as thick by the naked eye. Lymphatic dilatation was less than in the previous group. Ascites was not present. There were thrombi in the hepatic cava in 5 cases.

Microscopically the majority of the livers showed marked fibrosis of the venous tree at all levels and small fibrous plaques extended out from the veins here and there into the liver (cf. Fig. 166). Usually small foci of fresh necrosis were also present. In 4 instances in which the cava had been narrowed less, by the ligature or by subsequent caval thrombosis, the sclerosis was similar to that in the previous group and the main alteration in the liver parenchyma was dilatation of

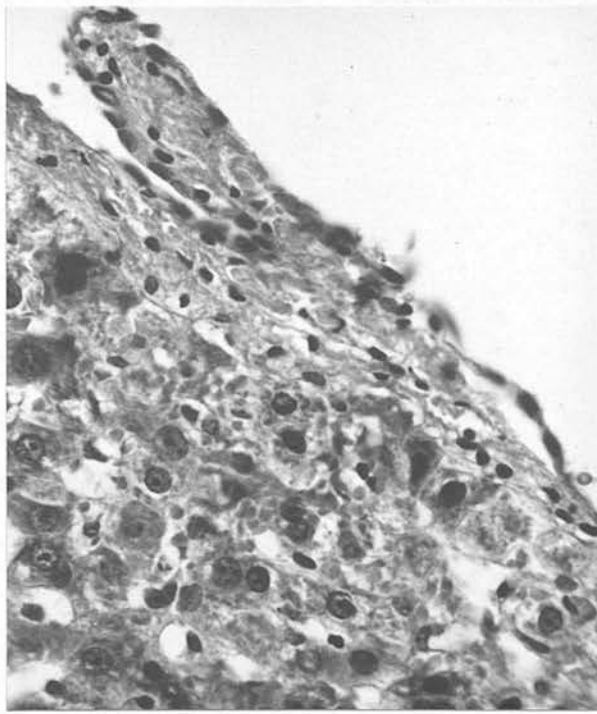


Fig., 163. RL 52 killed at 18 days. Ascites was present. A peritoneal fibrous tag. H. & E. x 420.

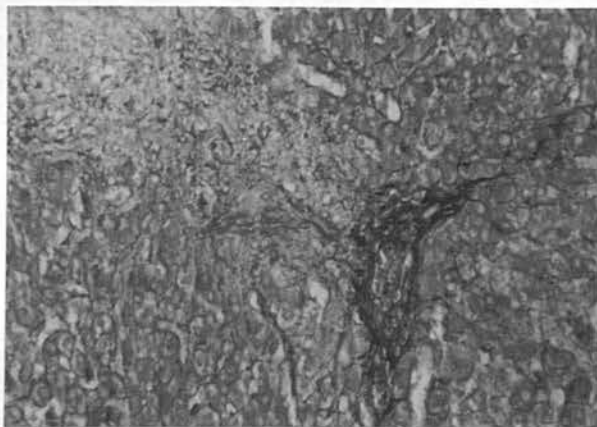


Fig., 164. RL 52 killed at 18 days. A focus of necrosis. Fibrous occlusion of intercalated vein associated with a focus of parenchymal necrosis. Carbacid-fuchsin, x 150.

terminal groups of sinusoids at central venules (cf. Fig. 170). In the worse affected livers, foci of centrilobular sclerosis or fibrous plaques round intercalated veins (Fig. 165) sometimes linked up neighbouring veins so that small fibrous septa formed, occasionally leading to an appearance approximating to pseudo-lobulation. The left lateral and median lobes (see Figs. 37 and 52) were generally worse affected than the right lobes. In a few instances early nodules of regeneration had developed and hepatocellular activity was prominent throughout these livers. Neoprene latex casts of the hepatic veins (Fig. 174) showed that the architecture was not greatly disturbed, but the vessels were more irregular, dilated and stumpy than normal and they were particularly irregular at the periphery.

Fibrosis had also begun in the subcapsular haemorrhagic zones and in these and other scars, foci of cholangio-fibrosis were found from time to time. Most of the subcapsular zones remained unorganised, however. They were extensive over many parts of the liver of a rat killed at 13 weeks, but particularly large in the left lateral lobe. The main hepatic vein from that lobe was blocked by an organised thrombus.

Group IV - 13 rats, 11 killed and 2 died at varying times from 14-46 weeks after operation.

The livers weighed about 1.25 times the normal weight. They showed varying degrees of congestion and were coarsely granular on the surface. The walls of the hepatic veins were thick and white. The hilar lymphatics were a little enlarged. There was no ascites. Thrombi were present in the hepatic cava in 7 cases.

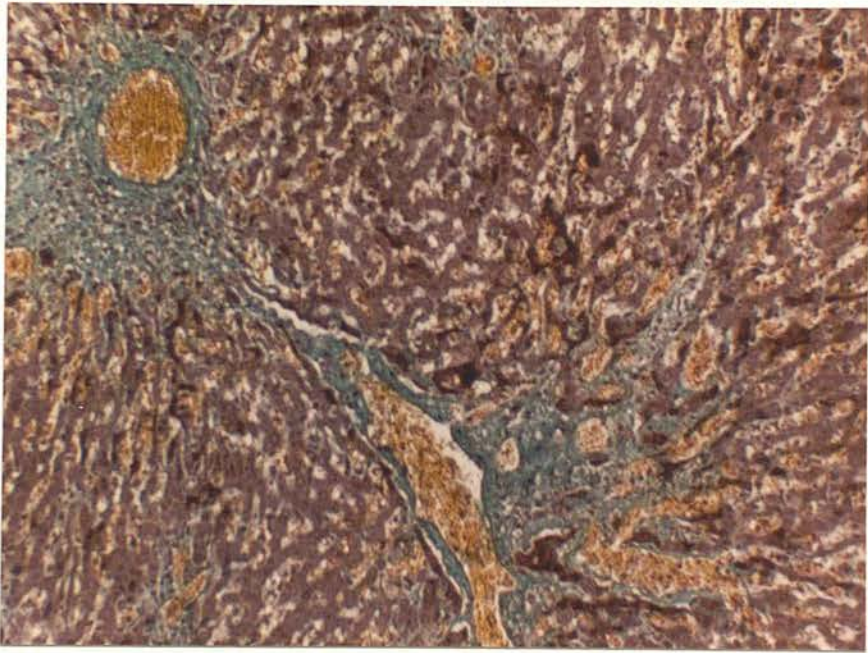


Fig., 165. RL 47 died at 9 weeks. Two intercalated veins are shown near their junction (cf. Fig., 44 for normal). Their walls are grossly thickened by collagenous fibrous tissue which extends out into the hepatic parenchyma and lines sinusoids, so that the fibrous plaque resembles those of centrilobular sclerosis in Chiari's Disease in the human liver (Fig., 128). This appearance, which approximates to the early stages of pseudolobulation, was rare in the experimental rats. Picro-Mallory x 120.

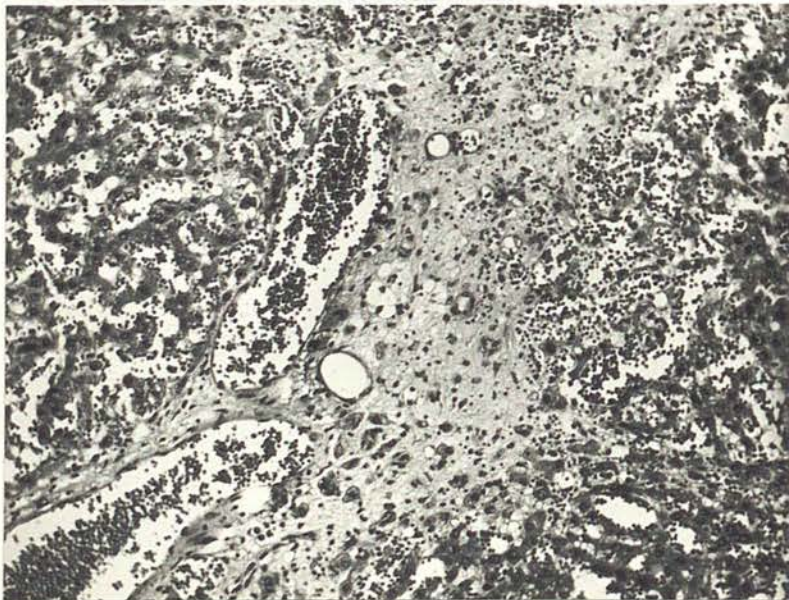


Fig., 166. RL 43 killed 18 weeks after operation. A fibrous scar at the junction of an intercalated and an hepatic vein, containing a few small cysts and macrophages (cf. Fig. 158). H. & E. x 125.

The histological features were similar to those in the previous group but were more uniform and more firmly established. In several livers cirrhotic features were present but they were not advanced in degree. The fibrous tissue was chiefly deposited in two sites namely as narrow collars extending irregularly into the immediately adjacent parenchyma (cf. Fig. 165) and secondly in the form of scars in the same locations as the necrosis described in the initial stages. (Figs. 166 and 167). The scars were sometimes dense and interspersed with hyperplastic liver cells and more often composed of loosely textured collagenous fibrous tissue. They were usually vascular and contained a few macrophages in which iron or lipofuscin pigment was present (Fig. 167). Foci of cholangiofibrosis were also found in the scars and near portal tracts (Fig. 175). There were also larger cysts of another kind (Fig. 168) which were lined by flat endothelium and were probably vascular in origin. Organisation of the areas of subcapsular haemorrhage had produced similar histological features in that zone (Fig. 167). The process was usually less advanced there and areas of haemorrhage persisted (Fig. 169). In parts of most of the livers, small foci of fresh necrosis were present.

Other features of the chronic disturbances of the liver architecture included terminal dilatation of groups of sinusoids and of central venules (Figs. 169 and 170). Liver cells round about the scars and to a smaller degree elsewhere showed hyperplastic changes. The portal tracts were slightly fibrosed and often contained macrophages with iron-pigment granules. This pigment was commonly found only in livers of animals surviving into the fourth period. Foci of haemopoiesis were present in

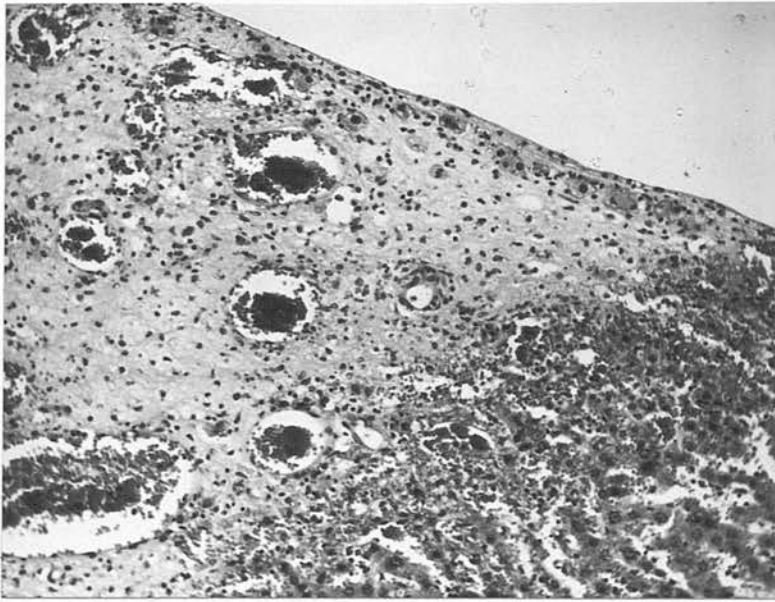


Fig., 167. RL 43 killed at 18 weeks. Vascular spaces in fibrous tissue organising a superficial haemorrhagic area, (cf. Fig., 169). H. & E. x 125.

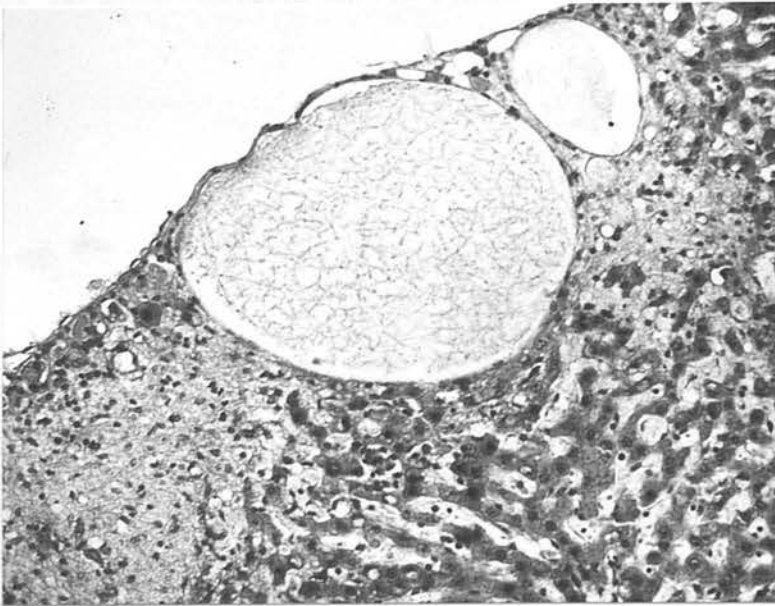


Fig., 168. RL 36 killed at 19 weeks. Large cystic spaces probably vascular, developed in the organisation of a superficial haemorrhagic area. H. & E. x 140.

several instances in the portal tracts and also to a less degree in foci in the parenchyma and in several of the vascular scars.

The lymphatics were dilated in all the usual sites (Fig. 171). Capsular lymphatics had not formed.

Ascites: Ascites was found only between the 2nd and 7th post-operative weeks and was always small in amount.

The first observation of ascites was in R118, killed at 12 days, in which resorption and organisation of necrotic foci had begun. The hilar lymphatics and lymph nodes were enlarged. The ascites amounted to about 3 ml. The findings were similar in 2 other animals killed during the period and in one of them, but not in any other rats, fibrous tags were present on the surface of the liver (Fig. 163). Lymphatic enlargement without ascites was found on killing 7 other animals of this group II. In 8 other rats, laparotomies were performed at from 2-3 weeks after operation. Although there was only a little fluid in the peritoneal cavities when they were opened, there was copious transudation of clear fluid amounting to a few ml. from all surfaces of the congested livers, when they were handled. Pleural effusions were not encountered in any animal killed more than a few days after operation.

Effects on the portal circulation: The rats were killed by an overdose of anaesthetic and the portal vein was often inspected before death. It was dilated. No attempt was made to define portal-systemic anastomoses.

The spleens were enlarged in nearly all cases; 27 were

weighed* and 43 were examined histologically. At death during the first few days after operation, enlargement up to double the normal weight was found, which was mainly due to congestion. Congestion diminished later in the week and the normal foci of haemopoiesis with megakaryocytes increased at the same time. In the second group (i.e. 1-6 weeks) weights ranged up to 3 times normal. The heaviest spleens were found in animals with severely damaged livers. There was considerable hyperplasia of the Malpighian bodies. The red pulp was enlarged through an increase in haemopoiesis and in "pulp cells". The latter were similar to reticulum cells with a basophilic and pyroninophilic cytoplasm. Similar staining characters were seen in cells that were most probably haemopoietic. Haemopoietic and pulp cells were present in the intima of the splenic veins. Brown pigments both positive and negative to Perl's reaction were often found in increased amounts. The histological findings in animals surviving longer (groups III and IV) were similar. Variable degrees of congestion were found and this influenced the weights. The weights were less than in the earlier groups being, on the average, one-and-a-half times normal. It was not possible consistently to relate the spleen weights to the liver weights or other indications of liver damage in these two later groups.

A little fibrosis of the splenic structure was seen in the animals surviving for several weeks or more, but considerably less than that commonly found in the fibroadenie of human portal hypertension.

* The weight of the spleen was found to be 0.28% (S.D. 0.08) of total body weight in 15 normal male rats and 0.32% (S.D. 0.22) in 32 normal females. These are slightly higher than the figures given by Reynell (1952).

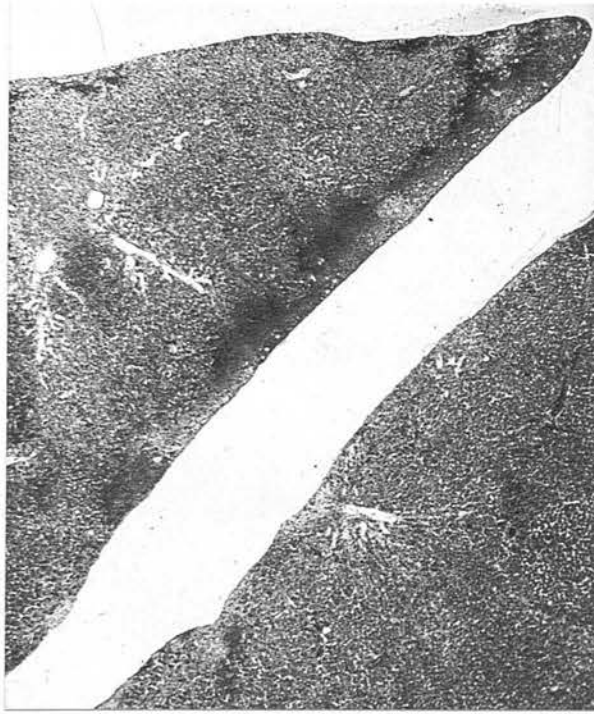


Fig., 169. RL 44 killed at 18 weeks. Persistent haemorrhagic areas along the surface of the left lateral lobe adjacent to the median lobe (below). Groups of dilated sinusoids and dilated central venules can be seen, (cf. Figs., 170 & 172). H. & E. x 22.

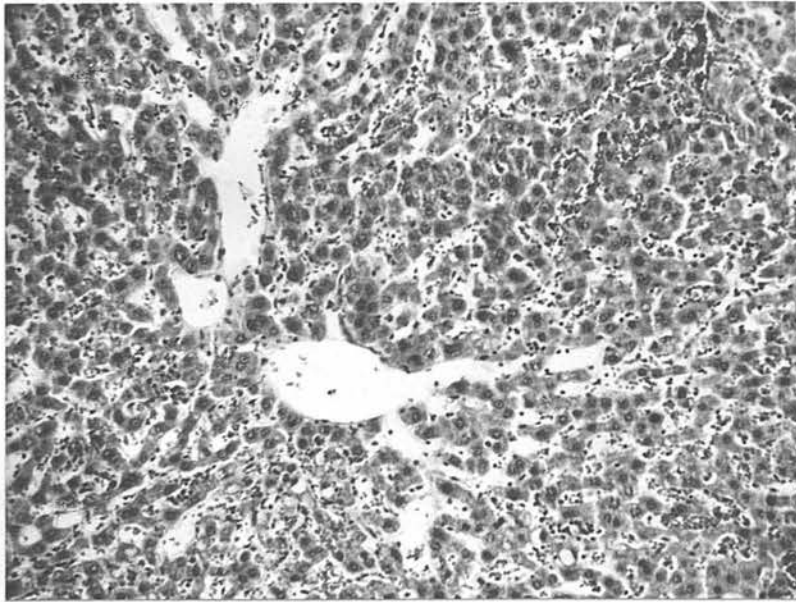


Fig., 170. RL 36 killed at 19 weeks. Dilated central venules and terminations of sinusoids. H. & E. x 125.

Discussion of experimental constriction of the thoracic inferior

vena cava in rats: It was found necessary to perform tracheotomy to permit reinflation of the lungs after thoracotomy.

This increased the hazards of the operation. Farris and Griffith (1949) state that tracheotomy cannot be carried out in the rat if the animal is to survive, and survival was probably achieved in the present series because of the use of penicillin. In other respects, the intrathoracic operation is preferable to an abdominal one. The effects of the caval obstruction on the peritoneal cavity and abdominal organs are not complicated by repair and other local results of an operation in this field.

The statement of Volwiler et al. that constriction of the inferior vena cava directly above the liver by cellophane in rats does not produce ascites is at variance with the recent work of Nayak et al. (1956). The latter authors also constricted the cava, between the liver and the diaphragm, and 21 rats survived the operation. Thirteen of the survivors had ascites which was greatest at 2-7 days and tended to disappear at 28 days. Nayak et al. reported a high protein content in the fluid and quantities up to 22 ml. They narrowed the lumen to 1/3 of its original diameter and the discrepancy in results may be due to different degrees of narrowing produced by the two sets of workers. The present experiments indicate that cellophane has a slow and a slight effect in causing fibrosis and subsequent narrowing of the cava in the rat. The degree of narrowing of the cava in the present experiments was often eventually as great or greater than that produced by Nayak et al., but ascites was earlier in appearance and greater in quantity in the animals of those workers than in the rats of the present series. This may be

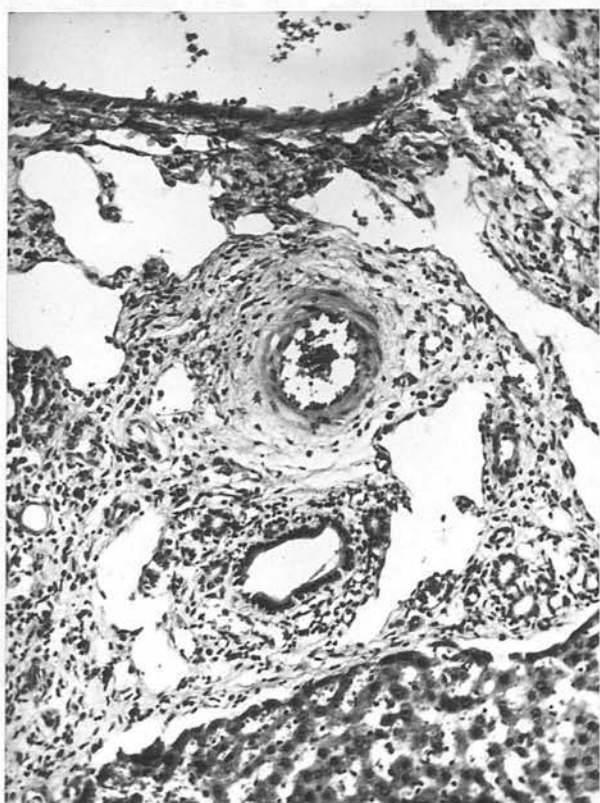


Fig., 171. RL 43 killed at 18 weeks. Dilated lymphatics round a hepatic artery in a large portal tract. H. & E. x 125.

due to trauma in the abdominal operation which the other workers used. In the experiments described in this thesis the ascites was increased greatly by the handling of the liver.

Although the peritoneum of the rat can absorb large quantities of fluid from the cavity, Nairn (1957) has shown that this absorption is often associated with hydrothorax which was not encountered in the experiments reported here. Spaces of Disse were not seen at any stage. They have been described in hepatic venous congestion in the cat (Bolton and Barnard, 1931). Fibrous peritoneal tags such as occur in Chiari's Disease (Figs. 80 and 114-116) and in the ascites of chronic venous congestion of the liver in man (Figs. 66 and 67) were rarely found in the rats. It is concluded that in the present experiments there was little transudation from the surface of the liver or elsewhere into the peritoneal cavity. On the other hand the lymphatics of the liver were grossly enlarged for a long time after the cava was obstructed. The lymphatics of the rat seem able to carry off successfully from the liver all the excess of fluid occasioned by the congestion of the organ and are perhaps more efficient in this respect than those of man or of the dog. The differences between the species may however be accounted for by the fact that lymphatics are virtually absent from the liver capsule of the rat, whereas they form an important part of the lymphatic system in other species. The latter explanation seems the more probable because the marked degree to which the superficial areas of the rat livers were damaged might be supposed to favour transudation from the surface. In a negative sense, then, the results of the present experiments favour the view that the ascites of Chiari's Disease and chronic venous

congestion of the liver in man are related to the excessive production of lymph or tissue fluid in the liver. In the latent phase of Chiari's Disease ascites is probably formed but does not accumulate because it is reabsorbed, whereas in the rat it seems that only small quantities of fluid are formed.

By the end of the 6th week after operation in the rats, there was no longer any tendency to form ascites, possibly because the lymphatics had enlarged sufficiently to deal with the increased flow. The lymphatics did not become any bigger in the ensuing weeks. The fact that the portal-venous branches of the rat are more muscular than the radicles of the hepatic vein (chapter II) may have some bearing on the difference in response between the rat and the dog in experimental venous congestion of the liver. The arrangement in the rat may permit a degree of compensatory reduction in the hepatic inflow which may not be possible in the dog. The ascites of hepatic congestion tends to remit spontaneously in dogs after many months, but the timing suggests that this is the result of the development of collaterals. Whatever the mechanism in the rat, a balance in the total circulatory arrangements of the liver was achieved by 7 weeks after the constriction of the cava.

A comparable balance was not struck in the case of the hepatic parenchyma, and foci of necrosis continued to form long after the original insult. The experimental procedure caused a slowly progressive liver lesion in which the features of cirrhosis eventually evolved, but it was not exactly the same as that described in the Budd-Chiari syndrome (chapter V) and in cardiac cirrhosis (chapter IV). In the human diseases, a cirrhotic pattern gradually developed, largely through the

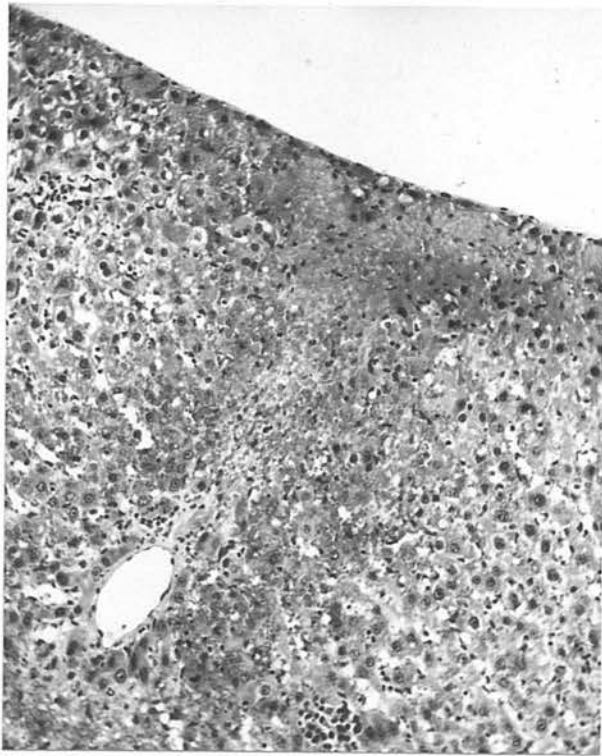


Fig., 172. RL 33 killed 42 days after operation (see also Fig. 151). A subcapsular haemorrhagic area extends out from a small intercalated vein. H. & E. x 125.

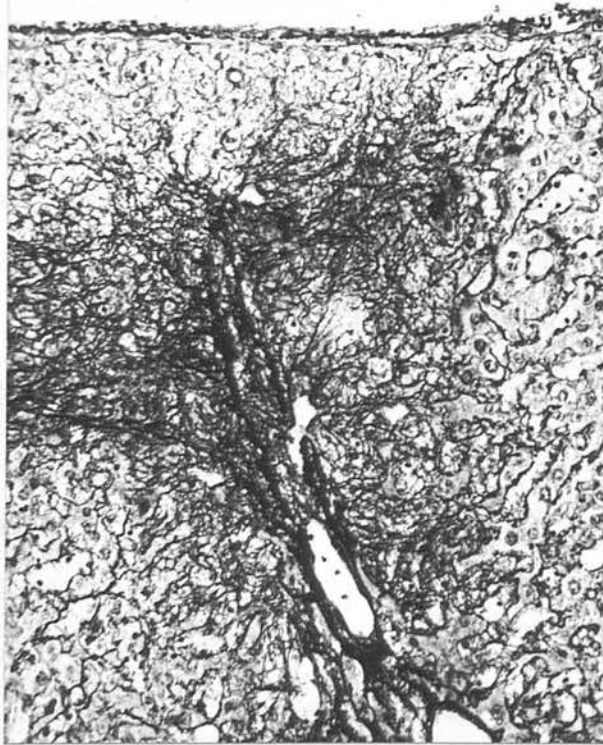


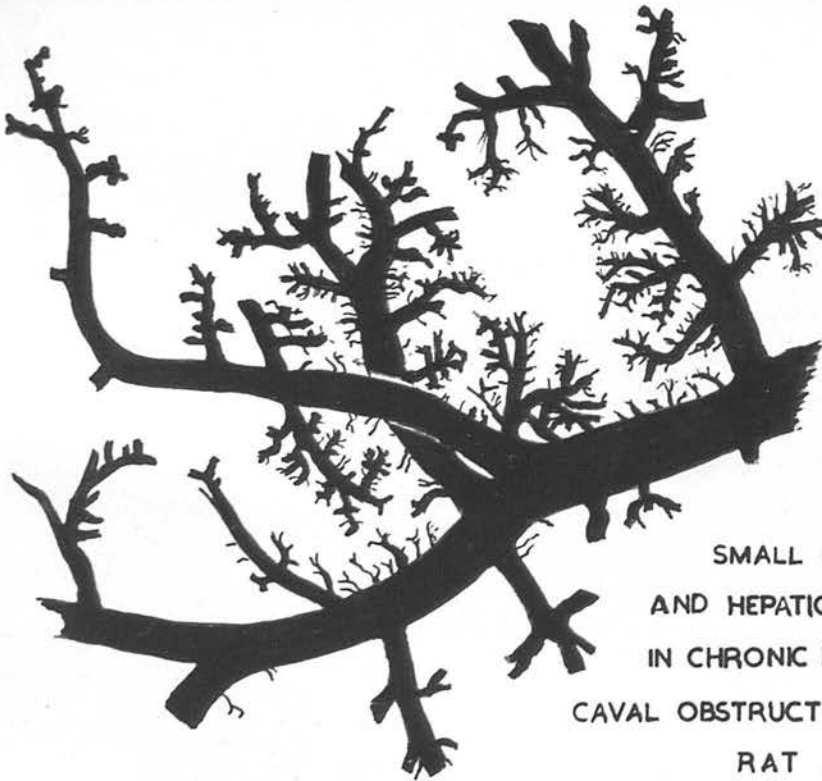
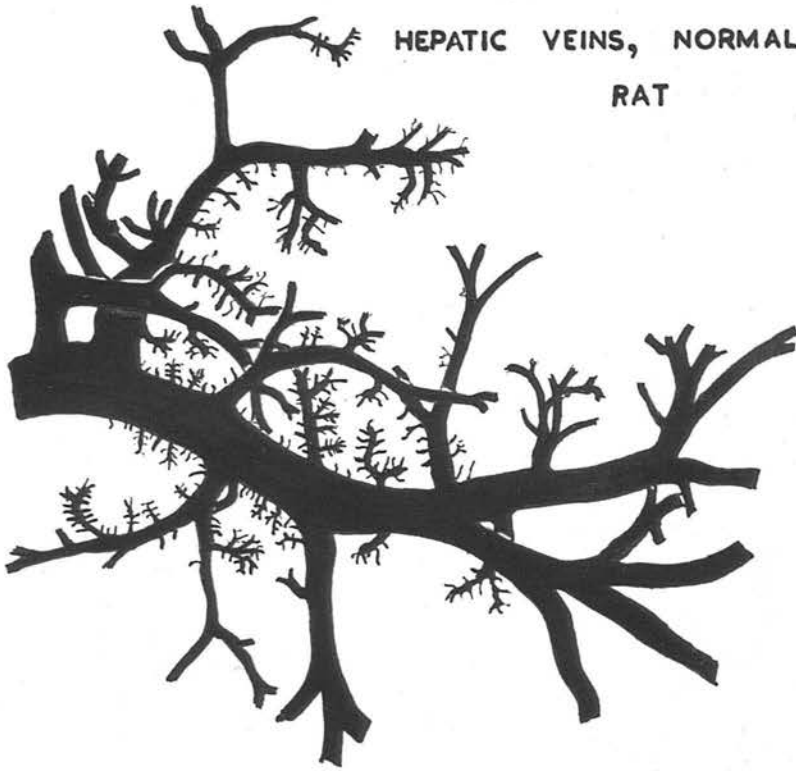
Fig., 173. RL 32 killed 31 days after operation. A similar field to figure 172, stained for reticulin. A central venule has been obliterated. Foote's stain x 150.

formation of fibrous septa uniting areas of centrilobular sclerosis to each other and to portal tracts (Figs. 126 and 128), and less often by the destruction of lobules through the closure of their central venules (Figs. 131 and 132). In the present experiments on the rat, it was the destruction of lobules or parts of lobules by necroses with or without closure of the central venules and other small veins (Figs. 172 and 173) and the subsequent scarring that were chiefly responsible for eventual hepatic fibrosis. While the experimental lesion resembled the human disease in the slow tempo of its progress and the minor development of nodular regeneration, the progression was due to recurrent necroses and not to a gradually increasing centrilobular sclerosis. Centrilobular sclerosis and the formation of septa, though found in some rats (Fig. 165) were infrequent. The liver tissue of the rats tended to react to the experimental procedure in a decisive fashion either maintaining its integrity to a greater extent than what is seen in chronic venous congestion in man, or undergoing repeated focal necrosis in a manner which is also not exactly the same as that in human disease. Some, though doubtless not all, of this difference may be related to the freer venous drainage of the rat liver and the absence of junctional constrictions. It may be because the liver cells of the rat probably function under potentially more varied conditions of venous pressure than the liver cells of man (see Chapter III) that species differences exist under the present pathological conditions. The occurrence of centrilobular sclerosis in human hepatic venous congestion corresponds to the fact that the area involved is a relative bottleneck in the venous drainage tract, for there is no other route of egress for

the blood from the lobule in man (see chapter I). In the rat on the other hand, sinusoids enter many vessels of larger calibre (Fig. 41 and chapter II). The closure of central venules and of intercalated veins by fibrosis which was sometimes observed (Figs. 164 and 173) might also be expected to embarrass the lobules of the rat liver less than similar lesions in man. A pattern approximating pseudolobulation was in fact rarely found in the present experiments and nothing closely resembling it was seen.

Although centrilobular necrosis was commonly found, it was often asymmetrical (Fig. 158) and the most susceptible areas appeared to be at the junctions of intercalated veins (Figs. 158, 165 and 166) and in the superficial portions of the liver. The reason for the localisation of venous junctions is not that stagnation is greater there, since venous drainage seems at least as good from such areas as from other parts of the rat liver. The necrosis may perhaps be the direct result of an elevation of the hepatic-venous pressure which might act more directly on the parenchyma at such junctions than elsewhere. The explanation for the preferential involvement of the superficial areas is not so hard to find. They are conspicuously haemorrhagic. Nayak et al. describe them as infarcts and they may be associated with venous closures (Figs. 172 and 173). A similar tendency to a more severe involvement of the superficial areas has been noted in venous congestion in the rabbit (Kawano) and in Chiari's Disease. It has been ascribed in the latter condition in chapter V to differences in the normal venous drainage of deep and central areas of the human liver (Figs. 25 and 26). Wakim and Mann (1942) observed long small

SMALL RADICLES AND
HEPATIC VEINS, NORMAL
RAT



SMALL RADICLES
AND HEPATIC VEINS,
IN CHRONIC INFERIOR
CAVAL OBSTRUCTION —
RAT RL62

Fig., 174. Camera-lucida drawings of neoprene-latex casts of the hepatic veins in an experimental animal (below), killed at 11 weeks, in comparison with a normal (above). Only a few sinusoids have been drawn.

veins in subcapsular areas of rat livers which they transilluminated, and it is the tissue normally drained by these terminal radicles that was most severely affected in the present experiments. This tissue is less well placed than tissue deeper in the liver to compensate for occlusion of its veins, because it does not benefit from sinusoidal anastomoses on all sides.

Abnormal vessels do not form freely in the thin liver capsule of the rat. It is not till the haemorrhagic zones become organised a long time after the caval obstruction, that wide vascular channels open up (Figs. 167 and 168). Since the left lateral and median lobes of the rat liver are thin (Figs. 37, and 169) the conditions in the superficial areas have a greater total effect on them than on the thicker right lobes or on the unified human liver. These thin lobes were the most affected portions of the livers in the present experiments. It is possible also that the liver cells in the subcapsular areas were further embarrassed by deviation of blood through central tissue via the short-circuit route of Daniel and Pritchard (1951) which might have operated under the experimental conditions of impaired circulation. In neoprene casts made of the hepatic veins of 2 animals killed at 10 and 11 weeks respectively, the peripheral portions showed an irregular vascular pattern, while the vessels in the central areas were normally arranged though irregularly dilated and stumpy in outline (Fig. 174). A similar appearance in a cast of human hepatic veins in chronic venous congestion is illustrated by Belli and Sprovieri.

Among other consequences of the caval constriction, foci of cholangio-fibrosis may be mentioned (Figs. 160 and 175). Their occurrence following a purely mechanical procedure is an

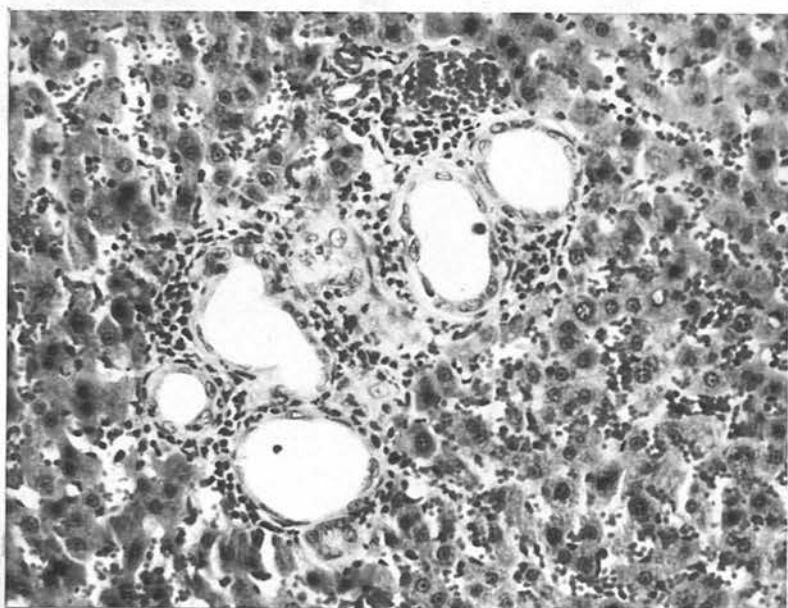


Fig., 175. RL 44 killed at 18 weeks. A clump of biliary cysts (cholangio-fibrosis). H. & E. x 230.

indication of the non-specific aetiology of this premalignant lesion of the rat. György (1954) states that "In general it may be assumed that all necrogenic hepatotoxic agents are potential carcinogens for the liver." In the present experiments the foci of cholangio-fibrosis apparently formed in the healing of foci of necrosis and they would appear to constitute one of the links between necrosis and carcinogenesis in the rat liver. The characters of the necrosis in the acute stage and of its resorption were non-specific and in general similar to the lesions seen at like periods after the insult in rats poisoned with senecio alkaloids. It is interesting to note that fibrinoid droplets were found in the liver cells in the experiments with senecio alkaloids reported earlier in this chapter as well as in those under discussion here. Bull et al. reported similar bodies as "protein globules" in descriptions of their findings with another pyrrolizidine alkaloid in rats, and considered them to be non-specific as they evidently are. Nairn et al. (1958) investigated cytoplasmic vacuolation of liver cells in several types of liver injury, by ultra-violet-flourescence microscopy and stated that the vacuoles in their sections contained material similar to blood plasma. It is possible that the fibrinoid droplets in the present material may be associated with the watery vacuolation found in the earlier stages of the necrosis (Figs. 156 and 157) and in chronic venous congestion of the human liver (Fig. 62b).

The formation of thrombi in the hepatic cava in the present series was probably the result of hepatic necrosis. The wall of the cava is thin where it passes through the liver, and adjacent hepatic necroses probably have an effect on the caval

endothelium. Thus the wall of the vessel may be altered as well as the character of the flow through it, by the ligature above. The fact that the hepatic lesions were not greatly enhanced by such additional occlusions was probably due to the possibility of collateral drainage provided by the diaphragmatic vein (Fig. 39 dv) which terminates in the end of the left ostium. Because of the small size of the rat, this and other collaterals are all close to the experimental obstruction. On the basis of these observations and of those in Chiari's Disease and other work referred to in chapter V, it may be postulated as a general rule that the closer a collateral is situated to the venous occlusion for which it compensates, the more effective is it likely to be.

Venous thromboses were not found in sites not directly affected by the operation in any of the experimental animals. This suggests firstly that where multiple venous thromboses are found in Chiari's Disease they are causally related to the hepatic venous occlusions and secondly that venous congestion of the liver per se does not induce extra-hepatic venous thromboses.

Enlargement of the spleen was found at all periods after the caval constrictions in a comparable degree to that produced by Reynell by subtotal constriction of the portal vein in the rat. Splenomegaly in Chiari's Disease, as in other forms of human portal hypertension is marked by sclerosis and varying degrees of hyperplasia of the white and the red pulp, but small foci of haemopoiesis are usually present. In the present experiments, the normal haemopoiesis of the rat spleen was sometimes massively increased and together with hyperplasia of white and red pulp accounted regularly for a considerable increase in

weight. Congestion was generally not severe after the first few days. The changes were similar to those described in ethionine-induced cirrhosis by Kent et al. (1957) who stress the use of the methyl-green-pyronine stain in the identification of the pulp cells, and many pyroninophilic cells of varying morphology were found in the spleens of the present series. A red staining of the cytoplasm by this technique probably also occurs, however, in primitive haemopoietic cells, since, in man at least, ribonucleic acid is present in the latter (Miale, 1958). On this and on morphological grounds, it is concluded that a variable but not inconsiderable proportion of the hyperplastic elements of the white pulp were haemopoietic; megakaryocytes were present often in large numbers. Cameron and de Saram (1939) came to the conclusion that splenic-pulp hyperplasia resulting from liver disease in the rat was independent of portal-venous hypertension and Kent et al. have sought to link it with an elevation in gamma globulin.

The fibrosing element was less in the splenic lesions of the present series than in the experiments of Kent et al. or in the more advanced cases of Chiari's Disease. Fibrosis probably indicates the degree of portal hypertension better than the reaction of the parenchymal cells of the pulp. The conditions of the present experiments in this respect are more like those of the early stages of Chiari's Disease (chapter V) than those of the later stages when splenic fibrosis is well established. Thus while the reaction of the rat spleen to the experimental procedure was similar to that found in the human condition, there were variations in the relative importance of the different elements of the lesion. These are probably due to a less persistent elevation of the portal pressure in rats as well

as to a species variation in the character of the splenic reaction. Reynell has shown that experimental portal hypertension tends to diminish spontaneously in rats.

Species variations: Bolton and Barnard (1928) who reported endothelial proliferations on the surfaces of the congested livers of the cats in their experiments associated these tags with the formation of ascites. The scarcity of such tags in the present experiments on rats can be related to the paucity of the ascites produced. The conditions on the surface of the liver are not the only considerations however. Apart from possible differences in the physiological methods of maintaining fluid balance, particular anatomical features of the liver and possibly of the hepato-duodenal ligament (Fig. 138) of certain species also play a part in causing variations in the reaction to hepatic venous congestion. From a comparison of the different species discussed in this thesis, it would seem that the two chief anatomical characters of the liver which may be related to these variations are the extent of the lymphatic network in the liver capsule and the degree of muscularity of the hepatic veins. These reach their greatest development in the dog. In the rat the liver capsule is thin and practically devoid of lymphatics and the hepatic veins contain very little muscle. In these anatomical respects the livers of the cat and of the rabbit apparently occupy a middle position and so resemble the human liver. Experiments by partial ligation of the inferior vena cava in the latter animals, which have already been referred to, resulted in ascites in amounts intermediate between those reported in the dog and in the rat. Probably experiments on the

cat and the rabbit provide the closest parallel to human hepatic venous congestion.

In one respect the experimental procedure reported here on the rat reproduces more closely the state of affairs in Chiari's Disease in man than do experiments on dogs. The unique anatomical characteristics of the canine hepatic veins favour the formation of ascites in venous congestion, and marked ascites invariably follows severe obstruction of the venous outflow. The rat on the other hand, after an initial period, can tolerate severe venous congestion without forming ascites, just as in Chiari's Disease the ostia can apparently be obstructed almost completely for long periods without overt ascites till the terminal phases of the disease. The ascites is kept in check in the rat, however, by a mechanism which is probably different from that in man, and experiments on both the dog and the rat must be kept in mind in considering the pathogenesis of ascites in human venous congestion of the liver. Since the rat liver can continue to function adequately and the animals remain healthy over many weeks during which the venous outflow from the liver is grossly obstructed, we can accept more readily the view that a long latent period can occur in Chiari's Disease in which severe ostial obstructions are present without symptoms.

The differences found in the hepatic and splenic lesions between the natural disease in man and the experimental condition in the rat are differences of emphasis rather than differences of kind, and processes occurring in one species may be recognized in the other, though not regularly to the same degree. If such differences are kept in mind, the procedure may be useful in the further study of chronic venous congestion as it occurs in man.

In another respect the slow tempo of progression of the hepatic damage and the absence of any extraneous toxin in its production might render the experimental lesion a satisfactory subject for biochemical study in the investigation of chronic hepatic disease.

SUMMARY

Several series of experiments designed to alter conditions in the hepatic veins of rats and rabbits are reported and discussed.

1. Experiments on rats with crystalline pyrrolizidine alkaloids - probably a mixture of jacobine and seneciphylline - from the common British ragwort did not result in a lesion suitable for study as a primary hepatic-venous phenomenon. The effects of these alkaloids on the livers of the rats over periods of short and intermediate duration were similar to those reported by most other workers with pyrrolizidine alkaloids and are greater in the male than in the female rat. In a few experiments on rabbits, the alkaloids were found to have an action on the liver similar to that in rats.

2. After trial of various methods of venous occlusion, partial ligation of the hepatic vein from the left lateral lobe was carried out in 29 rats. Variable amounts of liver tissue survived and partial regeneration often followed. The changes produced were not comparable to human chronic venous congestion and where regeneration occurred, the architecture of the normal liver was largely reproduced. The amount of liver tissue involved was such that hyperplasia of the undamaged liver compensated for the temporary impairment.

3. Partial ligation of the hepatic veins from the median and right anterior lobes of the liver in a few rabbits caused a lesion in these lobes similar to that in human chronic venous congestion or in Chiari's Disease. The difference between the results of the procedure in this animal and those in the rat are probably due partly to the relatively greater amount of

liver tissue compromised in the rabbit and partly to structural differences between the livers. In certain pertinent features the structure of the rabbit liver is more like the human organ than is the rat liver.

4. A technique involving thoracotomy and tracheotomy for partial ligation of the inferior vena cava in the thorax of the rat is described. The operation has a high mortality. Cellophane chiefly was used as the ligature; this caused a slight slow increase in the degree of stenosis post-operatively. An effective obstruction to the hepatic-venous outflow with reduction of the lumen of the cava by half its diameter was achieved with survival in 55 rats. This was often intensified by spontaneous thrombosis in the hepatic portion of the cava. A collateral circulation developed and protected the hind portions of the rats from venous stagnation. After the initial stages the animals remained in good health.

5. The livers of the rats were examined at periods up to 46 weeks after constriction of the thoracic vena cava. Zonal necrosis occurred soon after ligation but foci of necrosis continued to appear long after operation and caused a progressive liver lesion with scarring. Some special features of the location of the necrosis can be related to anatomical peculiarities of the rat liver. Parenchymatous tissue round the junctions of intercalated veins and under the external capsule in the thin lobes is particularly vulnerable. Lesions closely resembling the pseudolobulation found in other species were not encountered. Centrilobular sclerosis was much less frequent in the rat livers than in human chronic venous

congestion and the reaction of the liver parenchyma of the rat tended to take an "all or none" form - necrosis or survival largely intact.

8. Many of the foci of necrosis in the congested rat livers were repaired by scar tissue and the livers gradually became granular. Early nodular regeneration was found in the later stages. The hepatic veins became thick and fibrous. Occasionally thrombi formed in them; more often central venules and intercalated veins were occluded in relation to foci of necrosis. Splenic enlargement was common, due to pulp hyperplasia and haemopoiesis. Caval ligation in the rat thus partially reproduced the conditions of Chiari's Disease in man, especially the conditions of the earlier phases of the disease. The differences in the reaction of the organs are largely differences of emphasis rather than differences of kind.

9. Small amounts of ascites, greatly increased by handling of the liver, were found in the rats at from 1 to 6 weeks after constriction of the thoracic cava. The ascites was scanty and transient in comparison with that found in dogs subjected to a similar procedure. In this regard the reaction of the rat is more like that of man in whom severe obstruction of the ostia may be tolerated for a long time without ascites. The factors keeping ascites in check in man and in the rat are, however, probably different.

10. The varying propensities of different species to form ascites in venous congestion of the liver can be related to anatomical species differences in the extent of the lymphatic network in the liver capsule and the degree of muscularity

of the hepatic veins. In this respect the human liver occupies a position intermediate between those of the dog and of the rat. Consideration of the results of experimental venous congestion of the liver in both the rat and the dog is necessary to understand the pathogenesis of ascites in venous congestion of the human liver.

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APPENDIX A.

Chronic Urethane Poisoning in Rats:

By test the L.D. 50 of urethane by intraperitoneal injection was found to be approximately 250 mgm./100 gm. of rat.

I. Intraperitoneal Injection: 8 rats weighing from 200 - 350 gm.

Injections of a 10% watery solution of urethane were given over a period of 17 days, the doses being gradually raised from 0.5 ml. (50 mgm)/100 gm. of rat at the first injection to 1.0 ml. at the 9th. The rats slept after the injections.

At the 18th day all animals had lost 25% or more of their initial weights. Two were killed. The livers were congested and a little oedematous. There were slight abnormalities of the nuclei of the hepatic cells.

On the 19th day the six survivors were given a final (10th) dose of 1.1 ml. (110 mgm)/100 gm. and kept. Most of them had regained their original weights by the 40th day and all appeared well. Two died in the ensuing month. Necroses were found in the liver of one of these which died of pneumonia. The remaining four animals were killed at periods varying from 50 to 100 days after the start of the experiment. No important deviations from normal were seen in the livers or hepatic blood vessels of any of these animals.

II. Administration in the Drinking Water: 8 rats, 8 months old.

1% urethane was substituted for drinking water and at the estimated average daily intake of 10 - 15 ml. per day, the daily dosage was 20-30 mgm/100 gm. or rat.

Course - After 9 weeks all were unwell and two died. After 16 weeks, one died of pneumonia and two were moribund and killed. One of the latter had pneumonia and the other haematuria.

After 17 weeks, the remaining three rats were ill and were killed. One of them had pneumonia.

Liver was generally slightly larger than normal. There was a little oedema and sometimes congestion and variable degrees of irregularity in size and contour of hepatic cell nuclei which was never marked. Hepatic-vein lesions, blood-lagoon formation and erythrophagocytosis were not observed.

The chief effect of the poisoning appears to have been a non-specific reduction in immunity to intercurrent infection and hepatic-venous lesions were not produced.

APPENDIX B.

Experimental Anaphylaxis in Rabbits:

Antigen - Horse Serum.

"One dose" of horse serum is 1 ml./100 gm., rabbit weight injected at laparotomy into the spleen at the rate of 1-1.5 ml./min. (ether anaesthesia).

Rabbit No.	HS 1	HS 2	HS 3	HS 4	HS 5.
Weight	2,500 gm.	2,600 gm.	1,900 gm.	2,600 gm.	2,400 gm.
1st day	1 dose (into portal vein) Animal died of haemorrhage during first operation.	1 dose	1 dose	1 dose	1 dose.
12th day.		skin test positive.	skin test positive.	skin test positive.	skin test positive.
17th day.		1 ml. horse serum by i.v.i. (ear vein).	1 ml. horse serum by i.v.i. (ear vein).	1 ml. horse serum by i.v.i. (ear vein).	1 ml. horse serum by i.v.i. (ear vein).
19th day.		repeat one dose.	repeat one dose.	repeat one dose.	repeat one dose.
26th day		Animal died of shock at second operation.	animal killed	animal killed	animal killed.
AUTOPSY FINDINGS.					
Liver		contraction of hepatic veins; dilatation of central venules & central sinusoids; slight fibrosis & oedema of portal tracts; no arterial lesion.	marked portal-tract lymphocytic infiltrate; focal necroses; few arterial lesions.	marked arteritis; slight pallor centrilobular zones.	As H S 4, but more severe.
Heart		increased cellularity of interstitial tissue and focal muscle atrophy.	marked arterial lesions; moderate endocardial damage; focal lesions of myocardium.	As HS 3	As HS 3.
Other		lymphocytic infiltrate in lungs. No arterial lesion.	severe arteritis spleen	As HS 3 & arteritis in renal pelvis.	As HS 3.

There were no lesions in the hepatic veins or ostia or in any other systemic veins. All animals were in shock after first dose and severely shocked after second dose.

GENERAL SUMMARY AND CONCLUSIONS.

More detailed summaries have been appended to each chapter.

The anatomy and microscopical structure of the hepatic veins of man are described on the basis of personal observations. The main drainage territories do not correspond closely to the areas supplied by the portal-venous branches. Structural differences in the ostial portions of the veins permit considerable narrowing of the lumen there. The most important venous-barrier mechanism in the liver however, is probably that formed by junctional constrictions at the frequent terminations of central venules in hepatic veins.

The hepatic-venous system of the rat is fully described. Certain structural peculiarities are important in comparing histological changes in the liver of the rat with those in other species. The hepatic veins of some other mammals are also considered. Homologous lobes of the liver of different animals can readily be identified by their venous drainage and compared anatomically with portions of the human liver.

A review of the physiological studies of others and of the anatomical findings indicates that the hepatic-venous system of most mammals is capable of a vasomotor action. It is suggested that the clearest instance of a physiological action concerns respiration and the protection of the sinusoidal circulation of the liver and to a lesser degree the portal bed from the respiratory variations in caval venous pressure.

Some pathological conditions affecting the hepatic-venous system are reviewed. In the ascites of chronic venous congestion of the liver, fibrous tags form on the peritoneal surface. Similar tags are found in the Budd-Chiari syndrome. They probably mark the sites of transudation of fluid.

The pathological and clinical findings in 12 cases of the Budd-Chiari syndrome are described and discussed. The primary site of venous occlusion was shown to be at the ostia (Chiari's Disease) in five cases and was probably at this site in three others. A latent period of variable length apparently intervenes in many cases between the formation of the occlusions and the development of ascites and other symptoms. The pathogenesis is usually thrombotic and not inflammatory or congenital.

Several series of experiments designed to alter the conditions in the hepatic veins of rats and rabbits are reported. The administration of pyrrolizidine alkaloids from the common British ragwort did not yield lesions suitable for study as a primary venous phenomenon. The lesions caused in a lobe of the rat liver by partial ligation of its hepatic vein were not similar to those of human chronic venous congestion. A closer parallel was produced in similar experiments on rabbits. A technique for partial ligation of the inferior vena cava in the thorax of the rat is described. The resulting hepatic lesion differs from those of chronic venous congestion and Chiari's Disease in man in several respects. The

ascites resulting is transient in comparison with that produced in dogs by similar experiments.