THESIS ON

SPLENIC ANAEMIA,

WITH SPECIAL REFERENCE TO

HEPATOLIENAL FIBROSIS.

by

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'Tis directed against the spleen,
my worthy sirs.

Tristram Shandy.

PREFACE

Modern Medicine can never cease to honour the spirit of William Harvey who dared to challenge classical doctrine in quest of the ultimate truth. His lesson in critical reinvestigation of the bases of an unsatisfactory hypothesis may still be learned with advantage. Studies in the group of diseases known as "splenic anaemia" have too long been haunted by the spectre of "Banti's Disease", an ill-defined conception shrouded in an obscurity which has proved an insurmountable barrier.

The last account given by Banti of his disease was based on a study of 50 personal cases. Almost without exception, the writings on splenic anaemia since Banti's work became generally known, have been confused by attempts to correlate the findings with Banti's descriptions. This method of approach invariably led into a blind alley, owing to the rigid and highly individualistic views held by Banti. On the basis of pathological material from 89 cases of splenic anaemia, the writer has ventured to break away from this classical method of approach. The term "splenic anaemia" is used in its original historical sense as a generic term for a group of diseases. The commonest member of

this group is hepatolienal fibrosis. Banti's disease is relegated to a minor position as one of the syndromes which may occur among the varying clinical and pathological manifestations of this disease. This broader outlook has led to a new conception of the pathogenesis of hepatolienal fibrosis, which, if substantiated, may have its repercussions on the rationale of treatment. The value of splenectomy has been called in question.

As the primary object of the work was the elucidation of the pathology of the various diseases classed as "splenic anaemia", little new ground has been broken in the study of the clinical features. Nevertheless the mass of material has yielded data, which, though meagre on some points, may be of some value as a starting place for the further study of the manifold inter-relations of the liver, spleen and haematopoietic system.

The work has been rendered possible by the financial aid of the University of Edinburgh, (Goodsir Memorial Fellowship and Moray Endowment) the Beit Memorial Trust, and the Medical Research Council, which latter body defrayed the expenses of that portion of the work done in the University of Aberdeen.

The work has extended over three years

and has been carried out in the Surgical Laboratories of the University of Edinburgh (Professor Wilkie), the Department of Medicine, University of Aberdeen (Professor Davidson), and the Medical Unit, University College Hospital Medical School, London (Prof. T.R.Elliott). To the director of each laboratory I am indebted for the patience with which he awaited the results of a long and tedious research.

To the physicians and surgeons of the Royal Infirmary, Edinburgh, I am indebted for free access to case records and pathological material, and especially to Prof. J. Fraser, Mr J.W.Struthers, and Prof. Wilkie. Dr F.E.Reynolds kindly supplied the material from cases of Egyptian splenomegaly.

The physiological studies, detailed in chapters 7 and 8, were carried out at first in the Department of Physiology, University of Aberdeen, where the writer had the generous help of Prof. J.J.R.Macleod and Dr J.M.Peterson.

For facilities in the experimental study of hepatitis the writer has to express his thanks to Prof. T. Shennan and Dr J.Gray. For patient section cutting and other technical aid, thanks are also due to Messrs Knights, Henderson, Pettigrew and Nelson. The coloured illustrations in this work have been executed by Mr J. Grieve of Edinburgh,

with one or two exceptions.

Chapters 1 and 2 constitute an amplification of a preliminary study published in the Edinburgh Medical Journal in 1931. Chapters 7 and 8 are reproduced almost verbally from the Journal of Physiology. For permission to include this work, already published, I am indebted to the Faculty of Medicine, University of Edinburgh.

Lastly, a special debt is due to Dr J.W.McNee, who has taken the deepest interest in the work since its inception, and without whose generous help and practical advice , as well as unstinted kindness in the supply of pathological material and case notes, the work could not have been carried through to its present stage.

London, June, 1933.

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CONTRACTIONS USED IN THE BLOOD TABLES.

B. Basophil polymorphs.
C.I. Colour Index.
E. Eosinophils.
Hb Haemoglobin.
L. Lymphocytes.
M. Monocytes.
Mc Myelocytes.
N. Neutrophil polymorphs.
N.R. Nucleated red cells, as percentage of White cells (%W).
R.B.C. Red blood corpuscles.
W.B.C. White blood corpuscles.

SPLENIC ANAEMIA.

INTRODUCTION.

1. Historical Survey.

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SPLENIC ANAEMIA.

1. Historical Survey.

Splenic anaemia was first differentiated from leukaemia by Gretzel in 1866. The disease he described occurred in a child of ten months with dysentery and severe anaemia, with considerable enlargement of the spleen, and a lesser degree of enlargement of the lymph-nodes. The disease in question was not leukaemia, as was shown by the relatively crude methods of blood examination then employed. Although this case may easily have been one of Hodgkin's disease or of von Jaksch's disease, it served as the starting point in the study of a new clinical syndrome.

In 1871, H. C. Wood described a case, "Splenic variety of pseudoleukaemia", with enlargement of the spleen and severe anaemia, but without leucocytosis. In 1877, Strümpell described a case of splenic anaemia in a subject aged 25 years. This patient had four attacks of severe anaemia in the course of eighteen months. Each attack lasted about eight weeks, and was followed by an interval of comparative health. During each attack the spleen was enlarged and there was some temperature. The spleen diminished in size between the attacks. The patient died in the final attack. At post mortem the bone marrow was active and the spleen congested.

Strümpell emphasised the fact that the splenic enlargement was not determined by any hyperplasia of the spleen but solely by distention with blood. He considered that blood was being destroyed by the enlarged spleen. From the description given, this case was probably haemolytic jaundice.

In 1894, Guido Banti published his description of the disease which usually bears his name, under the non-committal title of "Splenomegalia con cirrosi epatica". This classical work was followed by other writings on the disease by the same author, not only in his own language, but in French and German. He thus drew the attention of physicians of the latter countries to what he considered a well defined clinico-pathological entity. Reference to his original publications reveals the painstaking nature of Banti's work. The clinical descriptions are clear and vivid, while the orderly description of the anatomical changes in the spleen form a marked contrast to many of the obscure descriptions written by others in later and more enlightened times.

Sir William Osler (1900) drew the attention of English speaking clinicians and pathologists to the disease "splenic anaemia", which he described as "a disease, probably an intoxication of an unknown nature, characterised by great chronicity, primary progressive enlargement of the spleen which cannot be

correlated with any known cause (primary splenomegaly), anaemia of a secondary type with leucopenia, a marked tendency to haemorrhage particularly from the stomach, and in many cases a terminal stage with cirrhosis of the liver and jaundice (Banti's disease)."

This definition of splenic anaemia may still be taken as representing the conception of many present day physicians. It gives clearly defined indications for the clinical use of the term. There is no attempt to clarify the exact nature of the condition, and the pathology and morbid anatomy are not discussed.

In the last thirty years writings on splenic anaemia have been profuse. Senator (1901) and Micheli (1906) held that there was no "splenic anaemia" which did not correspond to a stage of Banti's disease. This conception led to the use of the terms "splenic anaemia" and "Banti's disease" as synonymous.

Owing to the difficulties of assessing the nature of pathological changes in the spleen the descriptions of the morbid appearances in many of the published case records are almost valueless. It thus becomes impossible to say whether many of the reported instances correspond closely with Banti's postulates or not.

There are many examples of confusion with acholuric jaundice in particular. Certain cases, such as that described by Kidd (1913), in which the pathological examination of the spleen revealed no abnormality, and which was therefore called "simple hypertrophy" of the spleen, certainly cannot be included as instances of Banti's disease.

Quite soon after Banti had declared in detail the requirements for the diagnosis of his disease, questions were raised as to whether the Banti type of spleen could not be found in cases of ordinary hepatic cirrhosis. At a discussion in Rome in 1905, Banti was vigorously attacked by Marchiafava, one of his own compatriots, on this point. The final outcome of the argument was that Banti held that the venous sinuses of the spleen were more widely dilated in primary cirrhosis than in Banti's disease, and that the typical alterations in the follicles were absent.

In Germany, detailed studies were carried out by various workers on small series of cases, and many opinions were expressed. Chiari (1910) was of the opinion that Banti's "fibroadenie" could not be differentiated in any way from an ordinary fibrosis of the spleen. Klopstock (1907) believed that a spleen corresponding exactly to that described by Banti had never been found in cases of liver cirrhosis associated with splenome-

galy. In 1920 Mennet reviewed the literature up to that date with great care, and established to some extent the view of Klopstock. He found that many cases, while corresponding in a general way to Banti's description, deviated from it in some detail. Grave doubts became prevalent as to whether Banti's disease existed as a distinct and separate entity. Eppinger, in his monumental work, "Die Hepatolienalen Erkrankungen" goes into the question carefully, and his final statement is that he had only twice seen examples of Banti's disease, one in a German who had been a prisoner of war in Sicily, and one in an Albanian. He seemed inclined to believe that Banti's disease was a separate entity, but was limited geographically to the shores of the Mediterranean. In 1924, Durr, working in Aschoff's laboratory, made a careful comparative study of sections from cases of Banti's disease which he obtained from Banti himself, and from cases of hepatic cirrhosis. He came to the conclusion that there was no single pathological criterion whereby the spleens of Banti's disease could be distinguished from the enlarged spleen occurring in cirrhosis of the liver.

Further confusion, however, was added about this time by the "mycotic" school, which has flourished during the last decade, especially in France. It was claimed that "splenic anaemia" was caused by a strep-

ptothrix. The origin and explanation of this theory will be fully discussed elsewhere. It has nothing to commend it. The structures which were taken to be fungi are either elongated crystalloid structures, or hyaline collagenous threads encrusted with pigment. The pigment is probably derived from haemoglobin, and takes origin in old haemorrhages in the spleen.

The pathology of splenic enlargements is still somewhat bewildering, and in the absence of any satisfactory explanation of their origin, the subject of splenic anaemia still remains confused. There is, however, an increasing tendency to consider Banti's disease and splenomegalic cirrhosis of the liver as different manifestations of the same disease. Naegeli (1905) has held this opinion for many years. Erich Meyer (1913) and Lepehne (1930) are also quite clear on this point, and Eppinger (1926) in a recent publication states that "Bantis Annahme einer primaren Milzerkrankung als Grundlage einer bestimmter Zirroseform scheint uns ebensowenig das Richtige zu treffen wie die ursprungliche Theorie der Leberzirrose als einer ausschliesslichen Lebererkrankung."

The subject is undoubtedly complex, and all attempts to account for the etiology of the disease and its pathological manifestations have, hitherto, fallen

short in one or other respect. The hypothesis of fungus infection is unsatisfactory. Warthin's (1910) suggestion that splenic vein thrombosis was the cause of splenic anaemia in many instances, does not apply to all, and porto-splenic thrombosis is not of primary etiological importance. This will be discussed elsewhere. Norris and his colleagues (1918), Marchand (1907) and Chiari, have attempted to ascribe an important role to syphilis, which undoubtedly plays a part in some cases, but these are in the minority. While all these findings are of great interest and importance none has yet proved a satisfactory key to the problem.

From the foregoing account it is obvious that the term "splenic anaemia", in the sense in which it was first introduced, is merely a generic term for a group of diseases characterised by splenic enlargement with anaemia and leucopenia, or at least without leucocytosis. The term was applied by Strümpell to a case of haemolytic jaundice. Pathological advance in the past fifty years has recognised certain well defined entities which might have been entitled to the term "splenic anaemia" in the earlier days of its use. Gaucher's disease, acholuric jaundice, and aleukaemic leukaemia have been separated off as distinct clinico-pathological entities, but there remains a residue of diseases in which the term "splenic anaemia" is still somewhat

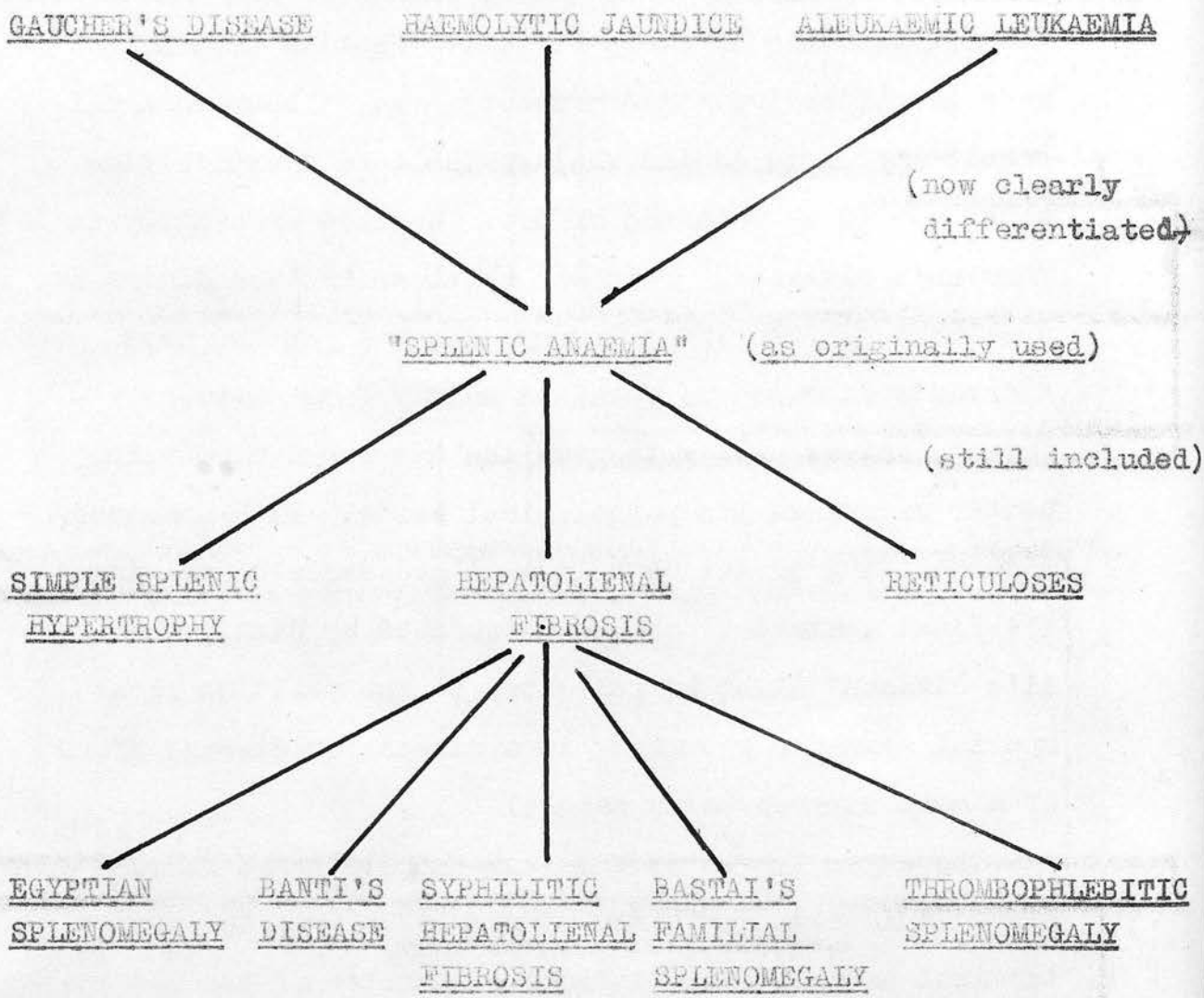
loosely applied. The use of the terms "splenic anaemia" and "Banti's disease" as synonymous is certainly to be deplored. "Banti's disease" is a form of pre-cirrhotic splenomegaly with certain well defined anatomical features in the spleen. As will be shown in the course of this study, only a proportion of the cases of so called "splenic anaemia" show these changes. The remainder of the cases belong to other disease groups, which are pathologically distinct from Banti's disease, although their clinical separation might offer some difficulties.

2. Terminology.

The confusion of terminology alone has led to misunderstanding. Banti's descriptions are quite clear from the clinical and pathological points of view, but as Mennet found, there are many cases which correspond generally to Banti's postulates, while not fulfilling the requirements in every detail. Banti's postulates were therefore too rigid probably, and it becomes a difficult matter to decide whether the term "Banti's disease" should be retained or not. We have an analogy in "Morvan's disease". Painless whitlows are not always a prominent feature of syringomyelia, and yet the term "Morvan's disease" is retained mainly from historic interest, but we prefer to give the disease a name which better expresses its pathological basis. With a better understanding of the pathological processes underlying the final anatomical changes described by Banti, "Banti's disease" might be relegated to the position of a special syndrome occurring in a disease or disease group of a more comprehensive nature.

Eppinger suggested the term "Hepatolienal fibrosis". This term certainly expresses briefly the common terminal pathological findings - increase of the connective tissue in the spleen and cirrhosis of the liver. The term has its drawbacks: there may be no fibrosis in the liver in Banti's first stage; there is probably also a stage in which there is no new connective tissue

TABLE I.


GAUCHER'S DISEASE
HAEMOLYTIC JAUNDICE
ALEUKAEMIC LEUKAEMIA
(now clearly differentiated)
"SPLENIC ANAEMIA" (as originally used)
(still included)
SIMPLE SPLENIC HYPERTROPHY
HEPATOLIENAL FIBROSIS
RETICULOSES
EGYPTIAN SPLENOMEGALY
BANTI'S DISEASE
SYPHILITIC HEPATOLIENAL FIBROSIS
BASTAI'S FAMILIAL SPLENOMEGALY
THROMBOPHLEBITIC SPLENOMEGALY

development in the spleen. But it conveys the impression that the liver and spleen are both involved in a disease process, which may ultimately lead to the formation of excess of fibrous tissue in both organs. As such it is undoubtedly the best pathological term for the disease group.

Naegeli wished the term "Splenic anaemia" to be discarded from medical literature as, in his opinion, it only led to confusion. It is a useful term to retain, however, if we understand that in making the diagnosis "splenic anaemia" we are not committing ourselves to an opinion on the pathology of the disease in question. A case of splenic anaemia may prove to be a case of hepatolienal fibrosis: on the other hand it may belong to another disease group which does not fit into the hepatolienal fibrosis class. The relation between these various conditions and groups is shown in the diagram.

"Primitive splenomegaly" is another term about which the same may be said as of "splenic anaemia". The term simply conveys the idea of enlargement of the spleen probably with no anaemia, and where there are no other features clinically to indicate the true nature of the disease.

3. General Survey of the Pathological Material forming the Basis of the Present Study.

The present study is based upon a series of cases of so-called "splenic anaemia" in the great majority of which the spleen was removed surgically. In a few instances only the pathological material was obtained at autopsy. The study of this disease group was begun in Edinburgh under the tenure of the Goodsir Memorial Fellowship, where the material was kindly put at the writer's disposal by the honorary staff of the Royal Infirmary, in particular by Professors Wilkie and Fraser and Mr. Struthers, to whom he is indebted for the pathological material and the case records of some forty cases in all.

During the past two and a half years the work has continued under the tenure of a Beit Memorial Fellowship, held partly in the University of Aberdeen, and more recently in the Medical Unit of University College Hospital Medical School, London. In the latter department the writer has had free access to Dr. McNee's unique collection of pathological material from cases of splenomegaly. From a personal study of this material and an analysis of the case records in University College Hospital, some twenty further cases have been added in which the details are sufficiently complete to warrant their

inclusion in this series.

The actual observations on pathological material alone have extended over not less than 89 spleens in all. In many of these, however, the case records were incomplete or unavailable, and the analysis here set forth has been confined to those instances in which the whole case could be exhibited.

The total pathological material examined was distributed somewhat as follows:

Hepatolienal Fibrosis.	59.
Acholuric jaundice.	13.
Simple hypertrophy of the spleen.	6.
Reticulo-endothelioses.	4.
Tuberculosis of the spleen.	2.
Gaucher's disease.	2.
Arterial angioma of the spleen.	1.
Sarcoma of the spleen.	2.
	89.

This table is in no way to be taken as a statistical analysis, as Dr. McNee's material was undoubtedly selected for submission to an expert opinion. Nevertheless, it tends to bring out the prominence of the hepato-lienal fibrosis class.

Of the hepatolienal fibrosis group only 41 cases have been selected for detailed examination. In the remaining 18 instances, however, the pathological material

left no doubt whatever that the condition belonged to this particular type of disease.

Pathologically and clinically acholuric jaundice is sufficiently well recognised and should be no longer retained as a type of "splenic anaemia". The microscopical picture is the most remarkably uniform in the whole range of splenic pathology, and should no longer be confused with the other types. Gaucher's disease is so rare and so well recognised pathologically when met with, and for the further reason that clinical details are lacking in both cases, it will not be described in this study.

The remainder of the types mentioned are still liable to be included under the term "splenic anaemia", and their clinical separation from one another may be a matter of some difficulty. Pathologically there is no doubt that they form distinct and separate disease processes, although the clinical pictures may be remarkably similar. These different types will be described and discussed.

The central point of the problem obviously lies in the hepatolienal fibrosis group, and this type will form the major part of the study to be presented. It is of interest to note that the number of spleens from this disease examined exceeds the number which formed the basis of Banti's last publication (1910). Banti's cases, collected over a period of more than twenty years, only totalled fifty. It is only as a result of the facilities for study of pathological material in three large medi-

cal schools that the present collection of cases has been made possible.

PART I.

HEPATOLIENAL FIBROSIS.

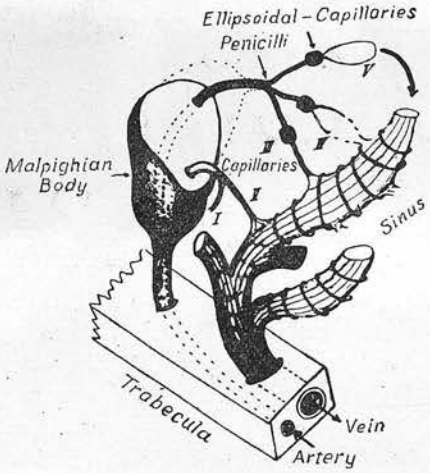


FIG. 1.—The circulation through the spleen. (After Braus.)

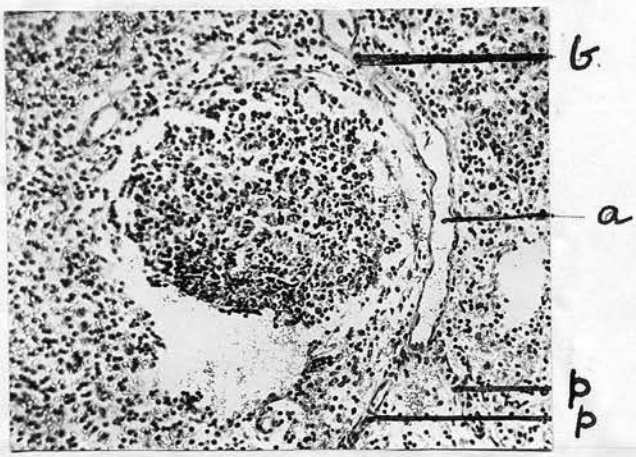


Fig. 2. (x125) Spleen of a child aet 6mos., injected with formalin via the artery. (a) shows an artery beyond the Malpighian body curving backwards from its bifurcation (b) around the Malpighian body to terminate in two penicillar arterioles (p). The splenic tissue has been ruptured by the force of the injection.

HEPATOLIENAL FIBROSIS

Chapter 1.

VASCULAR PATHOLOGY.

In the preceding section it has been noted that approximately two thirds of the cases of "splenic anaemia" fall into the hepatolienal fibrosis class. In making the diagnosis of hepatolienal fibrosis, the criteria adopted were:-

(1) The presence of certain characteristic vascular changes: viz.,

Any of the following four conditions;

a. Periarterial haemorrhage,

b. Periarterial fibrosis,

c. Siderotic nodules,

d. Peri-malpighian haemorrhages or fibrosis,

accompanied by

e. Dilated venous sinuses in the spleen with increase of connective tissue in their walls.

(2) The association of the splenomegaly with cirrhosis of the liver.

It is thus obvious that the diagnostic features in the spleen itself are determined essentially by changes affecting the local vascular system. A general knowledge of the mechanism of the circulation through the spleen is of fundamental importance for the understanding of the problems to be discussed.

THE CIRCULATION THROUGH THE SPLEEN.

The splenic artery, on entering the spleen, breaks up into smaller branches which lie in the trabeculae, each

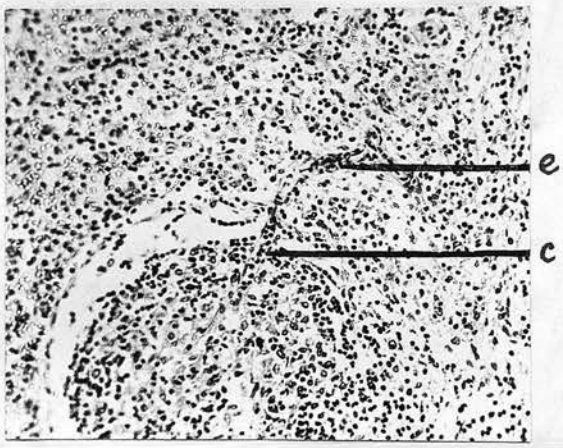


Fig.3 . (x120) Spleen of a child aet 6 mos showing an ellipsoid (e) in the immediate neighbourhood of the Malpighian body. (c) denotes a fine capillary passing in a radial direction from the Malpighian body.

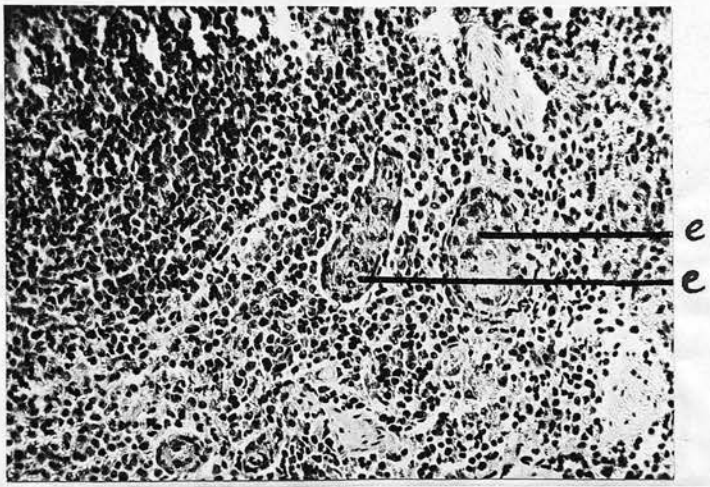


Fig. 4 . (x120) Ellipsoids (e) in the spleen of a fowl after the injection of India ink into the wing vein. The ink particles are caught up in the ellipsoids.

at first accompanied by a vein. Soon the vessels part company, so that many trabeculae carry only an artery or a vein. The artery finally leaves the trabecula and enters the pulp, where it receives a sheath of lymphoid tissue. This sheath becomes swollen in places to form the Malpighian body. Beyond the Malpighian body the artery loses its lymphatic sheath and breaks up in a dichotomous manner into several branches - the penicillar arteries. As Jäger (1929) has shown so beautifully, the penicillar arteries curve backward like the branches of a weeping ash, to encompass the Malpighian body, in the immediate neighbourhood of which they end. On following such an artery by serial sections, it abruptly loses its muscular coat and the surrounding splenic cells become condensed round the remaining endothelial tube to form an ellipsoid.

The ellipsoids are cone-shaped aggregations of cells resembling the reticulum cells of the spleen pulp, the only difference being that the interlocking protoplasmic processes of the cells are shorter and there is more cytoplasm surrounding the nuclei (Robison, 1926). The ellipsoids are much less marked in the human subject than in the cat and domestic fowl, for example.

The venous drainage system begins in the so-called sinuses, which form an anastomotic network and finally lead into the trabecular veins. The sinuses are

relatively wide channels, the walls of which consist of "parallel rows of endothelial cells loosely bound together by the protoplasmic processes of neighbouring pulp cells" (Robison) and by reticulin fibres. Between the cells lining the venous sinuses, there are slit-like stomata, the sinus wall being thus fenestrated.

As McNee (1929) has suggested, the ellipsoid forms a critical point in the circulatory system of the spleen. It may act as a sort of valve (Kapillarventil of Heidenhain, 1928), the condensed tissue of which it is formed collapsing over the end of the artery when attempts are made to force blood through the spleen from the veins to the arteries. It is also thought that it may protect the spleen pulp from sudden overflooding during rapid changes in the general blood-pressure. It is doubtful if this valvular action constitutes an important function however, for the same difficulty is met with in attempting to force fluid from the venous to the arterial side of the spleen in man , in whom the ellipsoids are only poorly developed, and often absent. The so-called "valvular action" is probably the result of increased pressure in the venous sinuses of the spleen pressing upon and collapsing the arteries and arterioles. It is easy to distend the venous sinuses in the spleen to the point of rupture by forcing fluid into the splenic vein under considerable pressure. Provided that the pressure is not raised too high or too suddenly, a flow in the backward direction can be achieved (Nisimaru and Steggerda, 1932).

(illegible). Tait and Cashin (1925) have shown that the ellipsoids filter off foreign particles in the blood stream. The true function of the ellipsoid is probably that of a plasma filter (Hueck, 1928). Nevertheless it is at this critical point, where the artery suddenly loses its muscular coat and merges into the fenestrated arterial capillary, that the "block" occurs, when the fluid pressure is suddenly raised in the venous system of the spleen. We shall return to this point later in discussing the effects of portal congestion. In the meantime let us take it that any local vascular catastrophe, occurring as a result of major changes in the pressure relations of the blood flow through the spleen, would tend to occur at this point.

In hepatolienal fibrosis the vascular changes observed fall into four distinct groups, and these will be discussed in turn:-

1. Hyaline Change in the arterial wall.
2. Perivascular haemorrhage, perivascular fibrosis, and the siderotic nodule: perimalpighian haemorrhage and fibrosis.
3. Endophlebitis of the Portal venous system, with or without thrombosis.
4. Dilatation of the venous sinuses of the spleen.

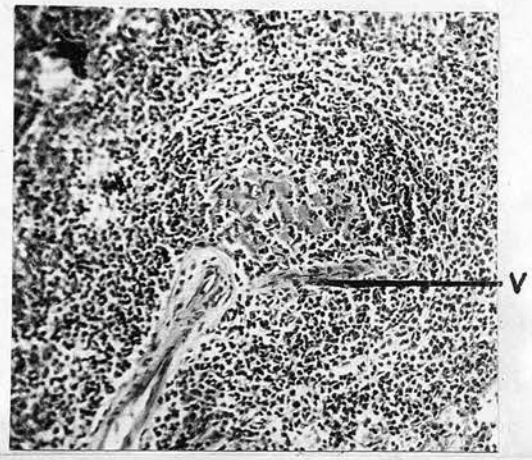


Fig. 5 .(x160) Hyaline deposits in the Malpighian body of an otherwise normal spleen in an adult male. Note the associated hyalinisation of a small vessel (v).

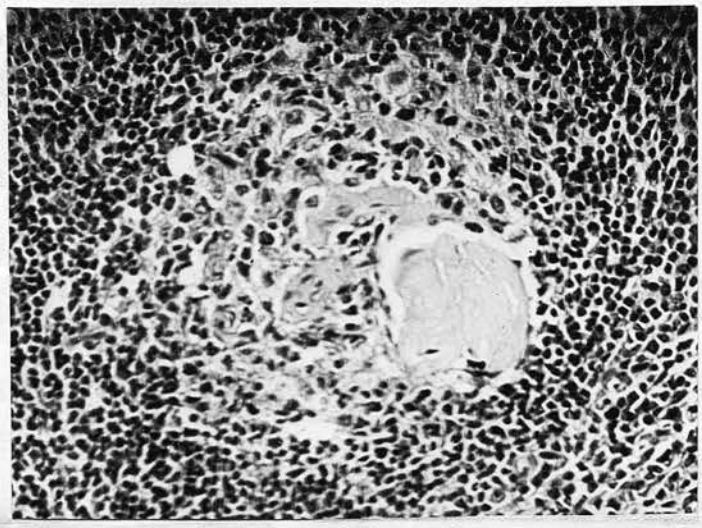


Fig. 6 . (x550) Hyaline deposits in the Malpighian body of a normal adult spleen.

1. HYALINE CHANGES.

Pathologists are quite familiar with the frequency of hyaline change in the arterioles of the spleen. In a series of twenty cases of hepatolienal fibrosis previously published by the present writer (1931), hyaline change was present in all the spleens examined with the exception of two, the latter being taken from young subjects under the age of fifteen years. It occurred in the blood vessels outside the trabeculae, and hyaline masses were frequently seen in the Malpighian bodies (figs 5,6). The change is included in this discussion as the frequency of the finding in normal spleens is not generally realised, and observations on hyaline changes have led in the past to faulty deductions.

Herxheimer (1917) examined 1140 spleens from autopsy material at all ages irrespective of the disease from which the patient suffered. He found that the small arteries in children under 10 years were usually unaltered or showed only slight hyaline alterations. Between the ages of 10 and 40 years, hyaline changes in the vessels were present in 50 per cent of cases to a marked degree, and this proportion increased at greater ages. Disease processes, with the exception of arteriosclerosis, seemed to have little influence on the incidence or extent of the disease. He concluded that

the cause of these extensive alterations must be dependent on the local conditions and especially on the peculiar vascular arrangements and special functional activities of the spleen.

Eppinger (1920) paid special attention to these changes in relationship to acholuric jaundice and pernicious anaemia. In the latter disease he found in the Malpighian bodies thick-walled central arteries, with hyaline deposits in the intima, in three-fourths of the cases. He suggested that these alterations were characteristic of pernicious anaemia. In haemolytic icterus he found similar changes, which he held to be responsible in some way for the intense congestion and extreme circulatory disturbance which characterises the spleen in that disease.

Dubreuil (1921) made observations on normal human spleens and observed the frequent presence of homogeneous "collagenous" masses in the Malpighian bodies. He concluded that such a mass represents an obliterated vessel replaced by a fibrous mass, and that "Colloidal" degeneration begins in the internal elastic lamina.

Matsuno (1922) examined 323 spleens and found small vessel alterations in 75.5 per cent. Among these he found the identical changes which Eppinger had regarded

as specific for pernicious anaemia. The alterations increase in frequency as age advances, and some of them may be related to ordinary arteriosclerosis. The follicular and penicillar arteries are affected most frequently.

Nakonetschky (1923) confirmed these findings of Matsuno and Herxheimer. He adds that it is important to differentiate the trabecular arteries from the other arteries of the pulp, since the former are subject to general changes affecting the systemic vessels.

While the presence of hyaline degeneration is thus well recognised, its actual significance is still in doubt. Until this has been explained the change will be liable to misinterpretation, such as occurred when it was considered by Eppinger to be a factor in the pathogenesis of pernicious anaemia and acholuric jaundice.

Hueck has put forward an interesting theory that hyaline change may be the normal process of obliteration of the active germ centres of the Malpighian bodies. The germ centre consists of a group of large pale cells in the centre of the Malpighian corpuscle, the cells of which often shew a process of active mitosis. The germ centres are indicative of activity of the central zone of cells in the formation of lymphocytes which lie in the outer zone. After adolescence

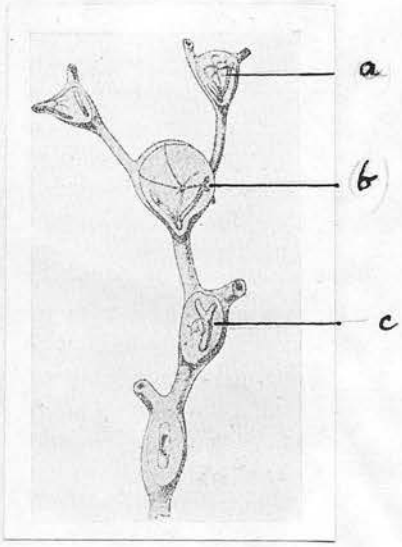


Fig. 7. (after Jäger) showing the evolution of the capillary network of the Malpighian body.
(a) The growing capillary loops of the developing germ-centre.
(b) The fully developed capillary system of the young active Malpighian body.
(c) The obliteration of capillaries in the involuted Malpighian body.

germ centres become relatively infrequent in the normal spleen.

The germ centre has an interesting developmental history. The lymphoid sheaths of the vessels are present before birth, but the active germ centres do not develop till after birth. They appear first as groups of large rounded protoplasmic cells at the margin of the lymphoid sheath. At the outer margin of such a cell group small lymphocytes make their appearance (Thiel and Downey, 1921). According to Jäger, Sabin (1916) and others, the development of the germ centre is preceded by the formation of a dense capillary network which leads to hypertrophy of the reticulum cells at the outer zone of the lymphoid sheath of the artery. At a later stage the capillaries of the node are obliterated by hyaline changes, which begin at the vertex of the capillary arch. (fig. 7)

The age periods of hyaline changes and the disappearance of germ centres show a close correspondence. Active germ centres are present in the lymphoid follicles in man up to the age of twenty. Thereafter they undergo involution and disappear (Hellman, 1928, Hellston, 1926). It is just at this age that hyaline changes begin to be common.

To regard hyaline change as an involution process falls into line with the generally accepted conception

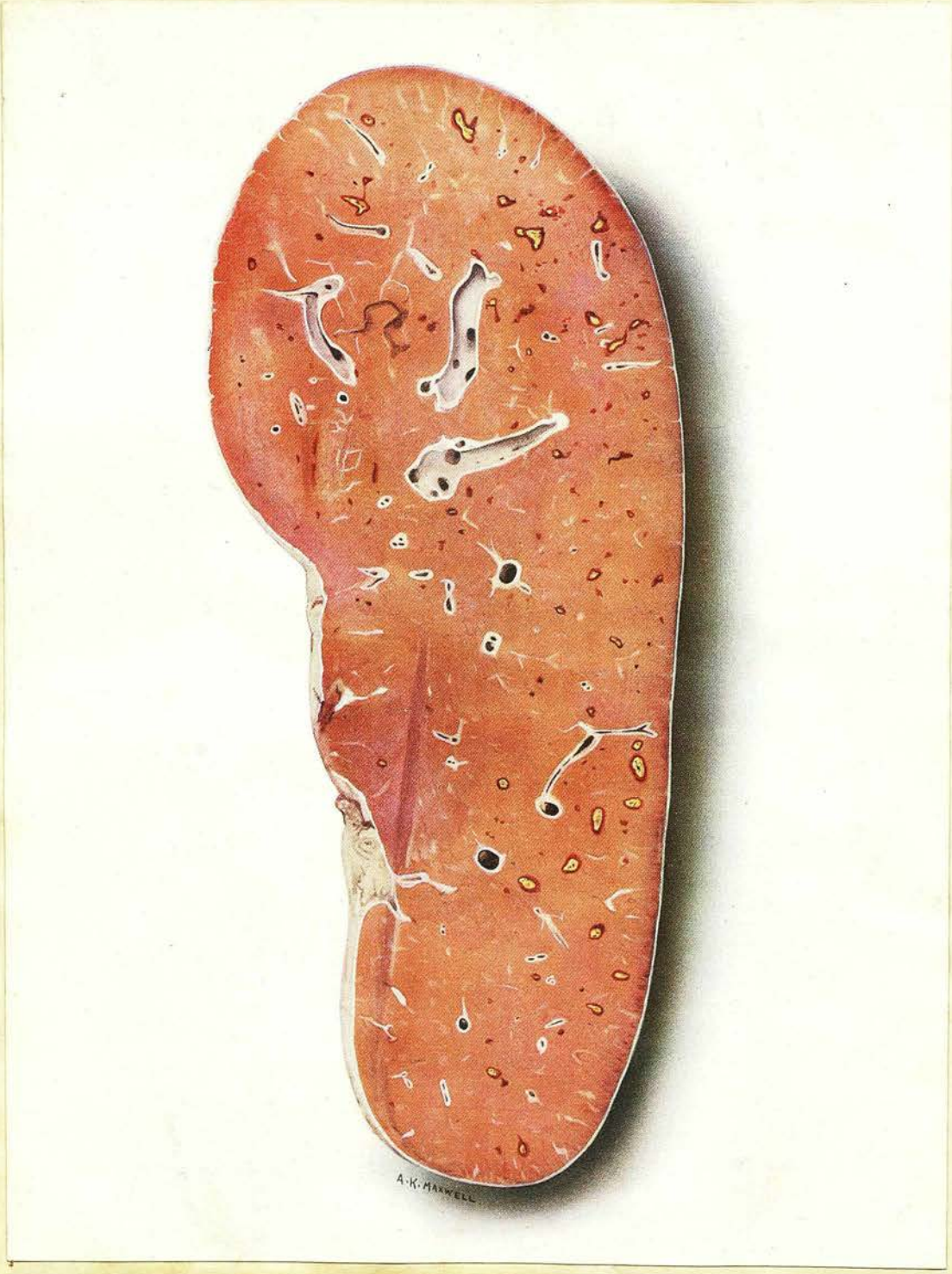


Fig.8 .(by kind permission of Dr J.W.McNee)
Spleen from a case of hepatolienal fibrosis, two-thirds natural size, showing siderotic nodules and periarterial haemorrhages.

of the significance of similar changes in the arteries of the uterus after the menopause.

The general inference is that hyaline degeneration in the blood vessels of the spleen along with hyaline deposits in the Malpighian bodies is to be regarded as a normal process probably related to the involution of lymphoid tissue in the organ. It may be widespread without having any pathological significance.

2. Perivascular Haemorrhage, Perivascular Fibrosis, and the Siderotic Nodule: Peri-malpighian Haemorrhage and Fibrosis.

McNee pointed out in 1929 that one of the commonest features of enlarged spleens in this country was the presence of rusty yellowish nodules on the cut surface. These nodules give a gritty sensation when cut with the knife. The unaided eye can usually distinguish a surrounding zone of haemorrhage. They vary in size from a pinhead to a split pea, and give a positive Prussian blue reaction, indicating the presence of iron.

Microscopically these areas are found to have a central artery with a diameter of 1/10th. to ½ mm. In the immediate neighbourhood of the artery there is a zone of considerable width which consists of branching hyaline connective tissue, the interstices of which

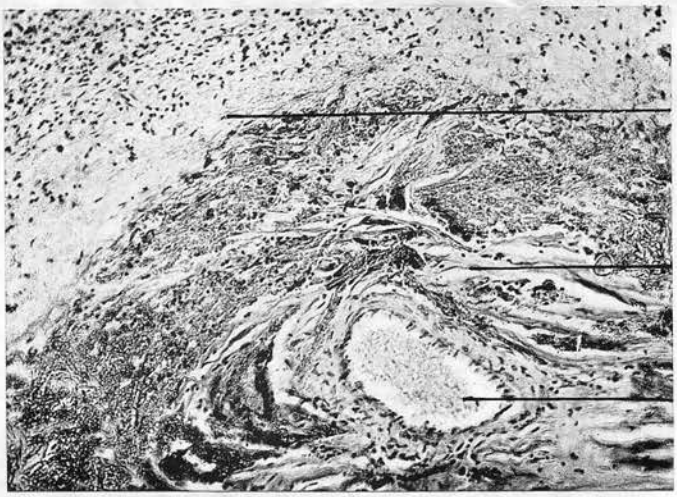


Fig. 9 .(from Case II.) Showing the general anatomy of the siderotic nodule. (a) The central artery, (b) the branching hyaline connective tissue with pigment caught in the interstices, (c) the outer zone of haemorrhage.

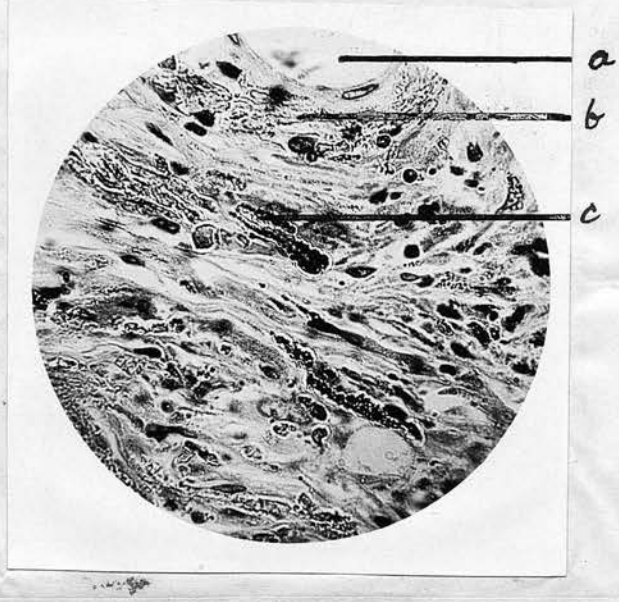


Fig. 10. (from Case XVIII) (oil immersion).
(a) the central artery. (b) crystalline pigment in the wall of the artery. (c) pigment crystals in the meshes of the hyaline connective tissue.

contain masses of golden yellow, pale yellow, and, in sections stained by haematoxylin, dark blue pigment. Outside this pigmented zone there is a zone of haemorrhage which separates the pigmented zone from the pulp tissue. (fig. 9)

The endothelium of the central artery is invariably healthy and the wall as a rule shows only hyaline change. Not infrequently, however, as noted by Sprunt (1911), narrow segmented bands of a golden yellow or yellowish green colour may be seen in the vessel wall outside the intima.

In the hyaline pigmented zone cell-nuclei are sparse and mostly of the small round type, resembling lymphocytes. A few, however, show the large clear stippled nucleus characteristic of the ordinary reticulum cells of the spleen. Some elongated cells are present lying along the connective tissue fibrils: these are fibroblasts. These cell types are obviously modified reticulum cells of the spleen pulp. A giant cell is occasionally encountered in these areas: its significance will be mentioned later. Haemosiderin pigment may be seen actually inside the reticulum cells and occasionally in the elongated fibroblasts.

The pigment of the pigmented zone consists of:-

(a) Amorphous rounded bluish-gray masses bearing a superficial resemblance to starch granules.

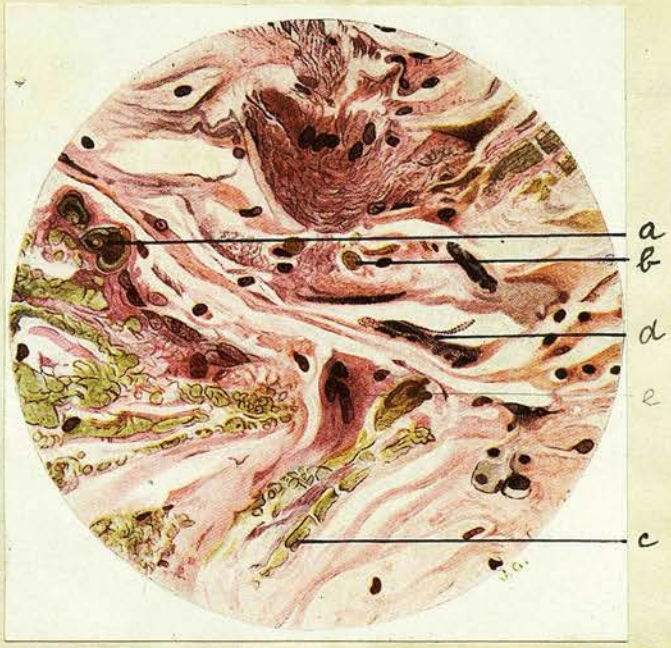


Fig. 11. (oil immersion) Colour drawing of a siderotic nodule, stained by haematoxylin and eosin. Note (a) bluish-grey concentric masses. (b) golden - yellow amorphous pigment. (c) elongated segmented yellow crystals. (d) bluish granular pigment along the hyaline connective tissue strands. (e) giant-cell.

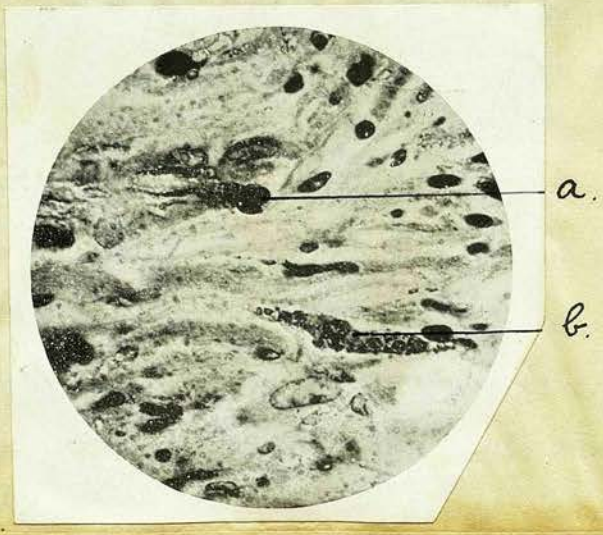


Fig. 12. (Oil immersion) Siderotic nodule. Note
(a) club-shaped end of an elongated crystal
(b) fibroblast containing haemosiderin pigment.

(b) Golden-yellow coarsely granular pigment, usually lying in rounded masses.

(c) Elongated, somewhat rectangular translucent, double-contoured, green, segmented masses lying along the hyaline fibrous strands.

(d) A pigment which stains dark blue with haematoxylin and with which the connective tissue fibres are encrusted.

In the outer haemorrhagic zone the majority of red cells are undergoing haemolysis, and fine pigment granules, possibly of haemosiderin, are seen lying among them. Just at the margin of the pigmented zone, where it abuts on the haemorrhage, the number of elongated fibroblastic cells is increased, and the golden-yellow pigment at this part is arranged in finer granules than elsewhere in the pigmented zone.

The history of our knowledge of these nodules has been reviewed by McNee (1929) and by Abrikossoff (1929). The condition was first described by Stengel (1904), but the first careful description was given by Gandy (1905). Since then various views have been expressed as to the nature of the lesion.

(1) The Mycotic Theory. Gibson (1914) attempted to prove by staining methods only the presence of a streptothrix in these cases, and he has recently reiterated his views in a book on the subject (1930).

Gibson's original work received little support until 1926-27, when Nanta (Algiers) observed these siderotic nodes in fifteen out of twenty spleens, and he considered some of the elongated crystalline structures to be the fructification organs of the aspergillus. In seven out of sixteen spleens removed by operation in Paris the same picture was present, and from two of these an aspergillus was cultivated. Simultaneously Schweizer (Geneva) examined five cases of Egyptian splenomegaly and found similar appearances in three. He concluded that this was a new group of spleen diseases-mycotic splenomegaly.

That the mycotic theory is improbable seems obvious for the following reasons:

(a) The nodules occur in a large number of different conditions in which the spleen is diseased: hepatolienal fibrosis, acholuric jaundice, Hodgkin's disease, leukaemia, syphilis and tuberculosis of the spleen (Jaffé and Hill, 1928). E. Weil and his co-workers, (1927) state that the aspergillus produces diseases which run different clinical courses. Mycotic splenomegaly thus expresses itself in six clinical forms - pure splenomegaly, splenomegaly with haemorrhage, with haemolytic icterus, with anaemia, with polycythaemia, and with ascites! The view that a single organism could cause such a varied group of patho-

logical conditions is wholly untenable.

(b) Injection into animals of any fungus that has been isolated from such spleens has failed completely to reproduce the disease. It produces an illness of a septic nature, which cannot be said to resemble any one of the numerous diseases of the spleen from which the fungus has been cultivated.

Oberling (1928) and Jaffé and Hill, while giving partial support to the mycotic theory, recognised the extraordinary variety of conditions in which the "mycelia" occurred. They are of the opinion that any fungus present must be a secondary invader and can have no pathological importance as a primary cause of splenic disease.

(2) The Mechanical or Chemical Theory. Sprunt (1911) expressed the opinion that iron compounds impregnate degenerated connective tissue fibres in a selective manner and that this may account for some if not all of the appearances. This view is supported by Christeller and Puskeppelies (1920). Gamna (1928) and Langeron (1928) state that the appearances are non-infective and are due to the impregnation of fibrin, connective tissue and elastic fibres by salts. Gandy and McNee draw attention to the fact that in spleens which show the nodules perivascular haemorrhage is invariably found and this appears to

Table II

Case	Perimalpighian Haem. or Fibr. Periart. Haem.	Periarterial Fibrosis.	Siderotic Nodules.	Venous sinuses	Portal vein and its Tributaries.	Haematemesis or melaena.
I.	+	+	+	+	D.F.	Very varicose. Thrombosis.	—
II.	+	+	+	+	d.f.	Endophlebitis (microscope)	+
III.	—	+	+	—	D.f.	Thrombosis. Varicosity of gastric veins.	+
IV.	—	+	+	—	D.f.	Old thrombosis Portal vein. Death from mesenteric throm.	—
V.	+	+	+	—	D.F.	Thickening of wall. Thrombosis and recanalisation of throm.	—
VI	+	+	+	+	d.f.	Dilated and thrombosed.	+
VII	—	+	+	—	D.f.	No mention.	—
VIII	+	+	+	+	D.F.	Dilatation of anastomotic veins in lower oesophagus	+
IX	+	+	+	—	D.F.	Dilated veins in abdominal wall and in spleen hilum.	+
X	—	—	+	—	D.F.	Caput medusae after opn.	—
XI	+	+	+	—	D.f.	Distended collaterals in abdominal wall.	—
XII	+	+	+	—	D.F.	Distended veins in abd.wall	—
XIII	+	+	+	+	D.F.	Veins not specially mentioned. N.B. Cirrhosis and ascites	+
XIV	+	+	+	—	D.F.	No mention. N.B. Cirrhosis	—
XV	+	+	+	+	D.F.	Dilated veins at lower end of oesophagus.	+
XVI	+	+	+	+	d.f.	No special mention, N.B. ascites	+
XVII	+	+	+	+	D.F.	Veins tortuous and thickened.	+
XVIII	+	+	+	+	D.F.	Great enlargement of veins in splenic pedicle.	+
XIX	+	+	+	+	D.f.	Distended veins round umbilicus	+
XX	+	+	+	+	D.f.	Distended tortuous and dilated	+
XXI	—	+	+	+	D.F.	Varicosity of veins.	+
XXII	NO VASCULAR	~~D.F. No mention~~. LESION:					—
XXIII	NO VASCULAR	LESION : Proliferative change only.					—
XXIV	+	+	+	+	D.F.	No mention.	+
XXV	+	+	+	—	D:f.	Enlarged veins.	+
XXVI	—	+	+	+	D.F.	Enlarged veins in spleen hilum	+
XXVII	—	+	+	—	D.F.	No mention	—
XXVIII	+	+	+	—	D.F.	No mention.	—
XXIX	—	+	+	—	D:F:	No mention.	—
XXX	+	+	+	+	D.F.	No mention.	+
XXXI	+	+	+	—	d.f.	No mention.	—
XXXII	+	+	+	—	D.	No mention.	—
XXXIII	+	+	+	+	D.F.	Enlarged veins.	—
XXXIV	+	+	+	—	D.f.	Enlarged veins in abd, wall and in spleen hilum.	—
XXXV	+	+	+	—	D.f.	No mention.	—
XXXVI	+	+	+	—	D.	No mention.	+
XXXVII	+	+	+	—	D.f.	No mention.	+
XXXVIII	+	+	+	+	D.F.	No mention.	+
XXXIX	+	+	+	—	D.f.	No mention.	—
XL	+	+	+	—	D.F.	Veins very hard.	—
XLI	—	+	+	—	D.	No mention of veins. Atheroma of artery(splenic)	—

be the earliest stage of the process.

An attempt has been made in the present study to throw some light on the nature and mode of origin of the siderotic nodules by:-

(1) A study of sections from spleens showing the nodules, including serial sections in one marked case:

(2) Observations on similar pigmentary changes in infarcts of the spleen:

(3) A study of the organisation of haemorrhages and infarcts in the spleens of experimental animals:

(4) A chemical study of the pigments of the siderotic nodules.

(1) The Sections.

The microscopic description given above agrees with the findings in all the fully developed siderotic nodules. In the spleens of the hepatolienal fibrosis group which showed the nodules perivascular haemorrhages were invariably found. A common association was the presence of periarterial fibrosis of concentric arrangement with interstices in which red blood corpuscles and haemosiderin pigment were frequently found. The incidence and relationship of

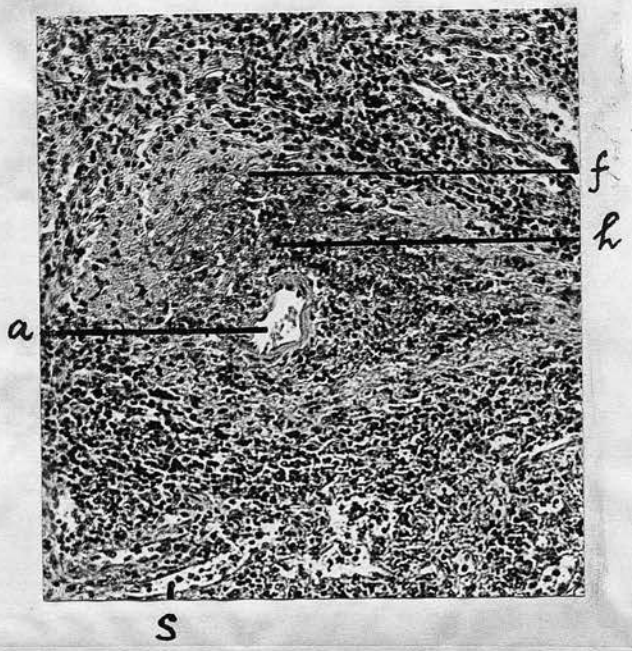


Fig. 13 .(x135) from case XX. Periarterial haemorrhage (h), with early fibrosis (f) round the margin. Note the central artery (a) with healthy walls. Dilated sinuses (s).

these changes is shown in the table.

Periarterial Haemorrhages are usually easily visible on examining the stained section with a lens. They occur round small arteries of a size similar to those seen in the centre of the siderotic nodules, and the diameter of the whole haemorrhagic area varies from three to ten times the diameter of the artery in the centre. The haemorrhage seen round the outermost zone of the siderotic nodules is not included under this description, for the purposes of tabulation. Frequently in the sections quite extensive haemorrhages were visible which did not bear any definite relation to a central artery, but in these definite periarterial haemorrhages could be observed elsewhere as a rule. It was probable that these areas had been cut tangentially in relation to the artery. Among the effused blood corpuscles granules of golden-yellow pigment were not infrequently seen

The periarterial haemorrhages were often noted to occur round the small arteries beyond the malpighian bodies, where these arteries were curving backwards to end in the peri-malpighian zone. In fig. 15 this distribution of the haemorrhage is well seen in relation to its artery. In many instances however, the relation to the peri-malpighian vessels was not seen in the sections. This condition has been termed

2. The next stage appears to be collagenisation of the dilated sinus walls. Stained with van Gieson a little newly formed collagen is seen in the sinus walls, and in the later stages the collagen may be a pronounced feature. The early and late stages of collagenisation of the sinus walls are indicated in table by "f" and "F" respectively.

It is to be noted that the process of collagenisation of the sinus walls differs from "fibrosis". In fibrosis, which may be illustrated by that occurring in the organisation of a perivascular haemorrhage, we have a transformation of the cells in a localised area into elongated fibroblasts. An area of cellular connective tissue is formed in which collagen fibres are laid down by the fibroblasts. By contrast, collagen appears in the walls of the dilated sinuses without any fibroblastic transformation of the spleen cells.

The process in the pulp is evidently not primarily fibrotic in nature as such a process would tend to produce shrinkage rather than enlargement of the spleen. The spleen pulp never assumes the appearance of scar tissue in this disease.

Apart from these changes in the venous sinuses, there are no other changes in the pulp as a rule. There is no cellular alteration of note, the cells

peri-malpighian haemorrhage, and is obviously of the same nature as the periarterial haemorrhages already described. It is given special mention however, as it is an important and common association of more obvious periarterial haemorrhage. It has also a special significance in the consideration of the origin of these haemorrhages.

The pathological material on which this study is based yielded an abundance of microscopic pictures to illustrate the further development of these periarterial haemorrhages. Let us first take the changes which follow upon a relatively small haemorrhage: i.e. one which, in diameter, does not exceed about five times the diameter of the artery in its centre.

The red cells become lysed: a change similar to that which occurs in an ordinary infarct. The blood pigment is removed by the neighbouring spleen cells. Simultaneously the splenic cells which lie in the effused blood tend to become elongated, and resemble fibroblasts in shape. At a later stage a network of cellular connective tissue is formed, with a few red cells still entangled in its meshes, and which at its edge gradually merges into the surrounding spleen pulp. Later on the connective tissue, lying in concentric strands around the artery becomes hyalinised, especially in the central parts. Thus we see the gradual development of the stage which

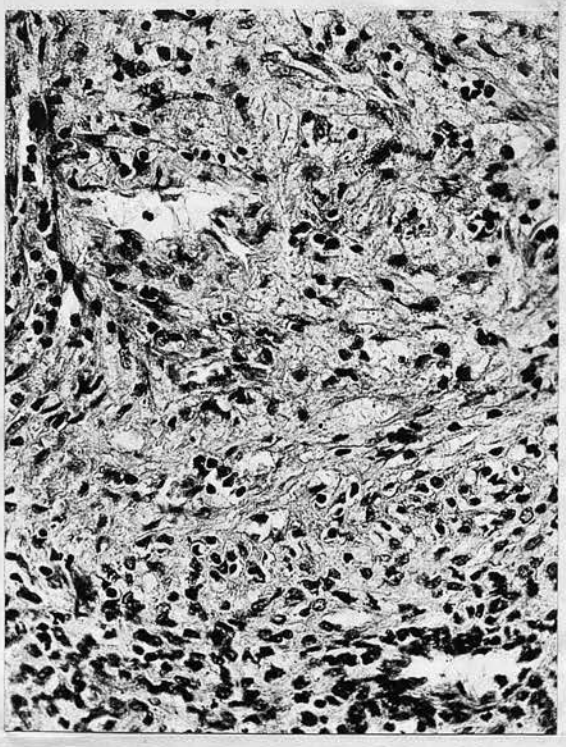


Fig. 16. (x 270) (From CaseII) The lower part of the picture to the point (p) is occupied by spleen pulp unaffected by haemorrhage. In the remaining part a periarterial haemorrhage has occurred. The red cells are undergoing haemolysis and the surviving spleen cells are becoming transformed into elongated fibroblasts in the organisation of the haemorrhage.

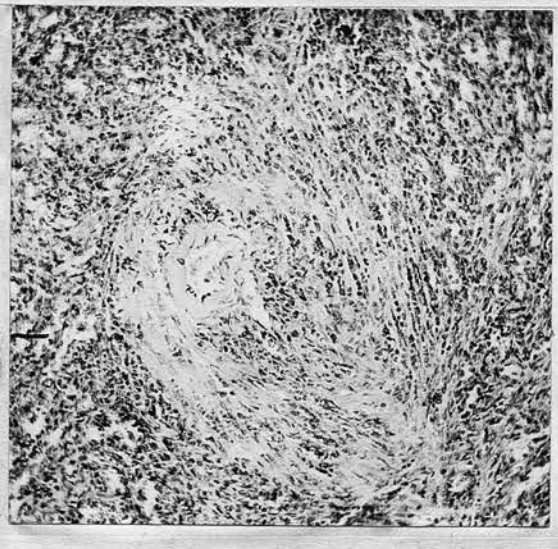


Fig. 17. (x 90) (From Case XII) showing the late stage of organisation of a periarterial haemorrhage. The concentric branching connective tissue strands have become hyalinised. The margin of the periarterial fibrosis gradually merges with the pulp on the right of the picture. Note also the dilated sinuses (s).

has been termed periarterial fibrosis.

The areas of periarterial fibrosis thus formed must be carefully differentiated from normal trabeculae. Two points usually suffice for the recognition of the pathological condition as contrasted with the normal. Firstly the trabecula has an abrupt clearly defined edge where it abuts on the pulp, while the area of periarterial fibrosis gradually merges with the surrounding splenic tissue, from some of the cells of which it has been formed. Secondly, the trabecula consists of a solid beam or strut of connective tissue. It has few or no interstitial spaces and never contains blood among its fibres: the area of periarterial fibrosis, on the other hand, has a concentric arrangement of its connective tissue strands containing in the interstices between the strands a few blood cells or even blood pigment.

The older areas of hyaline perivascular fibrosis are essentially "white infarcts". The nuclei of the cells lying among the connective tissue fibres are dark and rounded. The identity of periarterial fibrosis with Banti's fibroadenie will be discussed later (p.).

If we now follow the development of a larger zone of perivascular haemorrhage we find that the blood pigment liberated from the corpuscles in the central parts of the haemorrhage cannot be completely removed.

facing p. 32.

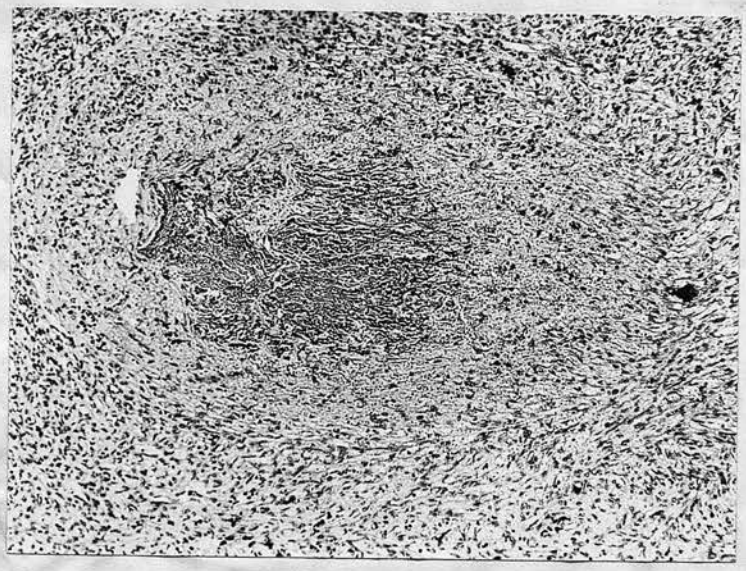


Fig. 18 . (x 90) (From case II) An extensive peri-arterial haemorrhage occupies nearly the whole field. The artery (a) lies excentrically and there is early fibrosis at the margin. Elongated rectangular crystals and other pigments have formed in the centre, their formation definitely preceding the local development of connective tissue fibres.

connective tissue fibres.

The haematin pigment becomes disintegrated into iron containing compounds which may adopt a crystalline or amorphous appearance (see p.). Fig. shows the appearance of such crystals, identical in appearance and staining reactions with the crystals found in the siderotic nodules, in the centre of an extensive zone of haemorrhage.

The further development of such a zone to the stage of the siderotic nodule merely necessitates the superaddition of the processes we have already described in the development of the zone of periarterial fibrosis. Hyaline connective tissue develops in the manner already described, and the pigment becomes locked in the interstices of the hyaline connective tissue or encrusted along its fibres. Frequently stages are seen in which the pigment formed does not show the variety of appearances we have described on p. 24, but simply consists of amorphous golden-brown masses of haemosiderin.

There is thus a great variety of appearances all of which develop from perivascular haemorrhages as the initial stage. The phases which we have tabulated (Table II) are merely convenient descriptive headings and naturally transition stages are common.

With regard to the site of origin of these periarterial haemorrhages, there is no evidence in any

TABLE III:

PERIARTERIAL HAEMORRHAGE

SMALL	LARGE
1. Lysis of red corpuscles.	1. Development of iron-containing pigments of varying types in the central parts of the haemorrhage.
2. Cellular connective tissue develops at the margin.	2. Superaddition of a process of fibrosis which enmeshes the pigments already formed.
3. Zone of young connective tissue around the artery enclosing a few red corpuscles.	
4. Hyalinisation of the peri-arterial connective tissue.	

spleen which has been examined of the rupture of an artery to account for the bleeding, and the trabecular veins have always appeared intact. We at once think of the "critical point" in the spleen circulation - the region of the ellipsoid, at the termination of the penicillar arteriole. Indirect evidence in favour of this site of origin is afforded by the frequent occurrence of a ring of haemorrhage or fibrosis round the malpighian body in those spleens which show peri-arterial haemorrhage. It is in this site, as already mentioned, that the penicillar arteries end.

As has already been noted the occurrence of sideriotic nodules is by no means confined to hepatolienal fibrosis. The nodules also occurred in instances of acholuric jaundice, tuberculosis of the spleen, etc. In these cases there was no fundamental variation in the anatomical findings to suggest any difference in the site of origin. The haemorrhages were always peri-arterial and there was never any suggestion of local arterial disease apart from "normal hyalinisation" to account for the bleeding. For this reason the writer feels justified in accepting direct evidence of the site of origin of the bleeding in one case as applicable to all spleens in which the haemorrhages occur.

The spleen chosen for a direct search for the site

facing p. 34

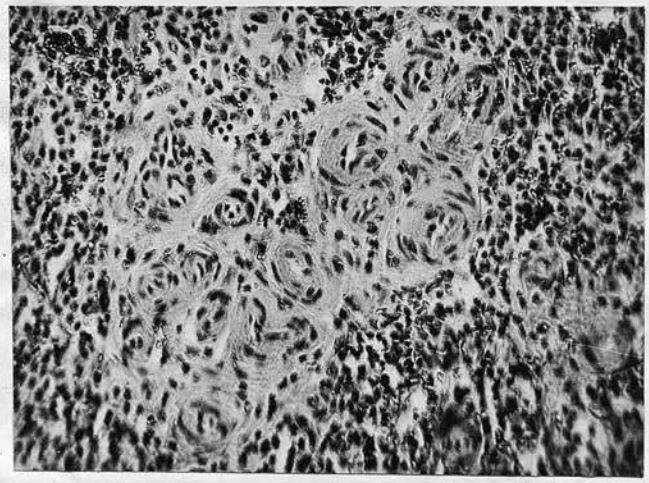


Fig. 19. (x 220) Arterial angioma of the spleen. Note the leash of arteries.

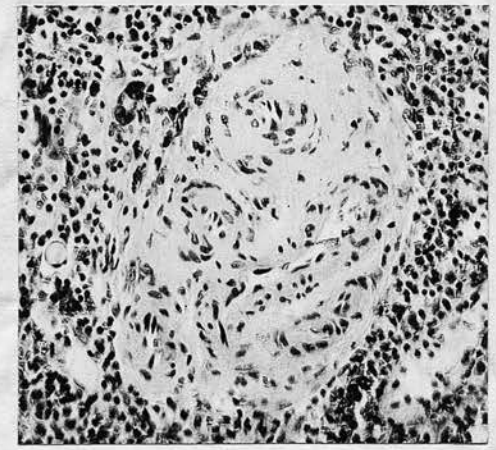


Fig. 20. (x 220) From the same case as the preceding illustration. Numerous arteries embedded in hyaline connective tissue.

of origin of periarterial haemorrhage, showed an exceptional number of nodules and peri-vascular haemorrhages. Owing to an anatomical peculiarity there were many more penicillar arteries than are usually found and it was relatively easy to follow any individual vessel by means of serial sections.

This case is not included as hepatolienal fibrosis as it was complicated by the presence of a duodenal ulcer with bleeding, and there was a congenital angiomatous abnormality of the intrasplenic arteries which were constituted by leashes of ten or twelve vessels. The latter circumstance, however, made it particularly favourable for study by means of serial sections, as the vessels were so numerous and easy to follow.

Donald M. aet 43, had a history of abdominal pain, vomiting, melaena and indigestion lasting over 14 years. In July 1927 a posterior gastroenterostomy was performed for duodenal ulcer. At operation the spleen was found to be 3-4 times the normal size. In February 1928 he complained of pallor and breathlessness with some abdominal pain. The blood condition was as follows:-

R.B.C.	4,400,000.
W.B.C.	2,400.
Hb.	75%
Neutrophils.	52%
Lymphocytes.	48%

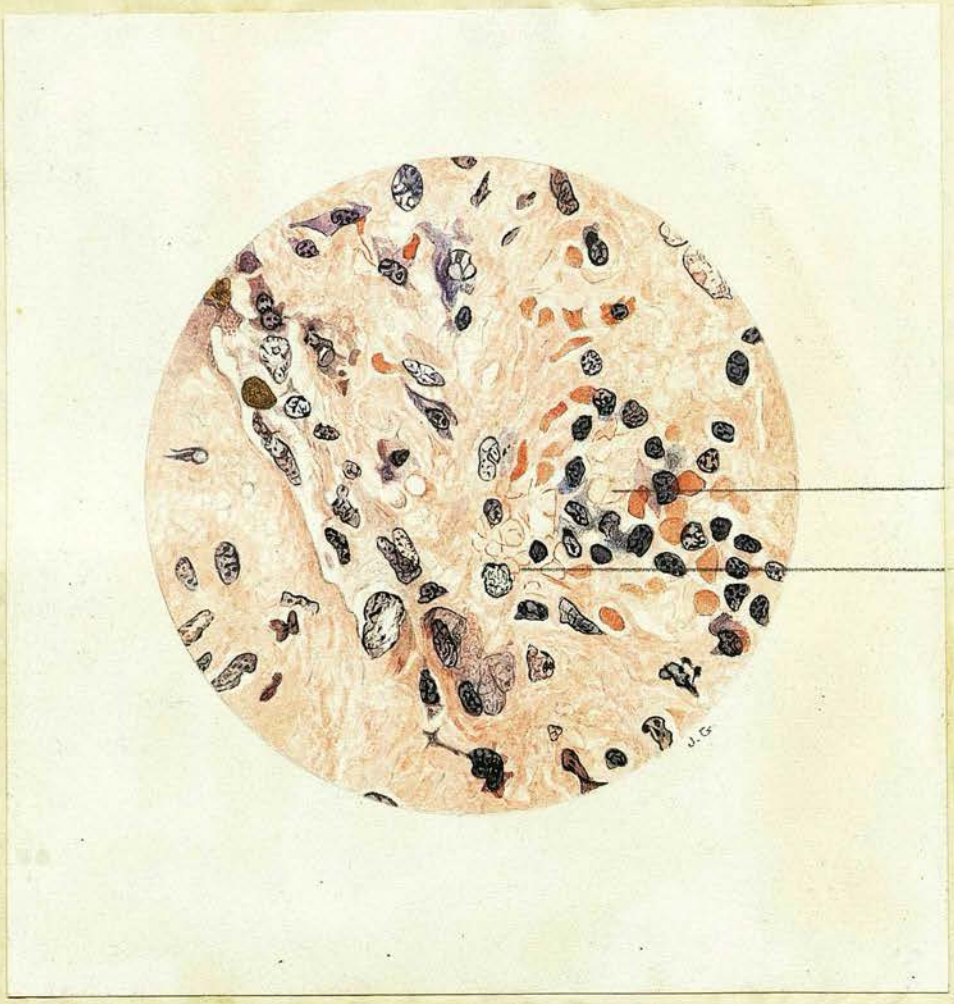


Fig.21. (Oil immersion) Showing the origin of a periarterial haemorrhage. The arrow (c) indicates the centre of an arterial capillary (oval ring of nuclei) at the point where it enters the pulp. Red corpuscles (r) have escaped at this point and are seen undergoing haemolysis.

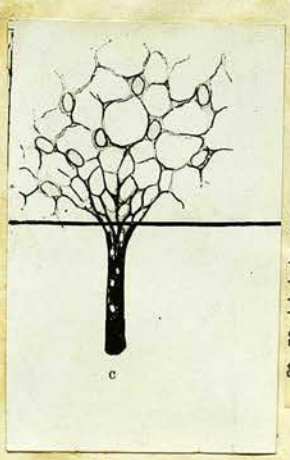


Fig. 22. (After Hueck) showing the mode of termination of the arterial capillary in the pulp. The section in the preceding figure passes through the arterial capillary in the plane (c).

Splenectomy was successfully carried out. The liver appeared normal at operation, but it was noted that the splenic artery was "large, tortuous and striated as if from early arteritis".

Spleen: Weight 18 ounces. Microscopically: capsule was thickened. The subcapsular sinuses are dilated and slightly fibrotic. The pulp sinuses are dilated with quite definitely fibrotic walls. Malpighian bodies show frequent hyaline deposits. The arteries show marked hyaline changes in the walls, and almost invariably are constituted by leashes of vessels. Periarterial haemorrhages, periarterial fibrosis and pigment deposits are frequent, i.e. siderotic nodules, and all intermediate stages in the development of these. Scattered through the pulp are small golden-brown refractile granules. These have a tendency to accumulate along the sides of the blood vessels. Phagocytes containing blood pigment are frequently seen in the pulp: these tend to be especially numerous in the region of the periarterial haemorrhages.

A small artery surrounded by a zone of haemorrhages was traced down to the point where it lost its muscular coat. At this point the arterial capillary was represented by a ring of "endothelial" cells without any visible connections with one another. Between these cells red corpuscles appeared to be escaping into the periarterial tissues, where they were undergoing haemolysis. (Fig.21)

The abrupt ending of the artery and its continuation for a short distance as a recognisable arterial

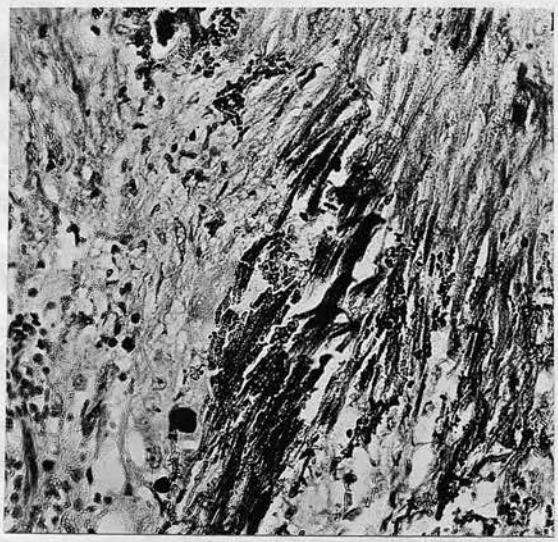


Fig. 23. (x 250) Elongated crystals and other pigments at the edge of an infarct of the spleen . (From a case of acholuric jaundice).

capillary corresponds to the anatomical descriptions of Weidenreich (1901) and Hueck. The latter draws attention to the absence of any demonstrable cement substance between the cells of the capillary wall. (Fig. 22) The cells are merely linked up by cell processes and the appearance of fenestrations between them is thus explained. Ellipsoids were not seen at this point, but, as Hueck points out, these are not present on all the penicillar arteries of the human spleen and in pathological spleens they are frequently absent.

(2) Infarcts of the Spleen.

In splenic enlargements infarcts are not uncommon findings, and in several of the spleens examined old infarcts were present. These contained types of pigment exactly similar to those found in the siderotic nodules. (Fig. 23) Large infarcts are usually white in the centre, but have quite a well-marked pigment deposit at the periphery. Abrikossoff (1929) made the same observations and in addition discussed similar pigmentary changes which are found in brown induration of the lungs, and in scars in the site of the corpus luteum of the ovary. He proved conclusively that each individual type of pigment found in the siderotic nodules of the spleen also occurs in those other organs in the conditions mentioned.

(3) Organization of artificially produced infarcts and haemorrhages in the spleen.

We have noted above the stages in the organization of periarterial haemorrhages in the spleen of man. It has also been noticed that the crystals of pigment formed at the edge of infarcts in the human spleen are identical in appear-ance with those which occur in the siderotic nodules. It was thought that it might be profitable to follow the changes which ensued when haemorrhages and infarcts were produced in the spleens of experimental animals, with special attention to the mode of development of scar tissue and to the fate of blood pigments and its derivatives.

Haemorrhages were produced in the spleens of cats and rabbits by puncturing the spleen with a fine needle which was rotated slightly after its introduction into the substance of the organ. In rabbits, infarcts of the spleen were produced by tying in an inclusive ligature both the artery and the vein to one segment of the spleen. The infarctions produced were of the red variety. In rabbits quite considerable deposits of haemosiderin may occur in the spleen under normal conditions. When a general distribution of such pigment was found in the healthy portion of the spleen little emphasis could be laid on the

local pigmentary changes around the infarcted area. Such animals had therefore to be left out of account and attention was only paid to those experiments in which the pigment was obviously derived from the infarcted area. In cats, however, haemosiderin pigment is rarely seen normally in the spleen, and there was little uncertainty as to the mode of origin of any pigmentary changes which developed after a local haemorrhage.

Results of Experiment.

In the first few hours after the production of an infarct progressive death of the cells in the infarcted area took place, as was evidenced by pyknosis of the nuclei in the affected zone. Within 24 hours lysis of the blood cells in the affected area could usually be made out. Up to 24 hours little alteration was detected in the living cells at the margin of the infarct.

In 48 hours (Fig. 24) definite enlargement of the surviving cells was seen at the edge of the infarct; the nuclei of the cells became larger and the chromatin filaments were rendered more prominent. No phagocytosis of pigment could be seen at this stage.

Rabbit E. 11. Killed two days after ligature of splenic vessels to the lower pole of the spleen. The lower pole of the spleen was of a deeper red and softer than the rest of the organ, but otherwise no

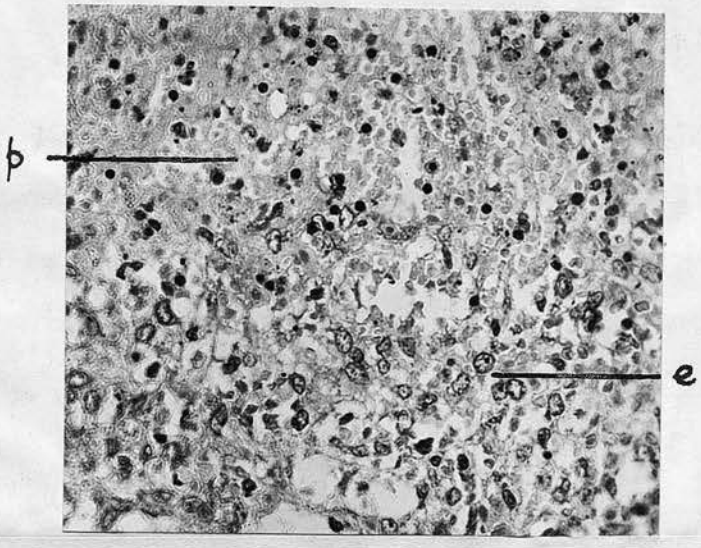


Fig.24. (x 350) 2 days after infarction of portion of the spleen. Note pyknosis of cell nuclei (p), and vesicular enlargement of cells (e) at the margin of the infarcted area.

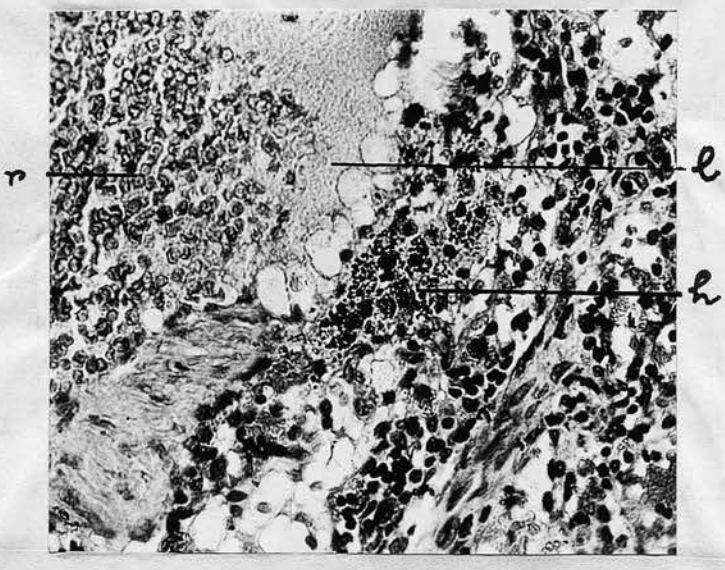


Fig.25. (x 350) 7 days after production of a haemorrhage in the spleen.
r intact red blood corpuscles.
l haemoglobin liberated by laking.
h haemosiderin laden cells at the margin of the haemorrhage.

abnormality could be seen.
Microscopically: The infarcted area was easily recognised by the diffuse eosin staining which was taken up by the red corpuscles and the haemoglobin pigment liberated in the process of haemolysis. The red cells had often lost their outlines and lay in conglomerate masses. The nuclei of the cells in the infarcted zone had become densely pyknotic. The surviving spleen tissue at the edge of the infarct showed no abnormality beyond the enlargement of the vesicular nuclei of the pulp cells. No pigmentary changes were seen. (Fig.24)

Between the second and the seventh day haemolysis of the red cells had taken place at the edge of an area of haemorrhage and the adjacent pulp cells had become laden with haemosiderin pigment.

Rabbit E. 1. Killed 7 days after the production of a small haemorrhage in the spleen. The haemorrhage had been so small that the naked eye could detect little abnormality. Sections cut through the part which had been punctured revealed a small area of haemorrhage with marked haemolysis at the edge. The adjacent spleen cells contained haemosiderin pigment. (Fig.25)

In the case of infarctions, the process had reached a similar stage at the end of a week so far as the absorption of blood pigment by the spleen cells was concerned. The formation of new connective tissue however was definitely advanced, while in the case of a simple haemorrhage new connective tissue had not

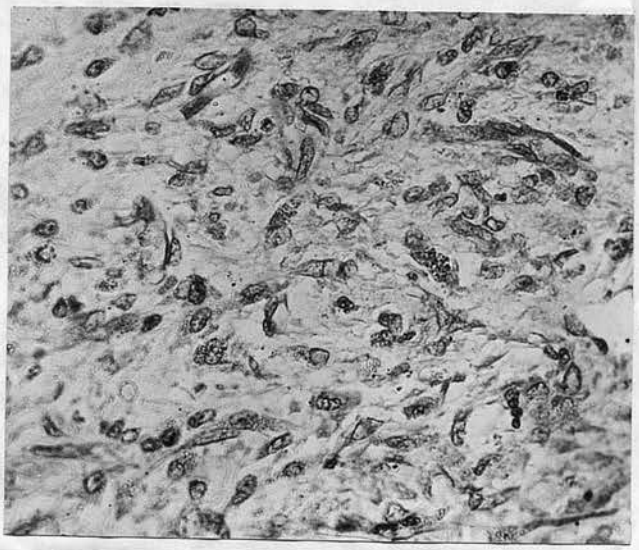


Fig.26. (x 350) 6 days after infarction. Formation of new connective tissue cells at the edge of the infarcted area: note the granular haemosiderin pigment in many of the cells.

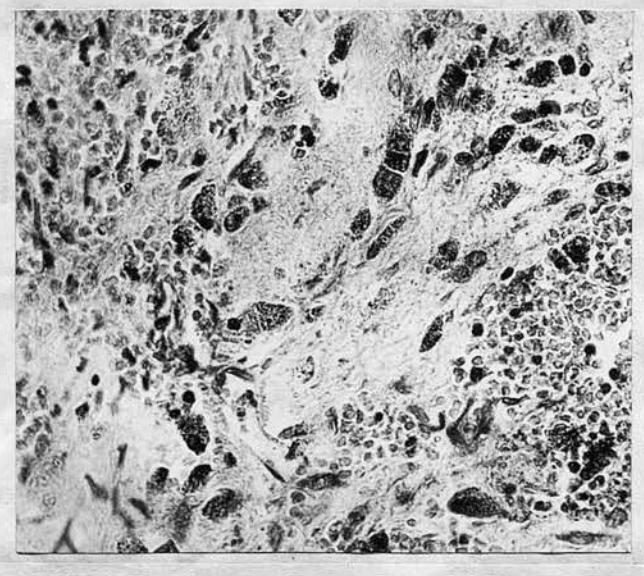


Fig.27. (x 350) 22 days after infarction. Note the haemosiderin content of the connective tissue cells, which are now less numerous than at the early stages (cf. preceding illustration).

yet made its appearance. The difference in the processes of organisation of haemorrhages and infarcts would appear to lie in the presence of dead spleen cells in the latter and not in the former. It is possible that the breakdown products of the pulp cells of the spleen form a greater stimulus to new connective tissue formation than those of red cells alone. While no interference with the oxygen supply of the cells round a haemorrhage may take place, there is probably an intermediate zone in the infarcted area where the collateral circulation is poor.

Rabbit E. 14. Killed six days after ligature of vessels to the lower pole of the spleen. The infarcted area was definitely red and more shrunken than swollen. Microscopically the striking feature was the formation of new cellular connective tissue at the edge of the infarcted area, many of the cells containing haemosiderin granules. (Fig.26)

By the end of three weeks the formation of new connective tissue had reached a more advanced stage. There was more ground substance in the connective tissue which took up the red van Gieson stain. The connective tissue cells still contained haemosiderin granules.

Rabbit E. 3. Killed 22 days after infarction. The new connective tissue cells at the margin of the infarct were fewer in number than those seen at the end of a week, and the formation of fibres and ground

Fig. 28. (Oil immersion) 21 days after production of an artificial haemorrhage in the spleen (h). Note the new connective tissue development with intracellular and extracellular haemosiderin.

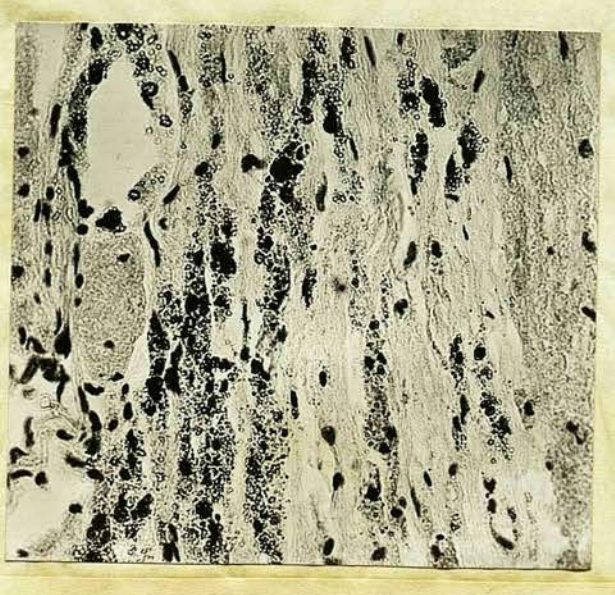


Fig. 29. (x 350) Hyalinisation of the connective tissue at the edge of an infarct, 60 days after its production. Note the large amount of haemosiderin pigment caught in the meshes of the connective tissue.

substance was much more definite. (Fig. 27)

Cat.E. 12. Killed 21 days after the production of haemorrhage in the spleen. A small area of haemorrhage the size of a pinhead could be seen in the spleen macroscopically. A section through this area revealed the appearance shown in Fig 28. New connective tissue was formed at the edge of the haemorrhage with haemosiderin granules lying both intracellularly and extra-cellularly in the interstices of the connective tissue.

It is difficult to tell whether this extracellular pigment was formed extracellularly or whether it was extruded by spleen cells which might have absorbed it previously. This is a point to which we shall return later.

The further stages of the process consist of the senescence and hyalinisation of the new connective tissue.

Rabbit E. 12. Killed 60 days after the ligature of the splenic vessels to one segment of the spleen. The connective tissue which has formed at the edge of the infarcted area has undergone hyalinisation of the connective tissue fibres and large quantities of haemosiderin pigment are caught in the interstices of the new connective tissue.

The above findings give some indication of the sequence of events ensuing upon the production of infarcts and haemorrhages in the spleen. It should be noted, however, that in many instances a haemorrhage

which had been produced at the initial operation could not be traced at autopsy. It appears that even considerable haemorrhages in the spleen may be absorbed and leave no detectable naked-eye trace: if the whole area were sectioned, no doubt a scar might be found to indicate the site of the old trauma.

(4) The chemical nature of the pigments in the Siderotic Nodule.

The appearance of the pigments seen in the siderotic nodule as stained by haematoxylin and eosin has already been described. There are four distinct types:

1. Dark brown amorphous rounded masses, which give the iron reaction. This pigment is often intracellular as well as extracellular.

2. Elongated, segmented, bamboo-like, translucent, pale, yellowish-green strands lying extracellularly. These do not give a strong iron reaction by the usual methods using weak hydrochloric acid and are variously described by different writers as sometimes giving the iron reaction and sometimes not.

3. Fine granular material which is often encrusted on the hyaline connective tissue strands of the nodule, and which takes up the haematoxylin stain.

4. Dark grey or grey-black bodies having a concentric laminated arrangement like starch grains.

Chemical Reactions in the Siderotic Nodule.

For the purposes of this chemical study, frozen sections were taken from spleens containing numerous nodules. The various reagents were applied while the sections were watched under the microscope. The following reactions occurred.

1. A positive iron reaction occurs with potassium ferrocyanide and hydrochloric acid. (Prussian blue reaction).

This reaction depends on the presence of free "ferric" ions. When iron is present in combination as phosphate or carbonate it gives no reaction with potassium ferrocyanide alone; the addition of hydrochloric acid, however, forms the readily dissociable ferric chloride, and the Prussian blue reaction occurs.

2. A positive iron reaction occurs with potassium ferrocyanide and acetic acid.

Ferric phosphate which was soluble in HCl (a "strong" acid) is not soluble in acetic acid ("weak"). The positive reaction with acetic acid is therefore due to the presence of carbonate. This reaction however was a very feeble one. The iron is therefore mostly present in the form of phosphate,

while a little is present as the carbonate.

3. The addition of potassium thiocyanate and acid gives a red colour. This is a further positive test for iron (ferric).

With potassium thiocyanate and "weak" acids (see section 5) the granular pigment encrusting the connective tissue strands only was stained red.

4. The Bell-Doisy test for phosphates was positive.

Macallum's test for phosphate which was used by Sprunt was found to present considerable technical difficulty owing to the necessity for very accurate measurement of the reagents used. The Bell-Doisy (1920) method was more satisfactory. A blue colour is obtained when a solution containing hydroquinone , molybdic acid and alkaline sodium sulphite is added to the nodules. This blue colour is a definite indication of the presence of phosphates in the siderotic nodules. I am indebted to Professor G. Barger for his help in applying this test.

5. The long rectangular yellowish crystals show the following properties:

(a) They are dissolved by oxalic acid, but not by acetic acid.

(b) They are soluble in hydrochloric acid.

The solubility in oxalic acid indicates that the crystals are composed of iron or a compound of iron.

For reasons already mentioned, the solubility in hydrochloric acid but not in acetic acid indicates that they are composed of iron phosphate.

These crystals give a variable reaction with the prussian blue test according to various writers. Using 5% HCl, the writer has found the reaction is invariably positive. With 1% HCl, the reaction may be only faint and confined to the margins of the crystals. With .5% HCl the crystals give no red reaction with potassium thyocyanate but the addition of 5% HCl brings up the reaction immediately. With weak solutions of acid therefore, especially when applied for a short time, the iron reaction may not be obtained.

6. Haematoxylin, applied to frozen sections, does not stain the rectangular crystals for the most past, but well-marked dark blue staining is produced in the other parts of the nodule.

Sprunt claimed that this reaction was due to the presence of calcium, as it persisted after the removal of iron by half saturated oxalic acid. In the nodules examined by the writer, however, the reverse was the case. On removal of iron by oxalic acid, no further reaction to haematoxylin took place. This is in accordance with the findings of Cameron, Muehlmann, and others that haemotoxylin indicates the presence of iron, and is not a test for calcium.

In order to test whether haematoxylin was more sensitive to the carbonate than the phosphate of iron, the carbonate was removed from the sections by acetic acid and washing. It was found that this procedure had no effect in preventing the appearance of the haematoxylin reaction. Since the crystals of iron phosphate do not take up the haematoxylin very strongly, it appears that iron is present in forms other than phosphate and carbonate.

7. Small amounts of a coarsely granular yellowish-brown pigment remain after removal of the phosphate and carbonate of iron by HCl.

This pigment however is removed by oxalic acid more slowly than the iron phosphate crystals, and after treatment with HCl, it will give the prussian blue reaction. It does not give the haematoxylin reaction however. There is no doubt of its iron nature, and the fact that it is sparingly soluble in HCl. Certain oxides and hydroxides of (ferric) iron possess this property of very slight solubility in acids, and it is possible that the pigment under consideration is one of these.

8. Von Kossa's test applied to the nodules gives a marked reduction of silver on the iron phosphate crystals and also on the other pigment particles.

As Cameron has noted, positive reactions are ob-

tained with calcium and ferric salts as well as with salts of other elements, such as strontium and barium, which are unlikely to occur naturally in human tissues. After the removal of the iron salts by means of oxalic acid there is virtually no reduction of silver by this test. There is therefore no deposit present which is likely to be calcium.

9. The application of alizarin S. gave no pink reaction. The addition of such mordants as phosphomolybdic acid and potassium alum failed to produce any reaction.

Cameron has shown that alizarin is a specific test for inorganic calcium, although some difficulty may be experienced especially with older deposits. The iron deposits gave a blackish colour which may mask the calcium reaction. Even after removal of iron by oxalic acid, no pink colouration could be obtained. There is therefore no positive evidence of the presence of calcium in the numerous nodules examined.

To sum up we may say that the long rectangular yellow crystals consist of ferric phosphate, while the yellowish-brown rounded masses possibly consist of ferric oxide or hydroxide. The other pigments staining with haematoxylin also contain iron, some of which is definitely present as carbonates. The granular pigment encrusting the connective tissue strands is probably

carbonate of iron.

We have been unable to confirm the presence of calcium which was claimed by Sprunt. An examination of the methods which he used to test for the presence of this substance shows that they were not sufficiently accurate. In denying the presence of calcium our findings are in agreement with those of Gigon (quoted by Macallum, 1924) and Jäger (1931).

DISCUSSION.

We now return to the consideration of our main problem - namely the details of the process of formation of the siderotic nodule and the various other results which may follow upon a perivascular haemorrhage in the spleen. We can consider the process under two headings:

1. THE FIBROTIC PROCESS:
2. THE PIGMENTARY CHANGES:

1. The Fibrotic Process. In this respect it should be noted that a periarterial haemorrhage of the type we have described is probably intermediate in nature between a simple haemorrhage and an infarct. The simple haemorrhage of the type we produced in animals forms a lake of blood banked by spleen cells, and containing no surviving cells of this type. The red infarct on the other hand contains a mass of dying spleen cells as well as blood. The perivascular haemorrhage occurring

in the pathological spleens under consideration consists when small of a considerable amount of blood, enmeshed among a number of spleen cells which probably survive, at least for a time, especially at the margin of the haemorrhagic area. The process of fibrosis resembles that occurring at the edge of an infarct, and may be stimulated to some extent by the death of some spleen cells in the centre of the haemorrhagic area. Provided the area taken up by the haemorrhage is relatively small, all the blood or blood pigment may be readily removed simultaneously with the process of fibrosis. As the fibrotic area ages, it tends to become hyalinised. It retains, as a rule, a concentric arrangement, and some blood remains, caught in the interstices.

2. The Pigmentary Changes. The chemical studies shown above seem to demonstrate conclusively that all the pigments which occur are constituted essentially by derivatives of iron. The origin of these pigments - all of them entitled to the term "haemosiderin" - is obviously haemoglobin.

It is difficult here to state the exact process which is at work. The formation of the pigments of a more complex crystalline appearance seems only to take place in the centre of relatively large haemorrhages, (see Fig. 18). The pigment which occurs most commonly, and which is often present to the exclusion of the other

types, is the golden yellow granular material - consisting most probably of ferric oxide. It is possible that this pigment is the precursor of the other types which may be derived from it by further chemical change. On the other hand both ferric oxide and ferric phosphate may be derived from a common precursor such as ferric carbonate. This, however, is mere speculation.

The details of the disintegration of haemoglobin into its derivatives are not yet settled and possibly the process may vary according to the circumstances in which disintegration takes place. Rich and Bumstead (1925) appear to favour the view that the process of breakdown of haemoglobin occurs intracellularly, and there seems to be little doubt that bile pigments have been identified conclusively in the reticulo-endothelial cells by these workers and also by Aschoff (1930).

On the other hand Leschke (1921) demonstrated the presence of ferments causing the change of haemoglobin into bilirubin in cell-free (centrifuged) cerebro-spinal fluid into which red blood corpuscles had been previously injected. The major part of the work on this problem tends to support the view that the process of disintegration of haemoglobin takes place for the most part extracellularly (Hueck 1921) There is no real proof that the intracellular disintegration of haemoglobin from

ingested red corpuscles is not a misinterpretation of the appearance which may be caused by the phagocytosis of damaged red corpuscles along with their disintegration products. It should be noted, however, that van den Bergh (1918) is against the "humoral" theory of the origin of bilirubin.

This question of bilirubin formation is intimately bound up with the fate of iron in effusions of blood. Hueck shows that the histological study of the breakdown of haemoglobin is beset with difficulties when he points out that in dilute solution both iron and bilirubin can be rapidly removed and excreted. It has been suggested (Neumann, 1904) that frequently in a blood effusion either haematoidin crystals or haemosiderin granules are visible, but not both. The nature of this reciprocal relationship is not understood. Neumann suggested that haemosiderin only becomes visible when the effused haemoglobin is in contact with living tissue at the margin, while haematoidin tends to be deposited in dead or dying tissues. Haematoidin is formed extracellularly (isomeric with bilirubin). Granular haemosiderin may be formed intracellularly in living cells, after the diffusion into them of soluble iron salts. This question is not yet settled.

From the direct observations we have been able to make, it would appear that the crystals of iron

phosphate tend to appear in the central parts of large haemorrhages, where there is little likelihood of contact with living cells. Granular haemosiderin (ferric oxide ?) tends to occur in contact with, or even within, living cells. Whether the granular haemosiderin which lies in the interstices of the connective tissue (Fig.[28]) has been formed extracellularly or has been formed intracellularly and has been extruded, it is impossible to say.

The Organisation of intrasplenic haemorrhages.

As we have seen in the experimental animals, effused blood or the blood in a red infarct, becomes laked and the iron moiety of the haemoglobin is taken up by the cells at the edge, within a few days. The second stage follows in which cellular connective tissue is formed, the fibroblasts often being derived from cells previously containing iron, which they may retain on assuming their new function. Haemosiderin pigment is also found in the interstices of the new connective tissue. Whether this is extruded from cells or formed extracellularly cannot as yet be decided.

In the pathological spleens we have noted that the process varies according to the size of the periarterial haemorrhage and that the process is intermediate between a haemorrhage and an infarct.

The process of organisation of a small periarterial haemorrhage has been outlined (p.). Any pigment li-

berated from the effused red cells tends to disappear - probably by a process of simple diffusion (Hueck.) All the red cells, however, are not lysed as a rule, and some remain to lie in the interstices of the new connective tissue which forms around the artery.

When the haemorrhage is larger, haemosiderin pigments are formed and come to lie either inside the cells of the spleen pulp or in the chinks of the connective tissue which is formed by these cells. In the central parts of a large haemorrhage the haemosiderin pigments assume different chemical forms - phosphate and carbonate of iron. What the original chemical state of the iron may be is unknown, but it is probable, following Hueck's idea, that the precipitation of these iron pigments depends on a greater local concentration in the centre of large blood effusions. Such high concentration might be caused by local difficulties of absorption.

The formation of these pigments precedes any definite connective tissue formation in this immediate neighbourhood. Definite connective tissue fibres are however formed in a week or two, and the pigments are caught in the interstices and become encrusted on the hyaline connective tissue strands.

It has been noted that the iron phosphate crystals sometimes appear to be encrusted on the hyaline wall of the central artery. There would appear to be a definite

affinity of hyaline tissue for iron salts, and the precipitation in this site is probably determined early. The hyaline arterial wall is there to be soaked by any iron salts which form in its immediate neighbourhood, while the formation of new connective tissue and its hyalinisation occupies a month or two (Fig.29).

The formation of giant cells in the siderotic nodule is probably similar to the formation of giant cells in relation to foreign bodies. The foreign body in this instance is of course the local crystalline pigmentation.

The site of origin of the periarterial haemorrhage.

There is little doubt that the bleeding takes place in the first instance from the ellipsoidal capillary. We have seen the effusion begin at this site. (Fig.21) Further indirect evidence is afforded by the frequency with which the haemorrhage and fibrosis occur immediately round the malpighian body. As previously noted, this is the site at which the penicillar arterioles end. Haemorrhage and subsequent fibrosis would occur at this site if the bleeding occurred round these penicillar arteries or their terminations.

The cause of the haemorrhage will be discussed later. (p.69)

Before leaving the subject of siderotic nodule, there is one other fact which is deserving of brief

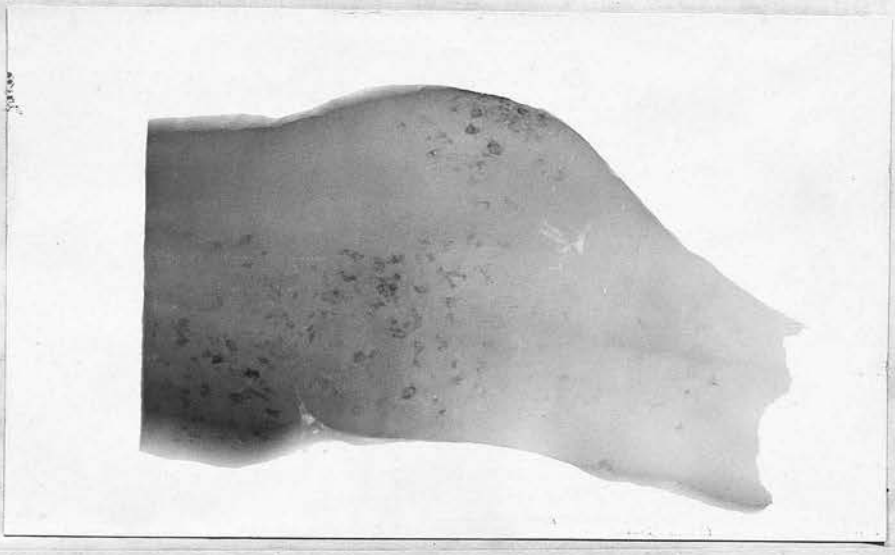


Fig.30. X ray photograph of a portion of a spleen with numerous siderotic nodules. The nodules are opaque.

mention. Although we have not been able to confirm the presence of calcium in the nodule, the iron compounds with which it is impregnated render it opaque to X-rays. The appearances are definitely positive when an excised spleen is X-rayed, but we have not had an opportunity of searching for the nodules by this method with the spleen in situ in the living subject. While the possibility is of some interest, it is doubtful if the procedure would be of much aid in diagnosis as the nodules are seen in a great variety of different pathological conditions in which the spleen is enlarged.

Chapter 2.

VASCULAR PATHOLOGY. (continued)

Having discussed the site of origin and the fate of the perivascular haemorrhages which occur in hepatolienal fibrosis, we now turn to a different, though related, aspect of the vascular pathology - the venous changes. These changes will be described under two main headings:

1. PORTO-SPLENIC ENDOPHLEBITIS AND THROMBOSIS.
2. DILATATION OF THE VENOUS SINUSES OF THE SPLEEN.

1. Porto-splenic endophlebitis and thrombosis.

The association of gross disease of the portal and splenic veins with liver cirrhosis is a well known textbook fact, and Banti noted it in his descriptions of "Banti's disease". Portal sclerosis was known to Virchow, but the first intensive studies of the condition were carried out by Borrmann (1897) and Simmonds (1912). These authors pointed out that disease of the portal vessels was independent of changes in the systemic arteries or veins, and that it occurs relatively frequently in youth, when changes in the systemic vessels are rare. They expressed the opinion that the different physical and chemical conditions in the portal system as compared with the systemic veins must have some relationship to its incidence.

Pathological Observations.

Out of the forty one instances of hepatolienal fibrosis under discussion, evidences of portal endophlebitis with or without thrombosis were found in six. (Cases I to VI inclusive). In five of these the condition was observed macroscopically either at operation or at autopsy. In the remaining instance, (Case II.) portal endophlebitis was only found after a systematic microscopic search. This microscopic search was carried out in six spleens in which naked-eye examination showed no sign of any gross vascular lesion of the portal tree; in five of these no vascular disease was found. It must be noted that the endophlebitis found in case II was discovered only by chance, as sections taken from other vessels at the hilum of the spleen in the same case showed no lesion. This finding in itself suggests that in hepatolienal fibrosis early changes in splenic veins are probably present with greater frequency than is generally suspected.

Taking the early changes found in case II, the findings are as follows (Fig.31):

The wall of the vein in general is somewhat thickened, the muscular tissue of the wall being slightly increased in amount. Occupying one side of the vein is a thickened plaque of intima overlying an area where the muscular coat is definitely thinned out. The deep-

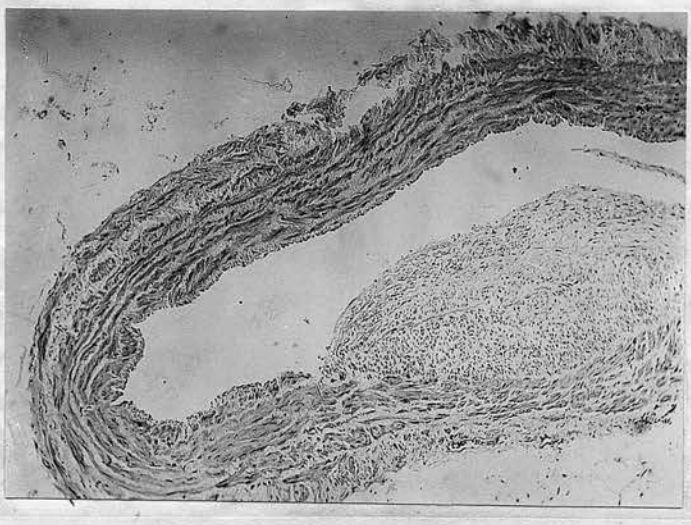


Fig.31 . (low power) Small vein from the hilum of the spleen of case II. Note the thickened plaque of intima overlying a thinned-out portion of the media, and the splitting of the internal elastic lamina.

er layers of the plaque consist principally of rather loosely arranged fibroblasts lying among strands of degenerated or hyaline connective tissue, the strands being cut in transverse section for the most part. In the more superficial part, i.e. next the lumen, the structure remains much the same with the addition of numerous wavy elastic laminae parallel to the surface. Intermingled with these there are elongated fibroblasts with many connective tissue fibres.

On purely histological grounds we cam make the following statements. Firstly, there is no microscopic evidence of any round-celled reaction to suggest a syphilitic or other chronic infective process, and there is no vestige of any more acute infection. There is no history of trauma. Secondly, there is a notable absence of foam cells or vacuolated cells such as are found in cases of nodular atheroma. It seems unlikely that the process has an inflammatory or a metabolic origin. The changes resemble those occurring in arteries in conditions of high blood pressure. It appears as if a reactive increase of the supporting elements of the vessel wall had taken place in response to raised intravascular pressure. The degenerative changes in the deeper parts of the plaque may be accounted for by poor blood supply, the same being responsible for the thinning of the muscle at this point. It is presumably in the degenerated connective tissue in the deeper parts of the plaque that calcification

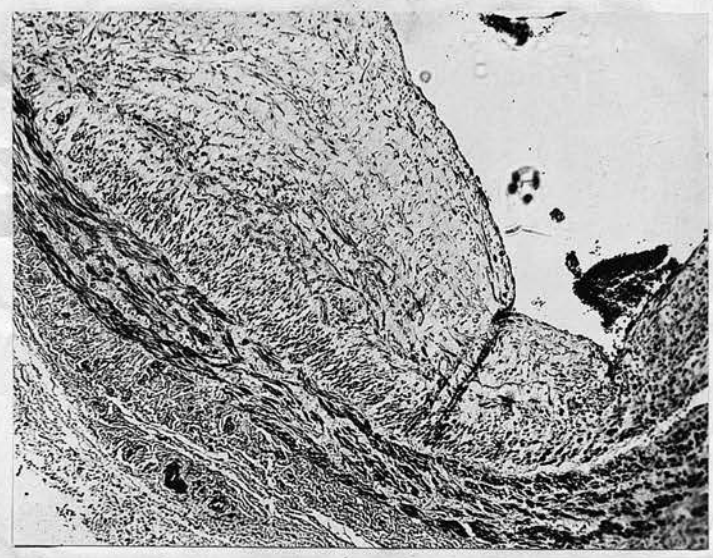


Fig. 32 . (x 21) Splenic vein from case I. Note the great connective tissue thickening of the intima with increase of elastic tissue fibres.

Fig. 33. (x 139) Section of a small vein from the hilum of the spleen of case VI. Note the thickened intima (i) as contrasted with a portion of normal intima seen on the extreme left.

might begin later. Such a thickened intimal plaque together with a congested and sluggish portal circulation would also predispose to thrombosis.

A more advanced stage of the endophlebitic change is seen in Fig. 32, taken from Case I, in which old standing thrombosis in various parts of the portal tree was found at autopsy. The process in this case had involved the large veins, and we find a more obvious development of intimal changes. There appears to be an increase of the connective tissue stroma between the muscle bundles of the media. The intima has undergone a connective tissue thickening with an increase of elastic fibres, the changes being much more pronounced than those in Case II.

The sections from the splenic vein of case VI showed similar changes in the vein wall, but with the superaddition of thrombosis. The muscular coat of the vein wall was thinned out under a plaque of connective tissue thickening. On the surface of the thickened intima thrombosis was superadded. Fig. 33 shows the changes in a small vein from the same case.

2. Dilatation of the venous sinuses of the spleen.

Before we discuss this change, let us first consider the anatomical and histological character of the normal spleen pulp. It is best to consider these features in a logical sequence, with reference to Hueck's diagram

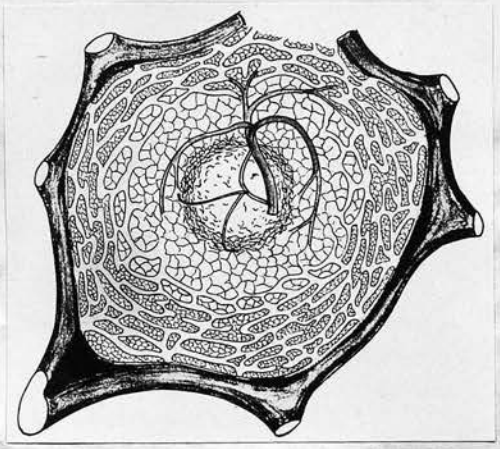


Fig.34. Diagram of the spleen lobule (Hueck). This represents the natural state. The venous sinuses are only seen at the periphery, and are narrow, while the pulp network occupies the major part of the lobule.

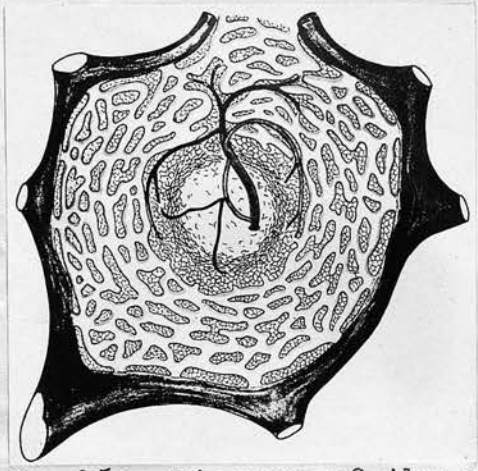


Fig.35. Diagram of the spleen in venous congestion. The venous sinuses are distended encroaching on the space previously occupied by the pulp network, and the pulp is crushed into a small space round the Malpighian body.

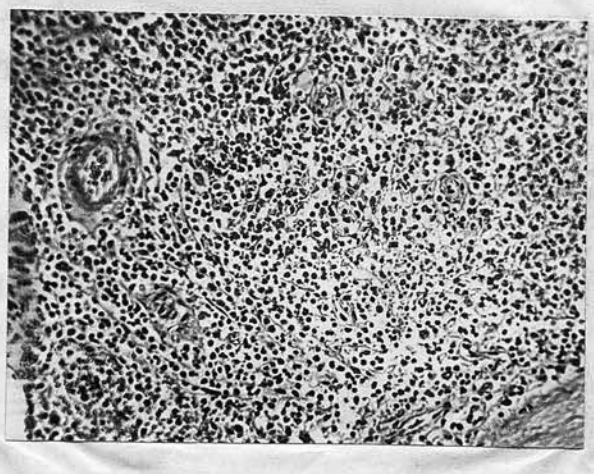


Fig.36. (x 130) Spleen of a child aet 6 mos. injected with formalin via the artery. The pulp network is evenly filled and distended, while the venous sinuses can scarcely be distinguished. This corresponds to fig. .

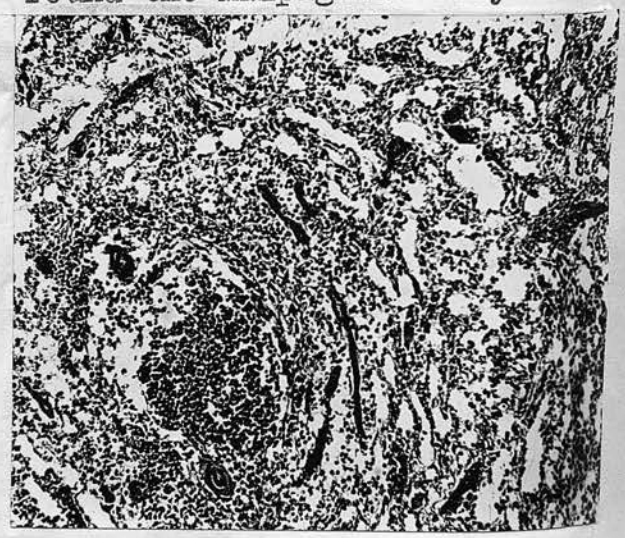


Fig.37. (x 100) Spleen of a child aet 5 mos. injected with formalin via the vein. The venous sinuses are markedly dilated and the intersinuous pulp tissue is crushed and condensed round the Malpighian body.

of the spleen lobule. (Fig.34,35)

The blood, leaving the arteries in the immediate neighbourhood of the Malpighian body which lies in the centre of the lobule, passes into the pulp spaces. These spaces are like the interstices of a sponge: they communicate freely with one another, and the spongework is held together by the branching processes of the pulp cells. The pulp cells themselves vary somewhat in size and appearance, according to their state of activity at the moment. The nucleus is usually rounded or oval, clear, with a few chromatin threads, while the cytoplasm is scanty. When the cells happen to be detached and lying free in the sinuses, their cytoplasm is more abundant, both cell and nucleus being rounded off, and the cell has the appearance of a macrophage. Only a few of the cells are definitely elongated and these resemble fibroblasts. In this loose meshwork the blood percolates slowly and is ultimately collected into more definite channels, the venous sinuses, which lie at the periphery of the lobule. These sinuses can usually be recognised as definite channels in the spleen pulp, especially in the neighbourhood of the trabeculae.

The cells which line them are somewhat elongated and have an oval nucleus which bulges into the lumen of the sinus. The lumen may contain one or two "active histiocy-

tes" (rounded potential macrophages). When stained by Bielschowsky's silver impregnation methods the whole spleen pulp is seen to be supported by a delicate framework of reticulin, and this is especially developed in the walls of the venous sinuses. Here the reticulin is thicker than elsewhere and transverse fibres can be seen to support those which run longitudinally, somewhat as the hoops of a barrel support the staves.

Although the sinuses are usually seen in an ordinary section at the periphery of the lobule and are more difficult to distinguish towards the centre, venous congestion or distension of the spleen by a fixative fluid injected into the vein, will so distend the venous sinuses that they encroach upon the area usually occupied by the pulp and extend centripetally as far as the Malpighian body. We thus see a section in which the sinus lumina alternate with intersinuous tissue consisting of compressed pulp. This state of affairs is illustrated by the diagrams and photographs. (Figs. 34 and 35).

In thirty nine of the forty one spleens from cases of hepatolienal fibrosis, the venous sinuses of the spleen shewed one of the following types of

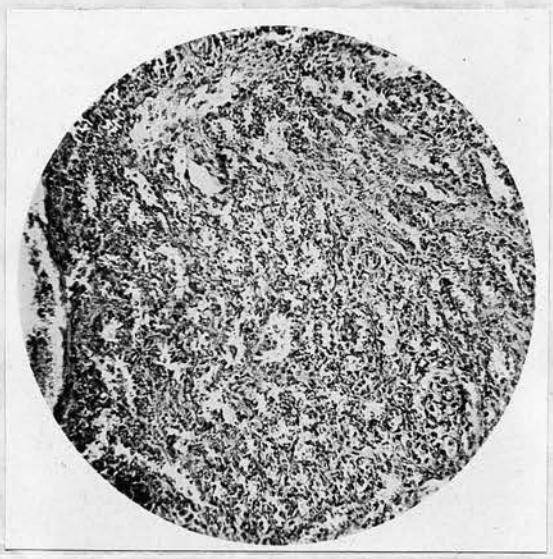


Fig. 38. (x 100) from case XXVII.
The venous sinuses are dilated , and the projection of the cell neclei into the sinuses gives the latter a "feathery" appearance.

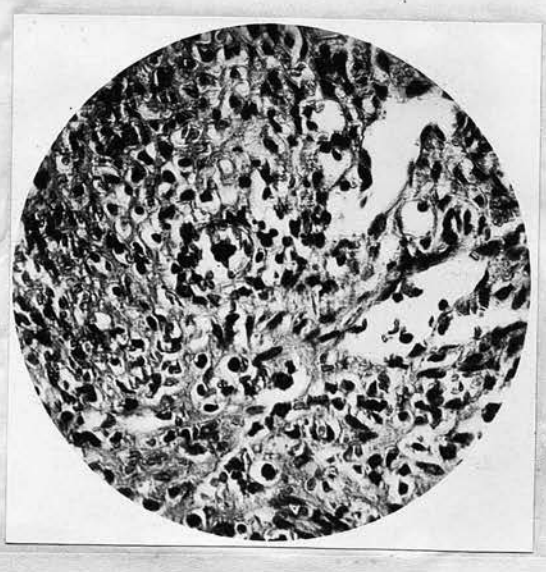


Fig. 39. (x 280) from Case XII.
Note the dilated venous sinuses with increased thickness of the supporting fibrils in their walls.

change.

1. DILATATION OF THE SINUSES.
2. DILATATION OF THE SINUSES WITH INCREASE OF COLLAGEN IN THEIR WALLS:

1. Simple sinus dilatation varied greatly in degree in the different spleens examined. In every instance the sinuses were distinctly dilated in the immediate neighbourhood of the trabeculae, and could usually be seen as definitely dilated channels extending centrally towards the perimalpighian zone. In some cases the sinus dilatation was extremely marked, giving the spleen an "empty" appearance. In table II , a mild degree of sinus dilatation is indicated by "d", and "D" is used when the dilatation is pronounced.

Simple dilatation of the sinuses without connective tissue increase leads to a "feathery" appearance of the sinus walls. This is shown in fig. 38 The appearance is due to the cellularity of the walls, the projecting nuclei of the cells lining the sinuses giving the "feathery" edge.

In the late stages of the disease the cellularity of the sinus walls undergoes an apparent diminution owing, mainly, to the elongation of the cells which thus become less prominent.

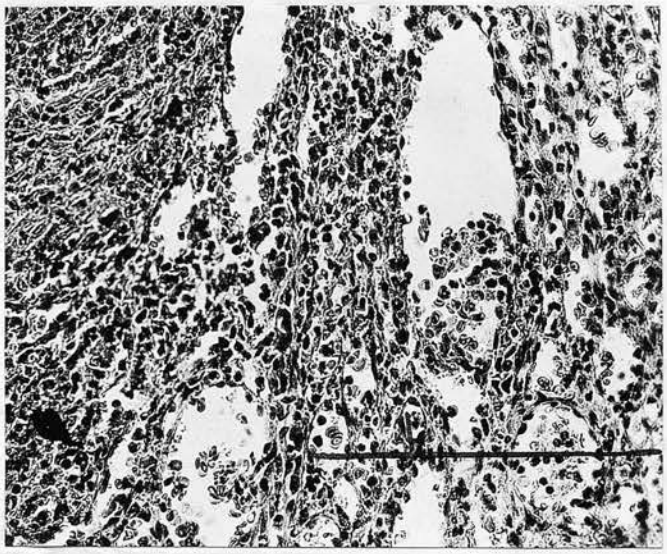


Fig. 40. (x 250) from case XXXIV.
Note the dilatation of the venous sinuses.
The dark fibres indicated by (f) took up
the red van Gieson stain, and are presumably
thickened reticulin fibres.

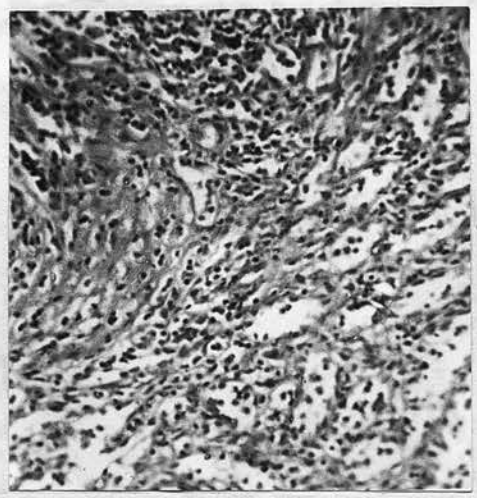


Fig. 41. (x 190). From case XXIV.
Note the dilated sinuses, with definitely
collagenous walls.

2. The next stage appears to be collagenisation of the dilated sinus walls. Stained with van Gieson a little newly formed collagen is seen in the sinus walls, and in the later stages the collagen may be a pronounced feature. The early and late stages of collagenisation of the sinus walls are indicated in table by "f" and "F" respectively.

It is to be noted that the process of collagenisation of the sinus walls differs from "fibrosis". In fibrosis, which may be illustrated by that occurring in the organisation of a perivascular haemorrhage, we have a transformation of the cells in a localised area into elongated fibroblasts. An area of cellular connective tissue is formed in which collagen fibres are laid down by the fibroblasts. By contrast, collagen appears in the walls of the dilated sinuses without any fibroblastic transformation of the spleen cells.

The process in the pulp is evidently not primarily fibrotic in nature as such a process would tend to produce shrinkage rather than enlargement of the spleen. The spleen pulp never assumes the appearance of scar tissue in this disease.

Apart from these changes in the venous sinuses, there are no other changes in the pulp as a rule. There is no cellular alteration of note, the cells

retaining their normal appearance for the most part. Very occasionally a multinucleated giant cell may be seen, but they are usually solitary and isolated. There is no evidence of iron or other pigment in the spleen pulp and myeloid metaplasia is absent.

The evidences of portal venous congestion.

In seeking a common factor to account for changes in the venous system of the spleen and the portal system of veins into which it drains, we naturally think of portal congestion, a time-honoured association of hepatic disease.

The evidences of portal congestion to be found in cases of hepatolienal fibrosis under discussion are many. If we refer to table II, we find that the thirty nine cases showing vascular lesions may be classified as follows:

Of 39 cases of Hepatolienal fibrosis showing vascular lesions:

Varicosity, enlargement or thickening of the veins in the spleen hilum; or dilatation of the collateral circulation between the portal and systemic veins occurred in.... 22

Of the remaining 17 cases, ascites occurred in.... 2

Of the remaining 15 cases, Haematemesis or melaena occurred in.... 5

Of the remaining 10 cases, Marked cirrhosis occurred in 2

Of the remaining 8 cases, Early liver changes occurred in..... 5

None of these lesions was shown by the remaining 3.

There is thus direct evidence of the anatomical effects of venous congestion, in 22 out of 39 cases. In the remainder, the veins are not mentioned, in the operation or autopsy notes; nevertheless, possible effects of portal congestion (haematemesis and ascites) occur in 7; while possible causes of portal congestion (gross cirrhosis or early hepatitis) are present in 7. Expressed in percentages:

Definite evidences of portal congestion	56.4%
Possible effects of portal congestion	18.0%
Possible causes of portal congestion	18.0%
No evidences to suggest portal congestion	7.6%

DISCUSSION.

As we have already mentioned in describing the early endophlebitic changes (p. 58), the intimal hypertrophy which occurs is neither atheromatous nor syphilitic. The former negation is suggested by the absence of "foam" cells characteristic of atheroma, while the latter is indicated by the absence of round celled infiltration of the media. Rather do the findings correspond to those occurring in the arteries in high blood pressure. Turnbull (1915) pointed out this type of intimal hypertrophy in general high blood pressure, and also in such a local high blood

pressure as that found in the pulmonary arteries in mitral disease.

The only other condition apart from high blood pressure which may lead to a similar intimal hypertrophy is local weakening of the vessel wall by disease primarily affecting the media. In such cases definite histological evidence of syphilitic inflammation is nearly always present in the media. In the absence of such signs of inflammatory change in the sections at our disposal it seems apparent that increased intravascular strain is the most probable cause. Adami (1912) also writes that "phleboscleros is not associated with any inflammatory condition, but is a strain fibrosis not due to irritation".

Dilatation of the venous sinuses of the spleen is in itself very suggestive evidence of venous congestion. Jäger (1931), in experiments to be described later, was able to maintain a condition of portal congestion in animals for periods up to two years. In sections taken from the spleen at the end of these long periods he found the picture to be dominated by the venous sinuses which were markedly dilated. The reticulin in the walls of the sinuses was irregularly thickened and the thickening of the reticulin fibres was noted to give way to collagenisation.

It appears therefore that not only the venous

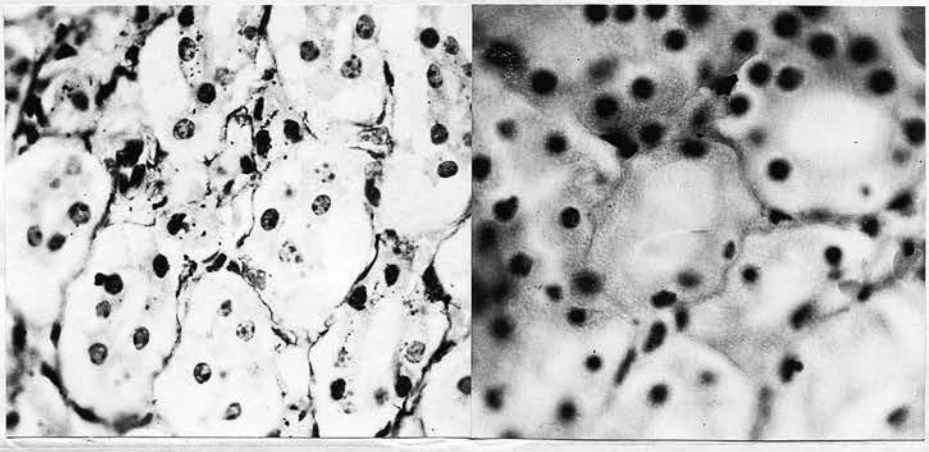


Fig. 42. (x 570) Kidney of guinea pig. Basement membrane stained by Foot's silver stain for reticulin, (left), and by van Gieson for collagen (right). Note that the basement membrane takes up both stains.

sinus dilatation but also the formation of collagen in the sinus walls may be referred to venous congestion. The formation of collagen from reticulin is probably merely reactive thickening of the supporting fibres in response to strain.

In his views on the relation of reticulin and collagen, Jäger obviously subscribes to the view of Nageotte (1930) who maintains that these two substances are essentially identical. In using Bielschowsky's silver impregnation methods for staining reticulin, the writer has frequently noted that fibres which take up the silver particles also stain red with van Gieson. An example of this may be found in the kidney tubules where the basement membrane takes up the silver strain and may also be stained red by van Gieson.

The factor which determines the identification of a fibre as reticulin or collagen appears to be its thickness. Very fine fibres will take up the silver deposit strongly, but will be only feebly stained by van Gieson. Thick fibres on the other hand are stained a deep red by van Gieson, but do not show the silver stain at all. Intermediate stages are of course found where the fibre is sufficiently fine to take up the silver stain, and is yet stained definitely red by van Gieson.

We may take it therefore that thickening of the reticulin fibres in the spleen will lead to their collagenisation. As we have already indicated the formation of collagen in the sinus walls in no way resembles the process of cicatrisation. The collagen appears to be formed independently of any local fibroblastic transformation. Jäger, in his experiments, noted that, in spite of the formation of collagen in the sinus walls, the reticulum cells of the spleen preserved a normal appearance. The retibulin thickening which occurs is therefore independent of local cellular changes, and is probably a result of increased intravascular strain in the sinuses of the spleen.

Matsui (1915) traced the changes in the reticulin framework of the human spleen in various disease conditions. In spleens from "Banti's disease", cirrhosis of the liver and syphilitic interstitial hepatitis, he found that the reticulin fibres underwent a marked increase in number and became definitely thickened.

There is thus ample evidence that the new formation of collagen in the sinus walls takes place from the thickening of reticulin fibres. The evidences of portal venous congestion are so strong that the writer accepts it as a fundamental feature in the pathology of hepatolienal fibrosis. In concluding this discussion of the vascular pathology of the disease, it

only remains to note the relationship of the periarterial haemorrhage to the portal congestion.

It has already been noted (p.17) that in attempting to force fluid through the spleen from the venous to the arterial side, a block occurs at the "critical point" of the circulation - namely the termination of the penicillar arterioles. In the event of venous congestion being sufficiently severe to lead to haemorrhage in the spleen, it is at this point that the effusion of blood would most probably occur.

As an experimental confirmation of this probability, Jäger found typical siderotic nodules and haemorrhages in the spleen in experimental portal venous congestion. It appears therefore that we are able to correlate portal venous congestion, not only with endophlebitis of the splenic vein and dilatation of the venous sinuses of the spleen with collagenisation of their walls, but also with the periarterial haemorrhages and their further developments - periarterial fibrosis and siderotic nodules. A case of simple obstruction of the portal vein will be described later in which these changes in the spleen were well illustrated.

Chapter 3.

THE RELATION BETWEEN PORTAL CONGESTION AND SPLENIC ENLARGEMENT.

It has long been recognised, and the point was stressed by Oestreich (1895), that the spleen of chronic venous congestion of cardiac disease is essentially very different from that in hepatic cirrhosis. Pribram (1902) showed that in experimental splenic vein congestion in dogs, the spleen did not remain permanently enlarged, but tended rather to shrink. As an explanation of this he assumed an active contraction of elastic and muscular elements. In the absence of strongly developed muscle fibres in the human spleen as compared with that of the dog, there is not the same ability to counteract the effects of congestion. There is, however, another factor which he did not consider, namely the diminution in arterial inflow to a part, the venous outflow of which is obstructed. (Wilson, 1933).

Artificial venous congestion was used by the original workers on the microscopic anatomy of the spleen, in their attempts to settle the question of a "closed" or "open" circulation. Basler (1863) found that even when he had distended the "veins" of the spleen pulp

with blood the pulp meshes could not be filled with red blood-cells. Sokoloff (1888) took up the subject again and confirmed the findings of Basler. The pulp spaces could not be filled by venous congestion, and, in fact, the pulp cells between the sinuses appeared to be more sparse than usual. He took it that the cause of this apparent paucity of pulp cells was a collection of oedema fluid which had filtered out from the dilated sinuses, while diapedesis of red cells occurred only after some time. Mollier (1910) maintained that the spleen circulation was essentially "open", but Sokoloff, as a result of his researches, took up the opposite view. The method used by Sokoloff to decide the question is open to criticism, but the observations arising therefrom as to the appearances of the venous sinuses are of interest in the question in hand. With regard to the size of the spleen after obstruction of the splenic vein, observations made by various workers have shown that the enlargement is only temporary and soon disappears. (Eppinger, 1920, Wicklein, 1891, Pribram, 1902).

The effect of distending the spleen via the veins by a fixative solution (formalin) is shown in Fig. 34. The venous sinuses are dilated and appear to fill up the whole lobule as far as the outer margin of the Malpighian body. As Weidenreich (1901) pointed out, the

venous sinuses are the most distensible portions of the spleen, and they may become so rapidly distended that they press upon and collapse the pulp spaces between the sinuses.

In the general chronic congestion of cardiac failure, this type of anatomical picture does not persist for any appreciable time. The venous sinuses are dilated at first as described. The later course of the splenic enlargement is modified by various factors. Hueck (1929-30) points out that in general, chronic venous congestion all exits from the spleen have their pressure raised, whereas in portal congestion, other exits from the spleen are still possible. Further, the arterial filling of the spleen is interfered with by the defect in the output of the heart. The spongework of the spleen becomes choked with red blood corpuscles, the arterial filling of the spleen, defective to begin with, becomes further cut off as a result of the venous obstruction, and stagnation occurs. The spleen becomes literally shut out of the circulation. It loses its storage material (iron, lipoids, etc.), and becomes atrophic. The lymph nodes are small, the trabeculae are relatively increased in numbers and there is a general increase of connective tissue at the expense of the pulp. The condition is well known as cyanotic induration.

It has frequently been claimed that portal obstruction and portal thrombosis may cause chronic splenomegaly.

Warthin (1910) made a careful analysis of the cases of porto-splenic thrombosis described in the literature up to that date. He showed the extremely frequent association of thrombosis of the splenic vein with splenomegaly and with liver cirrhosis. He illustrates fibrotic changes produced in the spleens of experimental animals as the result of portal obstruction. These bear some resemblance to the histological appearances in "Banti's disease". Warthin's conclusion is as follows:

"It is clear that in man the complex of splenic anaemia and Banti's disease, as formulated by Osler, is, in certain cases, if not in all, the result of an obstruction to the splenic and portal circulation, particularly the former, and that this obstruction is most commonly the result of an old thrombophlebitis of the portal vein and its radicles. . . .

"Until it has been definitely shown that the splenic anaemia or Banti's disease complex can exist without any evidence of obstruction of the portal or splenic vein, then my conclusion must hold that the complex is no disease entity."

The theory that thrombosis of the portal or splenic

vein may be a cause of splenomegaly with anaemia seems to have become established in many English and American textbooks, and the literature abounds with descriptions of cases considered to be of this type. Careful descriptions are given by Krull and Lossen (quoted by Mennet, 1920) Grützner, (1913), and Oettinger and Fiessinger (1907).

In all these cases the spleen was enlarged, varying in size from sixteen to forty three ounces; portal thrombosis was present in all; liver cirrhosis was present in many cases but absent in others. Oettinger and Fiessinger were actually of the opinion that in one of their cases portal thrombosis was responsible not only for the splenomegaly but also for the liver cirrhosis.

Wohlwill (1925) studied sixteen cases of portal thrombosis. The most notable of these was a patient with portal thrombosis but <u>without any splenic enlargement</u>. He considered that trauma at a previous operation and alcoholism were the responsible etiological factors in this case.

This observation emphasises two important points. Firstly, portal thrombosis can occur without splenomegaly. Secondly, if we are to accept portal thrombosis as a primary condition responsible for other changes, we must discover some cause for the portal thrombosis.

Among the etiological factors indicted in portal thrombosis, trauma is commonly included. Ledingham (1909), writing in Allbutt's System, says:-

"Many cases which showed symptoms of splenic anaemia or Banti's disease have presented a history of previous severe abdominal injury, and thrombosis of the portal vein with consequent splenomegaly, anaemia, and moderate cirrhosis of the liver has been proved on several occasions to follow injury."

The extreme rarity with which thrombosis of the superficial veins of the limbs results from the numerous knocks and bumps of every-day life, together with the deep-seated, well protected situation of the portal vessels, must be sufficient to make us exceedingly sceptical about any such cause.

Syphilis is another much quoted cause. It is certainly a factor in some cases of syphilitic cirrhosis and syphilitic splenomegaly, but in such cases portal thrombosis may occur as a secondary phenomenon. In any case syphilis cannot be seriously considered as a cause of phlebitis of the portal vein unless there is very suggestive local microscopic evidence of the disease.

Various inflammatory affections of the alimentary canal can, of course, lead to suppurative pylephlebitis, and it is just possible that mild infections may

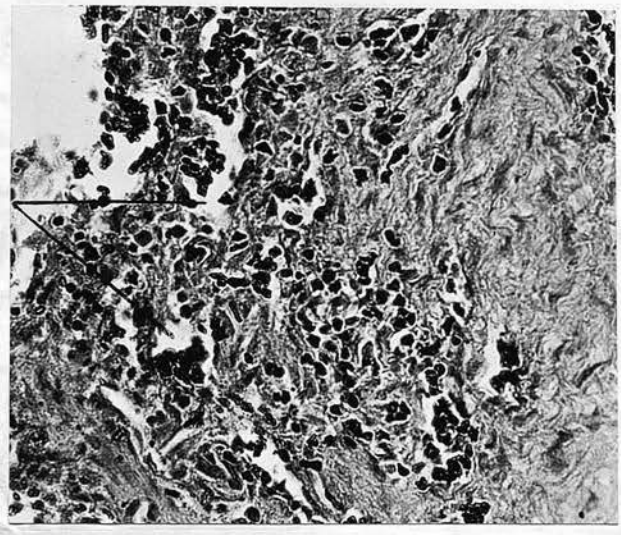


Fig.43. (x 300) Atrophied and fibrosed spleen of rabbit 4½ weeks after ligature of splenic veins. The sinuses are still recognisable (s).

be followed by a non-suppurative phlebitis and thrombosis.

To ascribe a primary role to portal obstruction as a cause of splenomegaly however accords ill with the observations already quoted, that portal or splenic vein occlusion tends to produce shrinkage of the spleen after the initial stage of congestion. It should be noted that Warthin, in his experiments on splenic vein occlusion in animals, did not obtain splenomegaly, although the histological picture bore some resemblance to that found in "Banti's disease".

Fig. 43 shows the result obtained after ligature of the splenic veins in a rabbit, where all possibilities of the development of a collateral circulation had been excluded. The animal was killed 32 days after the operation. A small nodule of scar tissue was found in the site previously occupied by the spleen. In a section the venous sinuses of the spleen could be recognised - "dilated and fibrotic" - and the great mass of the spleen was replaced by scar tissue.

In animals where the spleen is large (e.g. the dog) occlusion of the venous return leads to necrosis of the spleen.

A valid objection to these experiments is that the experimental occlusion of the splenic vein is sudden and complete, leading to early cessation

of the circulation through the spleen. In this way shrinkage, cicatricial contraction and even necrosis are brought about.

In human pathology we have to deal with either chronic continuous or remittant congestion. The most important observations up to the present date on the effects of chronic congestion are those of Jäger, which we have already described in part. His observations are so important that we shall take the opportunity to quote his methods and observations in some detail.

In experiments carried out in dogs, Jäger obstructed the splenic vein to one third of its cross section by a ligature to produce continuous congestion. In pathological portal congestion, conditions are probably rather different from the continuous congestion thus produced. Even the anastomoses show by their varicose tortuosity that they are not adequate for their purpose of conducting the portal blood into the systemic circulation. There is probably a residuum of congestion left. Any hyperaemia in the portal region, such as that occurring during digestion must lead to an exacerbation of the congestion. The portal circulation is then decompensated and the collaterals only relieve the situation when the flow of blood in the splanchnic area becomes less. The portal congestion in hepatic cirrhosis is

therefore most probably of a paroxysmal intermittent type.

Experimentally this type of congestion was reproduced in two ways. The portal vein was tied off to one third of its cross sectional area, and after a time only a sufficient number of collaterals were tied off to maintain a state of congestion. In a second group of dogs, the blood from the inferior vena cava was led through the portal vein by means of a reversed Eck fistula. Thus the amount of blood to be transmitted by the portal vein was enormously increased. When collaterals to the superior vena cava had developed sufficiently, the portal vein was tied off completely. The congestion was maintained over a period of 6 months to 2 years. Portions of the spleen for examination were taken at every operation. At the end of these long periods the spleen was somewhat smaller than in the state of acute congestion produced by the first operation.

In continuous congestion, thickening of the capsule and trabeculae was especially prominent, while the pulp and venous sinuses showed little alteration as compared with the normal.

In remitting congestion, the most striking point was not thickening of the capsule and trabeculae, but dilated venous sinuses. Thickening of reticulin

fibres had occurred in the sinus walls, and typical siderotic nodules were seen in the spleen.

It appears therefore that remittent portal congestion may lead to enlargement of the spleen, but to a degree not exceeding that produced by the initial acute congestion.

An estimate of the weight which might be reached by simple venous congestion of the human spleen can be made by distending the normal organ with saline via the splenic vein. When this is done it is found that the spleen enlarges to about three times its normal size. With an average adult human spleen weighing e.g. 150 grammes, the maximum weight which might be reached by means of chronic congestion alone would be about 450 grammes.

It appears obvious therefore that splenic enlargements over 1000 grammes which so often occur in association with hepatic cirrhosis are not to be accounted for by portal congestion alone. When hepatic cirrhosis is found along with porto-splenic thrombosis and splenomegaly over 500 grammes, the latter is not explained by portal congestion. Eppinger in discussing thromphlebitic splenic enlargements summed up the problem well when he said: "Dass sich gleich im Beginne der Stauung ein Milztumor entwickeln kann, ist selbstverständlich, warum es aber zu

einer dauernden Milzschwellung kommt, ist schwer einheitlich zu erklären. Offenbar spielt hier der Symptomenkomplex, den wir vielfach unter dem Namen Lebercirrhose zusammenfassen auch pathogenetisch eine grosse Rolle".

As so many of the recorded cases of portal obstruction are complicated by the coincidence of cirrhosis, an instance of portal obstruction in which the liver was macroscopically and microscopically normal will be discussed here.

Emily B.

Blood.

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
18.4.22	4,980,000	4,000	70	.7	60	36	3	1	0
10.6.22	4,200,000	3,000	72	.8	66	21	8	3	2
15.6.22	Splenectomy								
20.6.22	3,260,000	15,500	58	.8	65	20	9	5	0
5.7.22	2,060,000	10,000	32	.67	72	25	3	0	0
10.7.22	3,130,000	13,000	50	.79	65	21	9	4	1
2.8.22	4,670,000	7,600	72	.8	60	35	1	4	0
13.10.22	4,450,000	15,000	75	.87	57	37	4	6	1
9.3.23	5,000,000	13,600	65	.65	45	46	5	3	1
14.8.23	4,120,000	10,500	79	1.0	43	47	5	4	1
11.9.23n	3,860,000	12,400	80	.96	35	44	6	3	3
15.9.27	3,900,000	12,500	78	1.0	51	41	3	4	1
- .11.27	3,800,000	8,400	76	1.0	56	40	0	3	1
10,5,28	3,700,000	11,000	80	1.0	63	32	3	1	1

C A S E XLII.

Emily B. aet 22: Occupation Book-folder.
Admitted to hospital: 10.4.22.

History: The patient states that a year ago swelling of the abdomen and lower limbs appeared. About the same time menstruation ceased. She has always been short of breath but this has become worse during the past eleven months. Ten years ago she vomited blood and at this time the spleen was found to be enlarged. She has not vomited blood since then. Her appetite is usually good. Micturition is scanty in quantity. There is no history of alcoholism or of residence abroad.

Family History: Mother died of tuberculosis three years ago.

On Examination: The patient is slightly pale. Temperature 99.5. Blood pressure 130mm. Hg.

Abdomen: Uniformly distended. There is shifting dullness in the flanks and a fluid thrill. After removal of the fluid the spleen was palpable three inches below the costal margin. The liver could not be felt.

Cardio-vascular System: Nil to note.

Lungs: Crepitations were present at the bases posteriorly.

Urine: Albumen present .5% Epithelial & hyaline casts.

(14.9.23. Urea concentration test:

	Urea.	Volume.
7-30 a.m.	0.09%	48c.c.
8-30 "	1.25%	51 "
9-30	1.1%	56 "
10-30	1.2%	98 "

15.9.23. Blood urea 41mgs/100c.c.)

11.4.22. Paracentesis of abdomen: 22 pints. No organisms even on culture.
22.4.22. " " " 30 pints.
16.5.22. " " " 28 "
8.6.22. " " " 30 "
15.6.22. Splenectomy and abdomen emptied of fluid.
29.6.22. Paracentesis. 14 pints.
21.7.22. " 13 "

Blood counts are indicated in the appended table.

Wassermann Reaction: Negative.

15.6.22. Splenectomy. The spleen was enlarged to about three times its normal size. The liver was not examined. The abdominal wall was very vascular on account of an extensive collateral circulation.

Patient made a good recovery and was sent to a convalascent home from which she returned on 13.10.22. The ascites which had had to be tapped on two occasions after the operation had now disappeared. Oedema of the feet however was still present. Menstruation had returned after being absent for nineteen months.

2.3.23. Patient was readmitted with dropsy of the legs. There was no ascites and liver was not palpable. The result of the urea concentration test is indicated above, and the condition is now obviously renal in origin.

12.7.23. Some fluid made its appearance in the abdomen. The liver was not palpable.

6.9.23. Readmitted. Definite ascites and the feet swollen. The ascites was slowly reabsorbed and patient was again discharged from hospital. In December 1929 patient was admitted and died from renal failure.

Abstract of post-mortem notes. There was a great dilatation of the right ureter with no organic cause that could be found. This was associated with a congenital hydronephrosis of the right kidney. The left kidney was granular in appearance and showed an advanced degree of chronic nephritis.
The Portal Vein was closed at its hepatic extremity. The remainder of the splenic vein was widely patent as was also the superior mesenteric vein. The superior mesenteric vein joined the splenic to form a short ballooned portal vein which ended in a cavity at the entrance to the liver. From this dilated cul de sac several small vessels passed upwards to the hilum of the liver. The intrahepatic veins appeared to be normal. Large dilated submucous veins were present in the lower third of the oesophagus and there was also marked dilatation of the haemorrhoidal veins in the rectum and anus. The liver was natural in appearance and there was no macroscopic cirrhosis.
Microscopic Examination of the Liver. Apart from a slight cloudy swelling of the liver cells and a small degree of periportal lymphocytic infiltration there was nothing to note. There was no increase of connective tissue in the liver lobules or around the portal tracts.

The Spleen.	Weight 420 grammes.
Microscopic Examination.	
Vascular lesions.	Periarterial haemorrhages: periarterial fibrosis: perimalpighian haemorrhages and fibrosis: siderotic nodules all present.
Venous Sinuses.	Dilated with slight increase of collagen in the walls.

Malpighian bodies. Medium sized. Germ-centre seen occasionally.

The Pulp Cells. Showed little abnormality as compared with the normal except that the number of elongated fibroblastic cells in the sinus walls seemed to be increased.

DISCUSSION.

The anatomical picture presented by this case of a dilated ballooned portal vein ending in a 'cul de sac' with small collateral veins developed outside its wall, is a marked contrast to the picture of old-standing intravenous thrombosis and recanalisation. Not only was the familiar picture of the latter condition completely absent, but there was no vestige of the commonly associated, and probably causal, hepatitis.

Complete obliteration and disappearance of the upper portion of the portal vein of the type described is most probably the result of a congenital abnormality. The portal vein does not assume its full functions until after birth, when the umbilical vein and the ductus venosus Arantii, which communicate with it in foetal life, become obliterated. The veins at the hilum of the liver are thus situated at a region of developmental complexity where abnormalities of development may readily occur.

Analogous cases of congenital occlusion of the portal vein have been recorded in children by Wilson and Lederer (1929), and by van Creveld and Levy (1930) who discuss the literature.

So far as the spleen is concerned, the histological picture could be completely accounted for by portal congestion. Moreover the size of the spleen - about 2½ times the normal - might readily be explained by congestion alone. There were no evidences of hyperplasia. Histologically, the liver was quite normal.

We should hesitate to ascribe the ascites which occurred in the present instance to portal congestion alone. There was unequivocal clinical and pathological evidence of renal disease which would be a factor in the causation of oedema. In the presence of such an additional cause of dropsy, portal congestion would tend to bring about effusion into the peritoneal cavity. It is of interest to observe that van Creveld and Levy's case also had ascites in association with albuminuria.

A point of some importance may be the apparent cure of the leucopenia by splenectomy. The leucopenia which occurs in hepatolienal fibrosis seems to be in some way associated with the presence of an enlarged spleen (see p.). The present case affords some evidence in support of this idea although the post-operative picture is complicated by the presence of nephritis.

We may sum up this chapter by saying that portal obstruction is not necessarily followed by splenomegaly, and it may occur without any enlargement of the spleen. Under certain circumstances, however, it may bring about an enlargement of the spleen, the maximum enlargement reached in the human subject being about three times the normal size. Splenic enlargement over 600 grammes in an adult must involve some factor other than mere congestion. Portal congestion, however, is responsible for the vascular changes we have described in hepatolienal fibrosis.

Chapter 4.

The Changes in the Liver.

Before we can continue the discussion on the splenic enlargement in hepatolienal fibrosis, it is necessary to study some aspects of the associated changes in the liver.

A general survey of the case records shows the following association with liver disease:

	No. of cases
Cirrhosis of the liver present (in cases VI to XXIII inclusive)	18.
Early liver changes, e.g. mottling of the liver surface by scar tissue etc. (in cases XXIV to XXXII & case V. . . .	12.
Liver showing no abnormal macroscopic appearance. (in cases XXXV to XLI & cases I to IV) .	11.

Associated hepatic damage is therefore obvious to the unaided eye in 30 out of 41 cases, or in 73%.

It is necessary, however, to investigate the criteria on which we can definitely state that the liver is normal. In this respect we shall give some detailed consideration to Case I.

In this patient, as will be seen from the notes,

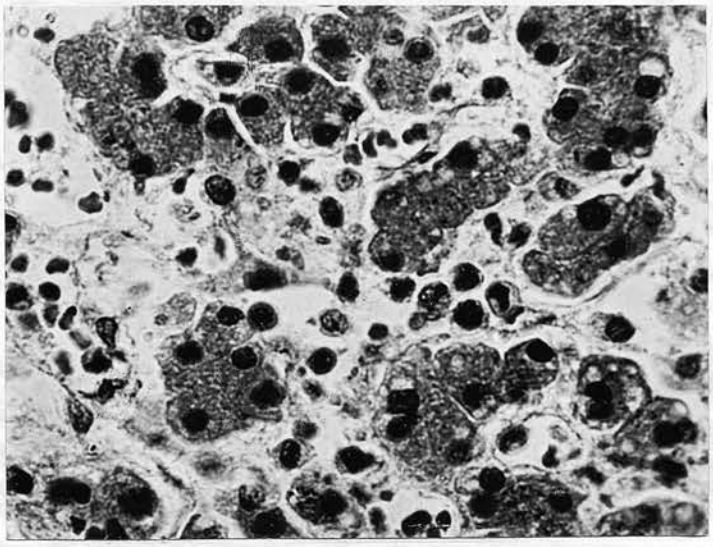


Fig. 44. (x 500) Section of liver from case I, which appeared "normal" macroscopically. Note the disintegration of the liver cell columns, vacuolation of liver cells, the separation of the cell columns by oedema, the leucocytic and large and small round-celled infiltration.

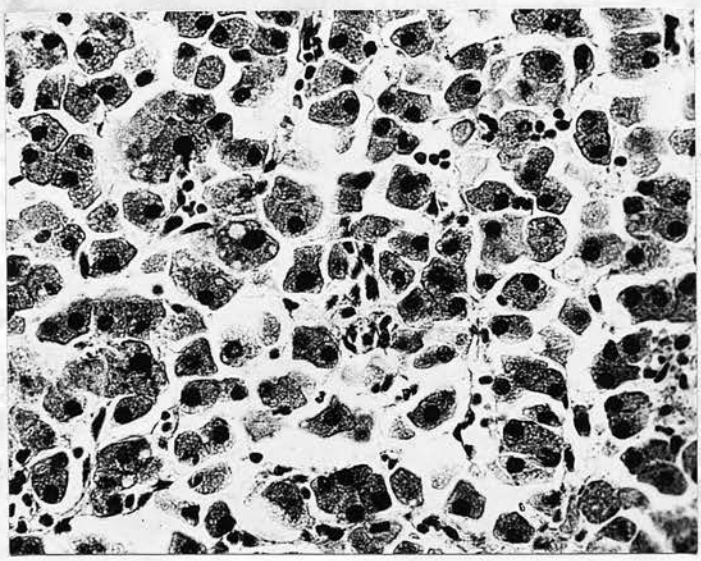


Fig. 45. (x 350) Liver from case I.
Note the disintegration of the cell columns, local round celled accumulations, vacuolation of the liver cells which show great variations in their size.

the liver appeared "normal" at operation. The patient died of porto-mesenteric thrombosis and infarction of the jejunum.

"The liver showed no naked-eye fibrosis". The pathologist, satisfied that sections of the liver were unlikely to reveal any lesion, omitted to take any. The physician in charge of the case, however, took a small portion of the liver for microscopic examination. By this fortunate chance we are provided with sections showing definite early hepatitis in a liver which was "normal" to the naked eye.

Histological examination revealed the condition seen in Figs.44 and 45. The liver cells showed cloudy swelling and fatty degeneration: the cell columns were broken up into isolated fragments consisting of one or more liver cells. Occasionally a liver cell was seen which seemed to be undergoing lysis. The liver cell columns were widely spaced out and the lymph space between the wall of the sinusoid and the liver cells appeared to be oedematous. A number of polymorph leucocytes were seen in the perisinusoidal lymph space, but small round cells and large round cells with abundant protoplasm predominated. Kupffer cells were difficult to identify. The degree of cellular infiltration varied slightly in different parts of the liver. In some areas it was pronounced (cf. Fig.44), while in others it was less marked (Fig.45). In the latter areas, however, focal cell infiltrations could still be seen, while the appearances of oedema, disintegration and separation of the cell columns were always much in evidence.

It is thus obvious that a liver which appears normal to the naked eye may yet show pronounced damage and inflammatory reaction on being subjected to microscopic examination.

From our case reports we may take yet another instance in which there was no definite clinical evidence of liver disease although at operation the organ appeared to be normal. In case XXXI, gross enlargement and tenderness of the liver were detected clinically, while the van den Bergh reaction and the icterus index showed a definite degree of jaundice. The liver and spleen both diminished in size during four weeks of observation. At the end of this time, when splenectomy was carried out, the liver had a normal appearance.

Although the liver appeared to be normal in case XXXVIII, and in case IV, both these patients were subject to transient attacks of mild jaundice.

Cases XLI and II had both been subject to epistaxis, the latter also to purpura, which, in patients suffering from this disease may possibly indicate hepatic damage (see p.262).

Microscopic and clinical evidence therefore would indicate that definite liver damage is present in hepatolienal fibrosis much more frequently than is indicated by inspection of the liver surface at operation or at autopsy. Taking the 11 cases in which

the liver was reported to be "normal", we have direct histological evidence of hepatitis in one instance, definite clinical evidences of hepatic damage (jaundice) in two, and possible indications of liver disease (epistaxis and purpura) in two. It is unfortunate for the elucidation of the pathology of hepatolienal fibrosis that biopsy material from the liver has not been taken more frequently. Excluding the two patients with epistaxis and purpura, we may state that definite evidences of liver disease have been found in 33 out of 41 cases, i.e. in 80%. Had sections been taken from the liver in the remaining cases, it is quite possible, from the lesson of case I, that evidences of hepatitis might have been found in every instance.

The absence of clinical signs of hepatic disease in the "precirrhotic splenomegalies" is therefore no evidence that such disease does not exist. It is well known that anatomical cirrhosis is the end result of a process which has lasted many years, or even a large proportion of a life-time, and which for years may be present without giving rise to symptoms. The term "cirrhosis" has however no place in the consideration of the earlier stages of the process of hepatic inflammation, where cirrhosis and sclerosis have not made their appearance. In this early stage

we must apply the term "hepatitis".

The conception of "hepatitis" has been coming more and more into everyday use in clinical medicine, especially on the continent. The first step towards the conception of hepatitis was made when catarrhal jaundice was removed from the category of an ordinary obstructive jaundice due to a cholangitis. The application of liver function tests indicated definite damage of the liver cells in catarrhal jaundice, but hepatic insufficiency was absent in cases of simple obstruction of the bile passages. Following the war, there occurred in Germany an extensive outbreak of epidemic catarrhal jaundice; in the vast majority of cases, however, the jaundice did not improve and the patients developed cholaemia, with purpura and central nervous system manifestations. Death occurred in these, and the pathological changes found were those of subacute yellow atrophy. In 1927, there occurred a similar but more extensive outbreak in Sweden. This outbreak demonstrated even more conclusively the diffuse nature of the liver damage in catarrhal icterus. In Stockholm alone, 89 cases of acute, subacute and chronic liver atrophy came to autopsy, in which the disease could be directly dated to attacks of catarrhal jaundice occurring at the height of the outbreak. (Bergstrand 1930).

While these cases are clear cut and indicate that the trend of modern opinion is correct in regarding catarrhal jaundice as hepatitis, the clinical appreciation of hepatitis is hampered by many difficulties. First among these is the remarkable compensating power of the liver. Experimentally seven-eighths of the organ can be removed, and all the functions of the enormous gland can be adequately carried out by the remaining eighth. In typhoid fever, for example, it is well known that areas of focal degeneration are almost constant in the liver at autopsy, and yet the clinical manifestations of liver disease, as they are recognised at present, are exceedingly rare.

The liver carries out all its functions without producing any easily available external secretion by which its work may be estimated like that of the kidney. Compared with the diagnosis of renal disease which is a relatively easy matter, the diagnosis of hepatic disease in its early stages is almost impossible, and its recognition will almost inevitably depend on future biochemical developments. In the absence of icterus, hepatic disease is,as a rule, only a matter of conjecture, and it will remain so until we have the desired refinements of biochemical technique.

Icterus, according to Eppinger, bears the same relation to hepatic disease as albuminuria to renal disease. While this is true in a general way, it

represents a state of knowledge on which we must improve. While albuminuria is almost constant in all stages of renal disease, icterus is by no means constant in hepatic disease. Icterus represents merely a disturbance in one function of the liver, and it is certain that degrees of liver damage may occur, in which the functions of bile-excretion remains more or less undisturbed. The idea of hepatitis without icterus is mentioned by Lepehne(1930) , who describes cases of liver enlargement with tenderness, in which jaundice is absent. Such cases occur during epidemics of catarrhal jaundice. The recent introduction of the bilirubin tolerance test by Eilbott (1927) has shown that acute liver damage may occur in the absence of jaundice. The test was positive, for example, in all cases of acute alcoholism within 24 hours of the alcoholic excess.

These considerations bring us inevitably to the opinion that hepatitis must occur with considerably greater frequency than is recognised at present. The absence of ordinary clinical manifestations of liver disease, and a liver which appears normal to the naked

eye cannot be accepted as evidence that the liver is undamaged.

Although hepatitis may be "silent" for years in many cases, we may be able occasionally to trace the earlier development of the disease. In case IX, for example, a syphilitic subject developed jaundice in the course of salvarsan treatment. The jaundice persisted for four months. During the succeeding five years he had transient attacks of abdominal pain with fever and slight jaundice. At the end of this time, "early" cirrhosis was just recognisable at operation. Case X shows a somewhat similar course but unrelated to syphilis. In case XV icterus began twelve years before his admission to hospital. In case VII the first clinical signs of hepatitis had occurred 23 years before she came under observation. It is certain that in the early stages these patients would have shewn no gross distortion of the liver to the unaided eye. It will be noted that cases of hepatitis with splenomegaly in which syphilis has been a precipitating factor (Cases VI, IX, and XIII) are included under the general heading of hepatolienal fibrosis. Clinically and pathologically these cases are identical with the others in which syphilis as a causal factor was excluded. The lesions in the liver and spleen in syphilitic subjects bore no identification marks of syphilis (e.g. gummata).

It would appear from the researches of Lindstedt (1919), Herxheimer and Gerlach (1921), and Bergstrand (1930) that syphilis instead of causing hepatitis per se, merely renders the liver especially liable to hepatitis of all degrees. This theory agrees well with the anatomical identity of the lesions in our syphilitic and non-syphilitic cases.

Apart from syphilis it is rare to find any definite etiological factor to account for the hepatitis. In case XXIII, cholecystitis appeared to play an undoubted part, and the sections from this case shewed an acute exacerbation of a chronic hepatitis, with a proliferative type of splenic enlargement.

The writer has seen one case of chronic hepatitis with splenomegaly (not included in the present series owing to lack of pathological material) which was undoubtedly related to an intensive course of atophan (phenyl-quinoline-carbonic acid) which had been given for chronic rheumatism. During treatment the patient developed jaundice; five years later the liver was definitely enlarged and hard, and associated with marked splenomegaly. It has been suggested that this hepatitis is essentially due to the coincidence of atophan with some other liver damaging factor (Starkenstein, 1932).

It would appear therefore that hepatitis tends to

assume the same anatomical forms irrespective of the causal agent involved, and that splenic enlargement may occur in association with hepatitis however pro duced.

Marchand (1895), Strübe (1897),and Bergstrand (1930) have noted splenic enlargement in association with acute and subacute yellow atrophy of the liver. Eppinger (1926) stresses splenic enlargement as a diagnostic point in acute ascending cholangitis with hepatitis. A moderate degree of splenic enlargement is commonly observed in association with catarrhal jaundice. Garnier and Reilly (1919) and Widal and May (1928) have observed splenic enlargements occurring in association with spirochaetosis icterohaemorrhagica.

We may conclude by saying that there is no decisive proof that the liver is undamaged in <u>any stage</u> of hepatolienal fibrosis. Positive evidence of liver damage was found in 80% of the present series of cases. In the remaining 20%, autopsy material was not taken, without which it is impossible to say that the liver is normal.

It appears that the liver cannot be exonerated from a share in the pathological process from the very beginning of the disease. The question with which

clinicians confront the pathologist at post-mortem, when considering a case of cirrhosis with splenomegaly, "Did the diseased liver or the enlarged spleen come first in this case?" begins to lose its meaning. The involvement of liver and spleen in all cases is probably simultaneous, and varies only in degree. The grouping of the various clinico-pathological variants under the heading "hepatolienal fibrosis" is an attempt to give more adequate expression to this modern hypothesis. The conception of hepatolienal fibrosis as a disease affecting both liver and spleen, and in which liver involvement is an essential feature from the outset, is the main thesis of this work.

Chapter 5.

The Cause of splenic enlargement in in association with hepatitis.

The natural opinion which was held up to the end of the last century was that splenic enlargement in hepatic cirrhosis was due to portal congestion. In the atrophic type of cirrhosis, which was frequently accompanied by ascites and oesophageal varices this explanation appeared to fit the case. This, however, is the very type of cirrhosis in which the spleen is often small, while, on the other hand, there are certain anatomical types of cirrhosis, e.g. the classical hypertrophic type of Hanot, in which the signs of portal congestion may be relatively inconspicuous, and yet considerable splenic enlargement is present.

Oestreich (1895) was the first to suggest that some factor other than congestion played the most important part in determining the enlargement of the spleen. He pointed out how markedly the "cirrhotic" spleen differed in its appearance from the spleen of ordinary venous congestion. According to him the spleen responds to some stimulating irritant and even in the early stages of cirrhosis there occurs a cellular proliferation - "hyperplasia pulpae" - which can persist into the later stage of the disease. Oestreich fur-

ther considered the possibility that in the later stages of the cirrhotic process, an indurative enlargement of the spleen might develop from the hyperplastic, so that the actual pulp became atrophied.

Senator (1901) thought that the substances which are responsible for cirrhotic alterations in the liver, also play a part in causing the enlargement of the spleen. Before Oestreich, Sieveking (1894) wondered whether connective tissue over-growth took place in the spleen in the same way as in the liver. He was unable, however, to determine any diffuse increase in the connective tissue in the spleen and therefore was unable to explain the splenic enlargement in this way. Rosin(1898) tried to explain the splenic enlargement on the same grounds as Sieveking. In the light of modern pathological opinion (e.g. Albot, 1931) which tends to regard the increase of connective tissue in the liver as secondary to damage of the liver parenchyma, all those theories based on the idea of a primary connective tissue overgrowth seem to be doomed to failure.

Strümpell (1900) ascribed the splenic enlargement of hepatic cirrhosis to chronic accumulation of bile in the blood. Weber (1897) suggested that the most marked enlargements of the spleen were to be found in those cirrhoses accompanied by the severest

jaundice. He suggested that toxic substances were retained and were responsible for the effects on the spleen. Hermann (1901) suggested that the enlarged spleen had a special etiological role and that it was probably overacting, possibly in an increased destruction of red corpuscles, so that its protective action was diminished, and toxins no longer fixed by the spleen flowed on to the liver and were responsible for the hepatic damage.

Bleichröder (1904) considered that there was a close relationship between blood diseases and hepatic cirrhosis, an idea which has recently been recuscitated by Epplen (1922). Bleichröder pointed out that in cases of liver cirrhosis, red bone marrow extended into the shaft of the femur, and Charcot Leyden crystals were also present, conditions which are both seen in blood diseases. He fails however to give any exact histological details, and at present with the lack of further positive evidence this view is not very helpful. The work of Hartwich (1912) was directly opposed to the view of Banti, and those other writers who regarded the spleen as the <u>fons et origo mali</u> in hepatic cirrhosis. He was unable to confirm the view that splenic enlargement might precede the changes in the liver. He regarded the liver change as primary, and the splenic involvement as secondary. The splenic

enlargement, in his opinion, however, was compensatory, and due to the fact that the spleen took over part of the work, usually carried out by the liver.

From the French writers the most extensive work was that of Gauckler (1905). He thought that the splenic enlargement was due to a true hypertrophy determined by a long lasting erythrolytic stimulation. This was especially dependent upon repeated intra-parenchymatous haemorrhages. The hyperplastic process was followed by the appearance of an atrophic sclerosis, so that the size of the spleen was determined by the intensity of the hypertrophic and atrophic processes. He concluded with the sentence:-

"La rate cirrhotique rentre dans le groupe des rates d'ordre haemolytique".

Gauckler claimed to produce appearances similar to those in cirrhotic splenomegaly by the use of haemolytic poisons, such as toluylenediamine. The most obvious objection to this hypothesis is that the spleen of haemolytic icterus in no way resembles the spleen of hepatolienal fibrosis.

Eppinger favoured this theory of excessive haemolysis as the cause of splenic enlargement in hypertrophic cirrhosis and developed the theory fully. In favour of the theory he adduces the presence of bi-

liary thrombi in the bile capillaries, extension of the red marrow into the shaft of the femur to bring about a compensatory overproduction of red corpuscles; the spleen, he admits, does not show the usual picture of haemolytic icterus, but nevertheless it is "blutreich" and contains iron pigment, so that "there is nothing against the assumption of increased blood destruction".

Reference to his illustrations of the pathological findings shows that the iron pigment present was definitely associated with periarterial haemorrhages and fully developed siderotic nodules. The congestion with blood was definitely due to an overfilling of the venous sinuses which are distinctly dilated.

One further point which Eppinger brings forward in favour of excessive haemolysis by the spleen in cirrhosis, is the beneficial effect of splenectomy on the jaundice. He admits however a hepatic element in the jaundice which may interfere with the favourable results. In answer to this contention of Eppinger, it is well known that jaundice is a mild and frequently transient symptom in cirrhosis, and the results of splenectomy would require to be more striking before we could accept the theory that the jaundice of cirrhosis is splenogenic. Eppinger, however, stresses a fact which we consider of importance: in cirrhosis, the

liver cells are damaged primarily, and the other features of the disease seem to bear some relationship to this primary damage. He also attempts to bring into line with the splenomegaly of cirrhosis the splenic enlargement of catarrhal icterus, which may be dependent on similar causes.

To be added to these various hypotheses which have been put forward to account for the splenic enlargement of cirrhosis, is the recent tentative suggestion given by McNee (1932) in his Croonian lectures. He described how, in gross cirrhosis, McIndoe (1928) had shown that the portal blood might be deviated from the regenerated "lobules" and pass straight on to the hepatic vein. By this means metabolic products from the intestine might reach the general circulation. The spleen might enlarge to deal with these. While this hypothesis raises problems of far-reaching interest, it does not account for the precirrhotic splenomagalies, in which an identical type of enlargement of the spleen is present long before there has been any such gross distortion of the liver circulation as McIndoe found.

The above brief review of the various attempts which have been made to account for the splenic enlargement of cirrhosis shows that up to the present no satisfactory hypothesis has been forthcoming.

In a study of material derived from human cases of hepatolienal fibrosis, it seemed to the writer that little attention had been paid to the response of the so-called reticulo-endothelial cells to liver damage. The well known accumulations of reticulo-endothelium in the liver, spleen, bone-marrow, and lymph glands is too well known to require any elaboration here. If we could find any common factor accounting for a possible histiocytic response in liver and spleen, such a factor might yield a clue to the problem of splenic enlargement in hepatitis.

Certain well known general histiocytic reactions, in which the Kupffer cells of the liver and the pulp cells of the spleen are simultaneously involved, may be mentioned. In lymphadenoma there is a proliferation of the reticuloendothelial cells of the body, which, particularly in acute cases, may affect the whole system. In Gaucher's and Niemann-Pick's diseases the reticuloendothelial cells of the liver and spleen are simultaneously involved by a primary disturbance in lipoid metabolism. In certain less defined cases, such as that described by Borissowa (1903) there is a proliferation of histiocytes, unchanged in their histological appearance, in the liver and spleen, Such cases are at present described under the name of "reticuloses" (Goldschmid and Isaac, 1922) or reticu-

lo-endothelioses (McNee).

The problem which we are to attempt to elucidate can be stated in the following questions:

1. Is there any evidence of a histiocytic response in hepatic cirrhosis or hepatitis, and if so what is the nature of the stimulus?

2. Does the spleen share in this response, and by what mechanism is it involved?

It will be seen that the writer prefers to follow the terminology suggested by Kiyono (1914) who would consider the cells of the spleen pulp and the Kupffer cells of the liver as "histiocytes".

"The ability of these cells to store colloidal dyes is combined with a tendency to become mobilised, to transform themselves into free amoeboid cells, giant cells and epithelioid cells, and to phagocytise" (Maximow, 1928). The microscopic appearance of histiocytes is strongly influenced by their functional condition. Generally speaking they may be found in a resting or an active state. The resting state corresponds with their fixed position, while active histiocytes show a more or less distinct hypertrophy and rounding-off, and may even become completely isolated from their neighbours and appear as free amoe-

boid cells. These active histiocytes may be distinguished from lymphocytes by their abundant, pale, sometimes acidophilic protoplasm, and the relatively small amount of chromatin in the nucleus.

The hyperplastic process in the human spleen.

In those spleens of the present series which were weighed (28) the average weight was 878 grammes. Only three were under 500 grammes while the maximum weight seen in a spleen from a case of hepatolienal fibrosis was 2,700 grammes (case XLI.a). In practically every instance therefore, cellular hyperplasia of the spleen must be invoked to account for the enlargement.

In cases XXII and XXIII histological examination of the spleen revealed no vascular lesion which might have resulted from portal congestion. In these two instances the size of the spleen is due to hyperplasia alone.

In case XXIII we have an example of an acute exacerbation of a chronic hepatitis, due presumably to cholecystitis. A section of the liver (Fig. 46) shows a definite leucocytic infiltration of the liver lobule associated with an accumulation of small and large round cells. This acute change coincides with

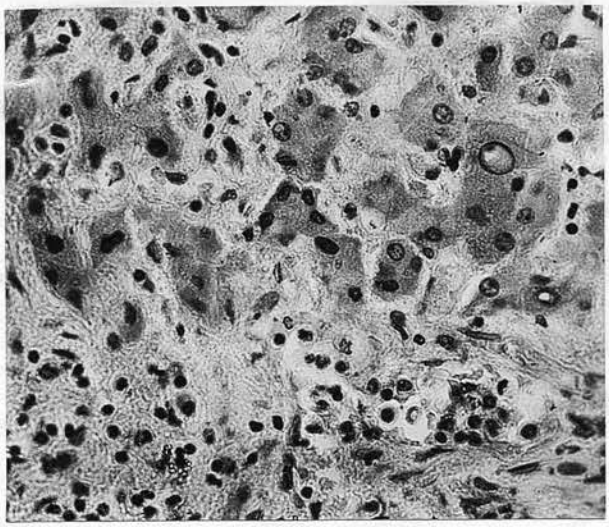


Fig.46. (x 350) Liver from case XXIII.
Acute hepatitis associated with acute cholecystitis. Note the intense leucocytic infiltration throughout the lobule.

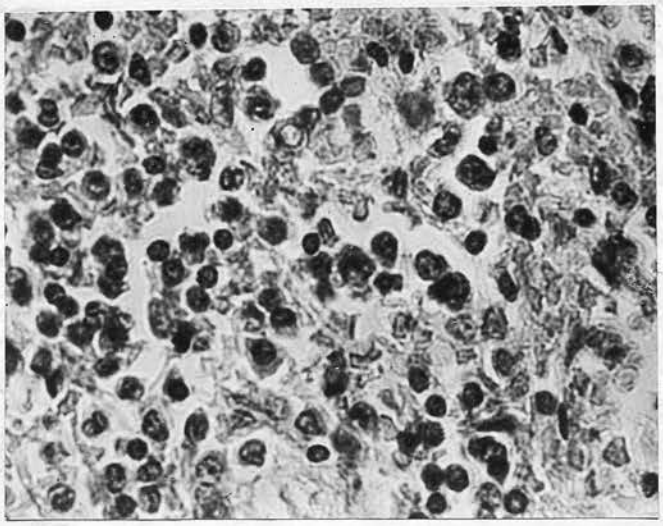


Fig.47. (x 600) Spleen from case XXIII.
Note the large numbers of rounded active histiocytes in the pulp spaces and in the sinuses.

old standing fibrosis and periportal sclerosis.

The spleen from the same case (Fig.47) shows a change reminiscent of that which is found in the enlarged spleen of acute infections. The sinuses are scarcely distended at all, and are filled by large round cells with a varying amount of cytoplasm - active histiocytes. This type of change is diffused through the spleen pulp and is suggestive of generally increased activity of histiocytes which in their resting phase constitute the cells of the normal spleen pulp.

When the acute phase has passed over, however, these active histiocytes may regress to the resting stage and we are left with a spleen, considerably enlarged, but in which the appearance of the pulp cells corresponds to that of the normal spleen. This is the appearance which we find in the spleen from case XXII. In spite of enlargement to 820 grammes, this spleen showed little histological abnormality of the individual cells.

If we look at Fig.37 which illustrates an artificially produced venous congestion of an otherwise normal spleen we see that the distended sinus walls are usually not much more than two cell layers thick. In the spleens from cases of hepatolienal fibrosis the intersinuous walls are often four or five cells thick, which is probably an index of proliferation of the

p 60.

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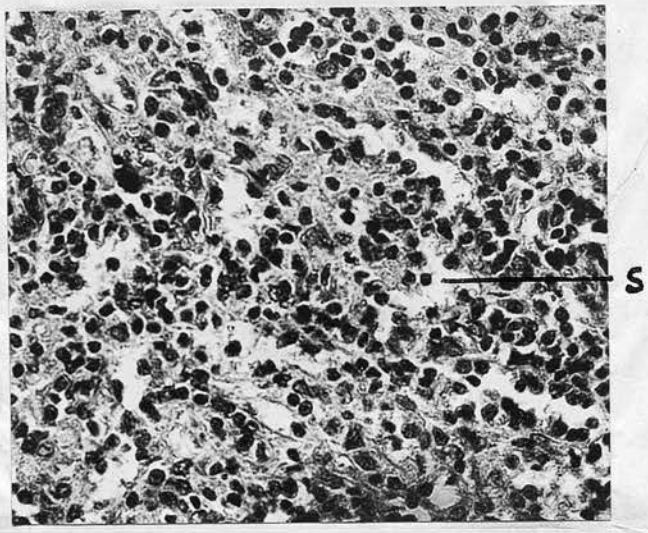

Fig. 48. (x 350) Spleen from case IV. Note the dilated sinuses (s) with increased cellularity of the pulp tissue between, and proliferation of new cells into the sinus lumina.

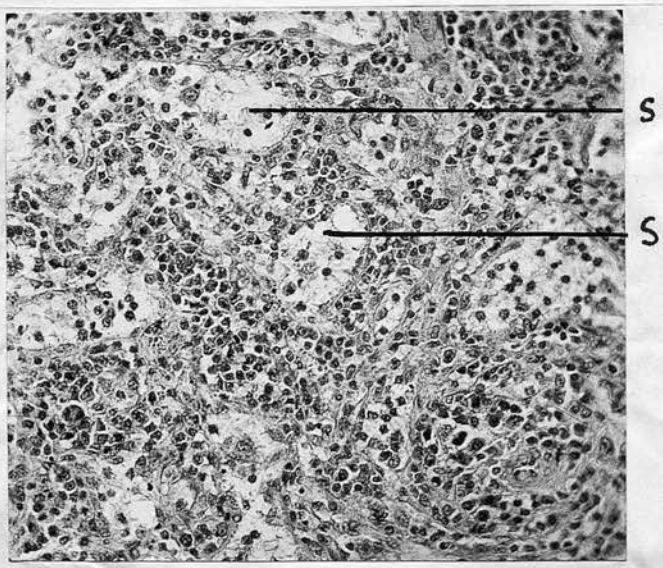

Fig. 49. (x 250) Spleen from case XLIa. Sinuses are denoted by (s). There is a great increase of cellular tissue between the sinuses, and also there is definite proliferation of active histiocytes into the sinus lumina:

pre-existing pulp tissue (Fig.48). Fig.49 also shows a similar cellular thickening of the intersinuous walls, but in addition there is also a proliferation of cells into the lumen of the dilated sinuses.

Occasionally another evidence of histiocytic activity may be seen, i.e. phagocytosis of red cells. This is particularly well defined in case XLIa. The section shows dilated sinuses in which active histiocytes are seen , frequently containing red blood corpuscles or fragments of these. It is to be noted that this phenomenon of erythrophagocytosis is not an index of excessive haemolytic activity on the part of the spleen, but is merely an index of excessive local activity of the spleen cells(Lauda,1928). It may be seen,for instance, in the splenic enlargement which accompanies typhoid fever, where there is no evidence of exeessive blood destruction.

One other proliferative change which is indicated in the same spleen (Case XLIa) is an increase in the number of lymph-nodes, which seem to extend into the pulp along the penicillar arterioles. Small new masses of lymphoid tissue are seen here and there in the pulp.

So far as the spleen itself is concerned therefore the principal evidences of cellular hyperplasia which we see are:-

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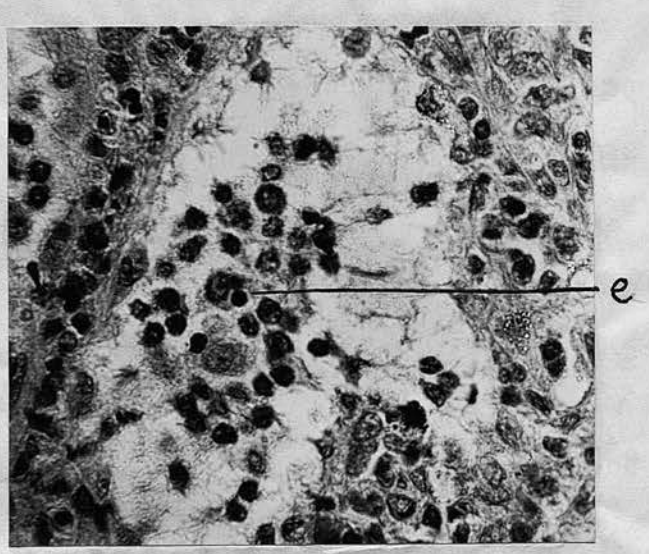

Fig. 50. (Oil immersion). Spleen from case XLIa. A dilated sinus is seen filled by active histiocytes, one at least of which contains an ingested erythrocyte (e).

1. Weight of the spleen over three times the normal i.e. more than can be accounted for by simple congestion.

2. Cellular increase in the intersinuous strands.

3. Proliferation of active histiocytes into the lumen of the sinuses, activity being indicated by the enlargement and rounded appearance of the cells and by erythrophagocytosis.

Another evidence of histiocytic proliferation may be found outwith the spleen itself, in the related splenículi.

These small splenículi, or accessory spleens, are identical with haemolymph glands. Normally they are small and difficult to find (Warthin 1901). In most cases of splenic enlargement examined by the writer there has been an associated enlargement of the splenículi in the hilum of the spleen. In cases of acholuric jaundice, Gaucher's disease, tuberculosis of the spleen and Hodgkin's disease, in which splenículi have been available for comparison with the spleen itself, the pathological changes in the splenículi have been identical with those found in the spleen itself without a single exception.

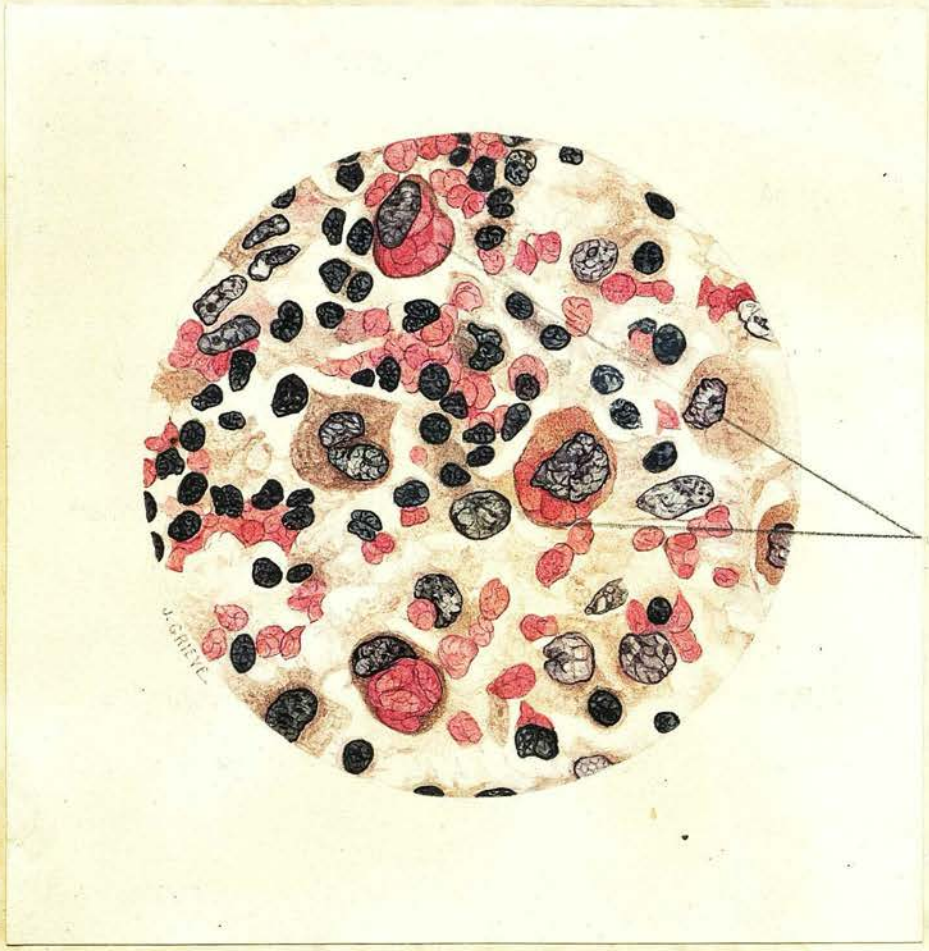

Fig. 51. (Oil immersion) Spleniculus from case XII. Note the great proliferation of large active histiocytes, and the cells containing ingested red corpuscles.

The evidence of these findings would therefore lead us to believe that the spleniculi and the spleen respond in the same way to the same disease processes.

In hepatolienal fibrosis however the changes in the spleniculi may offer a somewhat striking contrast to the histological appearances of the spleen. This is well indicated by the appearances in Case XII which are illustrated in Figs. 51, 52, and 53. The spleen it will be noted shows marked dilatation of the sinuses with thickening of the supporting fibrils. The cells of the spleen pulp show no histological deviations from the normal. The spleniculi on the other hand show a much more active type of change. The venous sinuses between the lymph-nodes are filled by active histiocytes, showing marked phagocytosis of red cells. In other parts of the spleniculus the formation of large endothelial giant cells has occurred.

Similar evidences of histiocytic proliferative activity were also found in spleniculi from cases IX, X, XI, and XXIV, and XLIa. These were the only cases of hepatolienal fibrosis in which spleniculi were available for histological examination.

It seems highly probable that the proliferative changes in the spleniculi are the counterpart of similar proliferative changes in the spleen, and are caused by the same agency. The only other possible

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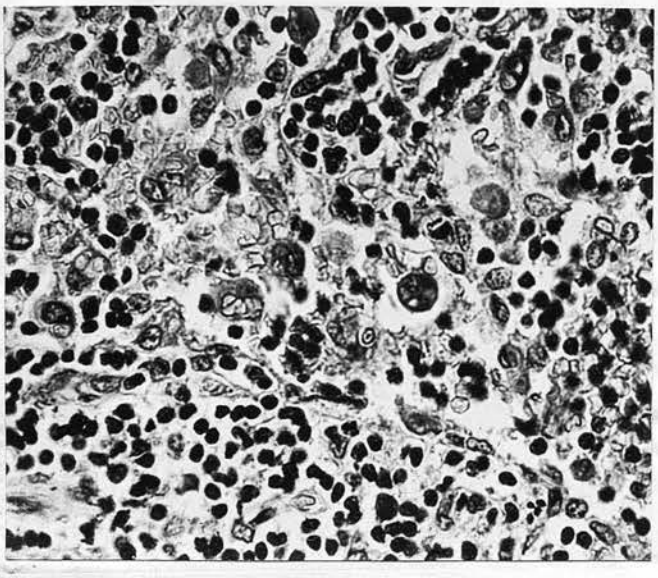

Fig. 52. (x 450) Spleniculus from case XII. Note the large active histiocytes with ingested red cells

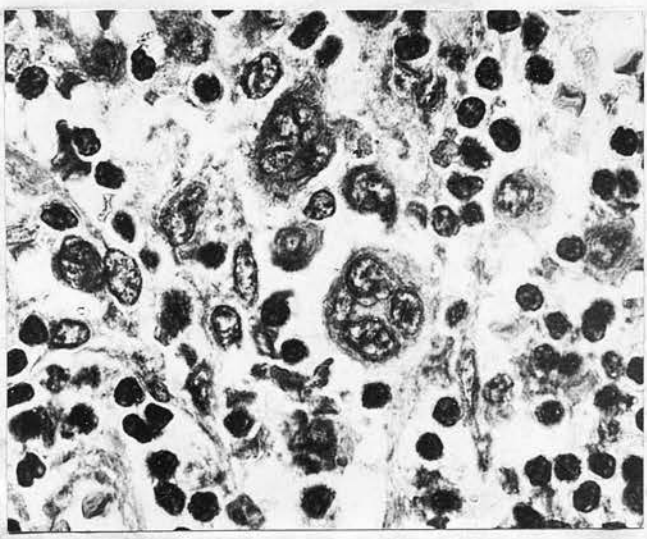

Fig. 53. (Oil immersion) Spleniculus from case XII. Note the formation of large giant cells.

explanation of enlargement of the spleniculi might be compensatory hypertrophy. The haemolymph glands are known to enlarge when the spleen is removed (Winogradow, 1882).

It is very unlikely, however, that this is the reason for the enlargement in hepatolienal fibrosis, for there is no evidence that the enlarged spleen is functionally impaired. As we have pointed out its cells are frequently histologically identical with those of the normal spleen, and there is no evidence to suggest that the hepatolienal fibrosis spleen cannot react in a normal manner to any calls made upon it.

Chapter 6.

The histiocytic Reaction and Splenic enlargement in Experimental Hepatitis.

Gye and Purdy (1922) noted an enormous enlargement of the spleen, and fibrosis of the liver as a result of chronic poisoning with colloidal silica. From a study of acute poisoning, however, it was apparent that the effect was primarily on the reticuloendothelial cells. These cells were loaded with silica which apparently stimulated their proliferation. The effect seemed to be a primary mesenchymal reaction, without the evidence of liver cell damage which is regarded as an essential feature of cirrhosis. It is to be noted that Albot (1931) claims to have demonstrated hepatic cell damage in colloidal silica poisoning as evidenced by "margination of chondriosomes". The reticuloendothelial reaction is, however, quite out of proportion to the degree of hepatic cell damage, and it is unlikely that the liver cell damage is the primary effect.

Roessle (1929) recognises the desirability of postulating a mesenchymal reaction in cirrhosis to account for the splenic enlargement. He gets over the difficulty by suggesting that in some cirhoses the action of the toxic agent falls primarily on the mesenchymal

tissue and the spleen is thus simultaneously or even primarily affected. Such a hypothesis would in reality bring some cirrhoses into line with the other primary histiocytic reactions mentioned above - - lipoid histiocytoses, reticuloses, etc. As it has been amply demonstrated that in cirrhosis the damage in most instances is primarily of the liver cells, and that the spleen is enlarged in many such cases, the postulation of a primary increase of fibrous tissue elements does not really solve the main problem.

The object of this experimental work is to study the nature of the local mesenchymal reaction which occurs in experimental hepatitis, and the reaction of the spleen to liver inflammation.

Methods.

In the experiments to be described, .5% manganese chloride solution was given subcutaneously to induce cirrhosis of various degrees of acuteness and chronicity. The dosage given was somewhat less than that used by the Hursts (1928).

In rabbits, subacute and subchronic cirrhosis were readily induced by the subcutaneous administration of .025 gm. manganese chloride per kilo thrice weekly, and in some cases this dosage was only given on alternate weeks.

Rabbits were used, and according to the recommend-

ations of Findlay (1924), a few guinea pigs were used to control the observations. Spontaneous hepatitis was noted in one or two instances in the rabbits, but was quite easily recognised as a rule. In the great majority of the animals there was no evidence of any old-standing liver disease, and in the text of this description, except where otherwise stated the appearances were common to numerous animals, and could be ascribed definitely to manganese. An attempt was made to use cats, but in these animals the kidneys were much more severely attacked than the liver and death occurred from renal changes, while the hepatic changes were insignificant.

The animals in most instances were allowed to die of the induced disease, but sometimes they were killed by dislocation of the neck. In no instance was chloroform used. Tissues were fixed in formalin or Zenker, and sections were stained by Sudan III, haematoxylin and eosin, van Gieson , and eosin and methylene blue.

To determine the histiocytic reaction, vital staining was carried out by India ink. Higgin's ink was diluted one half, and 3cc. of the sterilised filtered solution was injected intravenously on two occasions. Three or four days later the manganese injections were started.

Results of Experiment.

Generally speaking, our experimental observations of the effects on the liver agreed with those already published by the Hursts. The effect of the poison was first manifested upon the cells in the periportal zone at the periphery of the lobule. In acute poisoning these cells underwent an acute massive coagulative necrosis; in the more subacute types various changes were seen from fatty degeneration to necrosis of the colliquative type. The local cellular reaction did not make its appearance until these degenerative changes were well developed and the earliest local reaction we have seen occurred at the end of 48 hours.

1. The local reaction to liver cell damage.

Early Changes.

In rabbits which died of a single large dose of manganese chloride no reactive changes were evident unless the animals had survived at least 48 hours. At the end of this time however some local cellular reaction was manifest in at least one instance.

Rabbit 11. Weight 3,260 grammes. A single dose of .163 gm. manganese chloride was given subcutaneously. Death occurred 2 days later. Liver pale and fatty: spleen enlarged and plum coloured (weight: 2.55 gms.). Microscopically there was marked fatty degeneration of the liver cells especially in the centre of the

lobule. In the peripheral parts, the liver cells had undergone necrosis and liquefaction. Among these disappearing liver cells the Kupffer cells remained and were swollen with debris. In the immediate neighbourhood of the portal tract some of the Kupffer cells appeared to be elongated like fibroblasts. The sinusoids at the periphery of the lobule were congested.
Spleen: showed intense vascular congestion, but there was no endothelial proliferation.

In animals which received daily doses leading to death within a week cellular reaction and bile duct regeneration were quite pronounced.

Rabbit 18. Weight 2,900 grammes. Died on the sixth day after receiving .35 grammes manganese chloride in the preceding five days. The liver has a pale mottled appearance. The spleen is small.

Microscopically: There is a diffuse deposit of fat throughout the liver. Owing to vacuolation of the cells, the surviving Kupffer cells are especially distinct. They are active in contrast to the degenerated liver cells and appear to be increased in numbers. A good deal of new cellular connective tissue has appeared round the portal tracts which appears to link up with the surviving Kupffer cells where these can be definitely recognised. In the portal spaces there is definite bile-duct regeneration and proliferation. Round the bile ducts there is definite round

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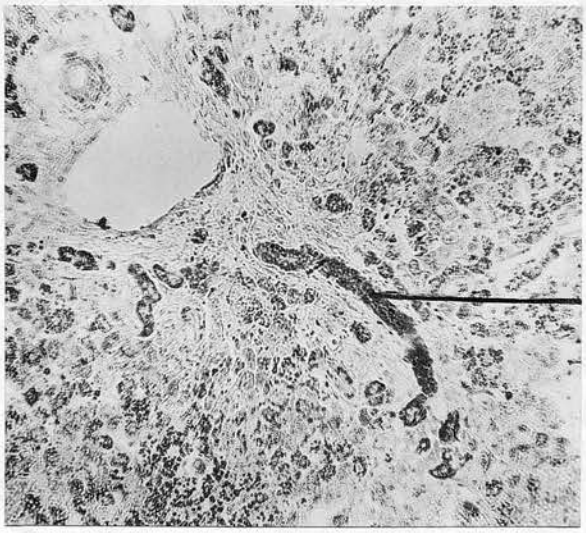

Fig. 54. (x 90) Rabbit 19: liver. Stained: Sudan III. Note the infiltration of the liver cells with fat, and the fat content of the bile-duct epithelium.(b).

celled infiltration. At the periphery of the lobules a few large hyperchromatic liver cells are seen (regeneration ?).
Spleen: No obvious abnormality.

Rabbit 19. Weight 3,100 grammes. Killed on the eighth day after receiving .2 grammes manganese chloride in the first five days. Liver pale and mottled. Spleen 1.65 grammes. Appears red and fleshy.
Microscopically: All degrees of fatty degeneration seen in the liver cells, and fat was also found in the bile duct epithelium. At the periphery of the lobule necrosis and autolysis of liver cells had taken place, and the surviving Kupffer cells were undergoing proliferation. Mitotic figures were occasionally seen in the Kupffer cells. Polymorph leucocytes were scattered diffusely through the lobules.
Spleen. A good many new rounded active histiocytes were seen in the sinuses.

In the first week relatively massive doses of manganese lead to acute and drastic changes in the liver. The first effect is manifested in the cells of the outer zone of the lobules and is usually a definite necrotic change, while the inner portions of the lobule undergo less severe degenerations. With the disappearance of the necrosed liver cells at the periphery, the Kupffer cells enlarge to deal with the debris, and definite proliferation of the

Kupffer cells may be seen with mitotic figures. There is a generally increased vascularity of the peripheral zone of the lobule which may be in part explained by the shrinkage of the noble elements and consequent widening of the sinusoids. New cellular connective tissue is formed in the latter half of the first week, only in relation to the acutely degenerating liver cells at the periphery of the lobule. Periportal round celled infiltration and bile duct proliferation are also obvious at the end of the first week.

Subacute and Chronic Changes.

The above acute changes are too gross for a detailed study of the origin of the new mesenchymal cells which appear in relation to the damaged liver cells. We have noted however the survival of Kupffer cells and their proliferation, and the fact that the new young connective tissue cells appear at the periphery of the lobule in relation to the damaged liver cells. In this site the new cells may take origin from the histiocytes of the portal spaces or from the Kupffer cells between the liver cell columns.

In animals dying about the end of the second week, the changes are much less acute.

Rabbit U. 3. Weight 2,100 grammes. Died on the 14th. day after receiving .18 grammes manganese chloride in six doses between the first and twelth days. Liver slightly mottled. Spleen 5 grammes.

Microscopically the liver shows amorphous degeneration at the periphery of the lobule and fatty degeneration which is most marked towards the centre. There is extension of cellular connective tissue from the portal zones between the degenerated liver cellsat the periphery of the lobule. The portal zones show increased vascularity and the sinusoids at the periphery of the lobule are over distended. There is new bile duct formation, and round celled infiltration in the portal spaces. In the larger portal tracts dilated lymphatics are often visible.

At the periphery of the lobules large darkly staining liver cells are frequently seen, often with 3-4 nuclei (regeneration).

Spleen: Pulp cell nuclei are large and clear and cytoplasm is swollen. The sinuses contain clumps of leucocytes and numerous rounded macrophages. No new formation of lymph nodes.

Acute massive necrotic changes at the periphery of the lobule tend to be replaced in milder intoxications by a type of degeneration termed "amorphous" in which the normal granularity of the liver cell disappears and the homogeneous cytoplasm stains diffusely with eosin. The swelling of, and absorption of debris by, the Kupffer cells seen in the very acute stages

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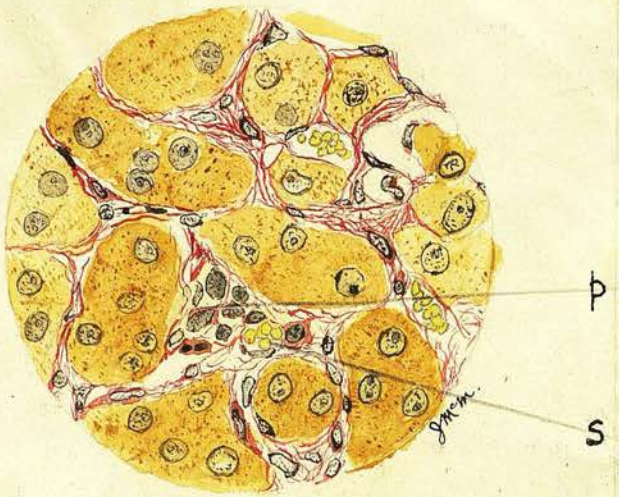


Fig. 55. (Oil immersion) Liver from Rabbit 16. Note the formation of collagen fibres among the liver cells, and the proliferation of new connective tissue cells between the sinusoid (s) and the liver cells. The new cells are indicated by (p).

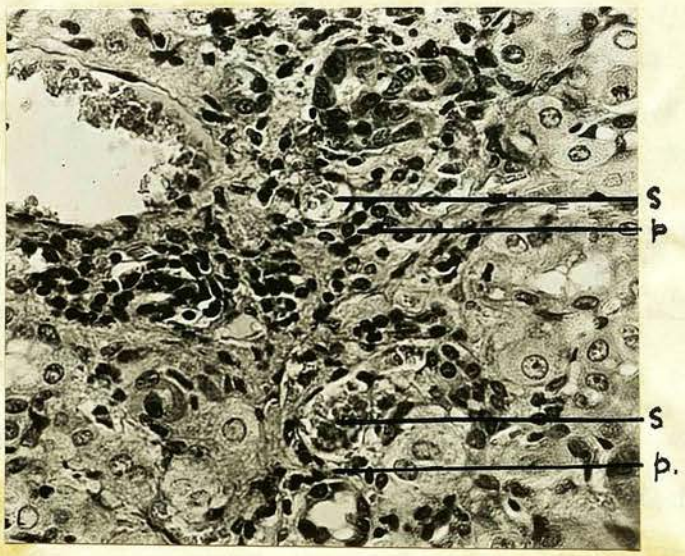
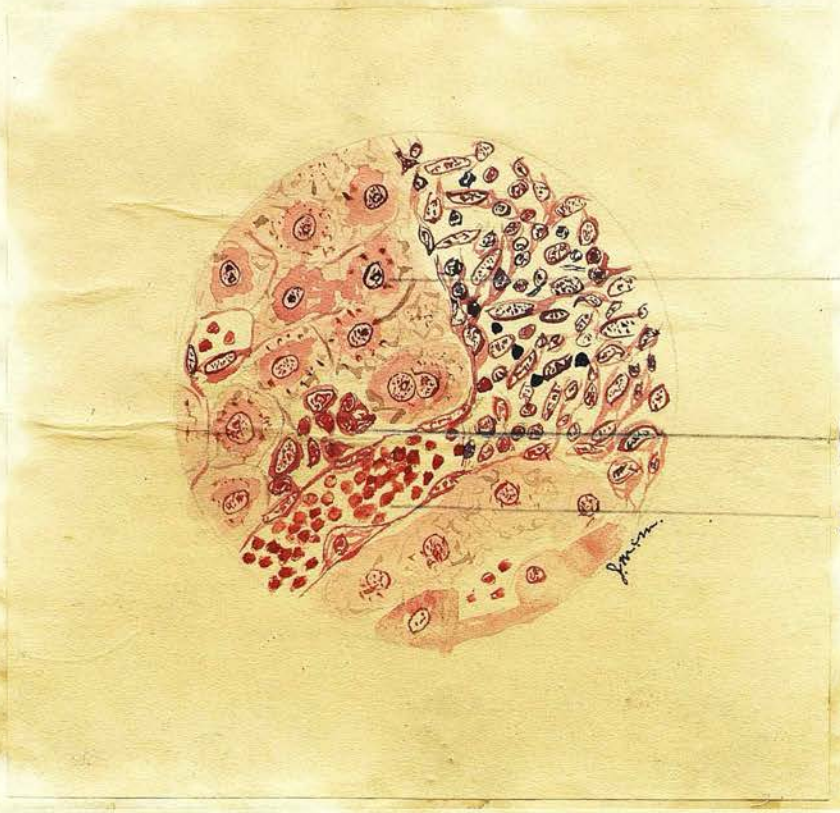


Fig. 56. (x 350) Liver of rabbit 16. Sinusoids are denoted by (s) and the new histiocytes by (p).

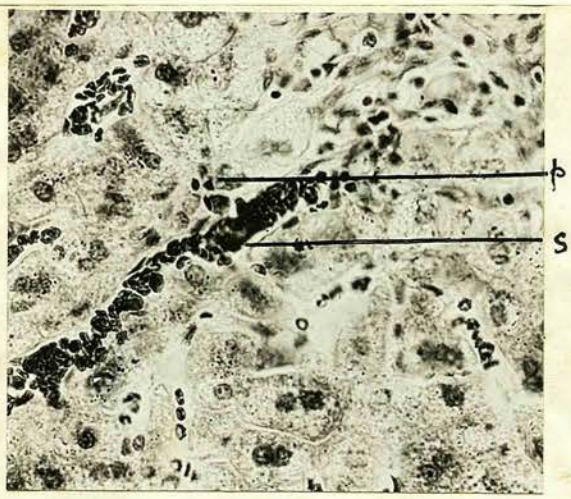
becomes less prominent, but nevertheless new primitive connective tissue cells make their appearance in relation to degenerated liver cells.

The origin of these new cells is better brought out in a more chronic type of liver change.

Rabbit 16. Weight 2,100 grammes. Received .425 grammes manganese chloride in 38 days. Liver had a greenish yellow appearance with a morocco leather surface. Spleen weighed 1.4 grammes. Microscopically: Liver shows little or no fatty deposit except in the regenerated bile ducts at the periphery of the lobule. The most striking feature is a diffuse extension of the connective tissue of the portal spaces in and between the liver cells. Apart from slight granularity the liver cells show very slight evidences of degenerative change. The liver cell columns are broken up by the new connective tissue and a fine pericellular cirrhosis is seen. Collagen fibres are abundant between the liver cells, and the new connective tissue cells have appeared between the sinusoidal capillary and the liver cell itself, i.e. in the perisinusoidal lymph-space. Bile thrombi are seen here and there in the bile canaliculi between the liver cells. There is increased vascularity of the portal tracts. Spleen: is not specially congested. A good few large rounded macrophages are seen in the sinusoids.



Figs. 57 and 58. (x 500 and 350) Drawing and photograph of the same portion of the liver of rabbit 33.
s sinusoid .
p proliferation of new histiocytes outside the wall of the sinusoid
a amorphous degeneration of the liver cells at the periphery of the lobule.



It appears therefore that the new cellular connective tissue tends especially to appear in the perisinusoidal lymph space in the first instance. In one instance of prolonged mild manganese poisoning, cellular proliferation in this site was seen at an earlier stage.

Rabbit 33. Weight 2,100 grammes. Given .1 gramme manganese chloride in every third week. Killed at the end of 210 days. Liver pale and slightly mottled. Spleen 2.3 grammes. Microscopically: Liver shows amorphous degeneration of the cells at the periphery of the lobule. Definite young connective tissue cell formation round the portal tracts in association with the areas of amorphous degeneration. A few of the cells at the periphery of the lobule have undergone necrosis and antolysis. The histiocytic infiltration appears to be related to the autolysis of cells at the periphery of the lobule and has not occurred in relation to those cells which have undergone fatty degeneration at the centre of the lobule. The new cellular formation has every appearance of occurring outside the wall of the sinusoid, i.e. in the perisinusoidal lymph space. Van Gieson's stain shows very slight new collagen formation among the histiocytes.

In those cases of prolonged mild manganese poisoning where we have been able to see the relationship of

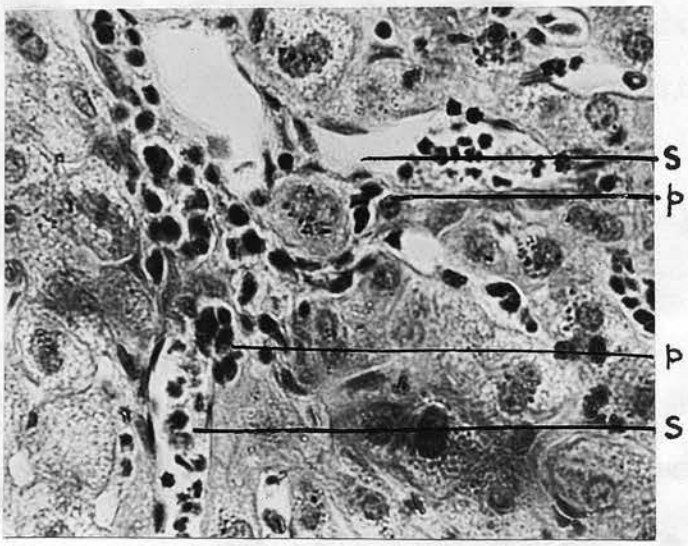


Fig.59. (x 550) Liver of rabbit 33.
s sinusoid.
p proliferation of new cells outside the wall of the sinusoid.

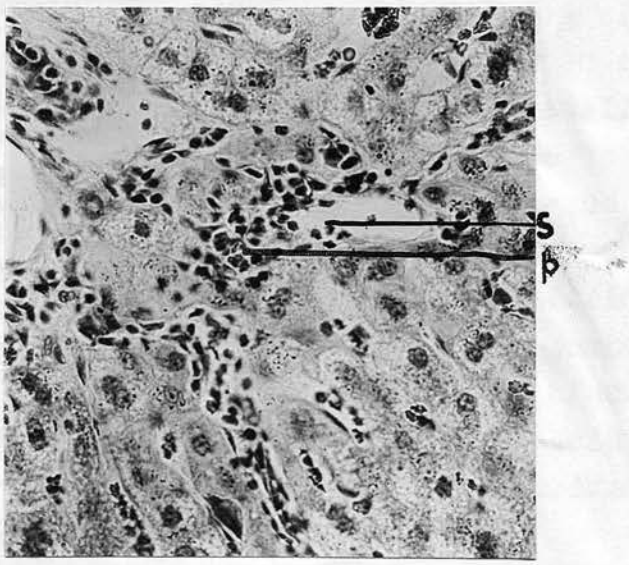


Fig.60. (x 400) Liver of rabbit 31.
s sinusoid.
p proliferation of new histiocytes outside the wall of the sinusoid.

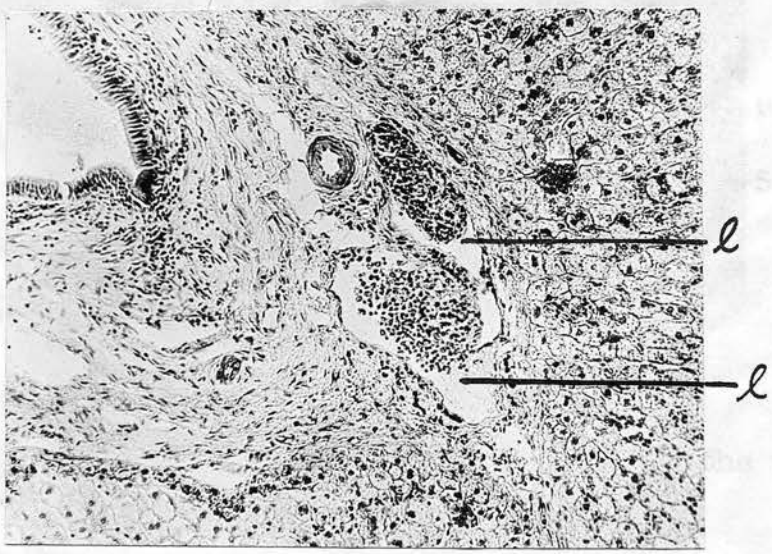


Fig. 61. (x 100) Liver of rabbit 31.
l dilated lymphatics, with proliferation of small round cells in their lumina.

the newly formed histiocytes to the wall of the sinusoid, the new cells have always tended to lie in the perisinusoidal lymph space.

2. The part played by the Kupffer cells in the local mesenchymal reaction to hepatic damage.

We have seen suggestive evidence that the Kupffer cells play a part in the removal of debris in acute liver damage induced by manganese. In the more chronic types of liver damage, it is impossible to state what part they play in the new formation of histiocytes. In order to solve this problem it is necessary to induce cirrhosis in an animal in which the Kupffer cells have been vitally stained.

The difficulties in assessing the reaction of the reticulo-endothelial calls in vitally stained animals have been well summarised by Cappell (1930). If we wish to determine the part played in an inflammatory reaction by pre-existing reticulo-endothelial cells, several points must be kept in mind. Firstly the cells of the reticuloendothelial system must be first filled with a suitable dye, which will persist in recognisable amount for the duration of the experiment. The readily diffusible dyes such as trypan blue disappear from the cells in about two weeks, and are thus unsuitable for studies of this kind. Further we cannot

use dyes which persist for some time in the blood stream and are only slowly absorbed. Such a dye as Isamine blue given subcutaneously forms a depot from which small quantities of dye may escape into the circulation over a long period, and may thus be taken up by newly formed histiocytes present in the body at the time. Pre-existing histiocytes might thus be obscured by the new-formed histiocytes which had taken up the dye in the course of the experiment. Thirdly an interval must be allowed to elapse to allow those portions of the dye which have been taken up by the circulating monocytes to disappear from the blood stream. Otherwise the monocytes of the blood might accumulate at the site of the inflammation and obscure the issue which we wish to illuminate. For many reasons, therefore, we select India ink as the most suitable dye. It is particulate, and is rapidly taken up from the circulating blood where histiocytes are in contact with it, as in the liver and spleen sinusoids. The active histiocytes in these organs are soon loaded up with the ink, while the histiocytes of the subcutaneous tissues and other parts more remote from the direct access of the circulating fluid bearing the dye particles, are not so readily filled by the ink.

In assessing the results of the experiments conducted by this method, it is also essential to remember that only a fraction of the total number of histiocytes in the liver and spleen are filled by the dye, no matter

how much may be given. It is on this basis that Maximow subdivides the histiocytes into "resting" and "active" types, the latter taking up the dyes when they come in contact with the cell membrane, and the former failing to take them up at all. Transition stages are, of course, to be seen, i.e. cells which take up the dyes in small amounts. When a histiocytic response is elicited by any method, we are not aware of the exact extent to which resting and active histiocytes respond. It may be that the formation of new histiocytes is principally carried out by the cells which were previously "resting". In such a case, the new histiocytic infiltration would reveal little or no dye, although it had taken origin from pre-existing histiocytes. Ordinarily in the liver stained by India ink, there are no particles in the histiocytes of the portal spaces, but at the end of a few weeks an occasional pigment laden cell may be seen in the portal spaces, whither it has been carried in all probability by the lymph stream from the liver sinusoids.

We may take it therefore that if newly formed connective tissue cells in the liver are seen to contain India ink after hepatitis lasting two or three weeks, these cells are derived in situ from pre-existing Kupffer cells.

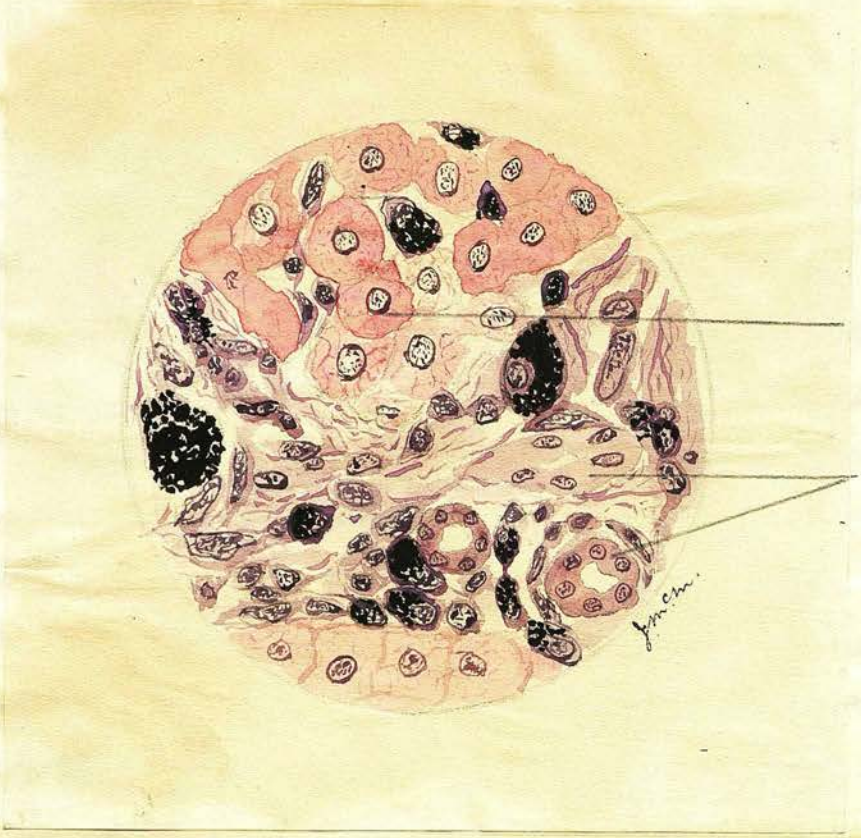


Fig. 62. (Oil immersion) Liver from Rabbit I 33.
a amorphous degeneration of liver cells at the periphery of the lobule.
b bile-duct regeneration in the portal tracts.
Note the numerous newly formed cells in the peri-portal tissue which contain india ink.

Fig. 63. (x 250) Liver from rabbit I 1.
Degeneration and necrosis of liver cells has taken place at the periphery of the lobule. There is a general increase of connective tissue cells in this site and many of these cells are seen to contain india ink. (c)

Rabbit R. 3. Weight 2,200 grammes. 3cc. India ink solution given on each of two succeeding days. 6 days later manganese chloride injections begun: .18 gms. given in twelve days. Death on the thirteenth day.
The liver is mottled and the lobes are ringed with black. Spleen 1.62 grns.
Microscopically: Amorphous degeneration of liver cells at outer zone. Some fatty degeneration in the central parts of the lobule. Marked increase of new cells in the outer part of the lobule. The India ink is heavily loading many of the Kupffer cells while others are quite unaffected. A proportion of the newly formed cells contains ink particles, but probably not more than about 30%. Van Gieson's stain shows the early appearance of collagen among the new connective tissue cells. The spleen is congested and shows some formation of new macrophages which do not contain ink particles.

Those cell reactions were studied in six vitally stained animals, and the results were similar to the above. The majority of the newly formed connective tissue cells did not contain India ink, but a certain proportion of them contained a variable amount of ink particles.

The reaction of the Kupffer cells to the introduction of foreign bodies has been studied by Biebl, (1929) in the formation of abscesses by Bloom, (1928) and in aseptic inflammations of the liver by Malyschew, (1927), Büngeler and Wald, (1928) and Higgins and Murphy, (1930). Biebl attributed the mononuclear reaction to foreign bodies to the Kupffer cells and the

polyblasts of the portal spaces. In the experimental abscesses studied by Bloom, no participation of the stellate cells in the formation of mononuclear phagocytes could be recognised. Bloom therefore regards these exudative mononuclear cells as being haematogenous in origin. Malyschew went to the opposite extreme and presented a picture of the Kupffer cell as an important primitive stem cell which could not only produce monocytes and fibroblasts,but also myelocytes and granular white corpuscles. All these might be seen in aseptic inflammation following a burn of the liver tissue, but the injection of trypan blue,(according to Malyschew), would prevent the development of myeloid tissue.

Büngeler and Wald repeated Malyschew's experiments and found that the response to the Kupffer cells was in no way interfered with by the use of intravital dyes. When the Kupffer cells were identified in this manner, they might be seen to play a part in the formation of local monocytic accumulations, but not in the production of granular leucocytes. Dye storage could be seen in the newly-formed granulation tissue at the site of a burn of the liver tissue. Higgins and Murphy, using the same methods as Büngeler and Wald to produce aseptic hepatic inflammations in rats, showed that the graphite-laden Kupffer cells tend to form a wall round the lesion and ultimately play a part in the formation of the fibroblasts which wall off the lesion.

Very little attention has been paid to the reaction of the Kupffer cells in cirrhosis. Moissejew, (quoted by Malyschew), mentioned that the Kupffer cells have a share in the formation of the connective tissue in human cirrhosis. In a paper by the Hursts on experimental manganese cirrhosis it is mentioned that the Kupffer cells survive and show signs of proliferation, an observation we have confirmed. The most recent French opinion is that of Albot (1931) who suggests that the histiocytic infiltration which precedes fibrosis takes origin from the periportal connective tissue. Fiessinger and Albot,(1929), however, mention that the Kupffer cells undergo swelling and proliferation, and their contention in this respect is supported by Martin, (1927).

Our results show that a small but definite proportion of the newly formed connective tissue cells contain ink particles. Our results differ from those of Higgins and Murphy, in that the lesion which we have produced is diffuse while that which they caused was a localised burn. While they obtained a mobilisation and migration of graphite-laden cells towards the lesion, no such local accumulation would be called for in the type of lesion with which we are dealing. On the other hand, the number of cells involved in a diffuse hepatitis would be much greater, and we should expect a greater

Table IV

Rabbit No.	Weight (grms)	Duration of Experiment. (days)	Weight of Spleen (gm)	Maximum Normal wt. (.5g/kilo)	Approx. times nor
R.I.1.	1900	14	2.15	.95	2.2
R.I.2.	2240	13	3.35	1.12	3.0
R.I.3.	2300	13	1.62	1.15	1.4
R.I.4.	2100	14	3.0	1.05	2.9
R.I.6.	1950	13	1.8	.97	1.8
R.10.	1950	24	2.1	.97	2.1
U.R.1.	2200	10	1.05	1.1	1.0
U.R.6.	2600	14	5.0	1.3	3.9
U.R.3.	2100	14	5.0	1.05	4.7
U.R.8.	2650	53	2.4	1.3	1.9
U.R.2.	2400	34	0.8	1.2	0.7
U.R.5.	2800	32	2.6	1.4	1.9
U.R.7.	2150	71	1.2	1.07	1.1
R.28.	1540	155	1.6	0.77	2.1
R.12.	2370	24	2.6	1.18	2.2
R.20.	2650	74	4.0	1.32	3.0
R.11.	3260	2	2.55	1.63	1.6
R.19.	3100	7	1.65	1.55	1.1
R.24.	1670	70	0.8	0.83	1:0
R.32.	1570	27	1.25	0.78	1.6
R.23.	1870	28	3.1	0.93	3.3
R.27.	2350	5	1.9	1.17	1.6
R.14.	2400	24	1.47	1.2	1.2
R.21.	1470	65	2.2	0.73	3.0
R.15.	3500	29	2.0	1.75	1.1
R.16 .	2100	38	1.4	1.05	1.3
R.22.	2420	226	2.7	1.2	2.2
R.33.	2100	210	2.3	1.05	2.2
R.19.	3100	7	1.65	1.55	1.1
R.31.	1670	210	3.0	0.83	3.6

mobilisation of resting histiocytes than would occur in a localised lesion. It is difficult to estimate what proportion of new connective tissue cells are derived from previously local active histiocytes in diffuse experimental hepatitis, but the number, from these personal observations, is probably not more than 20-30 per cent.

3. The reaction of the Spleen.

It has already been noted in one or two of the protocols given above that the spleen was somewhat enlarged. The normal spleen in rabbits weighs from .3 to .5 grammes per kilo (Krumbhaar 1926). Dunn, (quoted by Muir, 1932), found the weight of the spleen to be a little less than this. Taking the maximum normal expected weight as .5 grammes per kilo, we find decided enlargement of the spleen in a considerable proportion of our experiments. The weights in thirty experiments are given in table IV. In fourteen out of thirty rabbits with experimental hepatitis, the spleen was more than twice the normal maximum weight for an animal of that size. Seven of the thirty animals showed splenic enlargements to three or more times the normal size.

The enlargement did not appear to be accounted for by congestion alone, although in most cases the venous

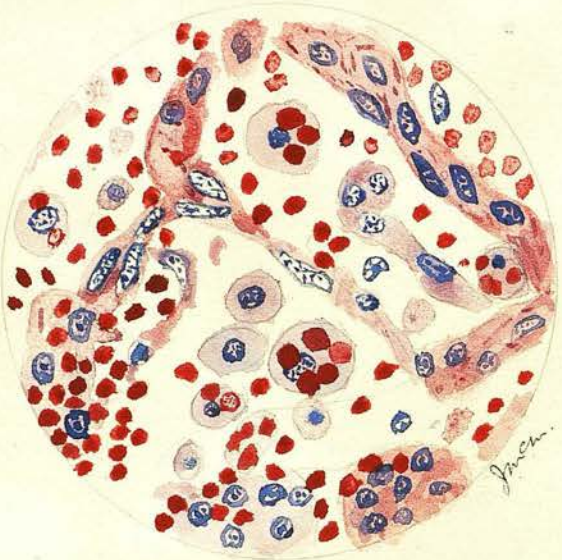


Fig. 64. (Oil immersion) Spleen of rabbit 23, stained by Eosin and Methylene blue. Note the proliferation of large endothelial phagocytic cells in the sinuses. Many of the cells contain ingested erythrocytes.

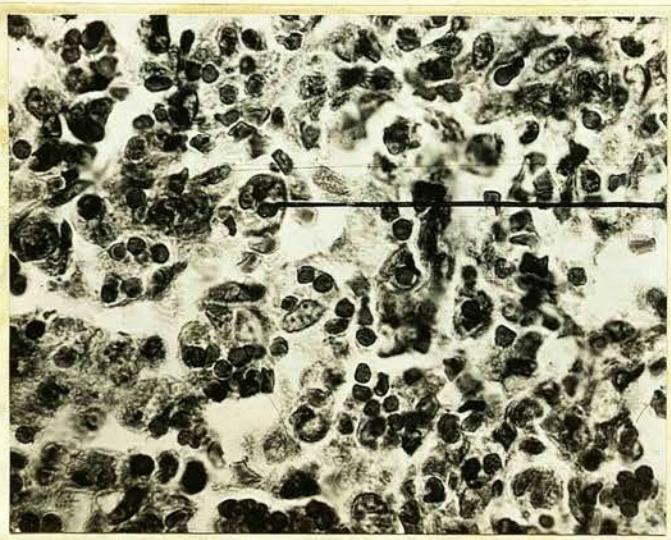


Fig. 65. (Oil immersion) Spleen of rabbit 23. Note the large phagocytes containing ingested red cells.

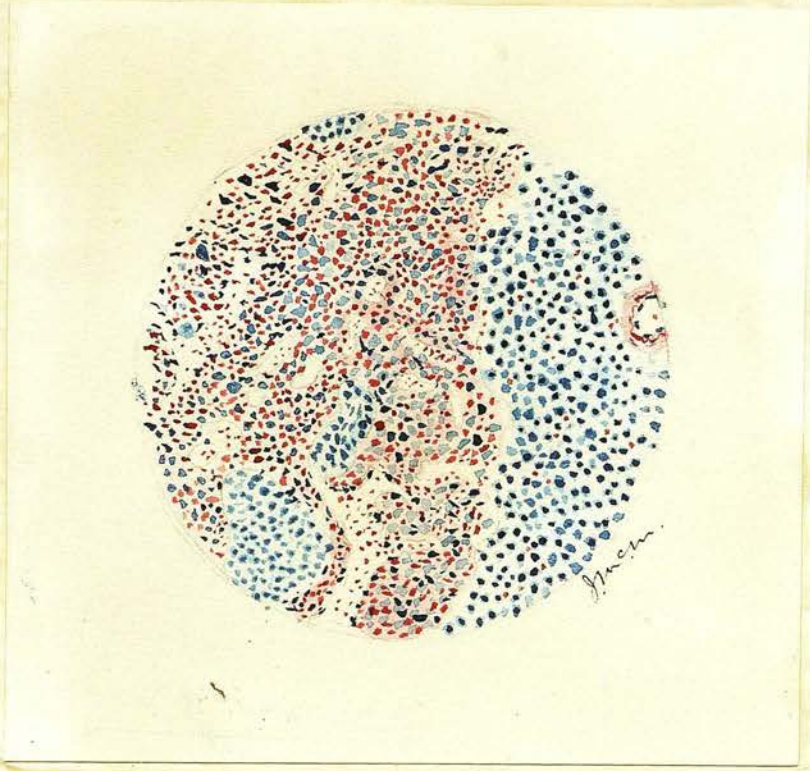


Fig. 66. (Low power) Spleen of rabbit 20. Note the proliferation of new lymph nodes. (Stain: Eosin and methylene blue).

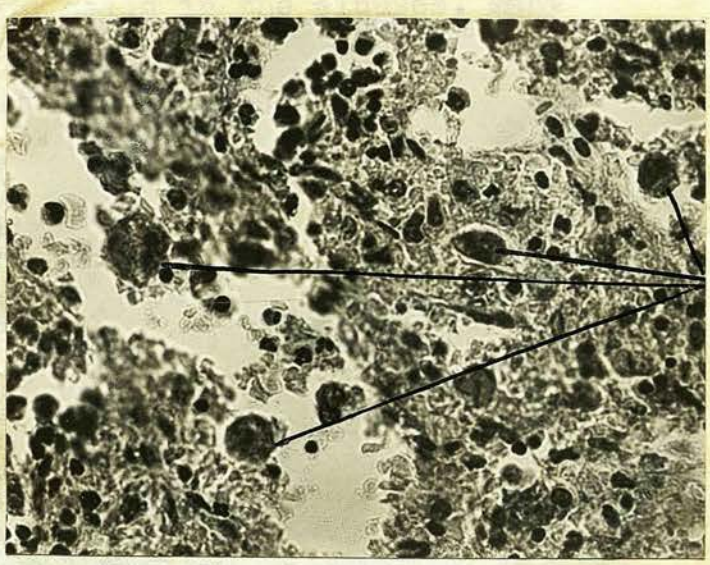


Fig. 67. (x 450) Spleen of rabbit 20. Note the proliferation of large rounded active histiocytes (p). One at least of these contains ingested red corpuscles.

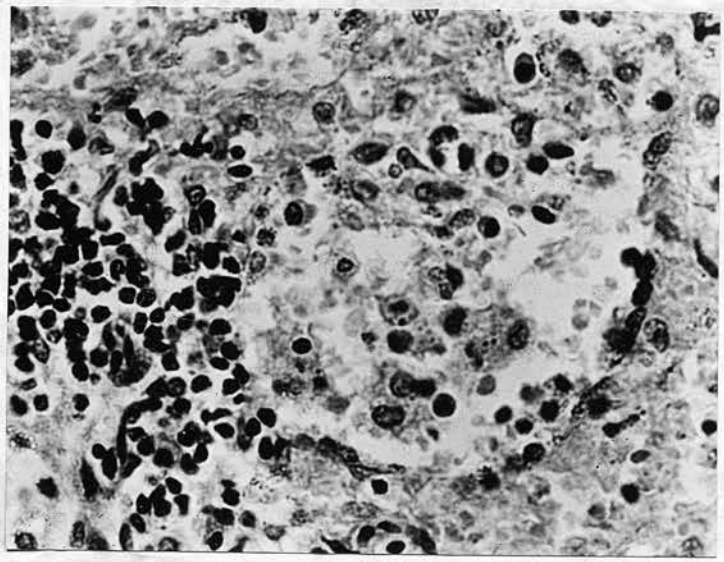


Fig. 68. (x 550) Spleen of rabbit 19.

Note the proliferation of large active histiocytes in the sinuses.

sinuses were dilated, and in one or two instances the venous congestion was intense. In most instances there was evidence of reticuloendothelial hyperplasia in the form of numerous large round cells in the venous sinuses, and in one or two cases erythrophagocytosis was also seen. In no cases was there any reticular thickening in the direction of collagenisation. In those spleens which had been stained intra-vitam with India-ink the new formation of large round macrophages did not appear to come from the ink-laden cells.

In one or two of the enlarged spleens the macrophage reaction was associated with the presence of clumps of granular leucocytes in the spleen sinuses. In one of the enlarged spleens there appeared to be a growth of new lymph-nodes which seemed to extend along the vessels from the neighbouring Malpighian bodies.

Some of the splenic changes are depicted in the adjoining illustrations.

(Figs. 64, 65, 66, 67, 68.)

DISCUSSION.

The experiments described illustrate a form of hepatitis caused by an agent (manganese) which has its primary action on the liver cells. Following upon the liver cell damage, a mesenchymal response takes place which involves a local proliferation of histiocytes in the liver

and frequently also in the spleen.

In the liver itself various types of cell damage are produced, one of the most striking of which is the "amorphous degeneration" of the French writers, which is said to result from the diffusion of lipoids through the protoplasm, (Robert-Chavis, quoted by Albot). Fatty degeneration is also seen, and of course various degrees of cloudy swelling. Necrosis of the liver cells occurs leading to rhexis or pyknosis of the nucleus, swelling and, ultimately, disappearance of the affected cells. During the first two days after the damage of the liver cells, very little cellular reaction has appeared. Nevertheless the Kupffer cells are seen to be the only surviving cells in the midst of the areas of liver cell necrosis. By the end of the first week all the reactive appearances are present. Attempts at regeneration of the liver cells appear during the second week, as evidenced by large hyperchromatic liver cells with multiple nuclei seen at the periphery of the lobule. These signs of regeneration are present together with the evidences of liver cell damage already enumerated. "Bile thrombi" may occur in association with the damaged liver cells.

Proliferation of bile ducts is also a striking feature.

Vascular reactions are difficult to interpret on account of the curious circulatory conditions within the liver.

In some of the experiments there is a greatly increased vascularity of the portal spaces, but this may be associated with the new connective tissue growth, rather than with the inflammatory process itself. In the earlier stages before there is any new connective tissue growth around the portal spaces, the sinusoids at the periphery of the lobule are often dilated, and leucocytic infiltration is seen. There may be also dilatation of the capillaries around the bile-ducts in the portal spaces, but leucocytic exudation is seldom seen here. One point which may be mentioned under this heading is the dilatation of periportal lymphatics which is a common and early feature.

We now come to the point which is our primary concern: the mesenchymal response. As has already been mentioned, the Kupffer cells appear to survive the onslaught of the toxic agent on the parenchymal cells. A few days after the liver cell damage has begun, the Kupffer cells may be seen in mitosis, and active proliferation of the cells is thus evidenced. Proliferation of new connective tissue cells or their precursors, whatever their origin, takes place in relationship to the damaged cells to the greatest extent, and ultimately an occasional surviving liver cell may be seen isolated in the midst of the connective tissue new growth. The new production of connective tissue cells does not as a rule extend beyond the

zone of damaged liver cells which is always at the periphery of the lobule.

Under favourable circumstances, new connective tissue cell formation may be seen to occupy an isolated area where a liver cell has undergone autolysis. This is seen in Fig. 57. In this particular instance, the Kupffer cells and the reticulin wall of the sinusoid could be made out, and the new histiocytes had made their appearance in the perivascular space between the sinusoid and the liver cell columns. This space is generally held to be a lymph space. In such a situation as this, the probability is that the cells took origin from the Kupffer cells lining that particular portion of the sinusoid. The only other possibility is that histiocytes grew from the periportal tissues into the perisinusoidal lymph-space, against the lymph-stream, and without leaving any "stem" to show the "root"from which they had grown. That the Kupffer cells play a part in the formation of the new connective tissue cells is shown by the vital staining experiments.

The lymphatic reaction.

It has already been mentioned that the lymphatic channels of the portal spaces are often dilated in the course of experimental hepatitis. In addition to this change there is often seen a round celled infiltration of the portal spaces, around the bile-ducts. This is so striking that Findlay took it to mean biliary inflammation

and went the length of saying that manganese cirrhosis was biliary in origin. Aschoff (1932) has reviewed this question of portal lymphatic infiltration, and points out that it occurs in many diseases which have nothing to do whatsoever with the biliary passages. In all cases it probably indicates some form of damage to the hepatic parenchyma. The metabolic products of the liver in so far as they do not leave it by the hepatic vein are carried by the lymphatics to the porta hepatis.

The Significance of the Mesenchymal Reaction.

Whatever the stimulus may be which leads to local histiocytic proliferation within the liver, it seems to be confined to the lymphatic system of the organ. This is evidenced in two ways:

1. The beginning of the process in the perisinusoidal lymph space.
2. The associated local increase of lymphoid cells in the portal spaces.

Dilatation of lymphatics in the portal tracts has also been noted in some of the experiments. In common with other inflamed tissues it is probable that the lymph flow from the inflamed liver is increased.

The writer considers the lymph from an inflamed liver to be an important factor in linking up liver disease with proliferative changes in the spleen. In a cat weighing three kilogrammes, the flow of lymph from

the thoracic duct may be about 2 cc per minute.

The great bulk of this lymph comes from the liver. (Starling, 1909). If the lymph flow from an inflamed liver is increased, then the amount of lymph carried from the liver into the blood stream must be enormous.

It is well known that the lymph from inflamed areas and the lymph from areas of cellular destruction (e.g. areas of tumour growth) carry a stimulus to the proliferation of the histiocytic elements which line the subcapsular corridor of the local lymphatic glands. From an inflamed liver such lymph may be passed directly into the blood stream.

"The spleen is the lymph gland of the blood". (Helly, 1903).

The proliferative changes which we have seen in the spleen may well be due to some factor carried in the lymph from the inflamed liver. In its course through the lymphatics of the liver, this factor may lead to local histiocytic proliferation and accumulations of round cells in the periportal lymphatics.

It may be of some importance, too, that such a blood borne irritant to the reticuloendothelial tissues of the spleen would come into contact with similar cells in the bone-marrow.

By this hypothesis many difficulties may be overcome which have always been outstanding in other attempts to

account for the splenic enlargement of hepatic cirrhosis. It will be realised that the degree of splenic enlargement will vary according to the degree of acuteness and the duration of the hepatitis. According to the amounts of the (?chemical) stimulant liberated in the lymph from the liver and the time such stimulating substances act on the spleen, so will the degree of splenic enlargement vary. It is quite comprehensible that hepatitis may exist without a sufficient stimulus to splenic enlargement being liberated at all.

Chapter 7.

THE PHYSIOLOGY OF THE PORTAL CIRCULATION.

In the above account of the pathology of hepato-lienal fibrosis, it is seen that considerable stress has been laid on portal congestion as a fundamental factor in bringing about certain characteristic vascular changes.

While the occurrence of such raised pressure innthe portal system may be readily visualised in the presence of a shrunken and distorted liver, it was nevertheless obvious during this study that the vascular changes occurred in the absence of gross cirrhosis. Indeed they were present in cases in which the liver, at the operation of splenectomy, appeared "normal". It seemed clear that the condition of "portal hypertension" which has been postulated to account for the appearances can occur in the absence of such gross and late changes as are found in a "hob-nailed" liver.

Even in the presence of gross cirrhosis the etiology of the raised pressure in the portal system is as yet imperfectly understood. Herrick, (1907), observed that the portal cirrhotic liver gave passage to an amount of portal flow in proportion to its weight, and that scar contraction caused no obstruction to the portal blood vessels, in the large portal cirrhotic liver.

On the other hand it was found that the portal pressure in cirrhosis was markedly influenced by the pressure at which fluid was passing into the liver through the hepatic artery. In the normal liver alterations in the hepatic arterial pressure had little effect on the portal pressure. In perfusion experiments on cirrhotic livers the addition of arterial inflow to the portal inflow markedly limited the latter, and for the portal flow to predominate, as in normal conditions, a portal pressure of 50mm. Hg. might be required. McIndoe, (1928), on the other hand, was unable to confirm these observations of Herrick. In the cirrhotic livers which McIndoe studied, he found that the liver cells were practically divorced from their portal blood supply and that the vessels appeared to run in the connective tissue bands between the islets of surviving liver cells. Slow obliteration of the porto-hepatic venous communications might occur here by scar contraction.

Whatever the explanation of the portal hypertension in the late stages of the disease, and both authors may be partially correct at such a stage, it is quite clear that raised portal pressure occurring before sclerosis has appeared cannot be dependent on scar contraction. If portal hypertension is present in the early stages of liver disease it must depend more on an alteration of physiological conditions of the portal circulation than on gross anatomical

changes.

The approach to the problem of altered physiology in disease must be made through normal physiology, and here we find information on the normal circulatory conditions of the portal circulation deficient and inconclusive.

The portal circulation presents a problem both from the anatomical and physiological standpoints, and the conceptions of its intrahepatic anatomy must of necessity influence our interpretation of the vaso-motor reactions in this system. It is obvious that there must exist some mechanism whereby the pressure in the hepatic artery is reduced to a level equal to that in the portal system when the two blood streams meet and mix in the sinusoids of the liver lobule.

Some of the earlier physiological observers, e.g. Burton Opitz, (1912), and Macleod and Pearce, (1914), seemed to accept the work of Gad, (1873), who considered that the hepatic arterial and portal venous streams met by a vascular connection at an acute angle whereby a wedge-shaped flap valve was formed at the angle of union. This flap was said to shift in accordance with the pressure brought to bear on its sides, so that an increased flow of blood through the hepatic artery would limit the flow of blood through the portal vein.

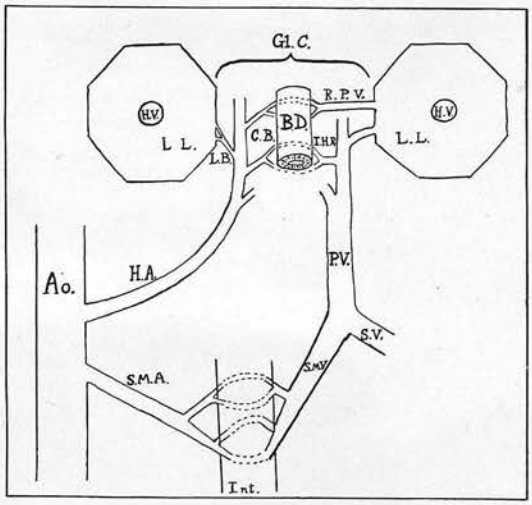


Fig. 69 Diagram of the hepatic and portal circulation. The dotted lines represent capillaries. Of the intrahepatic branches of the hepatic artery, the lobular branches are the least numerous and the smallest.

Ao. aorta. *B.D.* bile duct. *C.B.* capsular branches. *Gl.C.* Glisson's capsule. *H.A.* hepatic artery. *H.V.* hepatic vein. *I.H.R.* internal hepatic radicle of Kiernan. *Int.* intestine. *L.B.* lobular branch. *L.L.* liver lobule. *P.V.* portal vein. *R.P.V.* radicular portal vein (Ferrein). *S.M.A.* superior mesenteric artery. *S.M.V.* superior mesenteric vein. *S.V.* splenic vein.

This view, however, is not in keeping with the bulk of the anatomical evidence. Kiernan (1833) studied the intrahepatic distribution of the hepatic artery, and concluded that it sub-divides into branches which supply the bile-ducts, the walls of the portal veins and the tissues of the portal tracts (capsular branches, Fig.69).

From the capillary network thus formed, collecting venules gather the blood into the portal veins. These small intrahepatic radicles of the portal vein are termed internal hepatic radicles (Fig.69). This work of Kierman received authoritative support from the researches of Cohnheim and Litten (1876), Pfuhl (1922), Loeffler (1927), and Cameron and Mayes (1930). Loeffler draws attention to the fact that the blood supply to the intrahepatic bileducts corresponds in its anatomical arrangements to the vascular supply of the gall bladder, which develops as a diverticulum of the bileducts.

Cameron and Mayes admit, however, that an occasional small branch of the hepatic artery may pass directly into the liver sinusoids, and Olds and Stafford (1930) maintain that such branches constitute the main mode of distribution of the hepatic artery. If such branches are given directly to the lobule they must be of the nature of very fine arterioles to achieve a reduction of the pressure in the hepatic artery to a level corresponding to that in the portal vein.

The prevailing views of the French workers in this field are summarized in Poirier and Charpy's treatise (1905). While accepting Kierman's views, occasional small branches are described which pass directly to the liver lobule. The capsular branches of the hepatic artery, after supplying the structures in the portal tracts terminate not only in the internal hepatic radicles, but also link up with small veins which pass directly into the liver lobules without joining the portal vein. These small radicular portal veins were apparently discovered by Ferrein (1749).

These anatomical communications do not appear to have been considered in studies of the physiology of the portal blood flow. Clark (1928) and Bainbridge and Trevan (1917), for example, assumed that there were no true capillaries in the liver, while other writers do not commit themselves to any definite opinion.

The importance of keeping these anatomical considerations in mind cannot be over-emphasized in the study of the hepatic circulation. In perfusion experiments on the isolated liver, it is well known that, after about half an hour, the pressure in the portal vein must be raised to a level comparable to that in the hepatic artery, in order to maintain a flow through the organ. This suggests a free anastomosis between the two systems.

This anastomosis may take place by three possible routes:

(a) Via the lobular arterioles through the sinusoids at the periphery of the lobule.

(b) Via the capsular branches through radicular portal veins (Ferrein), and the peripheral sinusoids of the lobule.

(c) Via the capsular branches through the internal hepatic radicles of the portal vein (Kiernan).

It is difficult to simplify this statement further for the purpose of physiological considerations. One fact, however, is of paramount importance: an arteriolar system is a theoretical necessity in order to reduce the great arterial pressure of the hepatic artery to a level equal to that in the portal vein, for these pressures must be equal when the two streams reach the hepatic sinusoids. The balance of anatomical evidence is in favour of a capillary communication between the hepatic artery and the portal vein. Whether the capillary communication is physiologically important will be considered in this paper.

Keeping this knowledge of the hepatic circulation in mind, we approach the problem of the portal circulation from a new aspect. We conceive the portal venous system as having an outlet through the liver sinusoids and being fed with blood from the mesenteric arteries

in the periphery, and also having a central inflow from the internal hepatic radicles inside the liver. This central inflow joins the portal ramifications immediately before the point at which the portal blood passes into the liver sinusoids. Just beyond this point the portal stream is joined by a further inflow from the lobular arterioles and the radicular portal veins.

The object of the work to be detailed in this chapter is the elucidation of the effect of various vaso-motor reactions in the liver on the portal venous pressure, and if possible to form an estimate of the relative importance of the routes of anastomosis described between the hepatic artery and the portal vein.

TECHNIQUE AND METHODS.

Cats were used throughout the experimental work, anaesthetized with luminal (0.2 gm. per kilo intramuscularly) or with chloralose (0.1 gm. per kilo injected into the intestine after the cat had been anaesthetized with ether). There was no difference in the arterial or venous blood-pressure reactions with these two drugs, but with the latter the arterial pressure was more satisfactorily maintained. The arterial pressure was recorded from the carotid artery in mm. Hg. The portal pressure was

recorded from the stump of the splenic vein, the spleen having been removed. At first it was recorded with carbon tetrachloride in the manometer (S.G. 1.58) In the later experiments when technical difficulties regarding floats for the manometer had been overcome, a 5 per cent solution of sodium citrate in water was used to fill the recording system. A very satisfactory water manometer for ordinary purposes was made by C. F. Palmer Ltd., after the model suggested by Thompson (1930) for taking continuous blood-pressure records. A more delicate and accurate instrument was constructed for this work by Mr. Fraser of the Natural Philosophy Department, Aberdeen University. Once the cannulae were in position and the pens writing on the drums, the abdomen was closed as far as the requisite manipulations would permit. The component vessels of the portal circulation were rendered easily available by loops of thread passed round them, so that they could be clamped or otherwise obstructed at any time during the experiments.

The possible complicating influence of the return of the blood from the stomach to the portal vein was excluded by ligaturing the gastroduodenal branch of the hepatic artery. This procedure cut off the main blood supply to the stomach. The only

other tributary of the portal vein outside the liver is the cystic vein; this is so small as to be practically negligible. In one critical experiment, however, the cystic vein, too, was ligatured.

For the liver-volume observations a plethysmograph of the type suggested by Griffith and Emery (1930) was used, connected to a Macdowall volume recorder.

COMPONENT FACTORS MAINTAINING PORTAL PRESSURE.

In agreement with other investigators in this field, the blood-pressure in the portal system in cats was found to be on the average about 80-100 mm. water or 50-60 mm. carbon tetrachloride. The pressure undergoes fluctuations with the respiratory movements. It rises during inspiration and falls on expiration. According to Schmid (1909) these variations are due to changes in intra-abdominal pressure. They are not due to respiratory alterations in vena caval pressure near the heart, as these changes take place in the opposite direction, i.e. a rise during expiration and a fall on inspiration. The fluctuation is not due to the transmission of pressure from the arteries, as the respiratory change in pressure in the latter does not coincide absolutely with the respiratory movements, as the portal pressure does. Since the fluctuations

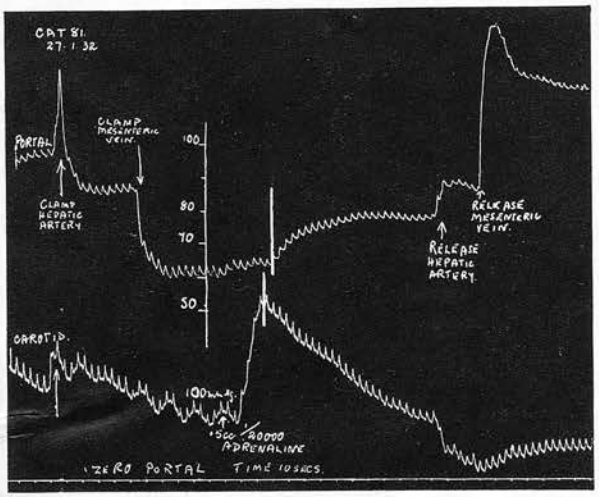


Fig. 10 Upper record: portal pressure. Lower record: arterial pressure. Chloralose anæsthesia. Hepatic artery clamped at the first arrow. This reduces the portal pressure by 15 mm. water. At the second arrow the mesenteric vein was clamped. The portal pressure is further reduced by 28 mm. water, but is still maintained at a relatively high level. The injection of adrenaline into the saphenous vein has no effect on the portal pressure until the arterial pressure has begun to fall. The slight rise in portal pressure is probably effected by increased inflow through collateral arterial channels from the bare area of the diaphragm. The removal of the clamps from the vessels allows the portal pressure to return to a high level.

are present when the abdomen is open the intra-abdominal pressure cannot be entirely responsible for the change. When the portal vein was guarded against direct pressure from the movements of adjacent viscera, e.g. the duodenum, the respiratory fluctuations were still present. It would appear, therefore, that under the present experimental conditions the factor responsible for the respiratory fluctuations may possibly be the downward movement of the diaphragm. This would produce a simple mechanical effect, the descending midriff gently squeezing the liver and causing a temporary obstruction to the hepatic circulation.

By producing a simple obstruction of the various component vessels of the portal circuit, various effects are obtained. Clamping the superior mesenteric artery or vein cuts off the splanchnic inflow and leads to an immediate fall in portal pressure, by some 30-40 mm. water. The pressure, however, does not fall to zero and a pressure of 50 mm. water is maintained. As the only remaining inflow to the liver after this procedure is the hepatic artery, it would appear that the latter pressure is maintained, in part at least, by a transmission of pressure from the hepatic artery to the portal vein. (Figs 70 and 73).

In comparison with the effect of clamping the mesenteric vessels, obstruction of the hepatic artery alone causes a slighter fall in portal pressure, usually amounting to 15-25 mm. water. (Figs. 70 and 72). This is not surprising, for, as Macleod and Pearce have shown, the hepatic artery brings about one-fourth to one-third of the blood which flows through the liver. Grab, Janssen and Rein (1929) estimate the proportion at much less - about one sixth. Three quarters or more of the blood flowing through the liver, therefore, comes from the mesenteric vessels.

Obstruction of the hepatic artery thus only cuts off a minor part of the inflow and the pressure is well maintained, although at a slightly lower level, by the mesenteric portal flow. It appears from this that under normal conditions the main driving force of the portal system is "vis a tergo" from the mesenteric arteries. But since the pressure in the intact portal circuit is about 80mm. water, and occlusion of both the hepatic and mesenteric components fails to reduce that pressure by more than half, (Fig. 70), we must assume that there is a resistance to the portal flow beyond the point of entry of the internal hepatic radicles of the portal vein. This resistance may be offered in the sinusoid bed of the

liver, but the degree of constriction of the portal ramifications in the liver before they enter the sinusoids, and of the sublobular venules, may influence the rate of escape of blood from the portal system. This hepatic resistance has the effect of reducing the portal pressure to the zero level which Bayliss and Starling (1894) recorded as being present at the point at which the hepatic veins join the vena cava.

The Effects of Adrenaline and Pituitary Pressor Extract on the Portal Blood Pressure.

1. Adrenaline.

This drug was used in quantities of 0.5cc. of a 1 in 10,000 or a 1 in 20,000solution given intravenously. The former strength was used where the animals were anaesthetized with luminal, while the latter was given when chloralose was used. The injections were given into the saphenous vein usually but for some special purposes, they were made intraportally. The exact mode of administration is indicated on the tracings or in the legends.

By injecting adrenaline into a systemic vein a rise in portal pressure is produced. This begins about seven seconds after the arterial pressure has

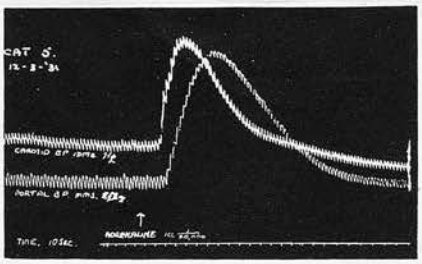


Fig. 71

Upper record: carotid pressure. Lower record: portal pressure (recorded in carbon tetrachloride). Luminal anæsthesia. At the arrow 1 c.c. 1/20,000 adrenaline injected into the saphenous vein. The carotid pressure begins to rise about seven seconds before the portal pressure. The portal pressure, however, continues to rise while the arterial pressure is falling.

started to rise, and it continues for several seconds after the arterial pressure has passed its summit. (Fig.11). The portal pressure rise has thus two phases: the first occurring while the arterial pressure is still rising, and the second while the arterial pressure is falling. As will be shown later (Fig.15) the rise in portal pressure after intraportal adrenaline begins immediately. We may assume therefore that the interval of seven seconds between the onset of the rise of arterial pressure and that of the portal pressure is due to a delay in adrenaline reaching the portal system. It reaches the arteries before the veins and the effect of the drug is therefore first manifested on the arterial pressure record. The rise in pressure thus produced in the portal system may be due either to an increased inflow into the mesenteric or hepatic radicles of the portal vein, or to an obstruction to the outflow through the hepatic branches, or to a combination of both. In comparison with alterations in inflow and outflow, constriction of the main trunk of the portal vein as a whole is not likely to occur to such a degree as to exert any marked effect on the portal pressure. This factor was ruled out by experiment (p.158)

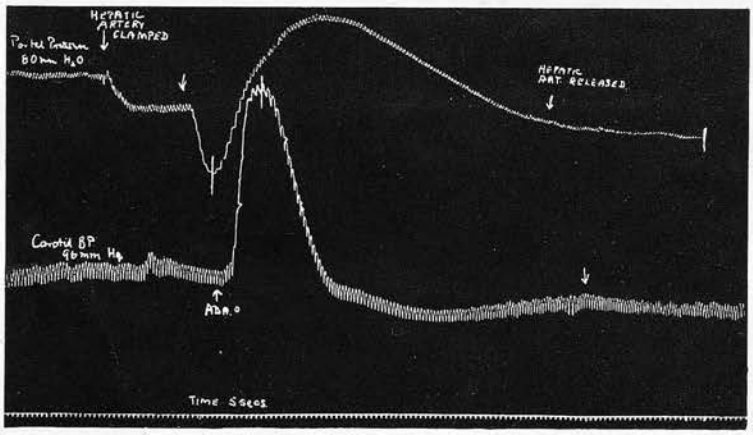


Fig. 42. Upper record: portal pressure. Lower record: arterial pressure. Luminal anæsthesia. At the first arrow the hepatic artery was clamped. At the second 0·5 c.c. 1/10,000 adrenaline was injected into the saphenous vein. As the arterial pressure rose the portal pressure fell. When the arterial pressure passed its peak, however, a rise in portal pressure began.

THE MESENTERIC COMPONENT.

If the portal vein is occluded partially by means of a ligature applied near the hilus of the liver, the portal outflow is so obstructed that the pressure sets itself at a higher level and alterations in pressure in the portal vein, dependent on intrahepatic effects of adrenaline, are prevented from manifesting themselves on the portal pressure record. By clamping the hepatic artery and thus preventing adrenaline from reaching the liver, the intrahepatic effects can also be abolished. Under these circumstances the injection of adrenaline is followed by an immediate fall in portal pressure, which begins as soon as the arterial pressure starts to rise. The moment that the arterial pressure passes its summit, however, the portal pressure begins to rise again and reaches its height about the time that the arterial pressure returns to normal (Fig.72)

Thus when the hepatic component is excluded from the recording system the rise in portal pressure is delayed. Since the only factor which can influence the portal pressure from the peripheral mesenteric radicles is the inflow of blood into the system, we assume that the inflow through the mesenteric capillaries is first diminished and then increased. Clark

has measured the flow from the mesenteric veins under similar experimental conditions, and finds that under adrenaline the flow diminishes until the arterial pressure has passed its peak "when an obvious increase occurs which returns to the original rate as the pressure falls".

The same observer states that "the fact that the outflow falls when the blood pressure is at its highest indicates that the constriction of the intestinal vessels is sufficiently intense to prevent the high pressure forcing more blood through the vessels. . . . This constriction, however, lasts a very short time and is rapidly overcome by the blood pressure. These observations and views have been confirmed by the writer using Clark's method of measuring the flow from a mesenteric vein by counting the drops. It appears obvious, therefore, that during the initial stage the portal pressure falls from diminished inflow, due to the active constriction of the mesenteric arterioles.

When this constriction passes off and the arterial pressure begins to fall there occurs an increased inflow of blood into the portal system. This increased inflow is facilitated by a dilatation of the arterioles and capillaries of the

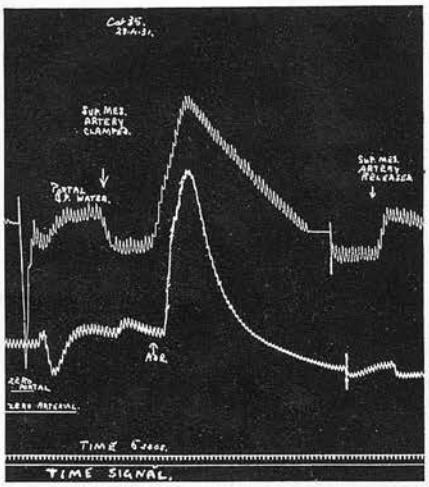


Fig 73 Upper record: portal pressure. Lower record: carotid pressure. Luminal anæsthesia. At the first arrow the superior mesenteric artery was clamped. The injection of adrenaline into the saphenous vein then causes a rise in portal pressure beginning a few seconds after the arterial pressure has begun to rise. The portal pressure is still rising when the arterial pressure has begun to fall.

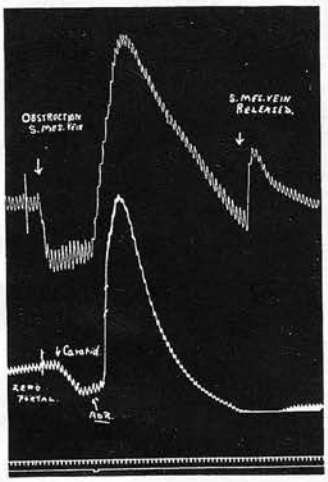


Fig. 74 Upper record: portal pressure. Lower record: carotid pressure. Luminal anæsthesia. The superior mesenteric vein was clamped at the first arrow. The injection of adrenaline into a systemic vein then causes the arterial pressure to rise, followed in a few seconds by a rise in portal pressure. The rise in portal pressure continues when the arterial pressure has passed its peak.

gut. Such capillary dilatation has been demonstrated by Clark, who considers it to be a passive phenomenon dependent on the increased pressure produced by adrenaline.

THE HEPATIC COMPONENT.

Having shown that the second phase of the adrenaline rise in portal pressure is due in the main to an increased flow into the system from the dilating mesenteric arterioles, it may be assumed that the first phase is due to an intrahepatic effect. This seems to be the case. If we occlude the return of blood from the mesenteric vessels, by clamping either the superior mesenteric artery or vein, the injection of adrenaline produces a rise of portal pressure which begins some 7 seconds after the arterial pressure has begun to rise. There is thus a short latent period exactly corresponding to that occurring with the portal circulation intact. The rise in portal pressure continues for some seconds after the arterial curve has passed its peak. (Figs. 73 and 74).

This rise of pressure in the portal system occasioned by the action of adrenaline in the liver may result from any of the following causes:-

1. A Venous Effect: (a) By constriction of the intrahepatic ramifications of the portal vein beyond the point at which they receive the internal hepatic radicles.

   (b) By constriction of the radicles of the hepatic vein.

2. A Hepatic Effect proper:

   Obstruction of the sinusoids either by

   (a) Swelling of the liver cells, or

   (b) Constriction of the liver as a whole by contraction of plain muscle in the capsule of Glisson, narrowing the sinusoids.

3. An Arterial Effect: By transmission of pressure from the hepatic artery into the portal vein.

The injection of adrenaline into the portal vein itself produces an immediate rise in portal pressure which precedes slightly the rise in arterial pressure (Fig.75). The adrenaline reaches the liver before it reaches the systemic circulation and thus its hepatic effect appears slightly before the systemic effect. Having reached a certain level a small plateau is seen on the portal pressure curve,

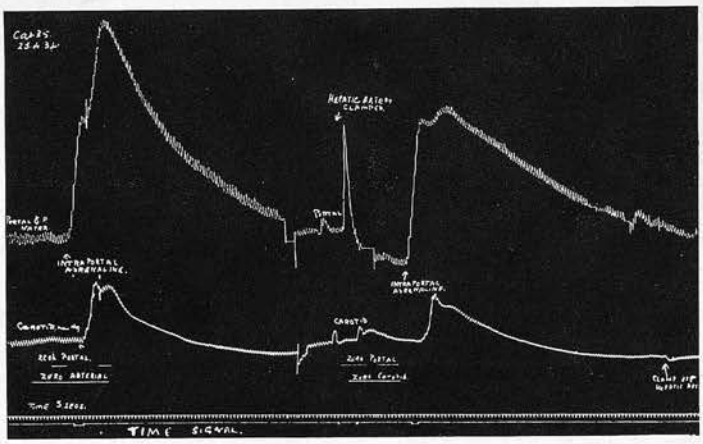


Fig 75 Upper record: portal pressure. Lower record: arterial pressure. Luminal anæsthesia. At the first arrow 0·5 c.c. 1/10,000 adrenaline injected intraportally. The portal pressure rises before the arterial pressure, and a secondary rise of portal pressure begins as the arterial pressure passes its peak. At the second arrow the hepatic artery was clamped. The intraportal injection of adrenaline was repeated, but the secondary rise in portal pressure was abolished.

and a few seconds later, when the arterial pressure passes its peak, a secondary rise appears. Since this latter rise occurs at the same time as the rise resulting from an increased inflow through the mesenteric arterioles, it might be expected to be due to a similar effect, i.e. an increased inflow into the portal system through dilating arterioles. This is the explanation, but the arterioles are not those of the mesenteric, but those of the hepatic artery. This is shown by the experiment with the hepatic artery occluded (Fig.75), when it is seen that the initial hepatic rise still persists but the secondary rise is almost negligible and is longer delayed than in the first experiment. It is noteworthy that the adrenaline effect on the systemic circulation after intraportal injection is much less than the effect produced by injection into a systemic vein. It would appear that the adrenaline is held up or altered in some way in the liver, so that a relatively smaller dose is passed on to the systemic circulation. In this way the mesenteric effect is also a minor one and only causes a slight rise in the portal pressure after the arterial pressure has passed its peak. It is possible that this slight secondary rise may also be in part explained by a slight blood flow into the liver

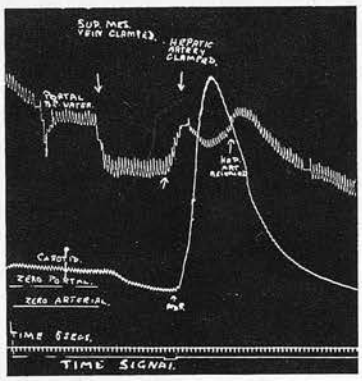


Fig. 76 (This record was taken from the same cat as Fig 74.) Upper record: portal pressure. Lower record: arterial pressure. Luminal anæsthesia. The superior mesenteric vein was clamped at the first arrow. At the second arrow adrenaline was injected into the saphenous vein. During the first phase of the adrenaline rise in portal pressure, the hepatic artery was clamped. This procedure abolished all further rise in portal pressure for the time being, and the expected peak (cf. Fig 74) was replaced by a trough.

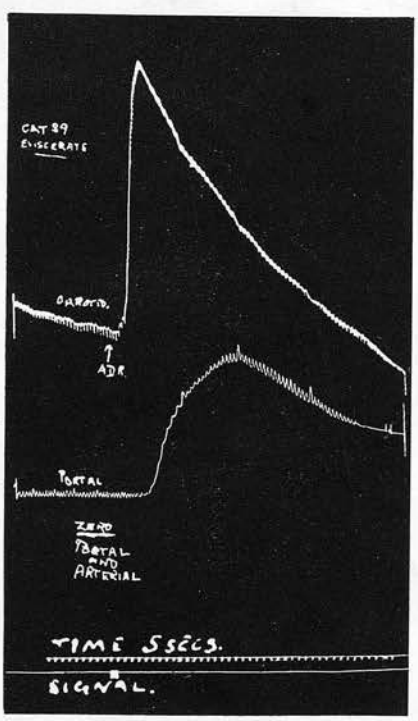


Fig 77. Upper record: carotid pressure. Lower record: portal pressure. Cat anæsthetized with luminal. In this cat the abdominal viscera had been removed with the exception of the liver. The injection of adrenaline into a systemic vein had no effect on the portal pressure until the arterial pressure had passed its peak. The rise in portal pressure then occurring is due to an increased inflow through the hepatic artery.

In this preparation the blood-pressure was falling rapidly, and the animal died a few minutes later.

through collateral arterial channels from the bare area of the diaphragm (cf Fig.70). In any case the main fact remains that the occlusion of the hepatic artery abolishes almost completely the secondary rise in portal pressure following the intraportal injection of adrenaline.

That the hepatic artery plays an important rôle in producing the hepatic part of the rise of portal pressure after adrenaline is further illustrated by the following experiments:-

If the mesenteric component is removed from the circuit by clamping the mesenteric vessels, and adrenaline is injected into a systemic vein, the portal venous pressure begins to rise, as we have seen previously (Fig.74). While this rise is occurring, obstruction of the hepatic artery will produce an immediate trough in the curve of the portal pressure. A very slight rise follows the trough which may be due to leakage through collaterals mentioned above (Fig.76).

Fig.77 shows the tracings of arterial and portal venous pressures obtained from a cat which had been subjected to removal of all the abdominal viscera with the exception of the liver. The portal pressure was recorded by means of a cannula inserted into the stump of the portal vein.

Under these circumstances the only inflow into the liver is through the hepatic artery. The injection of adrenaline into a systemic vein has no effect on the portal pressure until the arterial pressure has passed its peak. At this point an immediate rise of portal pressure is seen. This rise could only occur by transmission of pressure from the hepatic artery into the portal vein by increased inflow through dilating arterioles. It is worthy of note that this preparation was failing, and it is probable that considerable vasoconstriction of the hepatic artery was present before adrenaline was injected. This would so limit the inflow to the liver that adrenaline would not reach the portal vein, and hence no initial rise in portal pressure would occur. The rise only began when the hepatic arterioles were dilating with the fall in arterial pressure. With marked constriction of the artery limiting the flow through it, the portal pressure was still maintained at 15-20 mm water. This pressure must have been due to the resistance offered by the tone of the portal venous ramifications and the radicles of the hepatic vein. The reason for assuming pre-existing splanchnic vasoconstriction in the failing preparation will be elaborated later (p.).

The above facts present evidence which suggests very strongly that the second part of the hepatic component of the adrenaline rise in portal pressure is due to an increased inflow into the portal vein from the hepatic artery. How this increased inflow occurs, and the possible influence of intervening capillaries, will be discussed when we consider the action of pituitary pressor extract.

THE FIRST PHASE OF THE ADRENALINE RISE IN PORTAL PRESSURE.

The initial part of the adrenaline rise in portal pressure which occurs while the arterial pressure is rising, is still unexplained. There can be no doubt that it is an immediate direct effect on the venous or sinusoidal bed of the liver, for it precedes the arterial effect after intraportal injection.

It is conceivable that the action of adrenaline in producing the initial rise in portal pressure after intraportal injection might be due to a diminution in the calibre of the main trunk of the portal vein itself. To test this possibility the portal vein was partly obstructed by a ligature so as to delay the entry of adrenaline into the liver

after intraportal injection. This procedure also set the portal pressure at a high level which would not be influenced by any change in the calibre of the minute ramifications of the portal vein in the liver. Under these circumstances the intraportal injection of adrenaline was not followed by any rise in portal pressure. The injection of vasopressin under similar conditions produced a slight rise in portal pressure presumably due to contraction of the plain muscle in the wall of the vein. We assume, therefore, that with the doses of adrenaline used no appreciable effect is produced on the wall of the portal vein so far as its main trunk is concerned. This, however, does not exclude an intrahepatic effect of adrenaline on the portal ramifications.

The only method by which the cause of the initial rise of portal pressure can be settled is that of plethysmography. The interpretation of the results of liver plethysmography has given rise to considerable difficulty and confusion in the past. Bainbridge and Trevam (1917) considered that the liver volume increased under the influence of adrenaline, and they ascribed this increase to a swelling of the liver cells. They stated that the action of adrenaline in causing a rise in por-

tal blood-pressure could be simulated by the injection of distilled water into the portal vein. Distilled water would cause a swelling of the liver cells and thus the sinusoids would be obstructed. The writer has been unable to confirm this observation.

Clark (1928) on perfusing the excised liver, found that adrenaline caused a diminution of liver volume. Edmunds (1915) found that the action of adrenaline on the liver volume varied even in animals of the same species. The effect could be standardized to some extent by occluding the hepatic artery, after which adrenaline caused an increase in the volume of the liver. Edmunds is in favour of the view that adrenaline constricts the sublobular hepatic veins. Francois-Frank and Hallion, in 1896, observed that stimulation of the splanchnic nerves caused a diminution in liver volume even after ligature of the hepatic artery. This would suggest in contrast to Edmunds that the main site of action of adrenaline is on the portal venous ramifications.

During the past year valuable work has been done on this subject by Emery and Griffith (1930). They present incontrovertible evidence that the hepatic nerves act on the portal ramifications. Adrenaline produces a diminution of liver volume similar to that occurring with stimulation of the splanchnic

facing p. 160.

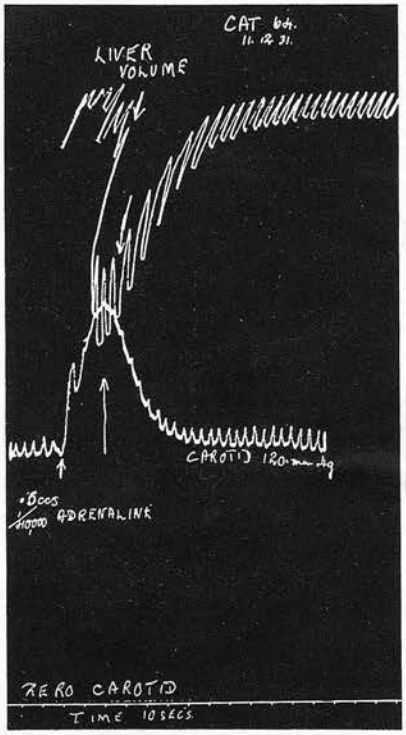


Fig. 78. Upper record: liver volume. Lower record: carotid pressure. Chloralose anæsthesia. Arrows mark corresponding times on the two curves. Following the injection of 0·5 c.c. 1/40,000 adrenaline into the saphenous vein the arterial pressure begins to rise, and almost immediately afterwards the liver volume diminishes markedly. The liver begins to swell again as the arterial pressure begins to fall.

nerves. If the preparation was failing and the blood-pressure low, then the volume of the liver increased with adrenaline. Otherwise the initial effect of adrenaline was always a diminution in the volume of the liver.

This work carried conviction in that the experiments were carried out with the liver in situ in the anaesthetized animal, and thus the criticisms which can be directed against observations made on the excised organ are countered.

The writer has repeated the experiments of these observers so far as adrenaline is concerned, and finds himself in entire agreement with their main findings.

When adrenaline is injected into a systemic vein the liver volume diminishes markedly a few moments after the arterial pressure has begun to rise. As soon as the adrenaline effect begins to pass off the liver volume again increases (Fig.78).

It is obvious that an initial constrictor action of adrenaline on the sublobular hepatic veins would cause an increase in liver volume from retention of blood in the lobules. As this does not occur the initial venous effect of adrenaline must be on the portal ramifications. This view is confirmed by the fact that the intraportal injection

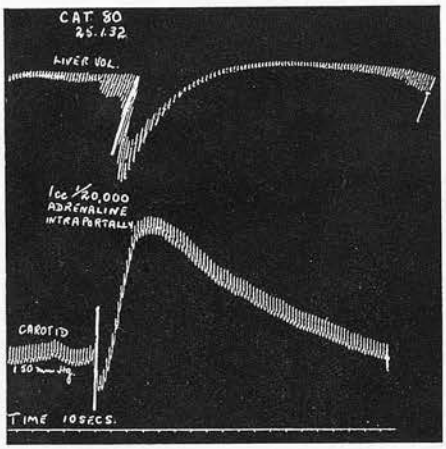


Fig. 79. Upper record: liver volume. Lower record: carotid pressure. Chloralose anæsthesia. The intraportal injection of 1 c.c. 1/20,000 adrenaline leads to an immediate diminution in liver volume. Some seconds later the carotid pressure begins to rise. The fall in liver volume is due to constriction of the ramifications of the portal vein.

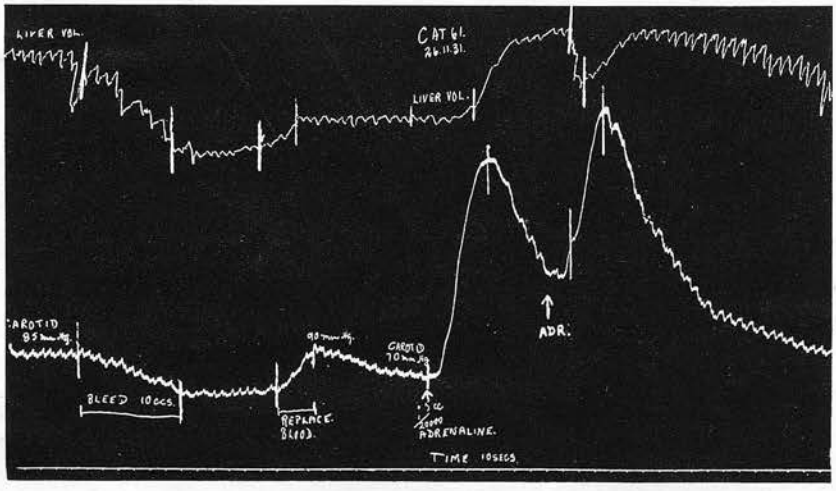


Fig. 80 Upper record: liver volume. Lower record: carotid pressure. Chloralose anæsthesia. Between the first two alignment marks 10 c.c. blood were withdrawn from the femoral artery into a heparinized syringe. Between the second pair of alignment marks this blood was reinjected into a saphenous vein. Subsequent injection of adrenaline into the saphenous vein caused no diminution in liver volume, but after the arterial pressure had begun to fall an increase in liver volume occurred. Note that the blood pressure was 70 mm. Hg when this injection of adrenaline was given. A second injection of adrenaline, however, caused a diminution in liver volume followed by an increase, as in the healthy preparation. Adrenaline fails to reduce the liver volume to the same degree as hæmorrhage.

of adrenaline brings about a diminution of liver volume before the adrenaline effect is manifested on the general circulation (Fig.79).

When the preparation is failing, as Emery and Griffith have also noted, there is little or no alteration in the liver volume while the arterial pressure is rising after adrenaline. As soon as the pressure begins to fall, however, an increased inflow occurs through the dilating splanchnic arterioles and the liver volume increases. If a second injection of adrenaline be given at this time, the volume of the liver diminishes with the rise in arterial pressure and again increases as the pressure falls (Fig.80).

Intraportal injection in the failing preparation gives a similar result. There is no effect on the liver volume until the splanchnic arterioles dilate, when an increase of volume occurs. A second intraportal injection then causes the liver volume to decrease.

These variations in the action of adrenaline on the liver volume require further elaboration. Reid Hunt (1918) made similar observations and noted that the animals which responded to adrenaline with an expansion of the liver appeared to be in a condition somewhat analogous to experimental shock.

He says:- "May not one of the features of experimental shock be a change in the blood-vessels of the liver such that they can no longer respond with a contraction to epinephrin?. . . . The expansion of the liver after epinephrin appeared to be passive; it was accompanied by a marked contraction of the leg..."

The fact that no alteration takes place in the volume of the liver of the failing preparation until the splanchnic arterioles dilate may have two possible explanations:

1. The liver sinusoids are already practically empty of blood, so that further constriction of the inflow cannot cause any diminution of the volume.

2. The inflow to the liver is already so restricted by splanchnic vasoconstriction that adrenaline cannot cause any further vasoconstriction.

The first hypothesis can be discounted, for we find that it is possible further to diminish the liver volume in such a failing preparation, e.g. by bleeding the animal. This is shown in Fig. 80. The second suggestion is probably nearer the truth, and is in accordance with Reid Hunt's theory. The record of portal pressure under the influence of adrenaline in a failing preparation shows neither the effect of diminished inflow through the hepatic artery, nor any constrictor effect of adrenaline on

the portal vein during the initial part of the rise in arterial pressure (Fig.77). That the splanchnic vessels are not merely refractory to adrenaline is seen by their response to the second injection of adrenaline in Fig.80. It would thus appear that considerable splanchnic vasoconstriction is present in a failing preparation. This may also explain the fact that although the arterial pressure may fall considerably from the level recorded at first, the portal pressure remains practically unaltered, for general splanchnic vasoconstriction would also cause constriction of the portal ramifications in the liver.

If this hypothesis is correct, it follows that the rise of blood-pressure from adrenaline in the animal with a low blood-pressure occurs by constriction of the blood vessels of the limb muscles and of the skin. This again is in accordance with Hunt's view. Vasoconstriction is already present in the splanchnic area and those vessels are only relaxed by the vasodilator impulses which bring about the fall in pressure after adrenaline.

The initial effect of adrenaline therefore is on the portal venous ramifications, where it causes venoconstriction. In the failing preparation this action may be masked by pre-existing vasoconstriction in the splanchnic area.

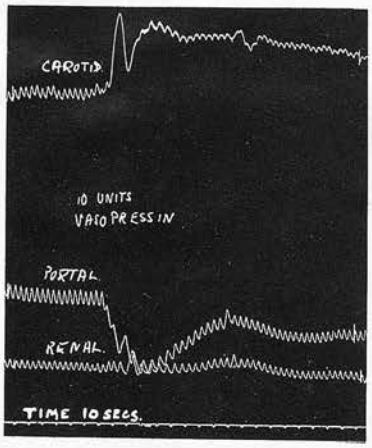


Fig. 81 Upper record: carotid pressure. Middle record: portal pressure. Lower record: vena caval pressure recorded from the renal vein. Chloralose anæsthesia. The injection of vasopressin into the saphenous vein leads to a rise in arterial pressure, accompanied by a simultaneous fall in portal pressure. The vena caval pressure remains practically unchanged.

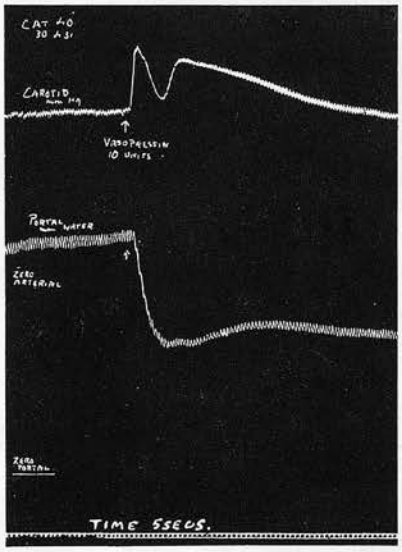


Fig. 82 Upper record: arterial pressure. Lower record: portal pressure. Luminal anæsthesia. The injection of vasopressin into the saphenous vein leads to a fall in portal pressure occurring simultaneously with the rise in arterial pressure. The portal pressure fails to recover its original level as the arterial pressure falls again.

2. THE ACTION OF PITUITARY PRESSOR EXTRACT.

Vasopressin, injected into the systemic veins produces a fall in portal pressure. This effect is due to the fact that vasopressin acts mainly on the capillaries and increases their tone (Clark, 1930, Krogh, 1929, Carrier, 1922.). As a result of this increase in capillary tone, the inflow of blood into the portal system is diminished and the pressure falls (Fig. 81.).

As Clark has noted, sometimes the portal pressure fails to recover its previous height after the injection of vasopressin. This effect is clearly shown in Fig. 82. Clark ascribes this to the fact that during the intra-abdominal manipulations there has been some loss of capillary tone which is restored by the injection of vasopressin and which remains after the effect of vasopressin on the arterial pressure has passed off.

The action of the first dose is always much more marked than that of subsequent doses. When the mesenteric vessels are excluded from the portal circuit, the injection of vasopressin produces a further fall in portal pressure exactly comparable to that occurring with the portal circulation intact (Fig. 83.).

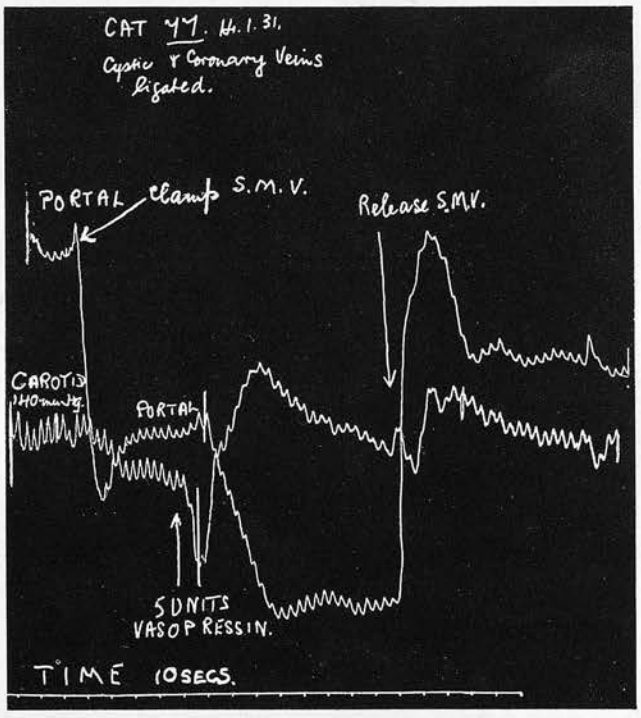


Fig. 83 Upper record: portal pressure. Lower record: carotid pressure. Chloralose anæsthesia. In this experiment special care was taken to ensure that there was no possible extrahepatic inflow into the portal vein, by ligaturing the cystic and coronary veins. At the first arrow the superior mesenteric vein was clamped. The injection of vasopressin into the saphenous vein then produced a very striking fall in portal pressure. On releasing the mesenteric vein the portal pressure did not return to its original level.

As this observation is exceedingly important, special care was taken to exclude all extra-hepatic communications between the hepatic artery and the portal vein, by ligaturing the cystic vessels from the gall-bladder and the coronary vein from the stomach.

This record is in marked contrast to the action of adrenaline under similar circumstances. As the arterial pressure passes its peak there is no rise of portal pressure comparable to that occurring with adrenaline. The action of vasopressin on the communication between the hepatic artery and the portal vein is exactly similar to the action of the drug via the mesenteric vessels. Therefore there must exist a capillary system between the hepatic artery and the portal vein inside the liver. It is unlikely that the liver sinusoids, with their incomplete lining, constitute a capillary system reacting like that in the intestinal wall. From this experiment we must assume that there is a closed capillary communication between the hepatic artery and the portal vein in the portal tracts.

This assumption is further supported by the experiment shown in Fig.76. During the venous part of the adrenaline rise of portal pressure

obstruction of the hepatic artery immediately abolishes any further rise for the time being. If the communication between the hepatic artery and the portal vein was via the sinusoids at the periphery of the lobule, no such effect would take place. The ramifications of the portal vein are constricted before their entry into the sinusoids. Limitation of arterial inflow into the sinusoids would therefore have no influence on the rising portal pressure.

<u>There must be a communication between the hepatic artery and the portal vein before the portal branches turn into the sinusoids.</u>

The difference in the effects of vasopressin and adrenaline is due to a difference of the action of the drugs on the arteriolar and capillary systems. When the splanchnic arterioles relax after adrenaline the blood-pressure is able to force blood through the capillaries, which may either dilate passively before the increased delivery of blood through the dilated arterioles, or they may conceivably undergo an active dilatation comparable to that observed by Hartman and his colleagues in 1929, in the capillaries of muscle when adrenaline is applied to them directly. In the case of vasopressin, since the

capillaries are actively constricted by the drug, the arterial pressure is prevented from having any appreciable effect on the portal pressure.

SUMMARY.

1. The portal venous pressure in cats averages about 80-100 mm water. It is maintained partly by the inflow through the mesenteric and hepatic arteries, and partly by a certain amount of tone at the outlet from the portal system.

2. These various components play a part in the vasomotor reactions occurring under the influence of adrenaline and vasopressin.

3. Adrenaline causes first a vasoconstriction of the ramifications of the portal vein in the liver, leading to a rise in portal pressure. A secondary rise occurs from an increased inflow of blood into the portal system through the hepatic and mesenteric arteries.

4. The initial venoconstrictor effect of adrenaline may not be seen in the failing preparation.

5. Vasopressin causes a fall in portal pressure by producing constriction of capillaries, the inflow into the portal vein being thus diminished. This effect is the same whether the drug is acting via the mesenteric or hepatic arteries.

6. The vasomotor reactions occurring between the hepatic artery and the portal vein in the liver are in all respects identical with the reactions occurring between the mesenteric artery and the portal vein. Indirect evidence suggests that the hepatic artery and portal vein are linked in the portal tracts by an arteriolar and capillary system.

Chapter 8.

THE PHYSIOLOGY OF THE PORTAL CIRCULATION.
(continued)

In the preceding chapter it was shown that adrenaline constricted the portal venous ramifications within the liver, thus confirming the views of others, e.g. Francois-Frank and Hallion, and Griffith and Emery, that the post-ganglionic splanchnic nerves passing into the liver carry constrictor fibres to the portal venules. In addition, it was shown that when the splanchnic arterioles dilated with the fall in arterial pressure after adrenaline injection, there occurred a secondary rise in portal pressure, due to increased inflow into the portal system.

It is desirable to know whether there is a parasympathetic supply having the converse effect of adrenaline and the sympathetic nerves on the hepatic vascular system. it was thought that acetylcholine might yield a clue to this problem, and the series of experiments detailed in this paper was therefore carried out, as a corollary to the work with adrenaline.

The work was carried out almost entirely on

cats under chloralose anaesthesia, and the dosage of acetylcholine ranged from 0.0005 to 0.5 mg for an average cat of three kilogrammes. The dosage and mode of administration of the drug is indicated in each tracing or its accompanying legend. The portal and vena cava pressures were recorded by water manometers connected to the stump of the splenic vein and the left renal vein respectively. The liver volume was recorded by a plethysmograph after the model devised by Griffith and Emery (1930). The flow from the inferior mesenteric vein was measured by a Condon's drop recorder. To record changes occurring in the stroke volume of the heart, a Henderson's glass cardiometer was used, connected to a tambour with a slack rubber membrane. As it proved difficult, and also unnecessary for the present purposes, to take records showing the diastolic heart volume, a side valve was provided on the connecting tube. In this way diastolic volume is not indicated in the cardiometric tracings, which only show the relative magnitude of the rapid change in volume which occurs in systole. In the cat it was found difficult to take more than three records of the type mentioned at any one time, but as the general

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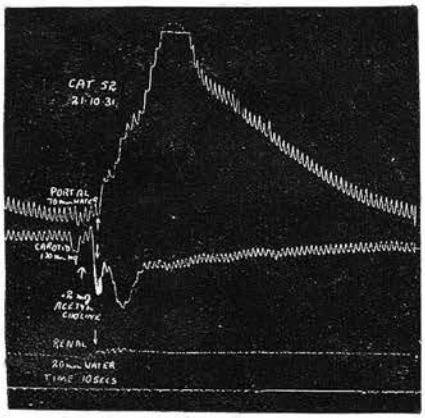

Fig. 84 Upper record: portal venous pressure. Middle record: carotid pressure. Lower record: vena cava pressure recorded from renal vein. Time record: 10 sec. At the first arrow 0·2 mg. acetylcholine was injected into the saphenous vein. The second series of three arrows indicates corresponding times about 6 sec. after the arterial pressure has begun to fall. At this time the portal venous pressure begins to rise, while little significant change occurs in the vena cava pressure.

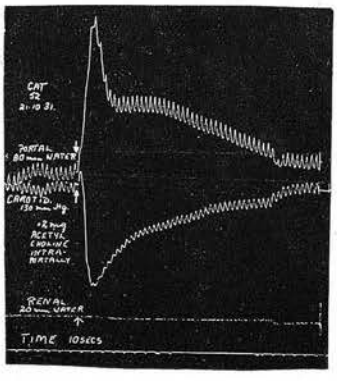

Fig. 85 Upper record: portal venous pressure. Middle record: arterial pressure. Lower record: vena cava pressure from renal vein. Time record: 10 sec. At the time marked by the arrows 0·2 mg. acetylcholine was injected intraportally. There is an immediate rise in portal pressure followed in a few seconds by a fall in arterial pressure. No significant change is seen in vena cava pressure.

nature of the changes did not vary, it is possible to piece the observations together into a composite picture, with some degree of certainty as to their value in relation to one another.

1. THE EFFECT OF LARGE DOSES OF ACETYLCHOLINE.

The injection of 0.2 - 0.5 mg acetylcholine into a systemic vein produces, as is well known, a marked fall in blood-pressure together with slowing of the heart. The portal pressure, after showing no change for some 5 to 6 seconds following the commencement of the drop in arterial pressure, then begins to rise (Fig.84). This rise in portal pressure is gradual during the first few seconds, and then it climbs more steeply, ultimately falling away as the arterial pressure returns to normal. The injection of a similar dose, or even of a somewhat smaller dose, directly into a mesenteric vein, invariably produces a steep rise in portal pressure, which occurs before any change is seen in the arterial pressure (Figs.85,86). It is probable therefore that the rise in portal pressure, caused by the injection of large doses of acetylcholine into systemic veins

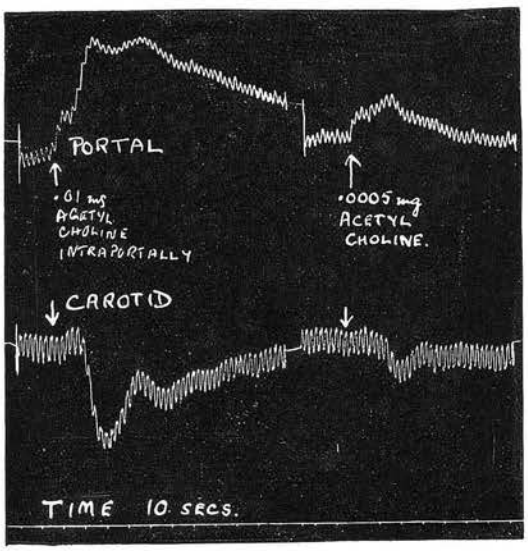

Fig. 86 Upper record: portal pressure. Lower record: carotid pressure. Time record: 10 sec. The intraportal injection of small doses is seen to bring about a rise in portal pressure, which results from a direct constricting effect on the vein.

is due to direct action on the portal vein, producing either constriction of the portal venous ramifications in the liver, or diminution in the calibre of the main trunk of the vein itself. Since there is no change in liver volume immediately after intraportal injection of the drug (Fig.89.) it is likely that the action is a general one on the musculature of the portal venous system. A somewhat similar effect was noted by Fleisch (1931), who observed that large doses of acetylcholine caused constriction of the mesenteric veins. Since this action is probably exerted directly on plain muscle, and is not related to the parasympatho-mimetic action of the drug, its nature will not concern us further in this investigation.

2. THE EFFECT OF SMALL DOSES OF ACETYLCHOLINE.

(a) The Portal Pressure Changes.

Doses of acetylcholine under one-fifth of a milligramme injected into a systemic vein produce a succession of changes in the portal pressure different from those described above. The first change takes place in the arterial pressure. (Fig.84.). This falls away steeply, while the portal pressure remains unchanged for some 6

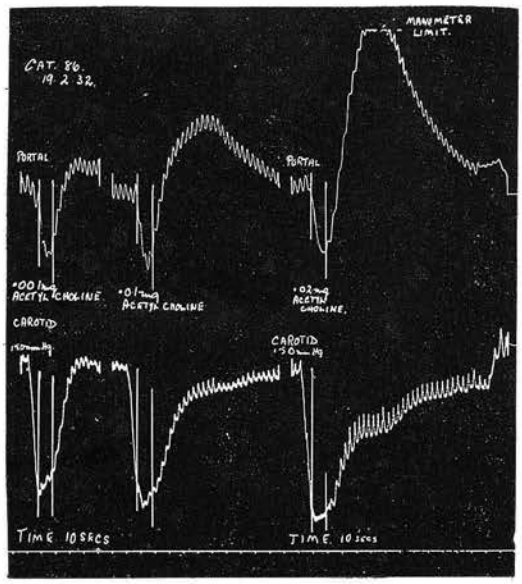

Fig. 87

Upper record: portal pressure. Lower record: arterial pressure. Time record: 10 sec. Three successive records from the same animal showing the effect of different small doses of acetylcholine into the saphenous vein. Vertical lines mark corresponding times. 0·001 mg. brings about a fall in portal pressure with a scarcely significant secondary rise. With increasing doses (0·01 and 0·02 mg.) the secondary rises become more marked.

seconds before it also begins to fall. As the cardiac slowing passes off it is followed by an acceleration of the heart beat above the normal for a few seconds. About this time the fall in portal pressure ceases, and is replaced by a rise. The extent of this rise is dependent upon the dosage of acetylcholine and the degree of the initial fall in blood pressure. With a dose of 0.02 mg. the blood pressure has fallen very considerably and the subsequent rise in portal pressure is correspondingly well-marked. With smaller doses of acetylcholine, the rise in portal pressure becomes less prominent.

Excluding general effects on the calibre of the portal vein as a whole, the cause of a fall in portal pressure may be either increased outflow or diminished inflow. In view of the work of Dale (1914), and the general acceptance of the hypothesis that acetylcholine dilates arterioles, thus causing an increased flow through these vessels into the veins, it was thought that the most probable cause of the initial fall in portal pressure would be increased outflow from the portal venous system. To investigate this possibility records were taken of the effect of these small doses of acetylcholine on the liver volume, and on the pressure in the vena cava.

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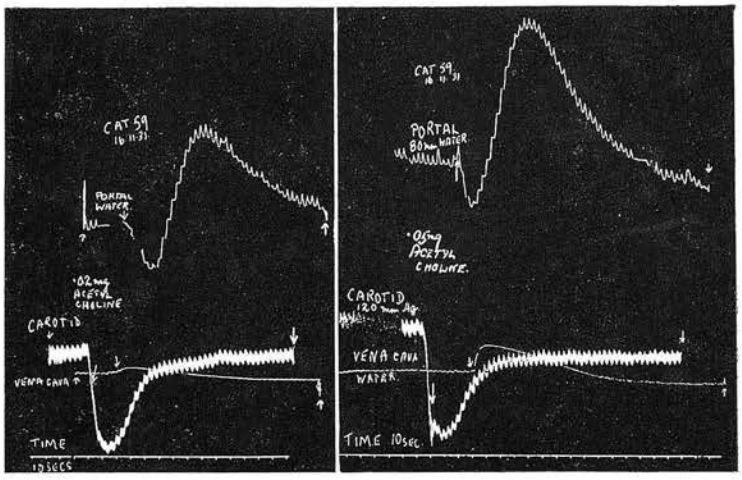

Fig 88

Upper record: portal pressure. Middle record: carotid pressure. Lower record: vena cava pressure. Time record: 10 sec. Note the abscissae marked by arrows on the right of each tracing. (*a*) 0·02 mg. acetylcholine into the saphenous vein. The portal pressure begins to fall 5 or 6 sec. after the arterial fall, and simultaneously (arrows) the vena cava pressure undergoes a very slight rise. (*b*) 0·05 mg. acetylcholine into the saphenous vein. The fall of arterial pressure is accompanied by marked cardiac slowing. Simultaneously (arrows) with the fall in portal pressure a distinct rise in vena cava pressure is seen.

(b) The effect of acetylcholine on liver volume and vena cava pressure. (See also section (g).)

With doses of acetylcholine ranging from 0.001 to 0.2 mg. the effect is constantly a diminution of liver volume (first part of fig. 98). This diminution in the size of the liver begins about 6 seconds after the arterial pressure has begun to fall, i.e. at the same time as the fall in portal pressure. Fig. 88 shows simultaneous tracings of arterial pressure, portal pressure and vena cava pressure. It is seen that, with smaller doses of acetylcholine (0.02 mg.), little change occurs in the pressure in the vena cava. Larger doses,however, cause a rise in vena cava pressure which occurs which occurs at the same time as the fall in portal pressure, and presumably also simultaneously with the diminution in liver volume. This rise in vena cava pressure is only present when cardiac slowing is marked. It was thought at first that this series of changes might be interpreted by assuming that acetylcholine exerted a dilator action on the hepatic vein, thus causing an

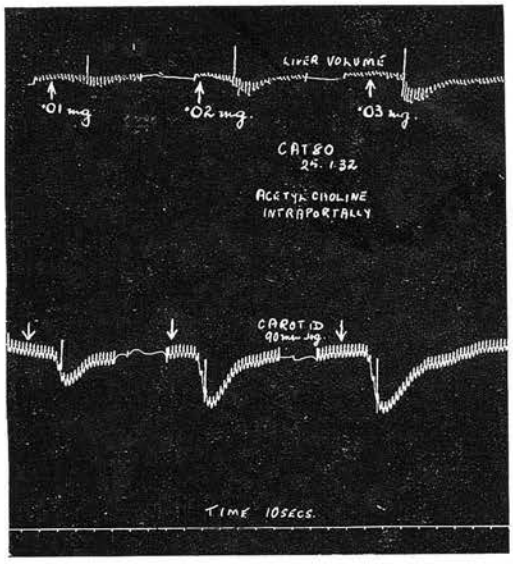

Fig. 89. Upper record: liver volume. Lower record: carotid pressure. Time record: 10 sec. Successive doses of 0·01, 0·02 and 0·03 mg. acetylcholine were injected intraportally. It is seen that no change occurs in liver volume until the fall in arterial pressure appears The diminution in liver volume is proportional to the degree of the fall in blood-pressure.

increased outflow from the liver lobules, with a consequent fall in the liver volume and portal pressure, and an increased inflow into the vena cava. This increased inflow into the vena cava would manifest itself as a rise in vena cava pressure, only in the presence of cardiac slowing: otherwise the heart would be able to deal with the increased delivery of blood quite efficiently, and the vena cava pressure would remain unaltered. Experiments carried out to test this hypothesis, however, showed that it was incorrect.

The invalidity of the assumption was at once proved by the experiment illustrated in Fig. 89. If acetylcholine dilated the hepatic veins, we should be able to demonstrate a fall in liver volume by the injection of a suitable dose into the portal system, and this diminution in volume should precede any effect on the general systemic circulation. As the illustration shows, this postulate is not fulfilled. No alteration in liver volume occurs until the arterial pressure has fallen, and further, the diminution in liver volume appears to be dependent upon the extent of the fall in blood-pressure.

The true explanation of the initial fall in portal pressure, and of the concomitant diminution

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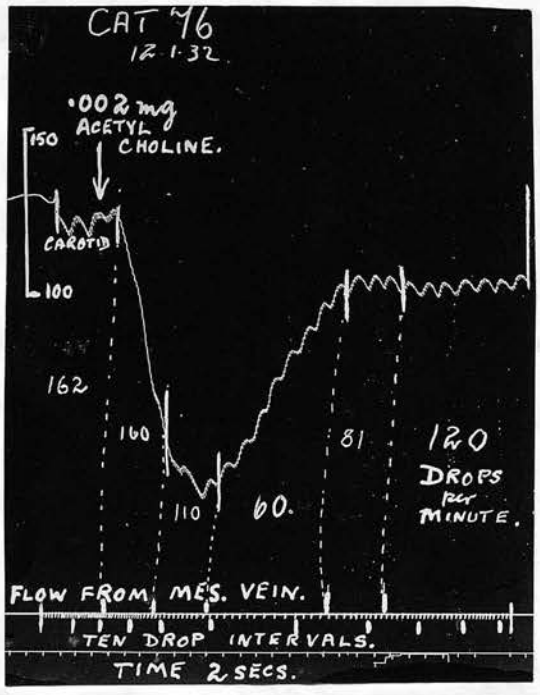

Fig. 90 Upper record: carotid pressure. Lower record: flow from a mesenteric vein in drops. Time record: 2 sec. Average rates are given in each marked interval. At the arrow 0·002 mg. acetylcholine was injected into the saphenous vein. During the first 6 sec. there is little change in the rate of flow. A distinct slowing then makes its appearance. When the arterial pressure begins to rise the slowing becomes still more marked, and the flow only begins to increase again when the blood-pressure approaches the normal level.

of liver volume, is therefore to be sought in the changes which occur in inflow rather than in alterations of the outflow from the portal system.

(c) The Flow of Blood through the Splanchnic Arterioles under the influence of acetylcholine.

Fig. 90 shows the type of result constantly obtained when the flow from a mesenteric vein is measured under the influence of acetylcholine. During the first 6 seconds after the arterial pressure begins to fall, there is little change in the rate of flow. A distinct slowing then makes its appearance, and becomes most marked about the turning point of the arterial pressure curve. As the pressure rises the slowing continues to be pronounced, and as the pressure reaches a level approaching its original height, the rate of flow again returns almost to its original rate. Thus the initial fall in portal pressure which occurs with acetylcholine appears to be dependent on diminished inflow into the portal system through the splanchnic arterioles.

This result was at first surprising, in view of the opinions generally held as to the action

of acetylcholine. It must be remembered, however, that the observations from which conclusions were reached regarding the action of the drug on the arterioles, were not as a rule made on the intact animal, but on isolated perfused organs and tissues. This finding does not therefore in any way invalidate the classical work on the vasodilator action of the "vagus-substance". It is of interest in passing to note the difficulty which Reid Hunt (1914) found in accepting the work of Dale (1914). The former writer was unable to detect vasodilatation with acetylcholine, and found himself forced to explain the fall in blood-pressure by diminished cardiac output.

Accepting the view, which has been amply proved by other workers, that acetylcholine dilates arterioles, we have two possible explanations for the diminished inflow into the portal system in the intact animal. The first is, that the vasodilatation may be more marked in the limb vessels, and the second, that the cardiac output may be diminished during the first stage of acetylcholine action.

(d) <u>The Flow of Blood through the limb vessels under Acetylcholine.</u>

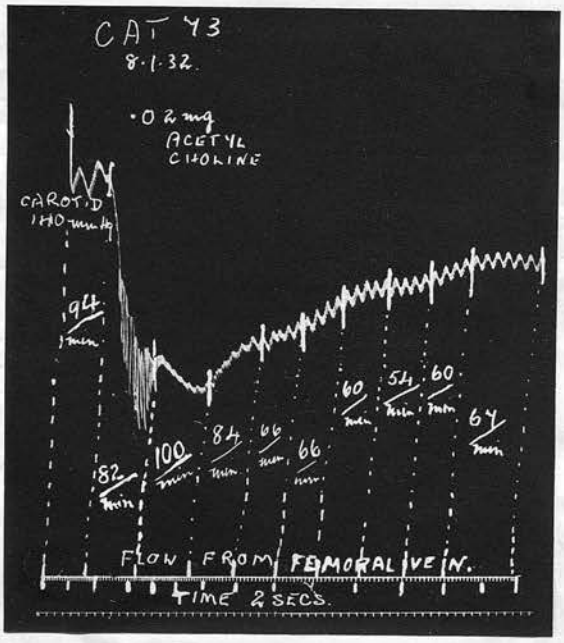

Fig. 91 Upper record: carotid pressure. Lower record: flow from femoral vein in drops. Time record: 2 sec. Following the injection of 0·02 mg. acetylcholine into the jugular vein the blood-pressure falls, and marked cardiac slowing occurs. During the stage of cardiac slowing, there is a diminution of the flow from the femoral vein. When the bradycardia passes off the flow is increased but is later diminished during the recovery of the blood-pressure.

Fig. 91 shows the flow of blood from the femoral vein under the influence of acetylcholine. During the stage of cardiac slowing the flow is somewhat diminished. As soon as this stage has passed off, however, a distinct acceleration of flow above the normal level is seen, which gives way to a slowing as the pressure begins to rise again. It appears then that the cardiac output must be diminished during the stage of cardiac slowing, since there is no acceleration of the flow either in the splanchnic area or in the limbs. The subsequent acceleration which occurs in the flow from the femoral vein indicates, however, the persistence of vasodilatation in the limbs until the pulse rate has begun to recover. Even in the intact animal, therefore, we find evidence of vasodilatation in the limbs, although this is masked by the diminution in cardiac output during the stage of cardiac slowing. In the intact animal there is no such evidence of vasodilatation in the splanchnic area, so that if such exists, it must be less marked than that which we have found in the extremities.

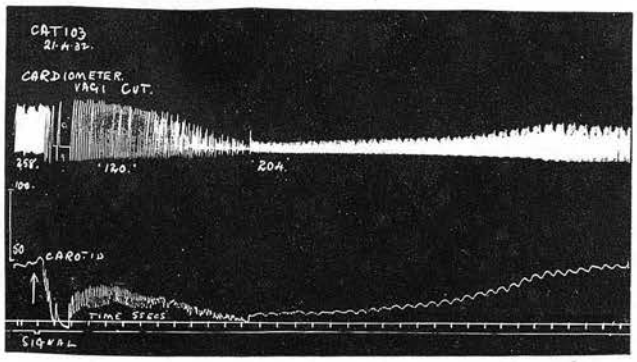

Fig. 92 Upper record: cardiometer. Lower record: carotid pressure. Time record: 5 sec. At the first arrow 0·2 mg. acetylcholine was injected. With the fall in blood-pressure, the heart is slowed from 258 to 120 per min., and the amplitude of each beat is increased. For a few seconds the heart beat becomes irregular, and at this stage the output per beat is markedly diminished. The blood-pressure then begins to recover, and the output per beat gradually returns to normal.

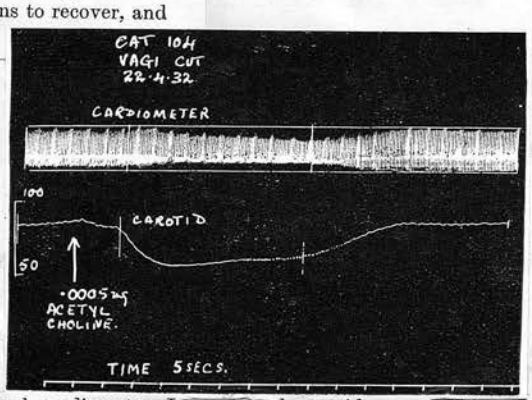

Fig. 93 Upper record: cardiometer. Lower record: carotid pressure. Time record: 5 sec. At the arrow 0·0005 mg. acetylcholine was injected. This dosage is insufficient to produce cardiac slowing. As the blood-pressure falls the cardiac output becomes diminished, and increases again as the pressure rises.

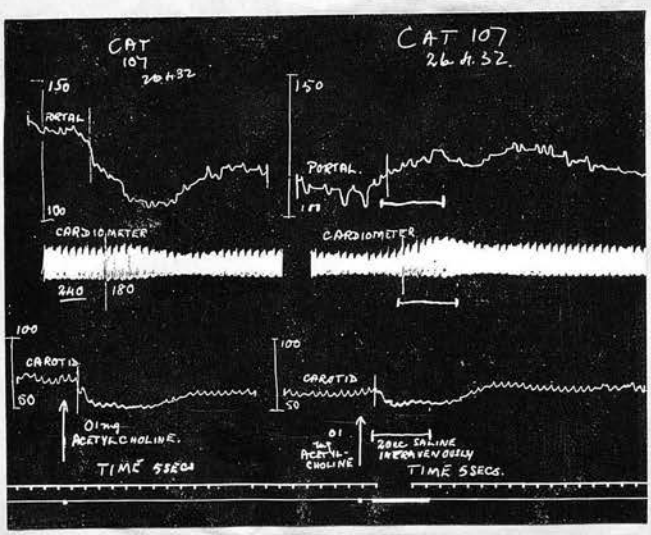

Fig. 94. Upper record: portal venous pressure. Middle record: cardiometer. Lower record: carotid pressure. Time record: 5 sec. At the arrow, 0·01 mg. acetylcholine was injected into the saphenous vein. The heart rate is slowed from 240 to 180, and as the slowing passes off, a diminution in output becomes evident. The fall in portal pressure corresponds to the stage of cardiac slowing with diminished cardiac output. The experiment was repeated with the injection of 20 c.c. saline into the circulation immediately after the acetylcholine injection. The cardiac output was raised with a corresponding rise of portal pressure.

(e) The Cardiac output under Acetylcholine.

The output of the heart under this drug may be influenced in various ways. The slowing of the heart itself may diminish the minute volume, although the stroke volume may be increased. Secondly we have the effect of peripheral vasodilatation in increasing the capacity of the muscular system, so that less blood returns to the heart, and its output is diminished.

Regarding the first possibility there can be no reasonable doubt. We have mentioned the evidence of diminished cardiac output in discussing the changes in flow through the limbs during the stage of cardiac slowing. There is also evidence of it in the rise in vena cava pressure, which has already been noted to occur, only when the cardiac slowing is marked (Fig.88). With the vagi cut to accentuate cardiac slowing from acetylcholine, the cardiometer shows an increased output per beat which, however, is insufficient to maintain the normal minute volume (Fig.92).

The second factor, i.e. increased capacity of the vascular system, is one which plays a special part in the failing preparation in which there is a condition of oligaemia. The volume of

the circulating blood is diminished, and vasodilatation in the periphery further diminishes the return of blood to the right heart, with resultant diminution in cardiac output independent of slowing (Fig.93). In the failing preparation the effect of acetylcholine on the portal circulation is modified, and the fall in portal pressure becomes the predominant feature, while the secondary rise is usually absent (Fig.94). The reason for this will be discussed later (p.). Under these conditions the portal pressure fall is seen to follow closely the diminution in cardiac output, and the portal fall is abolished when the cardiac output is artificially maintained.

Thus we see that the fall in portal pressure which occures after the injection of acetylcholine, is dependent on two factors: a predominance of vasodilatation in the limbs deflecting blood away from the splanchnic area, and diminished cardiac output.

(f) <u>The State of the Splanchnic Arterioles under Acetylcholine.</u>

Since we have detected no increase in the flow through the mesenteric arterioles, and since the portal pressure falls and the liver volume

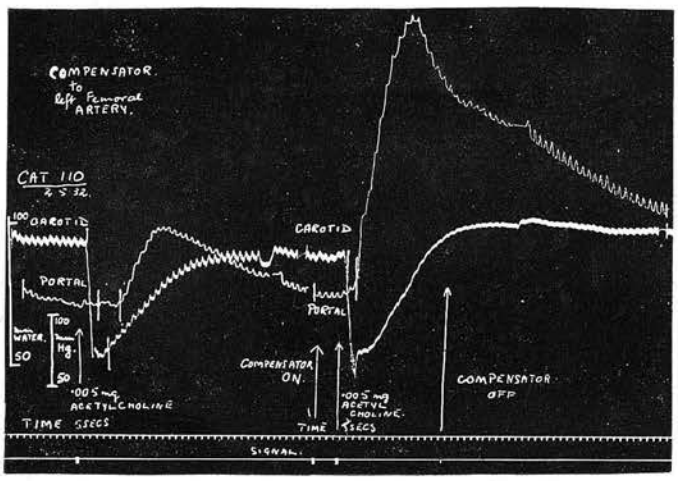

Fig. 95

Upper record: carotid pressure. Lower record: portal pressure. Time record: 5 sec. Bayliss compensator attached to the femoral artery. Acetylcholine (0·005 mg.) was injected into the saphenous vein. The usual fall in portal pressure is not evident, but after a delay a secondary rise is seen. With the compensator in the circuit, a marked rise in portal pressure begins immediately the carotid pressure starts to fall.

diminishes under acetylcholine, the assumption that the splanchnic vessels are dilated would be mere surmise. With a diminished flow through the splanchnic vessels in the presence of diminished cardiac output, these vessels may be dilated, contracted, or unaltered in calibre. If we could maintain the amount of blood in the arterial system at a constant level, vasodilatation in the splanchnic area, if present, should be demonstrable.

One way in which it would come to light, would be by an immediate rise in portal pressure as soon as the arterial effect of acetylcholine had manifested itself. These conditions can be achieved by the use of the Bayliss (1908) compensator. Fig.95 shows the effects of acetylcholine under these conditions. There is a prolonged delay, instead of a slight fall, in the first record of portal pressure under acetylcholine, and then the secondary rise is seen as usual. With the compensator in communication with the circulation, the effect is an immediate and pronounced rise in portal pressure at the moment when the arterial pressure begins to fall. The compensator was attached to the femoral artery, and under these conditions, tracings may not show the initial fall in portal pressure as one hind limb is out of the circulation and its function in deflecting blood from the splanchnic

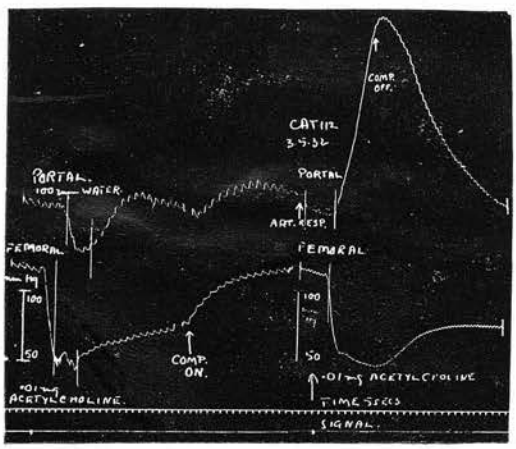

Fig 96. Upper record: portal venous pressure. Lower record: arterial (femoral) pressure. Time record: 5 sec. Bayliss compensator attached to carotid artery. Following the injection of 0·01 mg. acetylcholine a fall in arterial pressure is accompanied by a fall in portal pressure. With the compensator in communication with the circulation, a rise of portal pressure is seen as soon as the arterial pressure begins to fall, with the same dose of acetylcholine.

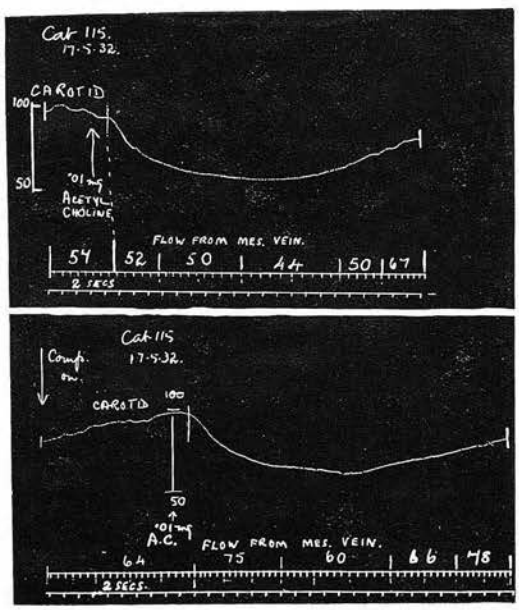

Fig 97. In both tracings: Upper record: carotid pressure. Lower record: flow from a mesenteric vein (in drops). Time record: 2 sec. Compensator attached to femoral artery. In the upper record 0·01 mg. acetylcholine injected into the saphenous vein brings about a fall in blood pressure with a concomitant diminution of flow through the mesenteric vessels. A few minutes later, with the compensator in communication (lower record), a similar dose of acetylcholine is followed by an immediate acceleration of the flow, with slowing later.

area is in abeyance. When, however, the compensator is attached to the carotid artery (Fig.96) the initial fall in portal pressure is still seen.

With the compensator in communication with the circulation, the fall in portal pressure is replaced by an immediate rise, beginning as soon as the arteriolar dilatation is evidenced by the drop in arterial pressure.

Fig.97 shows the effect of compensation on the flow through the mesenteric arterioles. The upper tracing shows the usual slowing of the flow as already described (Section c.). With the compensator communicating with the femoral artery, the initial slowing is converted into an increased rate of flow. There is no doubt, therefore, that the splanchnic arterioles are dilated by acetylcholine, and, when the arterial system is kept filled artificially, that they can transmit an increased amount of blood to the portal system, thus causing a rise in portal pressure.

The diminution in liver volume which was described in section (b) is due to diminution in the flow through the splanchnic arterioles. As in the reversal of the effects of acetylcholine on portal pressure and on flow from the mesenteric veins, the compensator also reverses this action on liver

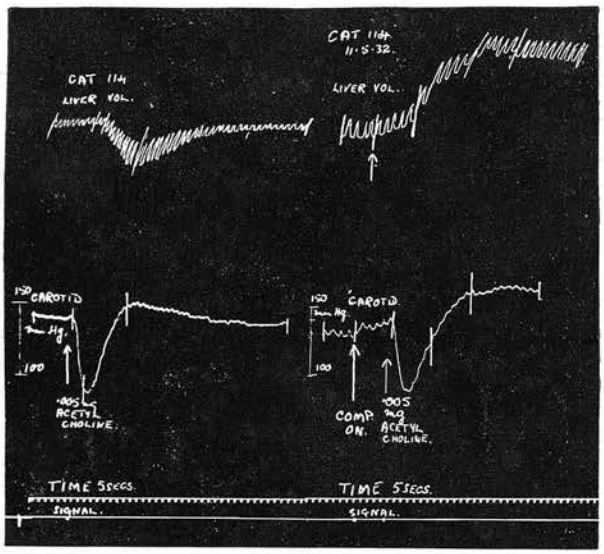

Fig. 98 Upper record: liver volume. Lower record: carotid pressure. Time record: 5 sec. Compensator attached to the femoral artery. 0·005 mg. acetylcholine into the saphenous vein gives a diminution of the liver volume beginning about 6–8 sec. after the fall in arterial pressure. The compensator is then connected to the circulation and, instead of diminishing, the liver increases in volume along with the fall in arterial pressure.

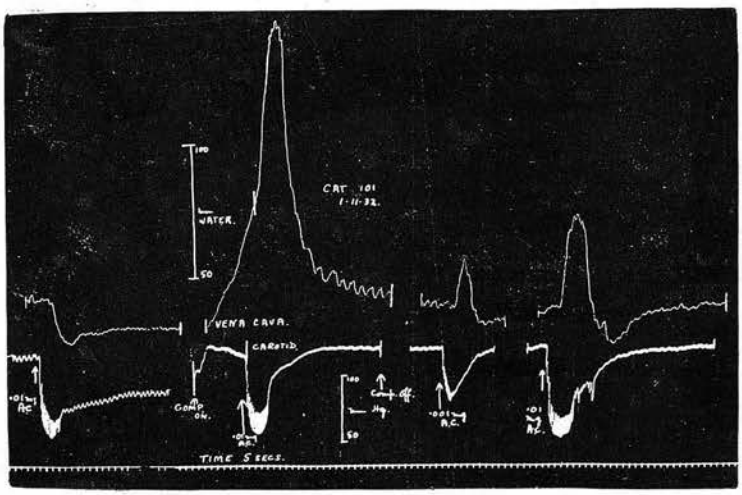

Fig. 99 Upper record: vena cava pressure. Lower record: carotid pressure. Time record: 5 sec. With the injection of 0·01 mg. acetylcholine a fall of vena cava pressure occurs. The arterial pressure does not recover in the usual manner. The compensator is then put into communication with the circulation, and a restoration of blood-pressure with a rise of vena cava pressure results. 0·01 mg. acetylcholine then causes a sudden and steeper rise in vena cava pressure, which ultimately returns to a normal level with the recovery of blood-pressure. The compensator is then excluded from the circulation and different doses of acetylcholine then produce rises in vena cava pressure which only last as long as the cardiac slowing.

volume. Instead of undergoing a shrinkage, the liver is seen to swell (Fig. 98).

(g) GENERAL VENOUS PRESSURE EFFECTS.

In Section (b), preliminary mention was made of the effects of acetylcholine on vena cava pressure. A rise in vena cava pressure is only seen in the presence of pronounced cardiac slowing. Slowing of the heart alone, however, is not sufficient to determine a rise in pressure in the vena cava, as can be seen from the first curve in Fig. 99. In this particular preparation, the volume of the circulating blood had to be increased before the rise in vena cava pressure became evident. Cardiac slowing then determined the extent and duration of the rise. With a slight degree of slowing, the rise of vena cava pressure was slight, and with more marked bradycardia the rise became correspondingly higher and more prolonged.

When the blood pressure falls with acetylcholine, the first effect of the compensator is to pour more fluid into the circulation. If cardiac slowing is present this excess of fluid brings about a rise of vena cava pressure. When theslowing passes off and the heart in consequence becomes more efficient, the excess of fluid is removed from the venous side of the circulation and the venous pressure falls (Fig. 100).

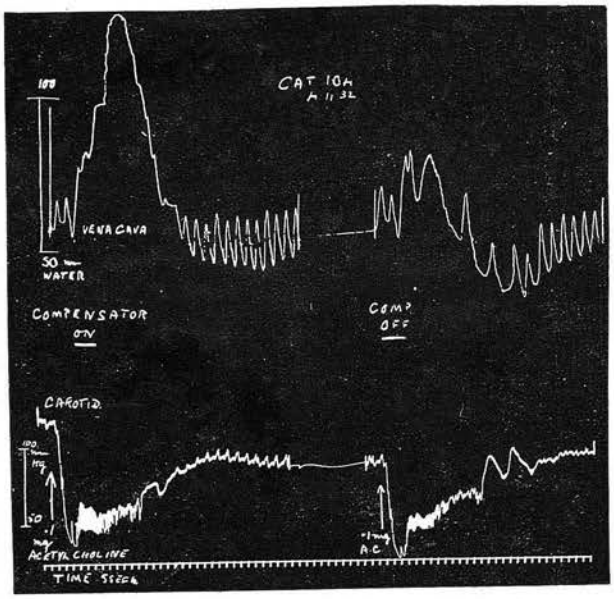

Fig. 100 Upper record: vena cava pressure. Lower record: carotid pressure: Time record: 5 sec. With the compensator in communication with the circulation 0·1 mg. acetylcholine was injected into the saphenous vein. During the stage of cardiac slowing, a pronounced rise of vena cava pressure is seen. When the compensator is excluded from the circulation this rise of vena cava pressure does not occur.

It is unlikely that these general venous pressure effects could take place without some influence on the portal pressure. If we take the initial portal pressure fall and correlate it with the changes of inflow which occur at the same time, we find that the inflow is reduced on an average (four experiments) from 136 to 99 drops per minute. The volume flow through the portal vein must be diminished in the same proportion. The initial portal pressure fall is about 20mm water as a rule, i.e. from 80 mm down to 60 mmwater. By Poiseuille's law, volume flow through narrow vessels

$$V = \frac{\pi r^4}{8\eta} p,$$

where r is the radius of the blood vessel, η the coefficient of viscosity of the fluid (blood), and p the pressure. With small doses of acetylcholine we have not found any evidence of change in calibre (r) of the portal venules within the liver, and the viscosity of the blood (η) presumably remains unaltered, so that

$$V = p K, \quad \text{or} \quad V \propto p.$$

A diminution of the volume flow from 136 to 99 would, therefore, account for a drop in portal pressure from 80 to 58 mm water. This approximates nearly to the fall of 20 mm water which was observed in the experiments.

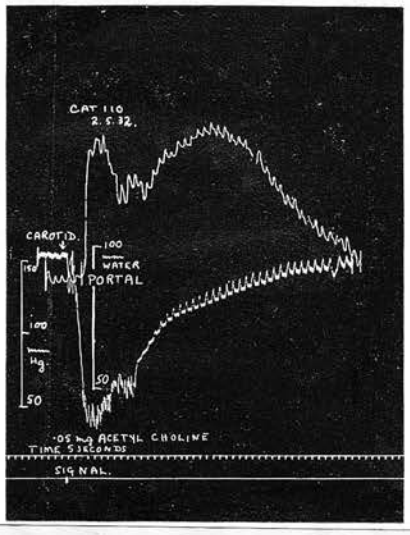

Fig. 101 Upper record: carotid pressure. Lower record: portal pressure. (Tracings subsequently cross.) Time record: 5 sec. Plethora had been induced by means of the injection of gum saline. Acetylcholine then brings about a rise of portal pressure in place of the usual fall.

With the compensator communicating with the circulation (Figs. 95, 96), the initial rise in portal pressure may amount to 70-100 mm water, and yet the only increase of inflow that could be detected was from 64 to 75 drops per minute (Fig. 94). This would account for a rise of portal pressure of only 15 mm water. It would appear probable, that the rise in general venous pressure produced by the use of the compensator with acetylcholine (Fig. 100), is responsible for the remainder of the rise in portal pressure.

From the same argument, part of the increase in liver volume brought about by the compensator, is probably due to the rise of pressure in the vena cava.

As shown in Fig. 99, when the vascular system has been overfilled following the use of the compensator, acetylcholine may continue to cause an initial rise in vena cava pressure: in the same way a rise in portal pressure may also be brought about (Fig. 101). This rise takes the place of the usual fall in portal pressure and is followed by a secondary rise.

It is thus seen that acetylcholine in the presence of plethora of the circulation may bring about a rise in general venous pressure in which the portal system shares. The type of curve then produced (Fig. 101) is mentioned particularly, as it was occasionally seen in cats (2 out of 70) where there had

been no artificial overfilling of the vascular system. In three experiments carried out in dogs, this type of portal pressure response to acetylcholine was present in all.

(h) THE SECONDARY RISE IN PORTAL PRESSURE.

In all animals where the circulatory conditions were good, and the blood pressure well maintained, a well-marked secondary rise in portal pressure was seen following the injection of acetylcholine. This rise begins when the arterial pressure is beginning to recover, and, generally speaking, the deeper the trough of arterial pressure and the steeper the subsequent rise, the more pronounced the secondary rise in portal pressure (Fig:87).

The fact, seen from the records of outflow from the mesenteric vein (Fig.90), that the portal pressure is rising when the inflow is markedly diminished, renders it obvious that the secondary rise in portal pressure must take place by a diminution of outflow from the portal system. It has also been noted that the cardiac slowing, brought about by acetylcholine, is often followed by a period of increased pulse-rate above the original level. These observations led to the thought that the sympathetic might

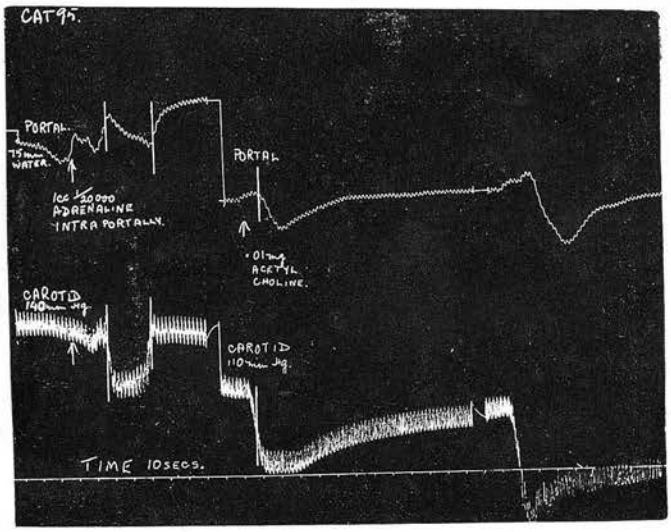

Fig. 102 Upper record: portal pressure. Lower record: carotid pressure. Time record: 10 sec. Following the administration of 20 mg. ergotoxine, 1 c.c. 1/20,000 adrenaline intraportally causes little significant change in the portal pressure, and, a few moments later, a falling carotid pressure results. Acetylcholine then brings about a fall in carotid pressure with gradual recovery and a fall in portal pressure with no secondary rise.

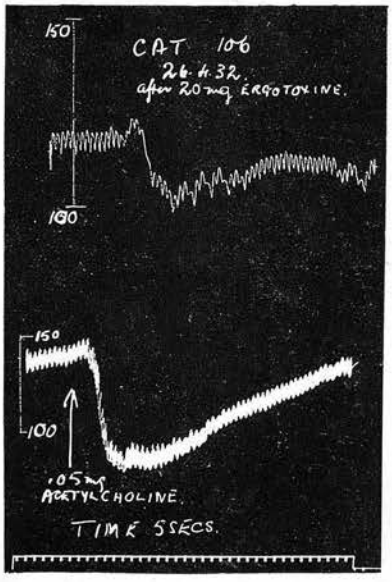

Fig. 103 Upper record: portal pressure. Lower record: carotid pressure. Time record: 5 sec. After 20 mg. ergotoxine the reaction to adrenaline had been reversed. 0·05 mg. acetylcholine brought about a fall in arterial pressure followed by a fall in portal pressure. The recovery of the arterial pressure takes place at a uniform slow rate and there is no secondary rise in portal pressure.

play a part in the recovery of blood pressure following its depression by acetylcholine. This hypothesis was put to the test by the use of ergotamine and ergotoxine to paralyse the sympathetic. Fig. 102 shows the result of this procedure.

It is seen that when the sympathetic is paralysed, the heart beats more slowly as a result of some loss of sympathetic tone. The injection of adrenaline into the portal system no longer leads to the immediate rise in portal pressure which would result with an intact sympathetic system. No significant change is seen in the portal pressure, (? no sympathetic dilator fibres), and the action of adrenaline on the arterial system is to bring about a fall in pressure. The injection of acetylcholine into the animal then brings about the usual fall in arterial pressure, accompanied by a fall in portal pressure analogous to the initial fall in the intact animal. The recovery from the depression of the arterial pressure is slow and gradual, while the secondary rise in portal pressure is absent. The conditions in this animal, and in that illustrated in Fig. 103, are such that a secondary rise of portal pressure might have been anticipated.

In the preceding chapter, it was pointed out that the splanchnic vessels in the failing preparation

were in a condition of greatly increased tone, which accounted for the absence of any further contraction with adrenaline. In particular, the adrenaline rise in portal pressure normally resulting from the constriction of the portal ramifications within the liver was absent. It is probable that the absence of the secondary rise of portal pressure in the animal with a failing circulation is due to the same circumstance. (See Fig.94)

The evidence therefore suggests that the secondary rise in portal pressure after acetylcholine is dependent on the integrity of the sympathetic system. When this is thrown out of action by ergot, the rise does not take place. The secondary rise does not occur when the sympathetic tone has been increased as a result of a failing circulation. It is also to be noted that in the animal with paralysis of the sympathetic system, the rate of recovery of the arterial pressure from the acetylcholine depression is slower than in the animal with normal circulatory reactions, such as that in Figs 87, 88. The recovery rate is also slow in the presence of a failing circulation. The association of the period of rapid recovery (Fig.90), with a diminution of flow through the splanchnic arterioles, is evidence of splanchnic vasoconstriction

at this stage. All these points are in favour of the hypothesis that the sympathetic plays a part in the recovery of the blood pressure after acetylcholine. Depending on the degree of sympathetic stimulation elicited, so does the secondary rise in portal pressure vary in extent.

Thus acetylcholine resembles adrenaline in calling out the opposing autonomic mechanism at the height of its action. Reflex vasodilatation and cardiac slowing are elicited at the point of maximum adrenaline effect. Acetylcholine at its point of maximum activity calls forth cardiac acceleration and splanchnic vasoconstriction.

DISCUSSION.

The results obtained in this investigation add some confirmatory evidence to the view of Griffith and Emery (1930) that the vagus nerve does not carry vasomotor fibres to the liver. These observers stimulated the vagus nerve, avoiding cardiac inhibition, and found no change in liver volume. The experiment described in Fig.102 would indicate, too, that as far as the portal vein is concerned, there are no sympathetic dilator fibres. The vasodilator reflexes in the liver obtained by Griffith and Emery were shown to be mediated through the splanchnics, and it is proba-

ble that any dilator reaction which occurs in the portal venules must be due to inhibition of vasoconstrictor tone.

Effects similar to those resulting from the intravenous injection of acetylcholine were obtained by Carnot, Gayet, and Merklen (1930), by stimulation of the vagus. They found an initial fall in portal pressure, which they ascribed to diminished inflow into the portal system, and a rise of portal pressure, which occurred as the arterial pressure recovered.

So far as the cat is concerned, there are anatomical reasons brought forward by Popper (1931) which indicate that the "Lebersperre" mechanism described in the dog by Mautner and Pick, and by Bauer, Dale, Poulsson and Richards (1932) is absent. In the dog, the muscular coat of the hepatic vein is much better developed than that in the cat or the human subject. Dale and his colleagues did not find any clear evidence of vagus control of the liver circulation nor did they record any significant results following the injection of acetylcholine. Grab, Janssen and Rein (1929-30) showed an increase rate of flow through the liver with atropine. Inflow and outflow were simultaneously increased, and thus there

is no reason to assume any immediate vagus effects upon the liver circulation. Such effects as are observed are entirely secondary to alterations in the general circulation.

In the experiments detailed in this and in the preceding chapter, outflow from the liver has not been measured directly. All the vasomotor reactions which we have obtained have been satisfactorily accounted for by the demonstrable changes in the circulation through the splanchnic vessels and the portal vein. In none of the experiments has there been any evidence of a controlling mechanism at the outlet of the liver lobule. This is in complete agreement with the observations made by Dale and his collaborators on the liver of the cat.

SUMMARY.

I. Large doses of acetylcholine bring about a rise in portal pressure by constricting the portal vein.

II. (1) With smaller doses of acetylcholine there is no direct constricting action on the portal vein. Two phases are usually seen in the portal pressure curve, viz. an initial fall, and a secondary rise of pressure.

(2) The initial fall in portal pressure is determined by diminished inflow into the portal system, due

to the predominance of vasodilatation in the limbs, and to diminished cardiac output.

(3) The diminished flow through the splanchnic arterioles, and the consequent fall in portal pressure, can be reversed by the Bayliss mercury compensator.

(4) During the stage of cardiac slowing, the general venous pressure may rise. This rise is exaggerated in animals which have been rendered plethoric; in such animals the portal pressure may rise in parallel with the general venous pressure, and the initial portal pressure fall is not seen.

(5) The secondary rise in portal pressure is due to constriction of the portal venules within the liver by the action of the sympathetic. It is absent when the sympathetic has been paralysed by ergot, and in the presence of a failing circulation.

III. There is no evidence of any parasympathetic dilator action on the portal or hepatic venules. The experiments with ergot also yielded no evidence of sympathetic dilator fibres to the portal vein.

Chapter 9.

THE PATHOGENESIS OF HEPATOLIENAL FIBROSIS.

In this chapter we shall sum up the findings of the preceding pathological and physiological observations and attempt to correlate them in a hypothesis of the pathogenesis of hepatolienal fibrosis.

Hepatitis is probably present to some degree in every case of the disease. During the stage of acute hepatitis, inflammatory products are carried from the liver by the lymph stream. These inflammatory products, which may be substances liberated by the breakdown of liver cells or in some instances possibly bacterial toxins, are carried by the thoracic duct to the blood stream. If they are present in sufficient amount for an adequate time, the spleen enlarges to deal with them. Under these circumstances cellular proliferation occurs in the spleen and various types of proliferative change may be seen. It is this hyperplasia of the spleen which is responsible for the great splenic enlargements (over 500 grammes) which are so often met with in association with hepatic disease. In short, the spleen acts as the lymph-gland of the liver.

The pure proliferative type of splenic enlargement is unusual in chronic hepatitis, and usually

there are superadded the effects of portal congestion. The effects of portal congestion may be seen in many cases where there are no gross evidences of liver disease, and certainly no evidences of scar tissue formation.

If we accept as a working hypothesis that portal hypertension may occur in the early stage of hepatic disease, we can account for all the anatomical manifestations in the spleen, (except enlargement), and in the portal vein, in a reasonable manner, and we can also correlate them with the clinical manifestation of haematemesis and bleeding from parts of the alimentary canal other than the stomach. How are we to explain portal hypertension in the early stage of hepatitis without invoking scar contraction, distortion and the other features of the grossly developed disease?

There are many possibilities to be discussed, and the vascular changes of hepatitis are but little known. The possibilities appear to be obstruction of the hepatic veins, obstruction of the sinusoids, and obstruction of the portal vein itself.

Gross obstruction of the hepatic veins by thrombosis is a rare occurrence in hepatic cirrhosis. It may occur as a separate condition when it gets the

name "Chiari's disease". Spasm of the hepatic veins is a possibility which must be considered in view of the work of Dale, Manwaring, and Mautner and Pick. These workers have shown that in the dog the musculature of the hepatic vein is particularly well developed, and responds to the injection of histamine, and to peptone by a powerful contraction. By this means the portal pressure may be raised very considerably.

It would therefore be conceivable that protein breakdown products liberated from the damaged liver cells might stimulate the muscular elements of the hepatic veins to contract. This, however, is an unlikely possibility for two reasons. The first is the anatomical nature of the hepatic veins in man which, in common with those of the cat, show very poor development of the muscular tissue (Popper). As a physiological parallel with the anatomical state of the veins, those of the cat do not respond to histamine and peptone in the same way as those of the dog. (Bauer et al.). By analogy those of the human subject would also, in all probability, fail to respond to this stimulus. Secondly, when contraction of the hepatic veins occurs, it is ac-

companied by a profound fall in the blood pressure, due to the damming back of large amounts of blood in the liver, spleen and portal area. Such a fall in blood pressure accompanied by swelling of the liver, is, as far as the writer is aware, unknown in liver disease of the human subject.

The second possibility is obstruction of the sinusoids. This appeared to be a possible result of swelling of the liver cells which is a common feature of degeneration and necrosis of these cells. In the course of a prolonged series of experiments on cats in which the portal pressure was measured, one animal was encountered, accidentally, in which marked fatty degeneration of the liver cells was present. The portal pressure in this animal was normal, while histologically the liver cells were definitely swollen beyond the normal size from the amount of fat with which they were infiltrated. Our observations on the degenerated livers of experimental rabbits have never shown an obliteration of the sinusoidal channels by the swollen cells. The liver is capable of considerable distension (cf. the cardiac failure liver), and swelling of the cells of an organ could only obstruct its circulation if the capsule were rigid and undistensible.

The portal circulation may be obstructed by spasm of the venules at the point where they turn into the lobules. The veins at this point have been shown to be supplied with sympathetic fibres, and respond to sympathetic stimulation and to adrenaline. It has also been shown that dilatation of the hepatic artery causes an increased amount of blood to flow into the portal system via the hepatic capillaries which communicate with the portal vein as well as with the hepatic sinusoids. (chapter 7.).

Pathologically, hepatitis probably has as one of its manifestations the condition of vascular dilatation which is common to all inflammationsmin other areas. In fully developed cirrhosis it is well known that the connective tissue bands representing the portal tracts are very vascular. The increased vascularity in the connective tissue results from the development of new capillaries in the young proliferating connective tissue.

The development of new capillaries is, of course a later stage of the inflammatory process. In the early stages of the process, the condition in the portal tracts may be vascular dilatation only; this would lead to raised pressure in the portal system. (chapter 7.)

The possibility that local vascular spasm may occur in hepatitis has been recently raised by Beneke (1932). He reports a case of acute yellow atrophy of the liver in which there was present endarteritis obliterans of the smaller branches of the hepatic artery, associated with a similar obliterative process in the hepatic veins. He points out that this change may result from diminished flow through the arteries (cf. the uterine arteries after parturition), and invokes spasm of the arteries as the ultimate cause of the degenerative changes in the liver.

Beneke also indicates the fact that there is a pronounced individual susceptibility of the liver to such poisons as trinitrotoluene and cinchophen,(or atophan). So far as the latter poison is concerned, some individuals have been reported (Beaver and Robertson, 1931) who have developed hepatitis after a total dosage of one gramme, while others may take as much as 480 gms without the slightest sign of trouble. In the acute cases the onset of acute yellow atrophy is sudden and massive, and the lesions resemble those produced by occlusion of the hepatic artery. It is suggested that the hepatic damage is not caused so much by the direct action of the toxic agent on the hepatic cells, as by

a reflex spasm of the vessels to the liver in individuals with a predisposition to angiospasm.

The bases of this argument appear to be somewhat loose, for one may equally well presuppose an individual susceptibility of liver cells as a special irritability of vessels. It is none the less interesting that Beneke should feel compelled to postulate vascular spasm within the liver by one process of argument, while the writer should reach its consideration by another.

Although raised portal pressure could be accounted for to some degree by local vasodilatation within the liver, such a rise of pressure would not be very high, and would probably be insufficient to cause large haemorrhages in the spleen and stomach. Local spasm of the portal venules must be kept in mind as a possible accompaniment of some forms of hepatitis. Beneke thought that spasm of the hepatic arteries might be a reflex mechanism via the splanchnic nerves. In such a case the portal venules would be involved as well, having the same vasomotor nerve supply.

The writer would not go so far as to ascribe to vascular spasm within the liver a causal role in hepatitis. In some cases, as we have seen, the local venous changes have been absent. It is quite

conceivable that local vascular spasm may occur as protective mechanism to shield the liver from noxious substances carried to it by the blood stream. We have as yet no direct evidence of portal hypertension in these cases of early hepatitis, but the evidences in favour of its presence are exceedingly strong. Just as we have to postulate coronary arterial spasm to account for anginal pain without local vascular lesions, we feel compelled to postulate that in many cases of hepatitis, local vascular spasm may be an accompaniment which leads to the manifestations of portal congestion.

Chapter 10.

CLINICAL VARIETIES OF HEPATOLIENAL FIBROSIS.

Banti's disease: Egyptian Splenomegaly: Bastai's Familial Splenomegaly.

1. Banti's Disease.

An excellent general account of Banti's final descriptions was given recently by McNee (1932) in his Croonian Lectures. In order to submit Banti's views to a detailed criticism it is necessary to restate some of the main points, stressing the more important details especially in the pathological descriptions. The following account is taken from Banti's German publications (1898 and 1910).

The course of the disease is chronic, and may last for many years. The first, or anaemic stage of the disease is characterised by a painless splenomegaly and subsequent anaemia. The anaemia may be severe from the onset and dominate the picture, or it may be a late appearance, and comparatively slight; or it may be completely absent. This stage lasts for three to five years, but it may persist up to twelve or more.

The second, or pre-ascitic stage. The liver becomes enlarged, and then gradually recedes. This stage lasts for several months, and it may be years,

during which time the urine contains urobilin.

The third stage. The liver now becomes smaller, ascites develops, and symptoms of an atrophic cirrhosis are added. Death ensues in six months to a year.

The blood picture is not pathognomonic. The red cells are diminished in number, but usually not below three millions. There is a marked deficiency in haemoglobin, and the colour index is consequently low. There is a leucopenia with an absolute or relative mononucleosis. Primitive red and white cells e.g. normoblasts and myelocytes are always absent.

Pathological Anatomy. The principal changes are found in the spleen. The bone-marrow is said to be indistinguishable from the marrow of ordinary secondary anaemias. The liver shows the changes found in the common type of portal or Laennec's cirrhosis.

The spleen is markedly enlarged. There is a connective tissue increase which is most marked round the follicular and prefollicular arteries. In the Malpighian bodies this process appears to extend through the follicle until the node becomes completely sclerotic. This change, which is termed

"fibroadenie", is the characteristic feature of the disease. There is a simultaneous thickening of the splenic reticulum, until the meshes are narrowed down to tiny holes, and this thickening has the appearance of a connective tissue increase.

The liver is unaltered in the first stage. In the second stage there is a slight hyperplasia of the connective tissue of Glisson's capsule, which gradually increases, and leads in the third stage to the typical picture of atrophic cirrhosis.

The splenic and portal veins often show a sclerosing endophlebitis. Banti assumes that the disease is of an infectious nature. A toxin reaches the spleen via the arteries and sets up the fibroadenie. In the spleen toxins are formed, either directly by the same agent, or indirectly by the disturbance of metabolism in the spleen. These poisons have the power of producing cirrhosis of the liver, anaemia and asthenia, while locally they determine further changes in the spleen and in the efferent veins. This hypothesis of the disease is supported by the fact that splenectomy in many cases of the disease brings about a cure, while without operation the disease assuredly leads to death.

Fibroadenie. This pathological change forms

the crux of the whole vexed problem. The last available note by Banti on this feature of the pathology of his disease is contained in a letter written to Professor Aschoff in 1922. Here he states:-

". . . . Banti's disease does not exist without fibroadenie, but fibroadenie can occur apart from Banti's disease. Fibroadenie begins round the prefollicular arteries or central arteries of the Malpighian bodies. The process spreads out into the follicles and also into the pulp which surrounds the prefollicular arteries. The affected follicles ultimately become sclerotic nodes. . . . The follicles are not all affected at the same time. They are affected successively, while a number remain normal. In cases of Banti's disease which have lasted for years, follicles are found at various stages, the fibrotic process just beginning in some and being advanced in others."

This description clearly indicates Banti's conception of the disease process so far as this aspect is concerned. In 1910, Banti gave the following histological details.

Many of the follicles are quite normal in appearance and show no serious structural alteration. Even in the first stage of the disease the

process of fibroadenie can be seen, and this process leads to the destruction of many of the follicles. Often the connective tissue growth is seen round the central artery merely as a somewhat broad fibrous ring. The fibrous area in the centre of the follicle can be of varying width, and may take up from one third to three quarters of the total cross section. The change consists of the development of coarse, fibrous, and often hyaline, connective tissue. In the connective tissue there are more or less wide elongated clefts arranged concentrically around the central artery of the Malpighian body. In these clefts or meshes there often occur nuclei with dense chromatin, of varying shapes. Where the change is not very advanced, cells may be seen which do not differ from those of normal lymphoid tissue. Banti calls these "chromoblasts". The clefts become wider towards the periphery of the follicle where they contain more cells. The network, from being hyaline in the centre, becomes more delicate towards the periphery until it finally fuses with the normal reticulum of the spleen. The process of fibroadenie can still be seen around the penicillar arteries where these terminate in the pulp. In the arteries themselves, not the slightest sign of arteriosclerosis is recognisable. Fibroadenie be-

gins, not as a progressive change spreading from the central artery of the Malpighian body, but around the penicillar arteries. The more advanced the course of the disease, the more arteries become affected. Thus it is possible to form an estimate of the duration of the disease. The fibrotic change can be followed even in the initial stage of the disease.

In many cases, instead of a germ centre, there may be found in the Malpighian bodies a necrotic hyaline mass of varying shape. Banti describes the staining properties of this substance in detail so that we can be certain it is not amyloid. These masses, according to Banti, may take origin from fused necrotic cells.

It will be noted that Banti shifts his opinion between 1910 and 1922 as to the site of the fibroadenie. In the latter year he states that it begins around the prefollicular arteries, while in the earlier publication he maintains that the process begins around the penicillar arteries. This is a common and somewhat troublesome feature of Banti's different descriptions, which, however, is scareely to be wondered at, as he was apparently uncertain of the exact mode of origin of the process, and his opinions on this point must have been wholly

speculative.

Taking the change which Banti described as "fibroadenie", there is little doubt that this corresponds exactly to the change we have described as periarterial fibrosis.

This point was confirmed by Professor Aschoff who kindly examined some of the writer's slides and photographs, and pronounced the change illustrated in Fig. 17 as being identical with that described by Banti, and which he had seen personally in Banti's own preparations. The thick hyaline appearance of the connective tissue, in the immediate neighbourhood of the artery, is well shown, as also the slits and interstices containing dense chromatin nuclei. The connective tissue becomes less coarse towards the periphery where it merges with the framework of the spleen pulp.

It would be difficult to assert and more difficult to prove that the fibrosis in this case had extended throughout the total area of a lymphoid follicle, leading to the disappearance of the latter. It is equally possible that the fibrosis has made its appearance around a prefollicular artery and by chance its area corresponds approximately to the size of a Malpighian body.

Banti's assertion that the fibrotic process occurs around the penicillar arteries is a fact to which Fig. will testify. With regard to the "thickening of the splenic reticulum and narrowing of the meshes down to small holes", these changes can undoubtedly be fitted in with our findings in the spleen pulp. We have already shown that the collagenisation of fibres which is seen in the sinus walls is probably a simple thickening of reticulin. The sinuses, though nearly always dilated, show a considerable variation in width, and may be quite narrow.

Banti assumed that the liver was normal in the first stage of the disease, because of the absence of "sclerosis". As we have seen, there are many cases in which the liver may appear normal to the unaided eye, and yet undoubted evidence of hepatitis may be present microscopically or clinically.

With regard to the hyaline masses which Banti mentions as occurring in the Malpighian bodies of the spleen in Banti's disease, these are in no way to be regarded as abnormal appearances. They may be seen in any spleen after the age of puberty.
(See p. 19).

The Splenogenic Theory of Banti. Banti's conception of the disease process was essentially one of primary splenic involvement by the causal toxins.

The liver was involved secondarily by toxins which had either been manufactured or stored in the diseased spleen. The principal support for this theory was the idea that the disease could be cured by splenectomy. If this were a fact, it would be a strong point in favour of the splenogenic origin of the disease. Unfortunately for Banti's hypothesis, splenectomy cannot be claimed to affect a cure.

The most extensive studies of the end results of the disease are those of Hanrahan (1925). Twenty seven cases were followed up of which sixteen had been splenectomised, and eleven had not been operated upon. Of the operated cases eleven were still alive, four of whom had survived for periods ranging from nine to twenty five years, while five had died between six months and four years after the operation. Of the unoperated cases, five were still alive, four of who had survived eleven to eighteen years after the diagnosis was made, while six had died one to five years after they were first recognised.

The Mayo Clinic figures were quoted by Moynihan (1921) in his Bradshaw lectures. Twenty seven cases had been subjected to operation five years or more previous to 1920, and of this number, only sixteen had survived. William Mayo admits that 10% of the cases which survived operation

died within the next ten years, usually from haematemesis. A. O. Whipple, in a personal communication to the writer, stated that he had lost a considerable number of cases from haematemesis some time after operation. Moorhead (1929) describes four cases of "splenic anaemia" which ended fatally at intervals varying from a few months to nine years, after splenectomy. The terminal symptoms in all these cases were of a haemorrhagic character. It appears, therefore, that the therapeutic results do not in any way favour the primary splenogenic theory of the disease.

Most clinicians of experience are familiar with cases of obvious hepatic cirrhosis in which the symptoms have not progressed over periods of many years. Professor Gulland has informed the writer of a cirrhosis which was found at operation for an unrelated abdominal condition, and in which the patient was alive and well 35 years later. In view of this spontaneous arrest which may occur at any stage of hepatic disease, it is exceedingly difficult to maintain that splenectomy has prevented death from cirrhosis in any given case. The positive evidence, therefore, is difficult to accept and there is abundant evidence to negative the idea that the cirrhosis is secondary to splenic involvement.

We may sum up our criticism of Banti's disease by asserting that Banti was incorrect in his assumption that the process of fibroadenie was inflammatory in origin. Fibroadenie is identical with the change we have decribed as periarterial fibrosis, which is one of the end results of haemorrhage round the splenic arterioles.

The splenogenic theory of the disease adduced by Banti has no clear evidence to support it, and appears to be improbable. The term "Banti's disease" can only be used in those cases where the splenomegaly is precirrhotic and shows characteristic periarterial fibrosis. Cases corresponding exactly to Banti's descriptions are difficult to find, and it would be better if the term were dropped and replaced by "hepatolienal fibrosis". The latter term gets over the difficulty of Banti's too rigid histological criteria and incorrect assumptions in respect of the pathogenesis.

2. Egyptian Splenomegaly.

An interesting account of this condition given by Ibrahim, Petridis and Stiven may be read in the reports of the meeting of the International Congress of Tropical Medicine and Hygiene held in Cairo in 1928.

Apart from the splenomegalies occurring in

malaria, which are common to all tropical countries, this form of splenic enlargement was first separated from the others by Day and Ferguson (1909), who described it as "a form of splenomegaly with hepatic cirrhosis endemic in Egypt". The condition occurs almost exclusively among the fellaheen of the poorer type, and is accompanied by all grades of bilharzial, pellagral, and ankylostomiatic infections. The symptoms begin at an early age, indigestion, sense of heaviness in the abdomen, and an irregular fever, with signs of an advancing anaemia. The disease advances by stages much as Banti's disase. The age of hospital cases ranges from 8 to 45 (Stiven).

Geographically, the disease is found throughout Egypt, being most prevalent in the region of the Nile delta, but according to Ibrahim, a similar type of splenomegaly occurs in Palestine, Syria, Turkey and Arabia. Gastro-intestinal disturbance and fever are usually the first symptoms. The fever is usually prolonged, and does not subside for some weeks or months, by which time the spleen is usually felt to be enlarged. Pain in the splenic area is common. The splenic enlargement is usually considerable and may reach as far as the pelvis, but it may be quite moderate. The liver may enlarge simultaneously

with the spleen, but it may also enlarge considerably with relatively slight splenic enlargement, or the liver may remain apparently normal in size while the splenic enlargement progresses. Ultimately, however, the liver becomes shrunken and cirrhotic. At any stage the disease may be arrested or even cured. Haematemesis is said to be rare although there may be markedly dilated veins visible on the abdominal wall.

The following pathological account is taken from the work of Day and Ferguson.

The blood count in forty cases averaged 2,635,000. The red corpuscles exhibit considerable variations in size in the more advanced stages of the disease. Nucleated red corpuscles are very rare. Leucopenia was the rule and the count averaged 4,500 per c.mm. The differential count showed 63% polymorphs, 25% lymphocytes, 5.5% large lymphocytes and hyaline cells, and 6.5% Eosinophils. The last feature is to be discounted in a tropical country where the parasitic infestation is so common.

The bone marrow is always more or less profoundly affected. The femur always manifests an active transformation of its marrow, the new marrow being anything from gelatinous red to a deep red colour, and of firm consistence. The hyaline non-granular ele-

ments of the marrow are very notably increased, with a relative reduction of the granular cells. There are seldom any evidences of nuclear activity in any of the types of marrow cells.

The usual type of cirrhosis is a fine diffuse variety without producing much, if any, external alteration of the organ. Microscopically there is a certain amount of cellular fibrillated tissue, mixed with lymphocytes, surrounding groups of lobules, and the liver cells are large, swollen and highly granular. Here and there minute isolated foci of necrotic appearance surrounded by collections of small mononuclear cells are met with. No parasites are found in the liver. In about half the cases multilobular or hob-nailed cirrhosis was present.

In consistence the spleen is firm, and frequently quite hard. It presents a uniformly and deeply congested pulp in which the Malpighian bodies are generally only detected with difficulty. There is hyperplasia of the lymphocytic elements of the pulp, general increase of connective tissue either in the form of a definite increase of the compact fibrous trabeculae, or in the larger spleens, an infiltration of spindle shaped cells diffusely distributed throughout the entire pulp. The vascular sinuses are dilated and distended with frequent interstitial haemorr-

hages . Active phagocytosis on the partbof macrophages towards red corpuscles and leucocytes may be seen.

No abnormalities of note are to be found in the intestine. Portal thrombosis has been found.

In a later paper, Day states that at the onset of the disease, and in infantile types, there may be a leucocytosis of 8,000 - 10,000.

The etiology is at present unknown. Ferguson and other investigators completely failed to find any parasites. It was suggested by Day and Ferguson that "the disease is probably produced by an infective agent as yet undiscovered which is more probably protozoal in nature than bacterial.

" . . . it corresponds most closely to Banti's disease and for the present we may be content to remark that closely comparable,if not identical,forms of splenomegaly with hepatic cirrhosis occur both in the south of Europe and in the Northern part of the Egyptian Delta."

Bilharzial infection has been said to be the cause of the disease (H.B.Day). A similar syndrome of hepatic cirrhosis and splenomegaly is said to occur in Japan. In dogs infected with Bilharzia.japonica, the transportation of eggs into the liver causes destruction of the portal spaces but no diffuse cirr-hosis of the liver was produced up to the 119th. day after infection. No definite changes in the

spleen were found. The evidence of this mode of origin is not convincing.

Siderofibrotic foci are found not infrequently in these spleens.

Results of Splenectomy. It is difficult to follow up these cases in a country like Egypt, but Stiven gives the following figures for a three-year follow-up of cases from whom the spleen had been removed.

No trace of the patient	6%
Poor indifferent health	5.5%
Death	19.5%
Good reports	69%

In this account we see a disease very similar if not identical with the cases of hepatolienal fibrosis which occur in this country. The involvements of liver and spleen appear to be simultaneous, and the hepatitis which occurs may apparently be present without much external alteration of the liver. Generally speaking the spleen appears to show proliferative changes to a marked degree, and the splenic enlargement is usually greater than that which occurs in Great Britain. The late results of

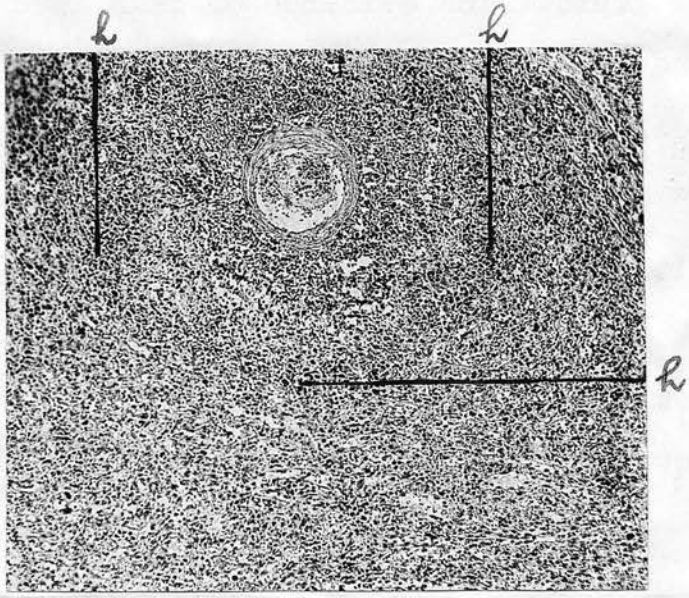

Fig.104. (x 85) Spleen from a case of Egyptian splenomegaly, showing a periarterial haemorrhage delimited by (h)

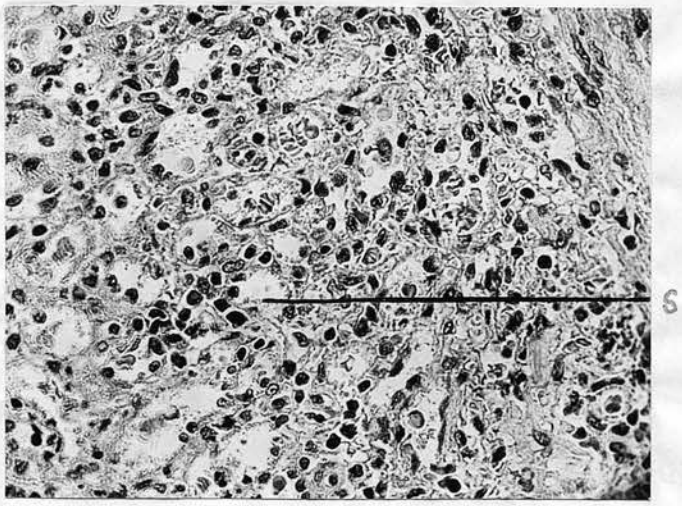

Fig.105.(x 350) Spleen from a case of Egyptian splenomegaly, showing dilatation of the sinuses (s).

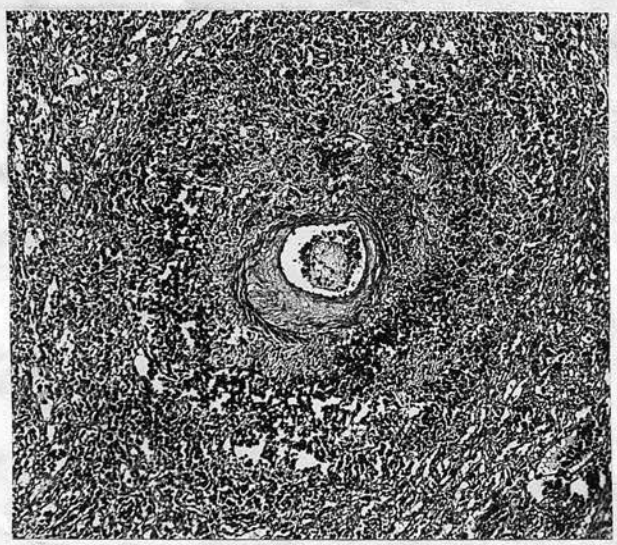

Fig. 105a (x 90) Spleen from a case of Egyptian Splenomegaly, showing an area of periarterial haemorrhage with commencing fibrosis.

operation indicate that the disease is not necessarily arrested by splenectomy.

Through the kindness of Dr. F. E. Reynolds, formerly professor of pathology in Cairo, the writer has obtained histological sections from two cases of Egyptian splenomegaly. The histological findings are illustrated in Figs. 104, and 105. Perivascular haemorrhages are seen to be present, while moderate dilatation of the venous sinuses also occurs. Proliferative changes are definitely present in the formation of rounded histiocytes in the splenic sinuses.

From the great enlargement of the spleen which occurs and the pathological descriptions of the liver changes given above, it seems that in Egyptian splenomegaly the hepatitis may be much more active and associated with more pronounced hyperplastic changes in the spleen than we see in this country.

Egyptian splenomegaly would appear to be a disease of a type exactly similar to hepatolienal fibrosis.

3. Bastai's Familial Splenomegaly.

Bastai (1922) described a disease which he called "Splenomegalia con cirrosi epatica familiare". Histologically, the spleen resembles that described by Banti, but Banti himself, who examined the sections would not admit them as "Banti's disease". Central sclerosis in the Malpighian bodies is described and also thickening of the pulp reticulum. Similar familial cases have been described recently by Ludbrook (1931) and by Leesmith (1933).

In Ludbrook's family, three out of five children had the disease. There was no gross cirrhosis, but the spleens showed "fibrotic" changes, and two of the children died from mesenteric thrombosis, 13 months and 2 years after splenectomy. Jaundice gave clinical evidence of liver damage in one of the patients, while another showed fatty degeneration of the liver cells.

In Leesmith's family, three children out of five were affected by the disease, and liver involvement appeared to be advanced. Two of the three cases suffered simultaneously from xerophthalmia. It is possible that allied dietetic defects may have been predisposing factors in the hepatitis in these patients.

By the criteria we have adopted, these cases

are simply instances of hepatolienal fibrosis in which members of one family have been subject to a common etiological factor.

CHAPTER 11.

The Clinical Recognition of Portal Congestion.

In 1751 Kvemff(quoted by Villaret and Besancon, 1928) noted the engorgement of the portal vein and the haematemeses of hepatic cirrhosis. Raikem in 1848 indicated other signs which he ascribed to portal congestion, namely ascites, haemorrhoids, and gastro-intestinal haemorrhages.

The subject of portal congestion was taken up in detail from 1899 onwards by Gilbert, and his pupil Villaret. Gilbert summarises his conclusions as follows:

"Whenever there exists an intrahepatic vascular obstruction, there occurs a series of symptoms which have been grouped under the name of 'the syndrome of portal hypertension'. The fundamental features of the syndrome are as follows:

Opsiuria, or delay in the elimination of urine,

Ascites,

Splenomegaly,

Haemorrhoids,

Gastro-intestinal haemorrhages, and

The development of the collateral circulation as seen in the anterior abdominal wall.

Of all the symptoms which constitute this syndrome, the earliest is opsiuria. The others vary in their order of appearance according to the type of case".

It is still maintained by the French writers (Villaret and Besancon) that the most delicate index of portal congestion lies in the delay in the elimination of ingested water by the kidneys. The following investigation was carried out in order to test the validity of this claim. In this work the writer was fortunate in having the collaboration of Dr F.H.Smirk.

I. Experimental Observations.

In order to ascertain the exact part played by portal congestion on the absorption and elimination of water, it was decided to produce simple mechanical congestion of the portal vein by partial occlusion of its lumen by means of a ligature. Rats were selected for these experiments, as the curve of diuresis following the administration of water to these animals has been found to resemble closely that occurring in the human subject (Heller and Smirk, 1932).

Technique.

The operations were carried out on rats under ether anaesthesia and with sterile precautions.

The abdomen was opened and a ligature passed round the portal vein above the entrance of the coronary vein of the stomach to produce partial occlusion of the lumen. The knot was tightened until congestion and slight cyanosis of the intestine became evident. Portal congestion having been produced in this manner, the abdomen was closed. Two series of control experiments were carried out. In one laparotomy was performed, but no large veins were ligatured. In the other series a ligature was passed round the inferior vena cava below the point of entry of the renal veins and tightened until venous congestion was evident.

The groups of animals studied include

1. Normal rats.
2. Rats with simple laparotomy.
3. Rats with laparotomy and portal congestion.
4. Rats with laparotomy and inferior vena cava obstruction.

The rats were given bread and milk for three or four days, and no food for several hours before the beginning of the experiment on water absorption and diuresis. Sets of animals from the above groups were weighed and given 5 p.c. body weight of warm water by a small stomach-tube (no.8 catheter). To determine the rate of water absorption, the animals were

killed by chloroform thirty-five minutes after giving water. The alimentary canal, from the cardio-oesophageal junction to the rectum, was dissected out and weighed together with its contents. The average weight of the gut plus contents depends upon the amount of water absorbed, and the alimentary absorption rates of the various groups of animals may thus be compared.

To determine the rate of urine formation, animals, which had had a previous diet of bread and milk as described above, were given 5 p.c. body weight of warm water by stomach-tube. The rats were kept in small wire cages during the experiment. On shaking the cage a rat will void its urine, which may be collected on a cotton-wool swab and weighed. The effectiveness of this method has been demonstrated by post-mortem examination of the urinary bladder.

Autopsies were made on most of the operated rats, and attention was given to the development of venous anastomotic channels and to congestion and cyanosis of the gut. Owing to considerable variation in the size of the spleen in normal rats, the weight of this organ was of no value as an index of the severity of the portal obstruction.

1. The Effect of Simple Laparotomy, on the previous day, on the Rate of Alimentary Absorption.

It has been shown by Heller and Smirk(1932, 1933.) that anaesthesia, and anaesthesia and laparotomy, in themselves cause for some hours a delay in the absorption of water from the alimentary tract. In order to control the observations upon animals with portal obstruction, a set of animals from the same batch were subjected to anaesthesia and laparotomy only. In seven rats the abdomen was opened under ether anaesthesia, the portal vein exposed, and the incision stitched up again. The following day these animals had a water diuresis test in the morning, while in the afternoon, i.e. twenty-four hours after operation the rates of water absorption were determined by the method already described. The results are shown in Table .

Table V.

The effect of simple laparotomy on the previous day on the rate of alimentary absorption.

Number of rats.	Condition	Time after giving water	Weight of the alimentary canals and contents as % of Body-weight.	Average.
8	Normal	30mins.	9.3,8.2,7.8,8.0 6.6,7.1,6.4,7.9.	7.7
7	Anaesthesia and laparotomy on previous day.	35mins.	6.2,5.5,7.0,8.1, 7.7,6.6,8.2.	7.04

The figures obtained in this series of rats indicate that the rate of water absorption does not differ materially from that in normal controls. Heller and Smirk found that the average weight of the empty gut in rats was 5.5 p.c. of the body weight. This would indicate that, in the rats which had been subjected to laparotomy, 1.5 p.c. body-weight of water remained unabsorbed at the end of 35 minutes. As the amount of water given initially was 5 p.c. of the body weight, it is obvious that 70 p.c. of the water was absorbed in 35 minutes.

It would appear therefore that the immediate effects of anaesthesia and laparotomy in depressing the water absorption rate have passed off on the following day.

2. The Effect of Laparotomy and Partial obstruction of the Portal Vein on the Preceding Day upon the Weight of the Alimentary Canal.

In the succeeding section the effect of partial occlusion of the portal vein upon the rate of alimentary absorption of water will be considered. The method employed does not distinguish between changes in the weight of the alimentary canal due to congestion and oedema of its wall, and those due to alterations in the amount of its content. Before we can

draw conclusions about the absorption rates from the weight of the gut, it is therefore necessary to ascertain whether portal obstruction causes any substantial increase in the average weight of the alimentary canal quite apart from the question of water absorption.

The necessity for such a control observation was evident in two animals which died a few hours after operation with complete obstruction of the portal vein. In these there was marked plum-coloured congestion of the gut with exudation of blood-stained fluid into the lumen. The guts plus contents were respectively 11.5 and 12.5 p.c. of the total body-weight, i.e., over twice the average normal value. Of this, about 2.8 p.c. body weight was represented by the blood-stained mucous exudate within the lumen.

In the animals which survived, venous obstruction was not nearly so complete, and the wall of the intestine showed a much milder degree of congestion. Under these conditions the relationship of gut-weight to body weight was as follows:

TABLE VI

The Effect of partial portal obstruction on the weight of the alimentary canal.

	Weight of gut as p.c. of total body weight.	Result of diuresis test.	Evidence of congestion and cyanosis.
5 rats with partial obstruction of the portal vein.	5.5	Definite delay	?+
	7.2	Slight delay	+
	6.7	Marked delay	++
	4.6	Slight delay	+
	5.9	Marked delay	++
Average	6.0		
10 normal control rats	6.0	No delay	None.
	5.9		
	6.1		
	5.0		
	5.1		
	5.1		
	6.2		
	5.7		
	5.2		
	5.0		
Average	5.5		

It is seen from this table that the average weight of the of the alimentary canal is increased from 5.5 to 6 p.c. of the body weight as a result of portal venous congestion.

3. The Effect of Laparotomy and Partial Obstruction of the Portal Vein, on the preceding day, upon the rate of alimentary absorption.

In these experiments the progress of water absorption was followed by weighing the alimentary canal and its contents, 35 minutes after 5 p.c. body weight of warm water had been administered by stomach-tube. The results are given in Table

TABLE VII

The Effect of Portal Congestion on the Absorption of Water.

Rat number	Weight of Gut - contents as p.c. body-weight 35 minutes after administration of water.	Stomach alone as p.c. body-weight	Congestion
1R1	10.1	5.9	++
1R4	7.9	2.5	+++
1R2	7.9	1.5	+++
1R6	10.3	1.9	+
104	13.2	Water mostly in stomach.	+++
1R3	13.6	Water mostly in stomach.	+++
2R2	10.5	Not noted	+
2G2	8.0	" "	+
2V1	8.3	" "	+++
2V2	8.3	" "	++
2V3	6.4	" "	+
Average	9.5		

It will be observed in general that there is a marked delay in water absorption as determined in this manner. Two experiments are omitted in which no evidence of portal obstruction was found at autopsy. The average weight of the gut plus contents, 35 minutes after giving water was 9.5 p.c. of the total

body weight. Remembering that the average weight of the empty gut in portal congestion is 6.0 p.c. body weight (Table VI), this would indicate that only 30 p.c. of the water given is absorbed in 35 minutes instead of the normal 70 p.c.

It appears that portal congestion is responsible for a definite delay in the absorption of water from the alimentary canal. Laparotomy and anaesthesia on the preceding day produce no such delay. The increased weight of the gut, from which delayed absorption is deduced, is too great to be accounted for by congestion alone which causes a relatively small change in the basal weight of the gut.

4. The Effect of a simple laparotomy on the preceding day upon the rate of water excretion by the kidneys.

As already mentioned in section 1, anaesthesia and laparotomy, or even anaesthesia alone, cause for a short time afterwards a delay in the absorption of water, which passes off at the end of twenty-four hours. It remains to be seen whether the delay in diuresis which occurs under these conditions has also passed off.

The following observations were made on the series of animals, which, four or five hours later, were used for the water absorption tests (Section 1).

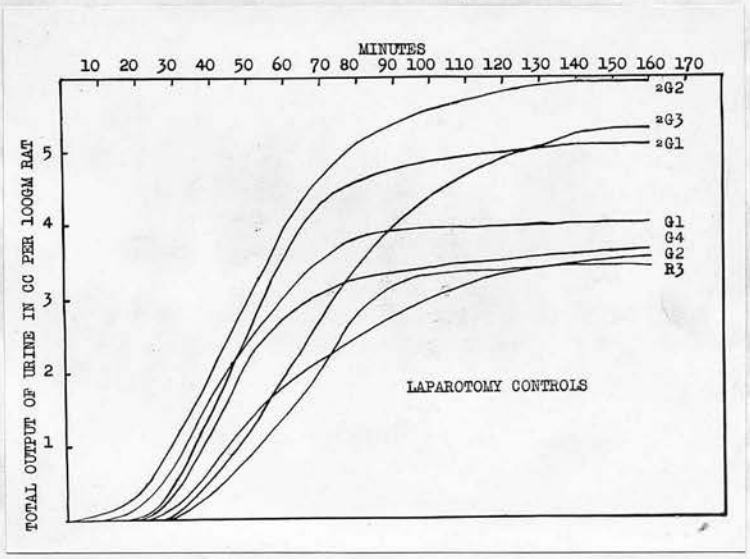

Chart 1.

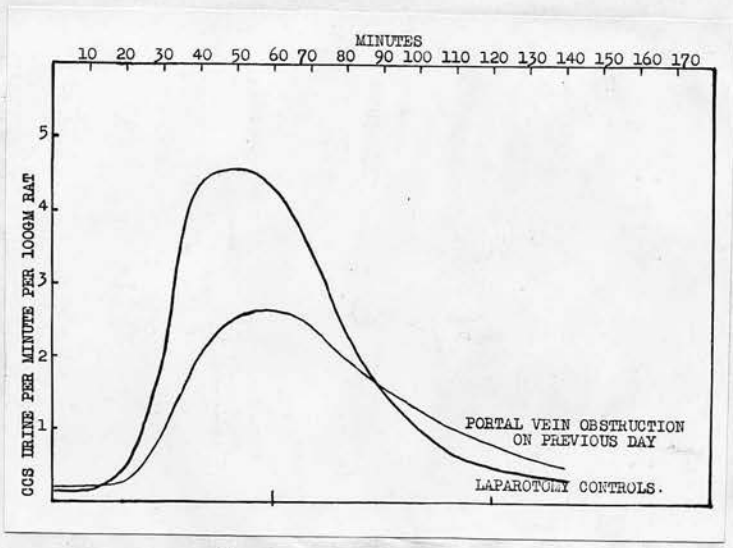

Chart 2.

Anaesthesia and laparotomy had been carried out on the previous day. 5 p.c. body-weight of warm water was given to each rat, and samples of urine collected at intervals of about ten minutes. The total amount of water excreted by individual rats at various times after giving water is represented on Chart 1, and the average of these results, expressed as rates of urine formation on Chart 2. It will be observed that, as an average the progress of diuresis is similar to that of a series of 18 normal rats investigated by Heller and Smirk, (1932) under the same experimental conditions. It may therefore be concluded that the rate of water excretion in rats is not greatly influenced by laparotomy under ether anaesthesia on the preceding day. This result is consistent with the observations made in section 1, that the rate of water absorption is relatively unchanged in these circumstances.

5. The Effect of Laparotomy and obstruction of the Portal Vein upon the rate of water excretion by the kidneys measured at various times after the operation

Two series of results have been obtained. In the first a group of animals with portal occlusion were compared with the animals of section 4 under uniform conditions. In the second diuresis experiments were performed on a series of rats before and

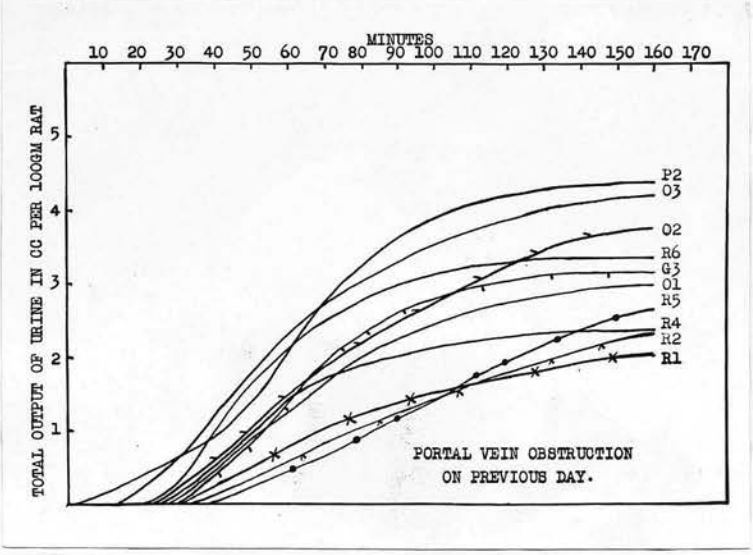

Chart 3.

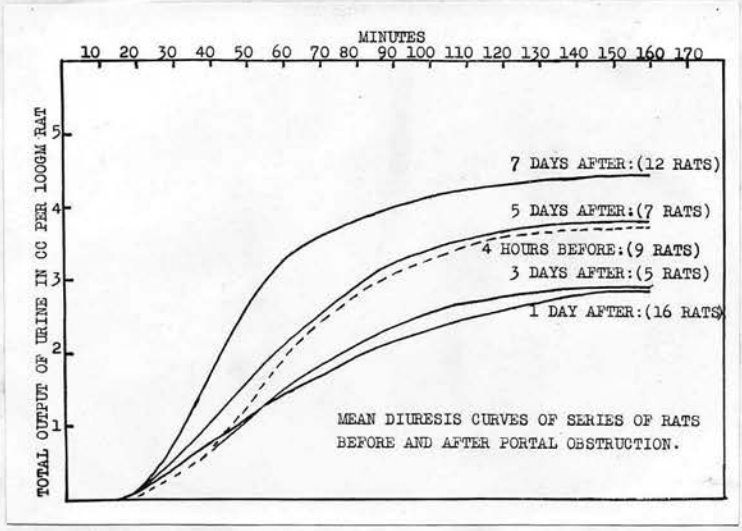

Chart 4.

at intervals of 1,3,5,and 7 days after the operation of portal ligature.

Group 1.

The individual diuresis curves from this series are shown in chart 3. It will be noted, however, that both in chart and in chart which records the average of the 10 experiments, that the rate of urine excretion is lessened, and the duration of diuresis is prolonged. At the end of one hour the average amount of urine excreted by the control rats is 2.6 cc, while only 1.4cc has been excreted at this time by the rats with portal congestion. In the control rats (chart 1) the average output at the end of two and a half hours is 4.4 p.c. body-weight, while in the animals with portal obstruction 3.13 p.c. had been excreted.

Group 2.

In this series of animals the response to 5 p.c. body-weight of warm water was tested before and 1,3,5,and 7 days after partial obstruction of the portal vein. The mean daily curves of the group are shown in chart 4. From a consideration of these averages it is quite clear that diuresis takes place much more slowly on the day after operation. By the fifth day the rate of urine formation had returned to normal. In the animals which survived

until the seventh day after operation, the progress of water excretion was rather above the normal rate.

5. The rate of water absorption one week after partial portal obstruction.

The question now arises as to whether the improvement which occurs in the rate of diuresis a few days after operation is to be related to a return of the absorption rate to normal.

In all the animals which survived to the end of a week post mortem examination revealed fairly well developed anastomotic channels between the portal and systemic veins, especially along the lesser curvature of the stomach, but also in the lumbar region. The appearances of congestion of the gut were not so obvious.

The result of a water absorption test one week after portal obstruction is shown in table .

TABLE VIII.

The effect of partial obstruction of the portal vein on the rate of alimentary absorption at the end of 7 days.

Number of rats.	Time after giving water.	Weight of alimentary canals - contents as p.c. body-wt.	Average.
9	35 minutes	9.8,9.8,8.6,8.0,7.3,9.3, 7.6,6.4,10.2.	8.5

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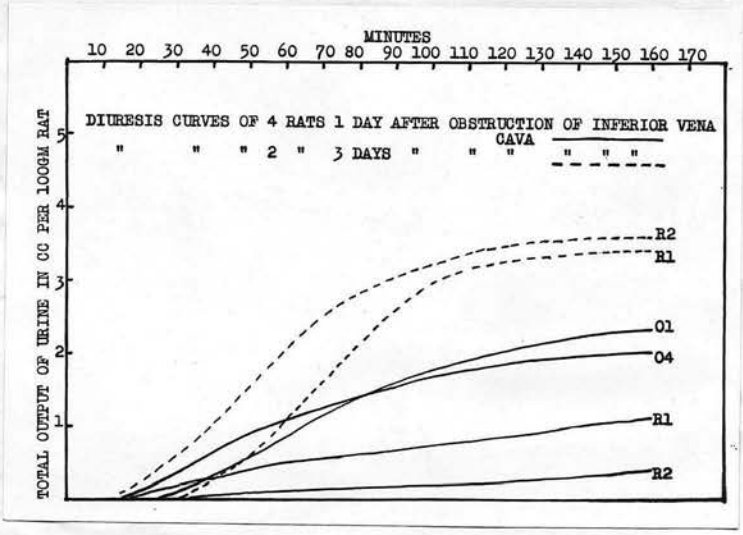

Chart 5.

It is seen that there is definite delay in the absorption rate, only 50 p.c. of the water having been absorbed as against the normal 70 p.c. in 35 minutes.

It appears therefore that a normal diuresis curve may occur in the presence of delayed absorption of water from the alimentary canal.

6. The Effect of Obstruction of the Inferior Vena Cava on the absorption and Excretion of ingested water.

From the experiments described in sections 4 and5 it is obvious that the delay in diuresis which is seen the day after portal obstruction, is not necessarily the result of slow absorption of water from the gut.

It was therefore decided to carry out an operation of similar type and severity on another series of rats. Under ether anaesthesia a ligature was passed round the inferior vena cava inferior to the point of entry of the renal veins, to occlude the lumen partially. Sixteen rats in all were thus treated. Twelve out of the sixteen gave a normal diuresis curve and a normal absorption rate on the following day., In four of the sixteen rats however , a marked delay in diuresis occurred on the day after operation. The water absorption rate in two of these four rats

was normal, when tested an hour or two after the diuresis experiment, 66 p.c. of the water given having been absorbed in 30 minutes. The other two rats which showed a delayed diuresis were allowed to survive until the third day after operation, when the administration of water resulted in a normal diuresis (Chart 5).

Discussion

In our experiments we have produced a condition of portal congestion, which was evidenced the day after operation , by cyanosis and increased weight of the gut.

At first we had some doubts as to the persistence of raised portal pressure 24 hours after its production by partial occlusion of the portal vein. Bolton (1907) showed that after obstruction of the inferior vena cava above the liver, the venous pressure, raised at first, fell to a normal level in an hour or two. This phenomenon Bolton ascribed to dilatation of the capillaries of the congested area. We have repeated Bolton's experiments and confirmed his observations, but have reached a different conclusion as to the mechanism involved in bringing about the fall of venous pressure. These observations will

be published elsewhere. Meanwhile we can state definitely that obstruction to the portal vein, or the inferior vena cava below the liver , thus damming back a smaller portion of the circulating blood than in Bolton's experiments, is not followed by a fall in venous pressure. Talma(1924) in experiments on portal congestion, also found that no significant fall in venous pressure occurred after it had been raised by partial occlusion of the portal vein.

Our experiments show clearly that portal congestion causes a delay in the absorption of water from the alimentary tract. This delay is still present at the end of a week although slightly relieved by the development of a collateral circulation.

In a number of animals in which water absorption tests were carried out after partial ligature of the portal vein, a considerable amount of water still remained in the stomach;as no gastric retention was observed in the animals with laparotomy only, a simple post-operative atony would hardly account for it. In addition to the water retained within the stomach an excess of water was also found in the intestine. It appears that both a gastric and intestinal component contribute to the delay in absorption.

The day after the operation of portal obstruc-

tion, there is a definite delay in diuresis in the majority of the animals. It is probable that the slow absorption of water from the alimentary canal is a contributing factor in this delayed excretion of water, but this is not the sole cause. A delayed diuresis may be seen in some cases (25 p.c.) of inferior vena cava obstruction, where the water absorption rate is not interfered with. Also a normal diuresis is the rule at the end of a few days after portal obstruction , when the rate of water absorption is still diminished.

This observation adds further confirmation to the observation of Heller and Smirk that the onset of diuresis is not an immediate direct result of the absorption of water , but involves some intermediate mechanism. Provided enough water is absorbed to start a diuresis, then even the slow rate of absorption which we have seen (section 5) would be sufficient to maintain a normal or nearly normal rate of water excretion.

It is obvious then that the mechanism of water excretion may be affected independently of defects in water absorption. Whatever the actual factor may be which leads to impaired excretion of water by the kidneys, it can be elicited in 25 p.c. of cases of experimental obstruction of the inferior vena cava. Heller and Smirk(1933) have shown that there may be an approx-

imate relationship between the severity of operative interference and the inhibition of the normal diuresis. Whatever the factor involved, rats with vena cava obstruction recover by the third day when a normal diuresis is seen.

In animals with portal obstruction therefore it is probable that at least two factors are concerned in causing the initial slow diuresis. Slow absorption from the alimentary canal is one factor. The second is the inhibitory effect of the abdominal operation which may play a part in the first day or two. At the end of a week after the operation, when the absorption rate from the alimentary canal is still considerably delayed, the curve of diuresis may be normal.

SUMMARY.

1. Rats, in which the portal vein has been obstructed, show, on the day after operation, a diminished rate of absorption of water from the alimentary tract and a delayed diuresis.
2. The delayed absorption rate improves in the course of the week following operation, but does not return to normal. A normal diuresis curve has been shown to occur even in the presence of slow absorption of water from the gut.
3. The delayed absorption rate is only one factor in bringing about the initial slow diuresis in portal congestion. A second factor is the severity of the operation, for a similar slow diuresis may be seen in 25 p.c. of rats with inferior vena cava obstruction, in which the water absorption rate is not interfered with.

2. CLINICAL OBSERVATIONS.

Diuresis tests were carried out on a series of hospital patients with various diseases. Cases were selected who were only moderately debilitated, and whose general condition was comparable with that found in an average case of hepatolienal fibrosis. The tests were carried out in three cases of the latter disease. In the cases which were used as controls there was no evidence of any gastro-intestinal disturbance such as might lead to delayed absorption of water, and the kidneys were apparently functioning in a normal manner.

Technique of the Diuresis Test.

Patients were given breakfast at 7-30 a.m., the only fluid allowed being a cup of milk. The bladder was emptied immediately after breakfast and the time noted. About 9-15 a.m., the bladder was again emptied and the urine measured. This quantity of urine, formed in a known time, gave the basal output which was usually in the neighbourhood of 45 - 50cc. per hour. Immediately the bladder was emptied, 1 litre of water was drunk. Thereafter the bladder was emptied at intervals of about 15 minutes until the resulting diuresis had passed off. The time at which the water was drunk is the zero point in the chart.

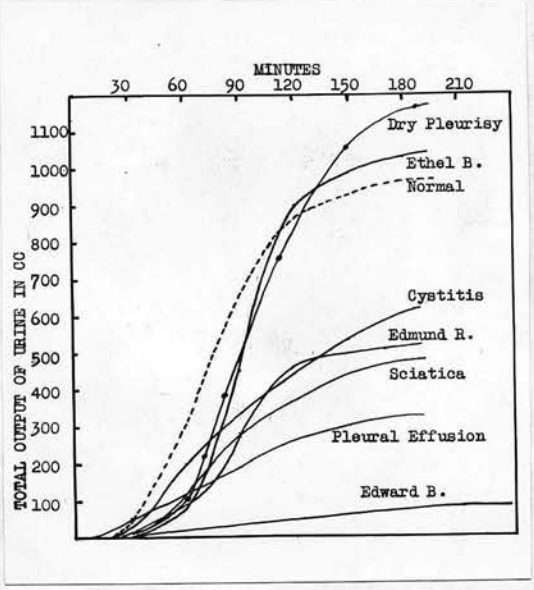

Chart 6.

Diuresis curves in a series of patients. Ethel B., Edmund R. and Edward B. were cases of hepatolienal fibrosis. A diuresis curve from a normal healthy subject is shown by the dotted line.

The total output of urine is followed as a curve.

Results of the Diuresis Test.

A normal diuresis curve from a healthy subject is indicated in the chart by the interrupted line. Taking the three cases of hepatolienal fibrosis, we see that Ethel B. (case XXXVI) gives a normal curve. The test was carried out two months after the spleen had been removed. Haematemesis had occurred before operation and the spleen showed the effects of peri-arterial haemorrhage.

Edmund R., aet 22, had cirrhosis of the liver with splenomegaly. There was no history of haematemesis or melaena, no ascites and no enlarged veins could be seen on the abdominal wall. The diuresis curve was well below the normal level.

Edward B., aet 51, had cirrhosis of the liver, moderate splenomegaly and ascites. His daily output of urine was very low. In the hour and a half before the water was given he only formed 12 cc of urine. The administration of a litre of water made no perceptible difference to the urinary output, and he only formed 104 cc urine in the next 5½ hours.

These variations are scarcely less striking however than the variations we found in the so-called controls. A patient convalescing after

pleural effusion gave a very poor diuresis, while another subject who had had dry pleurisy gave a curve above the normal. Patients with sciatica and cystitis (renal function tests normal) gave a poor diuresis.

It is obvious then that the curve of diuresis undergoes great variations in patients debilitated from any cause, and cannot be accepted as an index of portal hypertension. In the case of Ethel B., where we had good reason to suspect raised portal pressure, the curve of diuresis was normal. From our animal experiments it is certain that a normal diuresis may occur in the presence of slow absorption, so that we have no means of deducing from this test whether the portal pressure was raised or not.

In Edward B., on the other hand, ascites was present and the low urinary output was uninfluenced by such a large draught as a litre of water. The plasma proteins in this case were lowered to 5.5% and it is possible that lowered protein osmotic pressure of the plasma may play a part in the gross disturbance of water metabolism which occurs in these advanced cases of hepatic disease.

The factors influencing water exchange in health and disease are as yet too little understood

to allow of any conclusions from diuresis tests as to the pressure conditions in the portal circulation.

So far as our experimental and clinical investigations have taken us at present, we cannot regard opsiuria as an index of portal congestion. It would be unwise to say that the diuresis test is of no value, as the factors influencing water exchange offer a very fruitful field for further research. It is also possible that improvements in our methods may yield more accurate information on the rate of water absorption which may yet give a clue to the problem of portal congestion.

The other manifestations of portal congestion as enumerated by Gilbert are ascites, splenomegaly, haemorrhoids, gastrointestinal haemorrhages, and the development of a collateral venous circulation in the abdominal wall.

Ascites is not determined by portal congestion alone. In a long series of experiments on portal congestion in animals, Talma was unable to produce ascites. In spite of the evidences of portal congestion in 39 of the present series of cases, ascites was only present in 6 (cases, X, XIII, XVI, XIX, XX, XXII.).

It appears that some factor other than mere mechanical congestion of the portal vein must be present to account for ascites. Provided some other cause of oedema is at work, portal congestion would play a part in localising the dropsical effusion to the peritoneal cavity.

It is notable that the cases in our series which showed ascites all had gross and advanced disease of the liver. Moreover, one of our patients, (Case XVII.), showed oedema of the feet, without any ascites. Similar cases of hepatic disease are mentioned by Hetenyi (1931) in which oedema of the legs may precede the appearance of ascites.

What the factor may be which determines dropsy in hepatic disease is not yet known. Villaret and his colleagues (1925) showed the presence of hypoalbuminaemia in cases of hepatic ascites. Wallich (1930) has confirmed this and has shown that the reduction of plasma protein exactly resembles that found in nephrosis.

Lowered protein osmotic pressure of the plasma may thus play a part in the production of ascites in hepatic disease.

Splenomegaly has already been fully discussed and it is recognised that portal congestion plays a part in the production of certain histological appearances,

and to a less degree in producing the enlargement of the spleen.

Haemorrhoids are described as a manifestation of portal congestion. We have not paid particular attention to their occurrence in this study. They have never constituted one of the complaints in our series of patients, Considering the frequency of haemorrhoids in patients in whom there is no reason to suspect portal congestion, we do not feel inclined to stress them as an aid to the diagnosis of obstruction to the portal blood flow.

Gastrointestinal haemorrhages constitute a clinical manifestation of considerable frequency. Bleeding from the gastrointestinal tract occurred in 20 of our 41 cases, i.e. 48.8 per cent, and sometimes, as in case XXXVI and case II, it constituted the most prominent symptom of the disease.

This symptom is undoubtedly precipitated by portal congestion and frequently the site of origin may be seen in an oesophageal varix. A close relationship has been noted by the writer between the occurrence of gastrointestinal haemorrhage and fully developed siderotic nodules in the spleen.

Of the 20 cases in which gastrointestinal haemorrhage occurred, siderotic nodules were pre-

sent in the spleen in 15. Siderotic nodules were only present in 17 out of the 41 spleens under consideration. (see Table II).

It has already been shown (p.) that the local deposits of iron in periarterial haemorrhages in the spleen only occur if these haemorrhages are relatively large. It would thus appear that bleeding from the gastrointestinal tract in hepatolienal fibrosis is related to the occurrence of large periarterial haemorrhages in the spleen. Both might be determined by a considerable rise in portal venous pressure.

It should not be forgotten, however, that other causes of haemorrhage may be at work in association with hepatic disease. Epistaxis is a common symptom in cirrhosis, and all grades of spontaneous bleeding may be found up to fully-developed purpuras. It is easily understood that in any general increase of the fragility of the capillaries, bleeding would tend to occur most easily in a zone of high capillary pressure. Portal venous congestion might thus localise purpuric bleeding to the gastrointestinal tract. Observations have been brought forward by Klemperer, Leyden, and Mouisset and Beutter (quoted by Villaret and Besancon) that in hepatic disease the gastric or oesophageal mucous

membrane may show a general oozing of blood from the surface. The bleeding in Case XXII may have been of this type. The general tendency to bleeding in hepatic disease will be discussed in the next chapter.

The development of a collateral venous circulation in the anterior abdominal wall is unequivocal evidence of portal congestion and has already been discussed. (Chapter 2).

Chapter 12.

CLINICAL FEATURES.

The clinical manifestations of hepatolienal fibrosis may be summarised as follows.

The disease tends to occur most frequently in the first half of life and it may come on in childhood. The symptoms are often insidious in their onset, and the splenic enlargement may only be discovered accidentally. The patient may present himself on account of abdominal pain or discomfort, weakness and general lassitude, referable to the anaemia on account of haematemesis. The disease runs a very chronic course, and unless the patient is subject to repeated gastrointestinal haemorrhages, the anaemia is usually mild in degree and the disability is moderate. Most of the patients are able to work in spite of haemoglobin values as low as 50-60%.

When the disease leads to death, this may occur from liver insufficiency, haematemesis, or portomesenteric thrombosis. In many cases, however, the course of the disease appears to be arrested and the patients live for many years with very slight disability. Whether the course of the disease is influenced by splenectomy is as yet undecided, and we shall discuss this question in the final chapter.

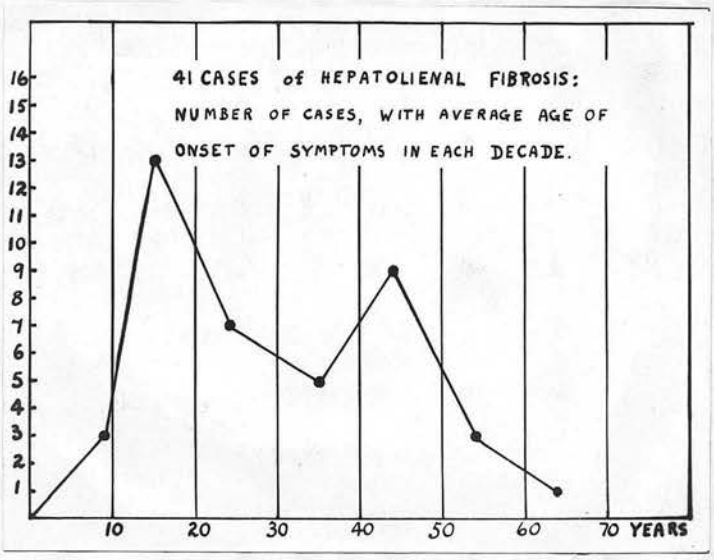
41 CASES of HEPATOLIENAL FIBROSIS:
NUMBER OF CASES, WITH AVERAGE AGE OF
ONSET OF SYMPTOMS IN EACH DECADE.
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
10
20
30
40
50
60
70 YEARS

Chart 7.

Age and Sex Incidence.

Of the 41 cases which constitute the present series, 20 were males and 21 females, giving an approximately equal distribution between the sexes.

The age at which the patients were first admitted to hospital does not give a true index of the age incidence in a chronic disease. The age of onset of symptoms, definitely referable to the disease, was taken for the construction of chart 7. It is notable that the disease begins most commonly in the second decade, and in more than half the cases, (23 out of 41), the symptoms began before the age of 30. The disease definitely predominates in the first half of life.

It is interesting to note that the age incidence corresponds to the period of life at which lymphoid tissue (Hellmann, 1926, Hellsten, 1928), has its maximum activity, and that the atrophic ("alcoholic") cirrhoses of later life are less frequently associated with splenomegaly.

Is it possible that there is a relationship between the reactive capabilities of lymphadenoid tissue and the occurrence of splenomegaly in hepatitis? It is of interest to mention in this connection that Minot and Isaacs (1926) noted a somewhat similar age distribution in Hodgkin's disease.

Anaemia.

Patients frequently present themselves with symptoms referable to anaemia - pallor, breathlessness, weakness, lassitude and so forth.

Red Cell Changes. The red cell count in 31 of the 41 cases ranged from 3 to 5.3 millions per cubic millimetre. The actual distribution of the average red counts in individual cases is as follows:

Red Corpuscle Count:	Number of Cases:
1--2 millions	2
2--3 do	8
3--4 do	17
4--5 do	11
Over 5 do	2

The cases which showed red counts below 3 millions were usually associated with a recent history of gastrointestinal bleeding: (Cases VI, VIII, XIII, XX, XXXVI, XXXVII.). In four instances, however, red counts below three millions were encountered where a history of haematemesis or melaena could not be elicited. Case IV., with a count of 2.1 millions, showed old portal thrombosis,and occult bleeding may have passed unnoticed.
Case XXXII. gave a history of "coughing" blood, while in case XXXIV repeated epistaxis had occurred. There was no blood loss in case XXXV., but here the count was 2.9 millions, very slightly under the 3

million level. It is unusual, then, for the red cell count to fall below 3 millions unless gastrointestinal haemorrhage is present.

The examination of a stained film reveals no change in the appearance of the red cells. In uncomplicated cases, nucleated red cells were not encountered, and reticulocytes did not exceed 1--2 per cent.

If a severe haemorrhage had occurred, however, signs of bone marrow activity were seen in a rise in the percentage of reticulocytes (case II). Polychromasia, anisocytosis and even nucleated red cells might be seen (cases VI., XIII.).

Fragility of the red corpuscles was examined in 15 cases. In six instances the fragility was normal, haemolysis beginning at .45 per cent saline, (cases IV., XI., XX., XXXI., XXXIV., and XLI.). In seven cases the fragility of the red cells was diminished as compared with a normal control, the corpuscles being completely resistant to haemolysis at .45 per cent saline, and only beginning to break down in .3 to .4 per cent. (Cases I., X., XV., XVII., XVIII., XXV., XXVI.).

In the remaining two cases fragility was increased, haemolysis beginning at .55 per cent,(Case VII.) and .6 per cent saline (Case XXXV.)

facing p. 25H.

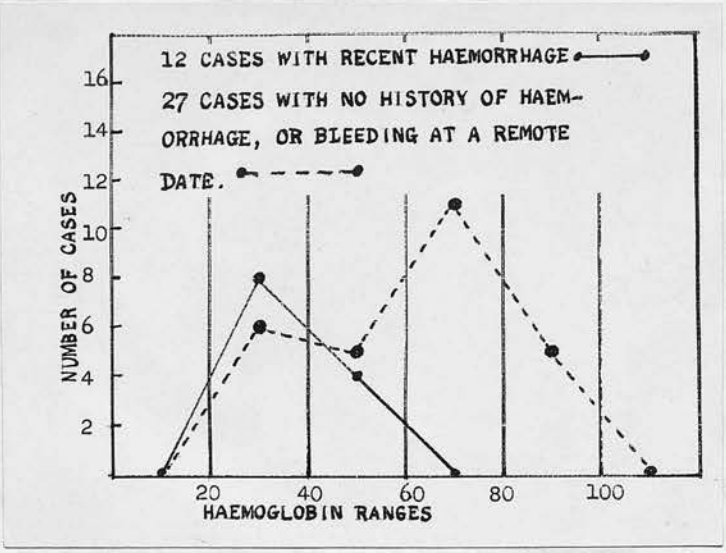

Chart 8

It is noteworthy that in the latter two cases there were no evidences of excessive breakdown of red blood corpuscles, and the histological findings definitely excluded any possibility of haemolytic jaundice.

Haemoglobin and Colour Index.

In our series, the average haemoglobin values in individual cases ranged from 25 to 85 per cent. Two groups of cases are separated in chart 8, those with recent gastrointestinal haemorrhage and those without. It is seen that, while a haemoglobin value under 40per cent is often found as a result of severe bleeding, there is also a small group of cases in this disease with similar low haemoglobin values, in which the cause cannot be ascribed to haemorrhage.

The colour index shows similar variations:

Colour Index Range:	Number of Cases:
.4 to .5	5.
.5 to .6	6.
.6 to .7	6.
.7 to .8	7.
.8 to .9	8.
.9 to 1.0	5.
1.0 to 1.1	2.

Low colour indices below .6 are found with or without a history of recent haemorrhage.

Before we discuss the changes in the leucocytes, it would be well at this stage to consider the possible causation of the deficiency of red blood cells and haemoglobin.

Several points stand out from the above account. Some patients, with over 4 million red cells and more than 80 per cent haemoglobin cannot be considered to be severely anaemic. Those who are definitely anaemic present an enormous variation, and may have either a high colour index anaemia or an anaemia associated with a low colour index.

There is no evidence to suggest that increased blood destruction by the large spleen is responsible for the anaemia, as the blood picture and pathological picture differ fundamentally from that found in haemolytic jaundice. There are neither signs of increased blood destruction (hyperbilirubinaemia, siderosis, etc.) nor evidences of compensatory hyperactivity of the bone marrow (reticulocytosis, circulating erythroblasts, etc.).

Further, splenectomy does not cure the anaemia (chapter 13.).

The defect would therefore appear to lie in blood formation. The bone marrow itself seems to be perfectly capable of responding. In 5 autopsies,

(Cases XV., XVI., XXI., XXII., XXV.) in which the bone marrow was examined, red marrow was found extending into the shaft of the femur in 4: in the remaining exception, the haemoglobin before death was 70 per cent. Further, in individual cases which had suffered from severe haematemesis, the anaemia was moderately well repaired (cases II., VIII., XIII.), the bone marrow being quite capable of manufacturing red cells up to a certain point.

The occurrence of so many high colour index anaemias in hepatolienal fibrosis recalls the recent observations of Gamna (1926, 1933) and Schulten and Malamos (1932) that a macrocytosis often occurs in cases of hepatic disease.

With regard to the low colour index anaemias, we may call attention to case VII, where a definite microcytosis was found by Dr. Price Jones. In this patient also an excessive fragility of red cells was present, a condition which has been noted in association with microcytic anaemias by Graham and Johnson (1932). Case XXXV also showed an extremely low colour index associated with increased fragility, but in this case the red cells were not measured. Case XXVII showed the association of a low colour index anaemia with achlorhydria.

It appears then that some of the anaemias

occurring in association with hepatolienal fibrosis may resemble closely the microcytic anaemias of Witts (1930). Others, however, may possibly be macrocytic in type. What the relationship of these anaemias may be to the hepatic disease is as yet an unsolved problem, but the relationship is certainly complex and probably varies in individual patients.

Leucopenia.

Leucopenia is the most constant feature of the blood picture in hepatolienal fibrosis. The lowest count we have encountered is 320 white cells per cubic millimetre (Case II). The average white count in this case, however, was 1,300.

Average Leucocyte Count:	Number of Cases:
1--2,000.	6
2--3,000.	4
3--4,000.	10
4--5,000.	5
5--6,000.	4
6--7,000.	6
7--8,000.	1
8--9,000.	3
9-10.000.	0
10-11,000.	0
11-12,000.	0
12-13,000.	1

Leucocytosis is therefore very exceptional and the patient mentioned in the above list who had a white count of 12,600 (case XXII.) was dying of

hepatic insufficiency. It is possible that superadded acute hepatitis may have been responsible for this leucocytosis. In case XXIII. a leucocytosis developed in association with superadded acute cholecystitis and hepatitis, although in the preceding quiescent stage there had been a leucopenia.

In dealing with the exceptions to the usual leucopenia, case III may be discussed, in which thrombosis of the splenic and portal veins had occurred, and in which a leucocytosis of 42,000 was found on one occasion. It appears that leucocytosis may occur in association with the onset of porto-splenic thrombosis, although it may not persist when the thrombosis has become chronic (as in cases I to VI.).

In Case XXXVII, leucocytosis was repeatedly observed, but portal thrombosis was not proven. We have no further observations on this possible cause of leucocytosis in hepatolienal fibrosis. A similar association of leucocytosis with portal thrombosis has, however, been noted in literature. Wilson and Lederer (1929) found leucocytosis up to 31,000 in a case of portal thrombosis. Opitz (1925) records one case with a leucocytosis of 11,500 at the acute stage. Ewald (1913) reported a case of porto-splenic thrombosis with a leucocytosis of 20,000. When observed at the chronic stage, however, the usual finding is

leucopenia, as in our six cases.

The leucopenia is practically always an evenly distributed diminution of all types of white cells, the proportions of polymorphs and non-granular cells being very slightly disturbed.

Polymorph percentage:	Number of Cases.
30---40.	1.
40---50.	1.
50---60.	7.
60---70.	16.
70---80.	9.

With regard to the causation of the leucopenia, it may be noted that the bone marrow is perfectly capable of responding to infection, with a leucocytosis (case XXXIII.). There is no evidence of any specific depression of granulo-poietic function.

On the other hand there is usually a sharp increase in leucocytes after splenectomy in hepatoliemal fibrosis. This in itself cannot be stressed as a point of evidence, for <u>temporary</u> leucocytosis occurs after splenectomy in normal animals (Pearce, Krumbhaar and Frazier, 1918). Nevertheless, in the disease with which we are dealing, the increase in the leucocyte count after splenectomy is usually permanent. In ten cases, (VII., IX., XII., XVIII., XX., XXIV., XXVIII., XXXII., XXXIV., and XL.) the leucocyte count

had remained normal or high (case VII.) at intervals of 2 months to several years after splenectomy. It appears to be quite possible that the enlarged spleen may be responsible for the diminution of the circulating leucocytes.

Changes in the blood platelets will be discussed under the heading of epistaxis.

Abdominal Symptoms.

The frequency with which patients complain of abdominal pain and discomfort is very striking. Of our 41 cases, 21 complained of considerable pain in the abdomen, and it was pain which drove patient XVI to suicide. Two patients (XV. and XX.) complained of abdominal discomfort short of actual pain, while in the remaining 18 patients, pain was not a symptom. With the exception of case XXIX, where there is a history of injury over the spleen, it is unlikely that pain is due to perisplenitis as this is a very infrequent pathological finding. Hepatitis is a much more probable cause of the abdominal pain. The relationship of pain to hepatitis seems fairly clear in case IX when the attacks of pain were associated with fever and jaundice.

Digestive symptoms commonly complained of are flatulence and diarrhoea, while vague indigestion and sickness are also mentioned occasionally.

In the case notes at our disposal it may be seen that flatulence was a complaint in six patients (cases III., XIII., XIX., XXIII., XXX., XXXIX.) In one of these patients (XXX.) the symptoms closely resembled those found in association with cholecystitis: flatulence, hyperaesthesia of the skin of the upper abdomen, pain passing round to the back and to the shoulder. It is possible that the feeling of distension which is so commonly complained of in gall bladder disease may be due to associated hepatitis.

Diarrhoea was a prominent symptom in cases XII., XVIII., and XXXVIII. Portal congestion and defective water absorption from the gut may account for this symptom.

Vague indigestion and sickness were complained of in cases XI., XVIII., XXVI., and XXVIII. In this connection it may be noted that in six cases in which test meals were investigated, two showed no free HCl (XVIII and XXVII.) while the others (II., VI., XIX., and XXXVI.) showed normal acid curves.

Symptoms referable to hepatic insufficiency.

Jaundice, when it occurs in association with hepatitis, is nearly always mild, and is frequently absent. Only very rarely is it severe. Apart from jaundice, a curious non-icteric type of sallow brownish pigmentation is sometimes seen, which was present

particularly in Case XXII. It is to be noted that pigmentation of this type in hepatic disease does not necessarily mean haemochromatosis, which was definitely excluded in this case.

Ascites and hepatic oedema have already been discussed (p. 242).

Epistaxis.

Epistaxis is a frequently recurring and important symptom. In the present group of cases it occurred 14 times, and twelve of these patients lay in the groups from cases VII. to XXXIV. where hepatic disease was readily recognised either at an early or advanced stage. Two cases (II. and XLI.) were outside this group. In cases II., XI., XV., XXII., and XXXIV., in which nose-bleeding occurred, the platelet counts were 33,000, 37,000, 74,000, 60,000 and 97,000 respectively. In cases II., XI., and XXII., there were other manifestations of thrombocytopenic purpura - purpuric spots in the skin, ecchymoses and prolonged bleeding time.

While the occurrence of spontaneous capillary bleeding is recognised in acute hepatic insufficiency (cholaemia), less attention has been paid to it as a manifestation of milder hepatic disease. A case has been recorded by East (1932) in which the purpuric manifestations constituted the "presenting symptom" of hepatic cirrhosis with splenomegaly.

The capillary resistance test was positive, and the changes in coagulation, bleeding time and platelet-count were in accordance with the diagnosis of "thrombocytopenic purpura".

Weil and his colleagues (1922) and Fiessinger and Diaconesco (1925) have shown that the tendency to bleeding in hepatic disease is of two types - purpuric and haemophilic. The latter, characterised by prolonged coagulation time used to be ascribed to the presence of bile salts in the plasma. While bile salts prolong the coagulation time in vitro, it has been shown that in hepatic disease there is not a sufficient amount of bile acids in the plasma to account for the delayed coagulation in this manner (Petren, 1920). The latter writer found that, in the haemophilic type of case, coagulation time could be brought to normal values by the addition of a watery extract of tissue juices in the same way as in haemophilia. These resemblances to haemophilia have been further amplified by the work of Hartmann (1927).

In the purpuric type of case, the bleeding is spontaneous, and probably dependent upon some primary capillary damage. In hepatic cases the capillary resistance test is frequently positive as has been shown by Fiessinger and Diaconesco. Emile

Weil and his co-workers have described failure of retraction of the clot associated with a low platelet count in hepatic disease.

In our cases we have not encountered the haemophilic type of bleeding. Purpuric manifestations, which were often seen, seem to be definitely associated with hepatic disease. The defect which leads to purpura probably lies in increased permeability of the capillaries, the deficiency in the circulating platelets being secondary (Tidy, 1928). The relationship of hepatic disease to capillary damage and capillary bleeding still remains to be elucidated.

Clubbing of the fingers was present in two cases (XVII, and XXII.) in association with hepatic cirrhosis.

A mild temperature is occasionally encountered, which may be due to hepatitis.

Table IX

TABLE OF CASES IN WHICH THE DURATION OF HEPATITIS COULD BE ESTIMATED.

Case No.	Total Duration of Hepatitis.	Result.
VII	28 years	Death from cancer of tongue 4 years after splenectomy.
IX	11 years	Alive 6 years after splenectomy. Had epistaxis and flatulence for some years after operation.
XIII	5 years+	Death from paratyphoid shortly after operation.
XV	12 years	Death from haematemesis a few days after splenectomy.
XVI	20 years	Suicide (no operation).
XVII	19 years	Death after splenectomy (?Haemorrhage).
XVIII	11 years	Well a year after splenectomy
XX	7 years	Well 2 years after splenectomy.
XXI	6 years	Death from haemorrhage the day after splenectomy.
XXII	12 years	Death from hepatic insufficiency (No operation).

Chapter 13.

TREATMENT AND RESULTS.

Since Banti first claimed that the cirrhosis and anaemia were splenogenic in origin, splenectomy has held the field as the means of treatment.

The objects of treatment in this disease must be

1. The arrest of hepatitis.
2. The cure or improvement of anaemia.
3. Relief of special symptoms such as haematemesis, and digestive disturbances.

The results of treatment may only be assessed by comparison with the normal course of the disease.

1. Hepatitis associated with splenomegaly seems to run an extraordinarily long and often benign course in the young subjects in whom this disease predominates. As we have already emphasised, hepatitis may remain latent for years. In only a few cases have we been able to date the hepatitis from some early symptoms. When it is seen from the adjacent table that the subjects of hepatitis may survive up to 24 years with their spleens, it is difficult to claim that splenectomy prolongs life by preventing further progress of hepatitis. Even gross cirrhosis may on-

facing p 266

Table X

TABLE OF CASES IN WHICH HAEMOGLOBIN VALUES ARE AVAILABLE BEFORE AND AFTER OPERATION.

Case No.	Hb range before operation.	Time after operation	Hb after operation.
V	50	3 years	54-62
VII	30-46	4 years	33-54
IX	70	2 months	80
XII	80	3 years	50
XVIII	80-90	1½ years	104
XX	28-32	2 years	50
XXIV	50	5 years	60-70
XXVII	30	1 month	60
XXXVII	21-30 (Haematemesis)	2 years	45-64
XL	60	4 years	70
XLI	42-45	2 years	72

ly be the residual scarring of a process long past its active acute stage.

Harrahan's series of cases, with and without splenectomy, has already been quoted (p.209). There was no essential difference in the expectation of life in the operated and unoperated cases.

2. Anaemia:

In evaluating the results of splenectomy on the anaemia, spontaneous fluctuations of the haemoglobin values must be kept in mind for comparison. Table X gives the haemoglobin values where these are available in the "follow-up" notes. Cases IX. and XXVII. are included, as they reported "well" and "much improved", 6 and 7 years after operation respectively. It should be noted, however, that cases XX. and XII. reported that they were "well" in spite of haemoglobin values of 50%! This fact demonstrates the extraordinary capacity of adjustment of the human subject to chronic moderately severe anaemia.

It is seen from the table that every case except one is still anaemic, and while some have improved, others have remained stationary, and one (Case XII.) was definitely worse. The single case with a haemoglobin of 104% had a haemoglobin value

as high as 90 per cent before operation. Such a change might have resulted from the spontaneous fluctuations which occur in the disease.

Table shows the changes in the red counts of 8 cases after splenectomy. With the exception of cases XX. and XXXIV., there was little significant change. In spite of the improvement in the red cell counts, Case XX. was still markedly anaemic, as can be seen from the haemoglobin value.

Case.	R.B.C. before Splenectomy.	Interval	R. B. C. after Splenectomy
VII	3.4--4.8	4 years	4.1--5.2
IX	3.7	2 months	4.4
XII	4.7	3 years	4.3
XVIII	4.0--4.2	1½ "	5.0
XX	2.1--2.6	2 "	4.5
XXIV	5.5	5 "	5.1
XXXIV	2.4--3.1	2 "	5.2
XL	4.6	4 "	4.3--5.0

As mentioned on p. 259 the leucocyte counts appear to rise and to remain at a higher level after splenectomy.

3. Special Symptoms.

Nose-bleeding, breathlessness, flatulence or recurrent jaundice were complained of in cases IX., X., XXXV., and XXXIX after splenectomy.

Haematemesis recurred after splenectomy, repeatedly, in Case XXXVII, and occurred for the first

time after removal of the spleen in Case XXVI. It should be noted in the histories of our series that gastrointestinal haemorrhage usually occurs only once or twice at intervals of years. In Case XX., haematemesis was definitely and frequently recurrent. So far as can be seen, haematemesis is not relieved by splenectomy. Portal congestion may still remain to precipitate haemorrhage from any part of the gastric mucosa.

One fact, however, remains: the subjective improvement frequently asserted by these patients after splenectomy. This may be to some extent psychological, but where the patients have had severe dragging pain due to the enlarged spleen, definite improvement in this symptom may result from removal of the spleen.

Operative Risks.

Of our 41 cases, 4 died without operation, from haematemesis,(VIII.), suicide,(XVI.), liver insufficiency,(XXII.), and acute cholecystitis and hepatitis,(XXIII.). 37 cases were operated upon:

Causes of post-operative deaths:

Peritonitis:	5.	(VI., XIV., XV., XIX., XXV.)
Liver insufficiency:	1.	(XVII.)
Intraperitoneal Haemorrhage:	2.	(XXI., XXX.)
Mesenteric Thrombosis:	3.	(I., III., IV.)

Unrelated to operation:
Paratyphoid: 1. (XIII.)

Excluding the last mentioned case, this gives an immediate post-operative mortality of 30 per cent. These patients are bad subjects for operation, not so much on account of anaemia, as on account of the liability to infection, and the tendency to mesenteric thrombosis.

Mesenteric Thrombosis:

In each instance in which this complication occurred, it was associated with old standing disease of the portal and splenic veins, which may lead to thrombosis quite apart from operation. Ludbrook (1931) records two cases which died of mesenteric thrombosis 13 months and two years after splenectomy. The operation of splenectomy is always followed by a rise in the platelet count, and this may further predispose to thrombosis. The most important factor, however, is probably local disease of the portal venous tree. In Case XI., platelets reached 790,000 without thrombosis. A case will be recorded later of reticulosis of the spleen in which the platelets rose to 800,000 after splenectomy without leading to thrombosis.

To sum up the results of splenectomy, we may

state that there is no proof that removal of the spleen either cures the anaemia or arrests the hepatitis.

The benefits which may ensue are:

1. Slight relief of portal congestion by cutting down a certain amount of blood-flow through the portal vein, and favouring the development of a collateral circulation at the raw area left after removal of the spleen.
2. Relief of discomfort due to dragging of the enlarged spleen.

To be weighed against this are the grave risks of the operation and the liability to infection, hepatic insufficiency, haemorrhage, and mesenteric thrombosis.

Medical Treatment:

Up to the present, the modern vigorous treatment of anaemia does not seem to have been applied to these cases. In the macrocytic anaemias, liver and vitamin B therapy should be actively carried out, while massive iron dosage might reasonably be expected to yield improvement in those cases with a low colour index.

The writer wishes to make a special plea for a more thorough investigation of the forms of anaemia occurring in hepatic disease, their spontaneous

fluctuations and their treatment by various methods.

Substances likely to damage the liver must be forbidden, e.g. alcohol, and in the case of operation there is a theoretical objection to chloroform. Treatment should also be directed against any bili-infections, on account of the associated hepatitis.

In prognosis, it should be remembered that the course of the disease is exceedingly chronic and in a number of instances the liver disease may be spontaneously arrested.

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A P P E N D I X

C A S E I.

Rebecca M. aet 42: Occupation: Nil.
Admitted to hospital: 3.11.23.
History: The patient gives a vague history of pain in the abdomen for three years. Her appetite has been good. No further details as to the history could be obtained as the patient's mental condition was very poor and she did not seem to understand questions.
Previous Health and Family History: Nothing of note revealed.
On Examination: The patient is thin, but there is no obvious pallor.
Abdomen: Appears to bulge especially in the upper part. The spleen is enlarged to within three inches of the umbilicus. A definite notch can be felt on the anterior edge of the spleen just below the costal margin. The liver is not felt and the liver dullness is apparently normal.
Other Systems: Nothing found.

Blood.

		Differential Count.	
R.B.C.	5,300,000.	Neutrophils	73.
W.B.C.	6,000.	Lymphocytes	17.
Hb.	84%	Monocytes	8.
C.I.	.79.	Eosinophils	2.

Wassermann Reaction: Negative.
Fragility Test: Haemolysis begins at .35%. There is no haemolysis at .4%. There is therefore an increased resistance of the red cells to haemolysis.
15.11.23. Splenectomy: The spleen was greatly enlarged, (weight 42 ounces); there were very few adhesions at the lower pole of the spleen. The veins

of the mesentery were very varicose so that it was difficult to find the splenic artery. The liver appeared to be normal.

18.11.23. Patient died with symptoms suggestive of haemorrhage into the peritoneal cavity.

Abstract of post-mortem notes: Old thrombosis was present in the splenic vein and the inferior mesenteric vein causing almost complete occlusion of the latter. Recent thrombosis of the splenic vein and of part of the superior mesenteric and portal veins was also present. Infarction of about three feet of jejunum had taken place commencing at a point two feet from the duodeno-jejunal flexure. The liver showed no naked eye fibrosis.

The Spleen:	Weight 1300 grammes.
Microscopic Examination.	
Vascular lesions:	Periarterial haemorrhages: periarterial fibrosis: perimalpighian haemorrhages and fibrosis: siderotic nodules all present.
Venous Sinuses:	Dilated, with definite increase of collagen in their walls.
Malpighian bodies:	Occasional germ centre seen.
The Pulp Cells:	An occasional giant cell seen. Apart from that, little abnormality in the type of cell present.
Liver:	Disintegration of liver cell columns with leucocyte and round celled infiltration.
Splenic Vein:	Marked intimal thickening and superadded thrombosis.

Miss C. Case II

Blood.

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M	E	B.
20.6.29	2,344,000	320	41	.9	No nucleated reds.				
	In the interval, 6 blood transfusions, X-ray treatment to the spleen, Liver diet, and arsenic internally. Recurrence of haematemesis in December.								
-. 12.29.	3,480,000	2,400	54	.84	Reticulocytes 3%				
	Liver and iron produced improvement. In January ecchymoses appeared over the thigh.								
11.2.30	4,200,000	1,400	65	.8	Reticulocytes .5%. Platelets: None seen in films: Bleeding time prolonged.				
1.3.30	4,200,000	1,000	70	.8	63	31	6		
	Platelets: 33,000. Reticulocytes: .5%								
5.3.30	Splenectomy: Spleen 920 grammes.								
8.3.30	3,970,000	16,200			85	13	3	0	0
	Reticulocytes: 2% Platelets: 220,000.								
14.3.30	4,300,000	11,400							
	Reticulocytes: 2% Platelets:380,000								

C A S E II.

Miss C. aet 27: Occupation: Nurse.
Admitted to hospital: 29.2.30.
History: In childhood the patient suffered from attacks of nose bleeding and purpuric spots. Epistaxis still recurs at intervals. She has always bruised easily. In the summer of 1929, she had a severe haematemesis when the spleen was found to be enormously enlarged. On gastric analysis no free HCl was found in the fasting juice but the acid curve was normal in later fractions. Only a trace of blood was found, and that at the end of the analysis. Haematemesis was repeated in December 1929. The spleen was enlarged to the umbilicus.
Blood Findings and the treatment are given in the appended table.
Operation: 5.3.30. Splenectomy was carried out. Some enlarged adventitious veins were seen passing from the spleen to the diaphragm. The liver appeared normal and there was no obvious disease of the splenic or portal veins.
Progress: 1933: Patient written to from time to time and says she is "very fit indeed".
Spleen: Weight 920 grammes.
Vascular lesions: Periarterial haemorrhages: periarterial fibrosis: perimalpighian haemorrhage and fibrosis: siderotic nodules all present.
Venous Sinuses: Moderate dilatation and slight increase of collagen in their walls.
Malpighian Bodies: Occasional germ centre seen.
Pulp Cells: No abnormality in the appearance of the individual cells.
Small Branch of Splenic Vein: Shows a plaque of intimal thickening, with splitting up of the internal elastic lamina.

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Amy P. Case III

Blood.

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
25.4.22	5,100,000	42,000	64	.65	79	20	1	0	0
8.5.22	3,020,000	8,200	40	.66	79	16	3	2	0
16.5.22	3,540,000	8,000	45	.6	78	16	3	2	1
31.5.22	3,890,000	8,500	60	.77	76	16	4	3	1
2.6.22	Splenectomy.								

C A S E III.

Amy P. aet 35: Occupation: Housewife.
Admitted to hospital: 1.5.22.
History: The patient complained of intermittent pain in the abdomen for eight months. Fourteen months ago her last child was born and since then she has had a feeling of lassitude. She is easily tired on the slightest exertion. Two weeks before admission she vomited a pint of blood and subsequently her motions were black for a day or two. Her appetite is poor and she is troubled with flatulence and acidity. Her doctor said that the splenic enlargement disappeared for three days after the haematemesis and then appeared again.
Family History: Two children were still-born.
On Examination: The patient is pale and anaemic.
Abdomen: The spleen is palpable and firm. It is enlarged almost to the umbilicus. The liver cannot be felt. There is no enlargement of the other organs and no tenderness elsewhere.
Cardiovascular System: Nothing abnormal found.
Other Systems: No abnormal physical signs.
Examination of Stool: Occult blood negative.
Wassermann Reaction: Negative.
Blood: counts are indicated in the appended table.
2.6.22. Splenectomy: The spleen was very vascular and decreased greatly in size at operation. (weight 750 grammes). Patient was apparently making good progress but eight days after the operation suddenly collapsed and died.
Abstract of post-mortem notes: Death was due to pulmonary embolism associated with ante-mortem thrombosis in the right auricle. Recent thrombosis had also taken place in the left internal iliac vein. There was

an old organized thrombosis of the splenic and portal veins. The veins of the stomach wall were varicose. The liver was pale (no sections were taken).

Microscopic Examination: There was advanced organisation of the thrombus in the splenic and portal veins. From the appearances, it was suggested that this thrombosis must be at least six weeks old if not more.

The Spleen: Weight 750 grammes.

Vascular lesions: Periarterial haemorrhage and periarterial fibrosis both present. No change in the perimalpighian zone and no siderotic nodules.

Venous Sinuses: Dilated with slight increase of collagen in their walls.

Malpighian bodies: No change in the individual cells beyond the flattened appearance of some of the pulp cells between the dilated sinuses.

Margaret M. Case IV

Blood findings.

Fragility test: No increase of fragility as compared with the normal.

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
15.8.31	2,140,000	6,600	25	.6	49	42	7	2	0
	Reticulocytes: .5% Platelets: 240,000								
21.8.31	Splenectomy.								
25.8.31	4,100,000	14,600	40	.48	74	26	8	0	0

C A S E IV.

Margaret M. aet 15.
Admitted to hospital: 15.7.31.
History: Parents have noticed for some time that she has been rather listless and pale. She has never complained of any pain beyond occasional headaches. Her appetite has been fairly good. She developed a slight yellow tinge every now and then, but her urine was never dark in colour. No history of epistaxis or melaena. Patient does not bruise easily.
Previous History: Always a fairly healthy child. She has never menstruated.
Family History: Nil to note. All the other members are healthy.
On Examination: Patient is small for her age. Weight 5 st. 10 lbs. Rather pale with a faint yellowish tinge in the skin. Mentally below average. Well nourished. Temperature normal.
Abdomen: Slightly protuberant. No hyperaesthesia. No rigidity or tenderness. Spleen projects downwards and forwards for about three inches below the costal margin. Liver is just palpable on taking a deep breath. No apparent free fluid.
Other Systems: Nil to note.
Wassermann: Negative.
Stool:

Total fat	18.2%
Split fat	44%
Neutral fat	56%

There was no excess of bile pigment in stool. Benzidine negative.
Blood Findings: see annexed table.
Operation: 21.8.31. Splenectomy: Liver appeared normal, gall-bladder not diseased. Spleen was

considerably enlarged - no adhesions.
23.8.31. Complaining of pain in the region of the wound. Some vomiting.
27.8.31. Rise of temperature. Pain in wound. Not looking well. No dullness at bases. Patient remained listless and failed to respond to treatment, and on 4.9.31. it was decided to reopen the abdomen.
Operation: 4.9.31. Abdomen reopened. No abnormality detected in veins or intestine.
15.9.31. Patient looks pale and dyhydrated. Breathing rapid and shallow. Pulse 160, very feeble.
Blood transfusion given. One pint of citrated blood from a compatible donor with 1 c.c. of coramine added. Responded temporarily but died at 7-30 p.m.
Post-mortem Examination revealed that death was due to mesenteric thrombosis. There was also an old thrombus in the portal vein.
Spleen:
Vascular lesions: Periarterial haemorrhage and periarterial fibrosis, both present. No perimalpighian change and no siderotic nodules.
Venous Sinuses: Dilated with a moderate increase of fibrous tissue in their walls.
Malpighian bodies: Germ centres predominant.
Pulp Cells: No special change in appearance, except for the presence of an occasional giant-cell.

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Helen P. Case V

Blood

Date	R.B.C.	W.B.C.	Hb	C.I.	N	Lym	M	E	B
1.4.27	4,010,000	5,330	50	.6	69	22	7	1	1
7.4.27	Splenectomy. Transfusion 600ccs blood.								
19.4.27	2,870,000	5,500	54	.9	76	20	1	3	0
22.4.27	3,520,000	8,500	60	.85	78	17	3	2	0
29.4.27	4,560,000	7,000	56	.62	72	22	3	3	0
-.10.27			55						
-. 8.29			62						
-.7.30			64						

C A S E V.

Helen P. aet 37. Occupation: Manageress.
Admitted to hospital: 1.4.27.
History: Patient complains of being devoid of energy during the past three years. During the last year she has got much worse and has had pain in the left side of the abdomen.
Family History: Mother and sister said to be anaemic.
On Examination: Patient is pale and sallow. Temperature rose to about 100 degrees at night before and after the operation. There is no actual jaundice.
Abdomen: The liver is palpable below the costal margin and feels slightly harder than normal. There is no free fluid. The spleen is enlarged to within one inch of the umbilicus.
Cardiovascular System: Haemic systolic murmur at the base.
Other Systems: Nil found.
7.4.27. Splenectomy: A little free fluid was found in the peritoneal cavity. The liver is not enlarged but is slightly pale and feels somewhat granular to the touch. Weight of spleen 17 ounces. Blood transfusion 600 c.c. Section of a vein at the hilum of the spleen showed endophlebitis with old standing thrombosis and recanalisation.
Progress: Patient made a good recovery. As can be seen from the table of blood findings the haemoglobin value did not improve appreciably. But, nevertheless, she was able to continue her duties which were somewhat strenuous.
July 1930: She reported and mentioned that she had had an "acute septic sore throat".
October 1930: Patient reported again on account of

the throat condition which was found to be cancer of the pharynx from which she died. There was no post-mortem examination.

Spleen: Weight 530 grammes.
Vascular lesions: Perimalpighian haemorrhages and fibrosis: periarterial haemorrhage and fibrosis: no siderotic nodules.
Venous Sinuses: Dilated with cellular walls: moderate increase of collagen fibres.
Malpighian bodies: No germ centres seen.
Pulp Cells: No abnormality in appearance.

Robert C. Case VI

Blood:

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M	E.	B.
15.1.27	2,070,000	3,000	36	.9	56	31	12	0	0
	Anisocytosis, Normoblasts and Polychromasia.								
28.1 - 31.1.27	Haematemesis and melaena.								
28.1.27	1,510,000	2,000	30	.8	70	22	7	0	0
	No malaria parasites.								
4.2.27	150 ccs blood transfused.								
8.2.27	1,730,000	2,500	26	.78	71	15	13	0	0
	Anisocytosis, Normoblasts, and polychromasia.								
9.2.27	Talma Morison operation:								
	Ascites and oedema of the legs persisted.								
23.2.27	2,253,000	3,100	30	.7	73	20	6	0	0
17.3.27	2,010,000	3,000	30	.75	57	35	5	0	0
24.3.27	Haematemesis.								
28.3.27	1,600,000	3,000	28	.88	78	14	6	0	0
31.3.27	Splenectomy. Spleen weighed 14 ounces.								
	Some adhesions. Marked hob-nailed cirrhosis.								
	Patient developed subphrenic abscess and died.								

C A S E VI.

Robert C. aet 42: Occupation: Carpenter.
Admitted to hospital: 11.1.27.
History: Until two days before admission the patient felt quite well and his appetite was good. He then had a sudden sharp pain in the abdomen which passed off after a few minutes. He felt giddy and an hour later he vomited some dark brown fluid. The following day he passed a black motion. In the afternoon he vomited blood again and had more maelena. He has never had a similar attack before.
Previous Health: Patient had syphilis twenty five years ago. Malaria in Greece 1917. He drinks three to four pints of beer at week-ends.
Family History: Nil to note.
On Examination: The patient is pale with a yellowish tinge. Temperature during his stay in hospital rose irregularly up to 100.
Abdomen: Is diffusely distended. The liver is palpable a hand's breadth below the xiphisternal junction in the mid-line. The spleen is felt three inches beyond the costal margin. There is a fluid thrill and shifting dullness in the flanks. There is no tenderness.
Test Meal: Free Acid .073%
Combined Acid .131%
X-Ray: The stomach is hypertonic: no ulcer.
Other Systems: Nil to note.
The Blood Findings are shown in the table.
15.1.27. Wassermann Reaction: Positive.
8.2.27. Oedema of the ankles was present.
8.3.27. Severe epistaxis.

Abstract of post-mortem notes: Slight atheroma beyond the aortic valves. Subphrenic abscess. Marked coarse cirrhosis of the liver. Thrombosis of the splenic vein. The small intestine was very oedematous. The oesophageal veins were dilated but no erosion was visible. Microscopically the liver showed general disassociation of the cell columns. Many cells had multiple nuclei. Old standing thrombosis of the splenic vein. The kidney showed chronic nephritis.

The Spleen: Weight 434 grammes.

Vascular lesions: Perimalpighian haemorrhage and fibrosis: periarterial haemorrhage and fibrosis: sideriotic nodules all present.

Venous Sinuses: Slightly but visibly dilated. Slight increase of collagen in their walls.

Malpighian bodies: No germ centres.

Pulp Cells: Crushed and somewhat flattened between the sinus walls.

facing p. 29th

Gladys H. **Case VII**

Blood.

Date	R.B.C.	W.B.C.	Hb	C.I.	N	Lym	M	E	B
22.11.23	3,400,000	5,500	30	.47					
14.12.23	4,580,000	4,000	46	.5	63	27	5	2	1
11.1.24	4,800,000	4,300	40	.41	59	24	12	3	2
29.1.24	4,530,000	2,300	42	.46	54	40	4	5	2
19.2.24	4,770,000	10,000	35	.37	71	25	6	0	0
20.3.24	Splenectomy:								
31.3.24	4,700,000	16,000	39	.42	19	5			
19.5.24	5,100,000	13,200	35	.34					
30.5.24	4,720,000	16,000	42	.44	60	28	10	1	1
20.6.24	4,100,000	11,200	33	.4					
19.7.24	5,000,000	11,000	42	.42	45	36	15	4	0
6.3.25	5,500,000	22,000	47	.42					
-.7.27	5,200,000	7,600	54	.52					
Feb.28	4,600,000	11,000	32	.38	Patient now has cancer of the tongue.				

C A S E VII.

Gladys H. aet 28.
Admitted to hospital: 4.12.23.
History: Patient complained of breathlessness on exercise, sleeplessness and a feeling of fatigue for the past ten years. She has also had attacks of nose-bleeding and headaches. The patient had an enlarged liver with jaundice when she was five years old. This lasted five weeks.
Family History: Nil to note.
On Examination: The patient is a well nourished woman but is definitely pale.
Abdomen: The liver can be felt one inch below the costal margin and its edge is somewhat hard. The spleen is palpable just beyond the costal margin. There is no enlargement of the other organs and no tenderness.
Cardiovascular System: There is a soft haemic systolic murmur at the base of the heart. No other abnormalities.
Other Systems: Nil to note.
Blood: The counts are given in the annexed table.
Wassermann Reaction: Negative.
Van den Bergh: Direct: Negative. Indirect: Positive 2.5 units.
Fragility Test: Haemolysis begins at .55% and is complete at .4%. Fragility is therefore increased.
Price-Jones Curve: Shows a microcytosis, the majority of the red cells measuring 6 to 6.5 (done after splenectomy).
20.3.24. Splenectomy: The liver is coarsely cirrhosed and enlarged. The spleen was adherent to the

under surface of the diaphragm. Its weight on removal was 400 grams.
A section of the liver taken at operation showed a regenerating nodule with slight chronic inflammatory changes round the portal tracts.
31.5.24. Haemolysis of the red cells begins at .55% i.e. there is no alteration in fragility as a result of splenectomy.
The Spleen: Weight 400 grammes.
Vascular lesions: Periarterial fibrosis with haemorrhage. No perimalpighian change and no siderotic nodules.
Venous Sinuses: Moderately dilated with slight increase of collagen in the walls.
Malpighian bodies: Nil to note.
Pulp Cells: No change in appearance of individual cells.

facing p. 296

Maud M.K.

Blood.

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
13.9.29	1,800,000	1,200	20	.5	75	22	0	2	1
18.9.29	3,140,000	5,100	21	.35	66	33	0	o	0
1.10.29	3,700,000	7,300	20	.3	62	36	0	2	0
16.10.29	3,020,000	5,400	29	.48	71	24	3	2	0

C A S E VIII.

Maud M. K. aet 65: Occupation: Housewife.
Admitted to hospital: 3.9.29.
History: Four months before admission patient lost her voice. On four occasions in the past nine months she has vomited blood, the last occasion being on 16.8.29. She suffers from shortness of breath on exertion. This symptom she has noticed for a year or two.
Previous Health: There is a long history of past illness with trouble in the right foot. Three years ago she had an operation for tuberculosis of the right foot. Patient's mother and one sister died of tuberculosis.
On Examination: Patient is pale. Temperature rises up to 99 at night.
Abdomen: Is diffusely distended. The liver can be felt one inch below the costal margin. Spleen is palpable two inches below the costal margin.
Examination of Stool: Occult blood negative.
Test Meal: Fasting Free HCl 0.
Total acid 8.
One Hour: Free HCl 0.
Total acid 24.
Chest: Coarse crepitations at the roots of both lungs.
X-Ray: Opacities in both hilar regions and at the left apex.
Sputum: T.B. Negative.
Larynx: Swelling of mucous membrane and granulation tissue on the posterior part with some oedema of the arytenoids.
Cardiovascular System: Mitral systolic murmur: no other signs.

Van den Bergh Reaction: Negative, direct and indirect.
Wassermann Reaction: Negative.
Blood findings are given in the table.
23.10.29. Patient began to vomit blood in large quantities. This continued all through the night and in spite of active treatment could not be controlled. Death occurred 24.10.29.
Abstract of post-mortem notes. The liver is definitely cirrhosed with a fibrous network of connective tissue passing through all parts of the liver. Microscopically the liver shows marked new growth of connective tissue around the portal tracts, in which infiltration with lymphoid cells is prominent. In the newly formed lobules degeneration and regeneration of cells is going on hand in hand. There is very marked infiltration with leucocytes in some of the degenerated areas. In other areas staining with bile pigment is prominent.
Oesophagus: There is dilatation of tortuous veins beneath the mucosa of the lower end of the oesophagus. The intestine is full of unaltered blood.
The spleen is enlarged, weighing 28 ounces.
There is chronic inflammation of the mucosa and submucosa in the neighbourhood of the vocal cords.
The lungs: show numerous scars of old tuberculosis.
The Spleen: Weight 870 grammes.
Vascular lesions: Periarterial haemorrhage: periarterial fibrosis: perimalpighian haemorrhage and fibrosis: siderotic nodules.
Venous Sinuses: Congested and dilated. Reticulin of the sinus walls is thickened to take the red van Gieson stain.
Malpighian bodies: No germ centres seen.
Pulp cells: No visible change in the appearance of these.

facing p. 292

Robert S.

Blood

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
14.9.27	3,700,000	3,400	70	.9	56	31	13	0	0
14.10.27	Splenectomy.								
21.10.27	4,100,000	7,600	82	1.0	61	29	6	3	1
28.10.27	4,640,000	7,000	74	.8	57	40	3	0	0
14.12.27	4,440,000	7,600	80	.9	55	40	5	0	0

C A S E IX.

Robert S. aet 33. Occupation: Draughtsman.
Admitted to hospital: 7.10.27.
History: Patient had syphilis five years ago and was under skilled treatment for 6 months. At the end of that time he developed jaundice which was said to be due to Salvarsan poisoning. He recovered in four months, but since then he has felt depressed and weak. His Wassermann reaction was quite negative after the course of treatment. His cerebrospinal fluid was not examined. Two years ago patient had a haemorrhage from the rectum, losing about a pint. He felt very weak afterwards. At this time it was found that he had an enlarged spleen.
Patient always feels heavy and depressed. About four years ago he began to have shivering attacks, with pains round the umbilicus. These were followed by weakness which lasted for about a fortnight. During these turns he sweats persistently for the first three days. He is sometimes a little jaundiced during these attacks.
Previous History: Dysentery. No history of alcoholism.
Family History: Nil to note.
On Examination: Patient is a little pale and somewhat depressed.
Abdomen: Appears a little full in the left hypochondrium. There is no cutaneous hyperaesthesia. The spleen is easily palpable, extending down nearly to the umbilicus. It is firm in consistence but not very hard. There is a little tenderness on pressure over it. Liver just palpable on deep inspiration, but not enlarged, the liver dullness being normal in extent.

No dullness in the flanks. Nothing else abnormal felt in the abdomen.

Cardio-Respiratory System:

B.P. S.105. D.60. Nil else to note.

Other Systems: No abnormality detected. No enlarged glands felt.

Blood findings are indicated in the table.

Operation: 14.10.27. Splenectomy.

Numerous dilated veins in abdominal wall suggestive of cirrhosis. The spleen was mottled and rather pale in colour, with smooth surfaces: no adhesions except at upper pole and extending a hand's breadth below the costal margin. The liver was slightly smaller than normal, with a rough morocco leather surface, not densely hard - a relatively early stage of cirrhosis. Numerous large veins were seen passing from the spleen and crossing over the splenic flexure of the colon. There were numerous enlarged glands in the splenic pedicle. Weight of spleen 1020 grammes.

29.10.27. Discharged. Condition very satisfactory.

Progress

14.12.27. Reported: in very good health: good colour: eating and sleeping well: in good spirits: no further sweating: firm scar. Is obviously putting on weight.

March 1930: He replied to a questionaire that since operation he was fit for work, had never vomited blood or had melaena: had occasional slight nose bleeding: no jaundice or swelling of the abdomen: suffers from flatulence, a symptom which he had before operation. He suffers slightly from breathlessness.

18.4.33. Wrote that his health was what he would describe as normal. About two years ago, itchy and watery headed shingles appeared on several parts of his body, eventually developing into patches. His doctor prescribed for him without benefit and in

despair he wrote to the National College of Health, Manchester, and was told that the condition was due to absence of his spleen. The treatment they prescribed has cured him and the patches are healed. (? Syphilis) An Insurance Company has recently accepted him for a Life Policy.

Spleen: Weight 1020 grammes.

Vascular lesions: Periarterial haemorrhage: periarterial fibrosis: perimalpighian haemorrhage and fibrosis: no siderotic nodules.

Venous Sinuses: Moderately dilated. Marked increase of collagen in sinus walls.

Malpighian bodies: Occasional germ centres.

Pulp Cells: An Increased proportion of elongated fibroblastic cells: otherwise nil to note.

C A S E X.

Euphemia A. aet 49: Occupation: Dressmaker.
Admitted to hospital: 25.4.28.
History: Until four years ago patient was in excellent health. She then began to have pain and swelling in the right side below the ribs, the pain being a dull ache and constant in character. She felt faint and weak and her legs and feet became swollen, so that she could not get her shoes on. She was in hospital for three months under medical treatment and was much better on discharge. About six weeks later she had a return of the same symptoms, most of the pain being on the right side, but occasionally there was sharp pain for days at a time in the left side. She could feel a large hard swelling in the left side. Her legs were again swollen and she was in indifferent health for many months. During her bad turns she became "yellow".
Previous Health: Muscular rheumatism, bronchitis and pleurisy. Erysipelas three times.
Family History: Nil to note.
On Examination: Intelligence average. Weight 8 stones. There is a slight malar flush and an icteric tinge in the skin. The mucous membranes and lips are pale.
Abdomen: There is slight swelling of the abdomen and noticeable fullness in the flanks. There is tenderness on both sides over the liver and spleen. Liver is palpable three fingers breadths below costal margin, smooth and tender to pressure. Spleen is palpable two fingers breadth below costal margin. It is hard, smooth and tender. A

fluid thrill can be elicited in the flanks. Friction is heard over the spleen.

Circulatory System: Nil to note.

Respiratory System: Coarse rhonchi heard in various parts of the chest. Nil else to note.

Nervous and Other Systems: No abnormality.

Blood Count:

R.B.C.	4,200,000
W.B.C.	7,200
Hb.	60%
C.I.	.71

Differential Count:

Neutrophils	60%
Large Lymphocytes	16%
Small do	23%
Eosinophils	.5%
Basophils	.5%

Fragility Test: No haemolysis above .4% Saline.

Coelioscopy: 11.5.28. Under scopolamine morphine narcosis. Coelioscopy revealed that the spleen was considerably enlarged with a rounded lower margin and no definite perisplenitis. The surface appeared to be a pale red colour, with numerous white pin points visible over it. The liver was next examined. It appeared to show a moderate degree of cirrhosis. The surface of the liver had an appearance, when seen through the cystoscope, similar to that of fat. This appearance was probably due to some degree of perihepatitis. The gall-bladder was clearly visible. It was large and probably thin-walled, having the normal green appearance. There was a small amount of fluid in the peritoneal cavity, and this rendered the examination difficult, owing to the fact that oxygen introduced by trocar and cannular bubbled up the fluid in the line of vision.

Operation: 14.5.28. Splenectomy.
Some free fluid in abdomen. Very marked perihepatitis over liver, which also showed definite coarse cirrhosis. Cirrhotic change less marked over left lobe. Spleen large, smooth, with rounded lower border. No adhesions. Slight perisplenitis.
Progress: After operation patient developed a bronchitis, and later parenchymal involvement of the lung with marked pyrexia, and large quantities of purulent sputum, occasionally blood stained. This complication cleared up in about three weeks. During that time, however, further trouble ensued. Oedema of the extremities was very marked, and both legs swelled to almost double their normal size. Patient looked very toxic and ill, slept badly, and was definitely suffering from liver insufficiency. The oedema of the extremities remained much the same until the administration of novasurol, ½c.c. weekly, was begun four weeks prior to discharge. After the fourth dose of this, tremendous improvement was noticed.
As regards the wound, this broke down a fortnight after operation and was re-sutured, but again broke down. On discharge the area had granulated well, and the abdominal wall was satisfactorily kept together by means of an adhesive belt with tapes.
21.7.28. Discharged.

R.B.C.	3,500,000.
Hb.	70%
C.I.	1.

20.3.29. Ventral hernia present, caput Medusae. Liver still very large. Early distention of veins. Getting about and feeling fairly well.
March 1930: Replied to a questionnaire that she was

only "slightly improved" since operation, and that she was somewhat jaundiced. She suffers from flatulence and indigestion, is slightly breathless and can only do slight work.
April 1933: Written to but no answer received.

Spleen:
Vascular lesions: Periarterial Fibrosis: No fresh periarterial haemorrhage: no siderotic nodules.
Venous Sinuses: Dilated, with increase of collagen in their walls.
Malpighian bodies: No germ centres seen. Hyaline masses prominent.
Pulp Cells: No change in appearance of individual cells.

Joseph F. Case XI

Blood

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
2.12.29	4,200,000	4,800	66	.79	55	36	7	2	0
19.12.29	3,040,000	Platelets 37,000							
27.12.29	Splenectomy								
29.12.29	4,050,000	28,000	Platelets: 310,000						
1.1.30	3,720,000	15,000	Platelets 540,000						
3.1.30	4,260,000	12,800	Platelets: 790,000						
8.1.30	4,420,000	10,000	Platelets: 590,000						

C A S E XI.

Joseph F. aet 13.
Admitted to hospital: 21.12.29.
History: Patient was quite well until five months ago when he vomited frequently for three or four days. The vomit was yellowish in colour and contained neither coffee grounds nor obvious blood. There has been no vomiting since then. A month later he was sent home from school feeling sick and shivering. This passed off in two days. His eyes were sore at nights; vision was good and there were no other eye symptoms. He has not felt this for some weeks.
Eight weeks ago, it was noticed that his abdomen was swelling. During the past three weeks he had noticed that his handkerchief had been bloodstained after blowing his nose. For four or five days his urine was smoky red in colour. For the past seven or eight weeks he has had many small reddish spots on the skin, especially on the chest. There has been no abnormal tendency to bruising. No history of melaena.
Previous Health and Family History: Nil to note.
On Examination: Patient is of good physique for his age and looks well. Conjunctivae show a very slight yellowish tint. There is no evidence of jaundice of the skin. Skin and mucous membranes show a slight degree of anaemia. There are a few small purpuric spots on the front of the chest, abdomen and arms. These are the size of pin-heads and do not disappear on pressure.
Abdomen: There is a general fulness, rather more pronounced on the left side. Slightly distended

veins are present over the upper part. Thespleen is enlarged to the midline and to a point one inch below and to the left of the umbilicus. It is firm and has all the characteristics of a splenic enlargement - notch, dull percussion note, and mobility on respiration. There is no dulness in the flanks. The liver is not enlarged.

The Blood Counts are shown in the table.

Fragility Test: Haemolysis begins at 0.45% saline.
complete 0.35% "

Van den Bergh: Direct reaction - positive delayed.
Indirect do - positive.

Blood Cholesterol: 118 mg% (low normal).

Wassermann: Negative.

Cardiovascular System: There is a faint systolic murmur at the base, otherwise nil to note.

Other Systems: Nil to note.

Operation: 27.12.29. Splenectomy.

The spleen was very large and firm, somewhat pale and a little puckered on the surface. The liver was small and hob-nailed, the left lobe extending very slightly beyond the middle line. The gall-bladder wall was thickened and opaque, whitish in colour, but no stones were felt. The stomach and duodenum were normal. Weight of spleen was 660 grammes.

7.1.30. Sudden acute pain to left of wound in morning. Lasted about one hour. Disappeared shortly after an enema had been given. Diarrhoea during the day.

11.1.30. Discharged.

Progress: Was killed in a motor accident 20 months after operation (August 1931). He had been quite well and going about.

Spleen: Weight 660 grammes.

Vascular lesions: Periarterial haemorrhage: peri-

arterial fibrosis: perimalpighian haemorrhage and fibrosis: no siderotic nodules.
Venous Sinuses: Marked dilatation. Very slight increase of collagen in sinus walls.
Malpighian bodies: Germ centres prominent.
Pulp Cells: No abnormality in appearance.

C A S E XII.

John T. aet 12.
Admitted to hospital: 30.12.29.
History: Patient dates his illness from two months ago when he began to lose appetite and energy and to feel sickly. He had some pain across the upper abdomen and vomiting on one or two occasions. His bowels moved 4 times a day and sometimes oftener. This tendency to diarrhoea has been present for years and he has passed motions up to 12 times a day. He often has a feeling of wishing to pass a motion but is unable to do so. During the past two months he has been troubled with nose bleeding. This lasts only a few minutes at a time with intervals of freedom of two to three weeks. The quantity lost is not large. He has not been able during these last two months to play football and the usual children's games, as he is too easily tired.
Previous History: Quite healthy apart from a desire frequently to go to stool. Two years ago he was "run down", and was said to be suffering from rickets. He was given malt and remained fairly well for about a year when he became seriously ill. He had then acute intestinal catarrh with colic and jaundice. He was ill for about a month and made a good convalescence.
Family History: Father and mother cousins, apparently healthy.
On Examination: Patient is a pale but well developed boy of 12. His face is plump and there are no signs of disease apart from the swollen abdomen.
Abdomen: The abdomen is distended to a considerable degree, being full anteriorly and in the flanks, and the lower ribs are splayed outwards over the distended upper part of the abdomen. On the skin of

the upper abdomen there are numerous distended veins running upwards from the umbilicus to the chest wall and as far as the upper ribs where they disappear. These veins fill rapidly from below, slowly from above, when emptied by pressure.
There are no signs of free fluid in the peritoneum. The liver is greatly enlarged, the lower border being palpable as a sharp even edge, a hand's breadth below the costal margin. The spleen also is greatly enlarged, reaching halfway to the umbilicus and with a notched anterior margin. There are no other abnormalities in the abdomen beyond a scar of operation for inguinal hernia on each side.
Cardiovascular System: The heart is pushed upwards. Faint systolic murmurs at mitral and pulmonary areas. Other sounds closed.
Other Systems: Nil to note.
Blood Examination:

R.B.C.	4,780,000
W.B.C.	8,300
Hb.	80%
C.I.	0.85

Differential Count:

Neutrophils	68%
Small Lymphocytes	20%
Large do	5%
Monocytes	7%

No abnormal types of W.B.C.

Coagulation Time	3½ minutes.
Bleeding "	4 do

Wassermann: (1st. report: weak positive) 2nd. and 3rd. reports: (after provocative dose of .3 gramme novarsenobillon): Negative.

Mother's blood Wassermann - Negative.

Operation: 21.2.30. Splenectomy.
There was no free fluid. The liver was found to be greatly enlarged, quite smooth though mottled in appearance and very firm like india-rubber. The gall-bladder was enlarged, and tense, with a fat-laden wall. The cystic gland was enlarged: stomach and duodenum normal. The spleen was enlarged to three times normal size. There were numerous enlarged fleshy glands along the splenic vessels, and several spleniculi. The lieno-renal ligament was unduly vascular. The falciform ligament was noted to be very vascular with several large veins and numerous tiny vessels. At its attachment to the liver, fine vessels were noted to run to it from the capsule of that organ. Weight of spleen was 600 grammes.

28.2.30.

R.B.C.	4, 800, 000
W.B.C.	17, 200
Neutrophils	78%
Large Lymphocytes	12%
Small do	8%
Eosinophils	2%

18.1.33. Reported. Slight dermatitis on back of both hands and feet. Sometimes blisters.
The condition was not considered to have any relation to abdominal one.
25.4.33. Reported (by request):

R.B.C.	4, 350, 000
W.B.C.	10, 600
Hb.	50%

Skin condition cleared up. Has been very well otherwise - playing games and never off school. Colour good. No visible signs of anaemia.

Mary B. Case XIII

Blood

Date	R.B.C.	W.B.C.	Hb	C.I.	N. Lym. M. E. B.
21.12.28	1,410,000	3,400	20	.7	Reticulocytes:1%. Platelets: Very few: Marked anisocytosis and poikilocytosis. Cells small.
1.2. 29	2,700,000	3,800	20	.4	Reticulocytes: 1%
26.2.29	Splenectomy. Free fluid in the abdomen, and thickening of peritoneum in gastrosplenic omentum. Liver enlarged and cirrhosis very definite: Blood transfusion after operation: Enlarged glands in the splenic pedicle. Wt. 710 gms.				
2.3.29	3,410,000	23,100	28	.4	Reticulocytes, 4.6% Platelets: 700,000
5.3.29	3,890,000	15,600	30	.4	Platelets:600,000
11.3.29	3,900,000	15,400	30	.4	Reticulocytes: 2.3%
22.3.29	4,200,000	11,200	35	.4	Reticulocytes 1% Platelets: 50,000

C A S E XIII.

Mary B. aet: 49. Occupation: Housewife.
Admitted to hospital: 17.12.28.
History: A week prior to admission patient suddenly felt a pain in the epigastrium which was relieved by vomiting. It was noted that the vomited material contained blood. The next day she noted that she pas-sed blood in the stools. Four days after this at-tack she again vomited blood, and her stools were black in colour. She had a third attack two days later in which the amount of blood brought up was greater than on the previous occasions.
Before the first attack of haematemesis, a week be-fore admission, patient had noticed a feeling of tightness across the epigastrium immediately after taking food. This discomfort had been present for about two months. Her appetite was poor, and she had a feeling of thirst occasionally: flatulence was troublesome. She has had no pain related to meals.
Five years previously the patient had an attack similar to the present one. A large spleen and a leucopenia were found then, and the Wassermann was triple positive. An ovarian cyst had been removed 19 years previously.
Family History: Mother has rheumatism and "gastri-tis". One sister died of a perforated peptic ul-cer. Father died of erysipelas.
On Examination: Patient is well developed. Very anaemic with a yellow pallor. Teeth artificial, gums healthy.
Abdomen: prominence on the left side which moves freely with respiration. There is some tenderness

for four inches below the costal margin on both sides, with increased muscular resistance over those areas. The liver edge is felt about one inch below the costal margin. The spleen is felt extending two or three inches below the costal margin. There are signs of free fluid.

Circulatory, Respiratory and Nervous Systems: Nil to note.

For two months after admission the patient was treated with arsenic, iron and liver. No rise in the haemoglobin values was produced, although the red cells increased without any reticulocytosis.

Wassermann: Negative.

20.2.29. Splenectomy.

Spleen: Weight 710 grammes.

Vascular Lesions: Perimalpighian haemorrhage and fibrosis: Periarterial haemorrhage and fibrosis: siderotic nodules.

Venous Sinuses: Dilated with increase of collagen in sinus walls.

Malpighian bodies: No germ centres seen.

Pulp Cells: An increased proportion of elongated fibroblastic cells. Nil else to note.

C A S E XIV.

David C. aet 19.
Admitted to hospital: 24.8.27.
History: Three months before admission the patient began to have a stabbing pain on the left side of the abdomen. The pain came in attacks lasting half an hour or so. He had no other symptoms of note at this time. About a month later he began to suffer from general weakness and lassitude, headaches, giddy turns, and slight breathlessness. During the last few weeks he has had several attacks of epistaxis and weakness has been increasing. There have been no digestive symptoms and bowels are regular. There has been no loss of weight.
Previous Health: scarlet fever and measles in boyhood.
Family History: Nil to note.
On Examination: The patient is pale and of poor physique but is not specially thin.
Abdomen: The spleen is enlarged to three inches below the costal margin. The liver is not obviously enlarged and cannot be felt. There is no free fluid.
Cardiovascular System: A soft systolic murmur was heard over the precordium.
Other Systems: Nil to note.

Blood:		
	R.B.C.	4,840,000
	W.B.C.	3,400
	Hb.	80%

Operation: 26.8.27. Splenectomy.
There were no adhesions. There were some enlarged glands in the splenic pedicle and in the mesentery. The liver was definitely cirrhotic.
Patient became irritable and sleepless following the

operation. Six days later the temperature had risen, with diarrhoea and rapid respiration. Typhoid was excluded by the usual tests. Pneumonia set in and death occurred on the eighth day after operation.

Abstract of post-mortem notes: The liver showed a well marked atrophic cirrhosis. There was well formed fibrous tissue in the portal tracts with focal necroses here and there. There was a low degree of generalised peritonitis. A mesenteric gland which was examined showed extensive central necrosis with a slight degree of acute inflammation. The bone marrow showed an extension into the shaft of the femur with a mixed leucoblastic and erythroblastic reaction. A fair number of megaloblasts were seen. Broncho pneumonia was present and had become confluent in the right lung. The left kidney was small and scarred ? Pyelo-nephritis. The right kidney was large and hypertrophied.

Spleen:

Vascular lesions: Periarterial haemorrhage and fibrosis: Perimalpighian haemorrhage and fibrosis: no siderotic nodules.

Venous Sinuses: Moderately dilated with increase of connective tissue in the sinus walls.

Malpighian bodies: Germ centres present.

Pulp Cells: No change in appearance.

C A S E XV.

George G. aet 26: Occupation: Inspector of Poor. Admitted to hospital: 15.2.30.

History: Two years ago patient awoke one morning feeling sick, and shortly afterwards vomited about half a pint of red blood. This was repeated on several occasions that day. This was the first warning he had of ill-health. He was treated for duodenal ulcer. Since then he has always had some abdominal discomfort, chiefly in the evenings, and has never really felt up to the mark - easily tired and not inclined to be energetic, but has had no specific complaint such as abdominal pain. Six months ago he had some nausea, but no vomiting, and thereafter for some days his stools were black in colour. Ten weeks ago he again vomited about a pint of bright red blood. Since then his lassitude and feeling of fatigue have been markedly increased. He has not felt fit for any work; he becomes breathless when he walks about, even on the level; he suffers from giddiness when he turns, stoops or rises quickly. Patient has always been pale and of a sallow complexion. He frequently has attacks of epistaxis.

Previous Health: An attack of jaundice lasting six weeks weeks twelve years ago.

On Examination: The patient is pale and of a sallow complexion. His eyes are rather sunken and have dark rings below them. There is a tinge of jaundice in his skin, and very slight icterus of the sclerotics.

Abdomen: Is rather full and appears larger above than below. There is a definite fullness in the left hypochondrium. The abdomen is soft, moves easily and rhythmically with respiration. On the left side there is a large firm swelling, reaching almost to the umbilicus, which moves downwards and forwards on

deep inspiration. It is firm in consistence, regular and smooth in outline and not tender on pressure. On the inner side a notch can be felt. The position, size, shape and consistence of this swelling render it obvious that it is the spleen. The liver is not palpable. No other abnormality was discovered on palpation of the abdomen. No enlarged lymph glands were felt on palpation of all the superficial groups.

Van den Bergh Reaction:

Direct: Positive delayed.
Indirect: Positive.

No bile ever appeared in the urine.

Blood:		
	R.B.C.	3,000,000
	W.B.C.	2,600
	Hb.	25%
	C.I.	0.42
	Neutrophils	71%
	Small Lymphocytes	23%
	Large do	5%
	Eosinophils	1%

Film: There is inequality in size of red cells, no nucleated red cells, no polychromasia. No myelocytes.

Reticulocytes	2%
Platelets:	74,000
Coagulation Time:	three and a quarter minutes.
Bleeding Time:	three minutes (Filter paper)

Fragility of the red cells was decreased. Lysis was not complete at .3%, and the cells were completely resistant at .45%

Blood cholesterol: 179 mgs %

Cardiovascular System: There were no murmurs, haemic or otherwise on auscultation.

Other Systems: Nil abnormal.

Operation: 11.3.30. Splenectomy.

Weight of spleen 1080 grammes. No adhesions. No free

fluid. Liver small and cirrhotic. Patient developed a bronchopneumonia to which haematemesis was superadded and death occurred on 20.3.30.

Abstract of post-mortem notes: Early peritonitis. Bronchopneumonia. Marked dilatation of veins at the lower end of the oesophagus. Liver much reduced in size. Whole of the left lobe had almost entirely disappeared. Right lobe roundish and very firm. Capsule showed fibrous tissue thickening and was finely nodular in appearance. Large smooth nodules like accessory livers on the under surface. Numerous haemorrhages scattered throughout the accessory livers. Section of the liver showed diffuse fibrosis.

Bone Marrow: The marrow of the shaft of the femur showed a replacement of the fatty tissue by a pale red erythroblastic tissue.

Spleen: Weight 1080 grammes.

Vascular lesions: Periarterial haemorrhage: periarterial fibrosis: perimalpighian haemorrhage and fibrosis.

Venous Sinuses: Markedly dilated. Increase of fibrous tissue in sinus walls.

Malpighian bodies: No germ centres seen.

Pulp Cells: No abnormality in the appearance of the individual cells.

C A S E XVI.

Robert R. S. aet 29.
Admitted to hospital: 13.5.28.
History: Since the age of nine years, patient was under observation with splenic anaemia. The blood counts throughout this period showed a secondary anaemia and leucopenia (counts not available). A sallowgreyish brown tint of the skin led to the diagnosis of Gaucher's disease, and on this account splenectomy was not considered. Throughout the illness the patient had repeated haematemeses. Intermittent attacks of jaundice occurred at first but later the jaundice was constant. He had severe dragging pains in the left side during the last few years and deep X-ray treatment was carried out. Spontaneous nose bleeding frequently occurred. The pain continued to be severe and on 13.5.28. the patient committed suicide by drinking lysol.
Abstract of post-mortem notes. The body was well developed and well nourished. There was no obvious oedema. The whole body showed deep jaundice. The mucous membrane of the oesophagus was desquamated in the form of a brown slough. The stomach and the upper part of the intestines showed marked necrosis of the mucous membrane.
The abdomen was moderately distended and contained eight to ten ounces of clear, slightly bile stained fluid. The liver was rather large and weighed nineteen hundred grammes. It was deformed by fissures and nodules. The outer surface of the liver showed numerous fibrous adhesions. On section, bands of fibrous tissue separated nodules of regenerated liver tissue. These nodules were considerably bile-stained. The gall-bladder contained one or two pigment calculi. There was no obstruction in the biliary passages which appeared healthy. The pancreas showed no obvious abnormality.

The spleen was enormously enlarged and weighed 1500 grammes. The peritoneal surface was an opaque white colour. The cut surface was somewhat paler than usual, and there were no signs of infarcts. The lymph glands of the gastro-splenic omentum were considerably enlarged and dark red in colour.

Bone Marrow from the shaft of the femur showed a marked reaction and was deep red in colour. Heart, aorta, lungs, and kidneys showed no abnormality.

The Spleen: Weight 1500 grammes.

Vascular Lesions: Perivascular haemorrhage: Perivascular fibrosis: Perimalpighian haemorrhage and fibrosis. Siderotic nodules.

Venous Sinuses: Slightly dilated with definite increase of collagen fibres in the walls.

Malpighian bodies: No germ centres seen.

Pulp Cells: No abnormality in appearance of the individual cells.

C A S E XVII.

Arthur W. aet 31. Occupation: Dental Surgeon.
Admitted to hospital: 23.9.30.
History: Epistaxis first occurred in 1911 and continued intermittently until 1922 despite cauterization. In 1922, following extensive cauterization the attacks were arrested and have not recurred since. In 1925 he had a severe gastric haemorrhage. A second haemorrhage occurred eighteen months later. The third haematemesis occurred April 1929, and was so severe that he nearly died. The last attack of haemorrhage from the stomach was on 26.6.30. For five years the patient has had swelling of the ankles and breathlessness.
Previous Health: Nil of importance. No history of jaundice or submucous haemorrhages or of bleeding from the rectum. While a student he was a heavy spirit drinker for two years.
On Examination: The patient is pale. There is marked clubbing of the fingers. Temperature is normal. There is definite but slight oedema over the skin of the legs.
Abdomen: The spleen is felt one inch beyond the costal margin. The liver is felt a hand's breadth below the xiphisternal junction in the midline. There is no free fluid and there is no tenderness or enlargement of the other organs.
Cardiovascular System: There is a soft systolic murmur at the apex, otherwise nothing abnormal found.
Wassermann Reaction: Negative.
Fragility Test: Haemolysis begins at .4% and is complete at .3% saline.
Van den Bergh Reaction: Negative direct and indirect.
Blood Count:

R.B.C.	3,330,000
W.B.C.	1,000
Hb.	66%
C.I.	.95

Differential White Count:		
	Neutrophils	65%
	Lymphocytes	28%
	Monocytes	4%
	Eosinophils	3%

Coagulation Time: One and three quarter minutes. (normal).

Laevulose Tolerance Test:

Fasting Blood Sugar	.106%
50 gms. Laevulose by mouth	
Half an hour after, blood sugar	.118%
One hour	.118%
One hour and a half	.118%
Two hours	.116%

Operation: 13.10.30. Splenectomy.
The liver was markedly cirrhotic. The spleen was not adherent. The spleen was large, measuring eight inches by four inches. (700 gms.) Splenic vein and artery were very tortuous and thickened. A blood transfusion was given. A few hours after the operation the patient died. There was no post mortem examination.
Spleen: Weight 700 grammes.
Vascular Lesions: Perimalpighian haemorrhage and fibrosis: periarterial haemorrhage: periarterial fibrosis. Siderotic nodules.
Venous Sinuses: Dilated with increase of collagen in the sinus walls.
Malpighian bodies: Nil to note.
Pulp Cells: No abnormality in appearance.

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Case XVIII

Fred. H.

Blood.

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
13.10.28	4,080,000	2,300	90	1.1	71	21	6	2	0
24.10.28	4,220,000	2,000	80	.95	70	20	5	5	0
29.10.28	Splenectomy								
21.11.28	3,200,000	6,600	58	.9	55	39	3	3	0
6.5.									
6.5.30	Readmitted for operation on inguinal hernia.								
8.5.30	5,030,000	7,000	104	1.0	62	29	8	1	0

Wassermann Reaction: Negative.
Van den Bergh Reaction: Negative.
Fragility Test: Haemolysis begins at .4% and is complete at .3% Saline.
The blood counts are indicated in the table.
Operation: 29.10.28. Splenectomy.
Great enlargement of the veins in the splenic pedicle. The spleen was large and measured 10" x 4" x 5". Early cirrhosis of the liver and ascites were present.
(Weight of spleen 1150 gms.)
After the operation the patient had some troublesome distension of the abdomen which was relieved by treatment. He was discharged 4.12.28.
Spleen: Weight 1150 grammes.
Vascular Lesions: Perimalpighian haemorrhage and fibrosis: periarterial haemorrhage and fibrosis. Siderotic nodules.
Venous Sinuses: Dilated with increase of collagen in their walls.
Malpighian bodies: Nil to note.
Pulp Cells: Compressed between the sinuses. No alteration in appearance.

Daisy M. Case XIX

Blood

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
14.4.25	3,040,000	3,560	65	1.1	71	12	16	1	0
1.5.25	3,893,000	2,660	72	.92					
21.5.25	3,530,000	2,500	56	.8	64	25	10	0	1
			Slight polychromasia.						
22.6.25	4,002,000	1,500	63	.78	50	33	17	0	0
25.6.25	Discharged.								
2.10.25	Readmitted.								
3.10.25	3,750,000	1,400	64	.86	76	14	10	1	0
15.10.25	Splenectomy and blood transfusion(1½ pints).								

C A S E XIX.

Daisy M. aet 44. Occupation: Housewife.
Admitted to hospital: 10.4.25.
History: Four months prior to admission the patient had ten teeth extracted after which she developed "influenza". A month later her liver was found to be enlarged, and she became pale and anaemic. Five weeks before admission her feet began to swell. The swelling came on during the daytime and subsided when the patient was in bed. Patient has always suffered from indigestion and flatulence. There is no history of alcoholic abuse.
Family History: Nil to note.
On Examination: There is pallor of the skin and mucous membranes. There is some oedema over the sacrum but none in the feet.
Abdomen: is uniformly distended. There is bulging of the flanks. No rigidity and no tenderness. The lower edge of the liver can be felt at the level of the umbilicus on the right side. The edge of the liver is smooth and sharp: its surface is firm and not tender. On the left side the spleen can be felt 2 inches beyond the costal margin. There is shifting dullness in both flanks and a fluid thrill can be elicited.
Cardiovascular System: There is an occasional dropped beat (extrasystoles). A systolic murmur is heard at the apex but is not propagated in any direction.
15.4.25. A trace of blood in the faeces.

Test Meal:

Fasting Juice.	
Free Acid	7.
Total Acidity	30.
After 1 hour.	
Free Acid	12.
Total Acidity	22.

X-Ray shows slow emptying of the stomach. There is a small residue after four hours.
While in hospital patient complained of pain in the back. Radiological evidence excluded the possibility of tumour growth.
Wassermann Reaction: Negative.
Van den Bergh Reaction: 8.5.25. Completely negative.
Trace of albumen in the urine. The patient ran a slight temperature, up to 100° in the evenings.
25.6.25. Patient was discharged from hospital.
2.10.25. Readmitted. While she was at home, the ascites had to be tapped four times, and the fluid was latterly blood-stained. There was now distension of veins round the umbilicus. No occult blood was present in the stool and the temperature was now normal.
15.10.25. Splenectomy. Three gallons of fluid removed from the abdomen. The surface of the liver was granular and finely cirrhotic. The spleen was enlarged and had one or two infarcts on the surface. One and a half pints of blood were transfused.
Patient ran a temperature after operation, and ascites had to be repeatedly tapped. Ultimately death occurred from peritonitis. 7.11.25.
Abstract of post mortem notes: Fibrino-purulent peritonitis. There was stenosis of the aorta between the superior and inferior mesenteric arteries. This was taken to be a congenital abnormality. There is a large irregular zone of degeneration under the capsule of the right lobe of the liver.
Spleen:
Vascular Lesions: Perimalpighian haemorrhage and fibrosis: periarterial haemorrhage: periarterial fibrosis. Siderotic nodules.
Venous Sinuses: Moderately dilated with cellular

walls. Very slight increase of collagen.
Malpighian bodies: Apparent new formation of lymph nodes along the penicillar arteries.
Pulp Cells: No abnormal appearances.

Thomas D. Case XX

Blood.

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
7.3.31	2,560,000	2,400	28	.58					
11.3.31	2,080,000	3,600	32	.75	80	12	8	0	0
		Platelets: 75,000.							
13.3.31	Splenectomy: Transfusion: 500ccs citrated blood.								
16.3.31	3,610,000	32,800	44	.6	Platelets: 164,000				
		Reticulocytes: 12%.							
24.3.31	3,750,000	12,600	46		Platelets: 123,000				

C A S E XX.

Thomas D. aet 26. Occupation: Warehouseman.
Admitted to hospital: 5.3.31.
History: Patient was perfectly well until January 1926, when he noticed that his abdomen was somewhat swollen. In April of that year he felt nauseated and on one occasion he vomited blood and at the same time his stools were black in colour. He has never had any vomiting since. Patient says that he was always rather pale after the haemorrhage, but the pallor became more marked and the abdominal swelling increased. He became very tired, sleepless and breathless, and had a feeling of heaviness in the left side.
After radiation of the spleen in 1926, he felt well and had no further symptoms except a feeling of weakness. He managed to carry on at his work until ten days ago when he again noticed that his abdomen was beginning to swell and the feeling of heaviness in his left side became more marked. Patient is troubled by breathlessness. appetite good. Bowels regular, no urinary symptoms. He has never lived abroad.
Smokes 30 cigarettes a day and takes a moderate amount of alcohol.
On Examination: Patient has a pale waxy appearance with a tinge of yellowness. Well nourished. Temperature normal.
Abdomen: Rather protuberant with slight fullness on the left side. No superficial or deep hyperaesthesia. There is slight tenderness below the costal margin on the left side. The spleen is greatly enlarged and extends almost to the umbilicus. Liver dullness is greatly diminished. There appears to be a little free fluid in the flanks.
Heart: Soft blowing systolic murmur in pulmonary

area. Nil else to note.
Lungs: Few crepitations at left base. Nil else.
Other Systems: Normal.
Wassermann: Negative.
Blood Counts: See table.
Van den Bergh: Direct delayed positive: indirect positive.
Icteric Index: 17.
Fragility Test: No increased fragility of red cells.
Coagulation Time: 4½ minutes (Capillary Tubes)
Bleeding Time: 6 do.
Operation: 13.3.31. Splenectomy.
A huge vein, as thick as a thumb, was seen crossing up from the umbilicus in the edge of the falciform ligament. All the veins encountered were distended, tortuous and dilated. The liver was small and showed an early stage of cirrhosis. There was a considerable amount of free fluid in the abdominal cavity. The spleen was large and had a mottled appearance. There were several adhesions, containing large veins, between the upper pole and the diaphragm. Patient was given 500 c.c. citrated blood. Weight of spleen 100 grammes.
25.3.31. Left side of chest aspirated and half a pint of straw coloured fluid withdrawn. Since operation patient has been running a slight temperature but feels well. He has been troubled by a slight cough but otherwise progress is satisfactory.
Progress.
25.4.33. Asked to report. Very well.

R.B.C.	4,500,000
W.B.C.	8,000
Hb.	50%

Spleen:
Vascular Lesions: Perimalpighian haemorrhage and

fibrosis: periarterial haemorrhage and fibrosis: siderotic nodules.

Venous Sinuses: Dilated and a moderate increase of collagen in their walls.

Malpighian bodies: Occasional germ centre.

Pulp Cells: No definite abnormality.

C A S E XXI.

Nicholas M. aet 29: Occupation: Miner.
Admitted to hospital: 10:4:17.
History: Weakness, vomiting after food, and pain in epigastrium; jaundice. The symptoms began five years ago. After three months in bed, all the symptoms disappeared except jaundice. Six months later, another attack similar in time and duration. Twelve months later, another attack similar to the others. The day before admission he had an attack of vomiting. Patient is addicted to alcohol. There is a history of haematemesis and melaena.
On Examination: Liver enlarged 3" below costal margin. Spleen much enlarged and notch felt.

R. B. C.	4,800,000
W. B. C.	1,600

Wassermann: Negative.
27.4.17.

R. B. C.	4,700,000
W. B. C.	1,600
Hb.	95%
C. I.	1.0
Height.	5 ft. 2"
Weight.	9 st. 3½ lbs.

No temperature: pulse slow: B.P. S. 104.

Treatment: Arsenic: hot baths.
Discharged after 12 weeks in hospital: still jaundiced.
Re-admitted: 5.2.18. With jaundice, pain in right hypochondrium, nausea, itching. Jaundice has never disappeared but has been renewed with fresh attacks which occur at approximately yearly intervals. Last attack 28.1.18.

On Examination: Well built and well developed adult

male. Very slow and dull in answering questions.
Abdomen: Skin pale yellow; distended, bulging in flanks, especially in the left. Many small bluish veins in skin, mostly in upper abdomen. Liver enlarged regularly to about 2" below costal margin. Edge defined and regular. No nodules palpable. Spleen considerably enlarged down and inwards; no notch palpable. Percussion confirms enlargement felt on palpation. Probably fluid in abdominal cavity.
Urine: Bile: otherwise normal.
Blood Count:

R.B.C.	3,700,000
W.B.C.	1,600
Hb.	70%
C.I.	.94

Operation: 26.2.18. Splenectomy. Spleen very much enlarged. Veins very friable and varicose.
27.2.18. The patient recovered from operation until ensuing day when he suddenly collapsed and died.

Notes from post mortem report. General jaundice. Haemorrhage from vessels at site of operation. Varicose dilatation of veins in lesser omentum. Liver surface shows slight irregularities. Increase of fibrous stroma but no definition of islands of liver cells characteristic of atrophic cirrhosis. The liver is deeply jaundiced.
Bone Marrow: there is no apparent replacement of fat by blood forming tissue.
Spleen.
Vascular Lesions: No perimalpighian changes seen.
Periarterial haemorrhage: periarterial fibrosis and siderotic nodules present.
Venous Sinuses: Dilated, with increase of connective tissue in their walls.
Malpighian Bodies: No germ centres seen.
Pulp Cells: No change in appearance.

C A S E XXII.

A.F. (Female) aet 26: No occupation.
Admitted to hospital: 10.6.31.
History: Since the age of 14, the patient has suffered from jaundice. The jaundice has always been mild and was associated with splenic enlargement. The urine contained urobilin and the condition was at first thought to be a haemolytic jaundice. There was no excessive fragility of the red cells, however. The patient has never menstruated. There has never been any haematemesis. Throughout her illness she has been subject to periodic nose bleeding. On examination the patient looks like an old woman. The hair is grey and there is a curious dirty-grey sallow appearance of the skin. There is a slight growth of hair on the face. These features indicate complete arrest of development of the usual secondary sexual characteristics of the female. There is oedema of the feet. Fingers show marked clubbing.
Abdomen: The abdomen is swollen. There is shifting dulness in the flanks and a fluid thrill can be elicited. The spleen can be felt extending downwards and forwards to the umbilicus. The liver is felt one inch below the costal margin and is hard and leathery in consistence.
Other Systems: Nil to note.
Blood:

R.B.C.	3,110,000
W.B.C.	12,600
Hb.	46%
C.I.	.74
Platelets	60,000

Differential White Count shows a relative increase in

the number of polymorphs, but otherwise no abnormality in the cell types. While in hospital the patient continued to have nose bleeding and purpuric spots developed over the chest and legs. Capillary resistance test induced the appearance of small pin-point haemorrhages in the skin. The vomiting became severe and was tinged with blood the day before death. The amount of blood, however, was not copious. The patient died on 24.6.31.

Abstract of post mortem notes. Theabdomen contained a large amount of straw-coloured fluid. There was no evidence of peritonitis. The stomach and intestines showed no mucosal haemorrhages. There was no evidence of dilatation of veins at the lower end of the oesophagus. The liver was small, weighing only 750 grammes. It showed a marked coarse cirrhosis, islands of regenerated greenish yellow liver tissue up to half an inch in diameter being set on a background of dense fibrous tissues. Both lobes of the liver were equally affected. The hepatic artery showed a little thickening.

The portal and hepatic veins appeared normal. There was no thickening or thrombosis of the splenic vein. The spleen was greatly enlarged (820 grammes). There were no adhesions round the spleen. On section there was no evidence of increase of connective tissue. The organ was soft and the pulp was of a homogeneous red colour. The splenic artery showed slight atheroma near its origin, but the three inches nearest the spleen showed marked diffuse dilatation with several local aneurisms. Here the vessel showed marked atheroma and there was calcification of the wall. The largest aneurism was about one inch in diameter and opened by a wide opening from one side of the parent artery. The aneurism contained some ante mortem thrombus. There was a soft

congested reacting lymph gland about half an inch in diameter in the hilum of the liver. The gall-bladder was normal.

There was no atheroma of the thoracic aorta. The heart was dilated and showed some fatty change. The bone marrow of the shaft of the femur was of a bright red colour and very soft. It showed an obviously extreme erythroblastic reaction.

Spleen: Weight 820 grammes.

Vascular Lesions and Venous Sinuses: Apart from hyalinisation of the splenic arterioles, no perivascular haemorrhages were seen and the venous sinuses could scarcely be distinguished.

Malpighian Bodies: were not especially prominent and no germ centres were seen.

The Pulp: Moderately congested, but not to the extreme degree which characterises acholuric jaundice. The pulp cells appeared somewhat swollen, and rounded active histiocytes were more numerous than usual.

Liver: Showed definite cirrhosis with marked connective tissue increases.

C A S E XXIII.

Henry D. aet 54.
Admitted to hospital: March, 1920.
History: Patient gave a history of general weakness and lassitude which had been present for some years. He had been subject to attacks of abdominal pain associated with vomiting but had never been jaundiced. He was troubled by flatulence, but apart from that had no digestive trouble. He never vomited blood and had never noticed his stools to be dark in colour.
On examination: The patient was rather pale. There was no jaundice.
Abdomen: The edge of the liver could be felt a hand's breadth below the xiphisternal junction. It was firmer in consistence than normal. The spleen could be felt reaching to a point midway between the costal margin and the umbilicus. There was no tenderness and no enlargement of the other organs.
Blood Count:

R.B.C.	3,600,000
W.B.C.	4,800
Hb.	62%
C.I.	.86

Differential Count: Showed no abnormality in the proportions of the various cells, and the red cells showed no abnormality apart from slight central pallor.
Other Systems: Nil to note.
While in hospital the patient began to have a slight temperature and became jaundiced. Tenderness developed under the right rib margin. A day or two after the temperature had risen, the fever was of a remittent type reaching 103-104% in the evenings. Leucocytosis developed up to 16,000. The jaundice was not very intense

and the icteric index was not more than 35. At the end of a febrile period of two weeks the patient died.
Abstract of post mortem notes: The liver was cirrhotic and the regenerated nodules of liver tissue were definitely bile-stained. The gall-bladder was full of stones and its wall was markedly inflamed. The spleen was enlarged red and soft in consistence and was about eight inches by five inches in dimensions. There was nothing of importance to note in the other organs apart from the usual effects of fever.
Spleen:
Vascular Lesions: No periarterial haemorrhages visible. No evidence of perivascular fibrosis or siderotic nodules.
Venous Sinuses: Scarcely visible and not dilated.
Malpighian bodies: No germ centres seen.
Pulp: A slight degree of arterial hyperaemia; numerous leucocytes present in the pulp spaces and a large number of large rounded active histiocytes present.
Liver: Old standing cirrhosis present as evidenced by the definite connective tissue increase. Recent acute hepatitis superadded with leucocyte infiltration of the portal spaces and liver lobules.

Case XXIV

Albert C.

Blood

Date		R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
2.3.28		5,500,000	6,000	50	.45	55	31	12	1	1
5.3.28		Splenectomy.								
5.3.28	5 p.m.		19,500							
	8 p.m.		21,600			86	13	1	0	0
6.3.28			30,200							
7.3.28		4,880,000	29,600	52	.53					
9.3.28			26,200			75	19	5	1	0
11.3.28			15,200			71	23	6	0	0
13.3.28		5,410,000		62	.54	75	14	7	4	0
14.3.28			13,800							
18.3.28		5,610,000	10,700	70	.63					
24.4.28		5,100,000	5,800							

C A S E XXIV.

Albert C. aet 20. Occupation: Coal Carrier.
Admitted to hospital: 25.2.28.
History: Patient was quite well until about one year and a half ago. He then became very pale and breathless on exertion and noticed that his stools were black like tar. He was in hospital about a year ago and improved very much. He has not worked since then, but he felt well until about six months ago, when he again became breathless and pale. He then noticed that his stools were very black in colour and a month later he vomited a cupful of dark red blood. He was again admitted to hospital on 19.12.27. He was extremely weak on admission but since then has improved steadily and is now feeling very well and quite strong.
Patient has never had any discomfort in the abdomen. He has had no flatulence or any feeling of fulness or weight in the abdomen. He often bleeds from the nose but there is no difficulty in stopping the haemorrhage, and if he cuts his skin there is no excessive loss of blood.
Previous Health and Family History: Nil to note.
On Examination: Patient is a little pale but otherwise looks healthy.
Abdomen: A little full, moves equally on both sides with respiration. There is no cutaneous hyperaesthesia. There is no rigidity or tenderness in any part. The spleen is easily palpable. It is greatly enlarged, its right border extending to the midline above the umbilicus. It is firm in consistence and moves freely with respiration. There is no evidence of perisplenitis. No friction heard on auscultation over the spleen. No free fluid in abdomen. Liver dulness normal in extent. Nothing else abnormal felt in the abdomen. No enlarged

glands felt in the axillae, neck or elsewhere.
Other Systems: Nil to note.
Blood findings are shown in the table.
Operation: 5.3.28. Splenectomy:
The spleen was very large. No adhesions to diaphragm. Liver somewhat firm but showing no definite evidence of cirrhosis. No gastric or duodenal ulcer. Some enlarged glands along the greater curvature of the stomach. The weight of the spleen was 1 lb., 9 ozs.
20.3.28. Discharged. Uninterrupted recovery.
Progress. 24.4.28. Reported. Feeling very well. Good colour, and has a well nourished appearance.
March 1931: Reported to a questionaire that he was feeling "much improved" and was fit for work. He had had occasional epistaxis and had been slightly jaundiced since the operation.
25.4.33. Reported by request. Feels well - unemployed but fit for work.

R.B.C.	5,150,000
W.B.C.	6,400
Hb.	60 - 70%

Spleen: Weight 780 grammes.
Vascular Lesions: Perimalpighian haemorrhage and fibrosis: periarterial haemorrhage: periarterial fibrosis. Siderotic nodules.
Venous Sinuses: Dilated with increase of collagen in their walls.
Malpighian Bodies: Hyaline deposits. No germ centres.
Pulp Cells: No abnormality in the appearance of the cells.

C A S E XXV.

Thomas N. aet 47. Occupation: Blacksmith.
Admitted to hospital: 10.8.29.
History: About May 1929, patient began to feel that he was tired and done at the end of his day's work. This gradually got worse, and about a month later his relatives noticed that he was losing colour, looking pale and unwell. He tried to continue his work in spite of breathlessness which was most marked on going uphill. There was no swelling of the feet at any time. About the beginning of July, he noticed pain in the left side of the abdomen and left hypochondrium. This pain was stabbing in character and was made worse by coughing: it still troubles him from time to time.
He has had no indigestion; no vomiting or haematemesis. About the middle of June he had some diarrhoea with very black tarry stools. He was not taking iron or bismuth at this time. He has had no diarrhoea since then, the bowels being quite regular. He has a slight cough, but this is not severe. He has been troubled by headaches for years.
Previous Health: "Epileptic fits" when a young man.
Family History: Nil to note.
On Examination: Patient is rather slow mentally and lacks energy. His conjunctiva shows slight anaemia and the skin is sallow.
Abdomen: Moves freely on respiration; there is no hyperaesthesia; on palpation there is definite enlargement of the spleen to 3 finger breadths below the costal margin. The spleen is tender on pressure. Percussion note over it is dull. The liver is felt one inch below the costal margin but is not unduly hard.
Cardiovascular System: Nil to note.

Lungs: There is no abnormality except the dull note at the extreme base of the left lung due to the enlarged spleen. Breath sounds here are diminished.
Central Nervous System: No abnormality detected.
Urine: No abnormal constituents.
Haemopoietic System: Spleen is enlarged, but there is no palpable enlargement of lymph glands.
Blood Examination:

R.B.C.	3,300,000
W.B.C.	3,800
Hb.	62%
C.I.	0.9

Film: Shows marked irregularity in size and shape. No nucleated red cells were seen.
Differential Count:

Neutrophils:	73.3%
Lymphocytes:	23.3%
Mononuclears:	2.3%
Eosinophils:	1.0%

Van den Bergh Reaction: Direct and indirect - Negative.
Wassermann: Doubtful Negative.
Fragility Test: Haemolysis begins at .3% and is incomplete.
Operation: 13.8.29. Splenectomy.
A large spleen with a rounded edge, and reddish pale in colour was found. Considerable bleeding took place from enlarged veins in the lieno-renal ligament, but these were secured by clamps. The liver was not enlarged, but the surface was slightly mottled by fibrous tissue.
Progress: The day after operation the patient developed bronchitis. A steam tent was fitted up. In the evening the pulse became rapid, but the colour was quite good. There was no sign of internal haemorrhage.
15.8.29. Patient had severe hiccough in the morning at 10 o'clock. By mid-day he had become distended and was vomiting. The distension affected the flanks mostly.

Blind caecostomy performed.
16.8.29. Vomiting continued unaffected by treatment. Enterostomy performed.
21.8.29. Death.
Abstract of post mortem notes: Peritonitis. Liver slightly enlarged. No obvious excess of fibrous tissue naked eye. Section showed areas of degenerative change in the parenchyma, with islets of round celled infiltration. Bone marrow showed a pronounced leucoblastic reaction.
Spleen:
Vascular Lesions: Perimalpighian haemorrhage and fibrosis: periarterial haemorrhage and fibrosis: no siderotic nodules.
Venous Sinuses: Dilated with slight increase of collagen in their walls.
Malpighian Bodies: No germ centres.
Pulp Cells: An increased number of elongated fibroblastic cells. Otherwise no abnormality.

C A S E XXVI.

Andrew R. aet 10.
Admitted to hospital: February 1930.
History: During the summer of 1929, it was noticed that the child's abdomen was getting large. He complained vaguely of abdominal pains and pains in the limbs. There was no vomiting, no jaundice, and no other symptoms.
Family History: No history of any familial complaint.
Previous Health: Nothing to note apart from scarlet fever, measles and whooping cough as a younger child.
On Examination: The child was well nourished and slightly pale. There was no fever. Spider telangiectases on the wrists and face.
Abdomen: The spleen was much enlarged and visible under the left costal margin beyond which it projected for three inches. It felt firm and was fairly smooth on the surface. The liver was not felt. There was no enlargement of the other glands. The other systems were normal.

Blood Count:

R.B.C.	4, 362,500 per cm.
W.B.C.	3,800 "
Hb.	50%
C.I.	.58

Differential White Count:

Small Lymphs:	6%
Neutros	55%
Large Lymphs	30%
Monocytes	9%
Platelets	37,804 per cmm.

No abnormal cells.

Fragility Test: Haemolysis begins at .39% complete at .33%
Van den Bergh Reaction: Direct negative: indirect Positive. 0.6 units.
Wassermann Reaction: Negative.

Operation: 25.2.30. Splenectomy.
There were many adhesions and the veins in the hilum of the spleen were greatly enlarged. The liver appeared to be slightly scarred and small white patches were seen on the surface. In consistence it was harder than normal. Following the operation the child had a severe haematemesis and vomited 2-3 pints of blood in the night. A blood transfusion was given and the patient made a good recovery.
Spleen:
Vascular Changes: No perimalpighian changes: periarterial haemorrhages: periarterial fibrosis: siderotic nodules all present.
Venous Sinuses: Dilated with increase of collagen in sinus walls.
Malpighian Bodies: Germ centres prominent.
Pulp Cells: No abnormality in the appearance of individual cells.

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Isabella McG. Case XXVII

Blood

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
29.10.23	2,640,000	6,400	30	.6					
8. 11.23	3,505,000	4,400	25	.35					
18.11.23	3,840,000	5,500	30	.4	67	27	4	2	0
4.12.23	Splenectomy:								
12.1.24	4,200,000	7,400	60	.8					

C A S E XXVII.

Isabella McG. aet 41. Occupation: Housewife.
Admitted to hospital: 3.12.23.
History: Patient has been "bloodless" since she had rheumatic fever at the age of eight. She has been weakly and breathless on exertion ever since. Otherwise her ordinary mode of life has not been interfered with. At intervals in the last three years she has had stabbing pain in the upper abdomen. The pain is worst on rising in the morning, but disappears after an hour or so. During the last six months the pain has been much worse. Menstruation has been very irregular and may last only one day.
On Examination: The skin is pale and slightly tinged with yellow.
Wassermann Reaction: Negative.
Test Meal: No free HCl: total acidity .8.
The Heart: Not enlarged. There is a blowing systolic murmur at the base.
Abdomen: The spleen is just palpable extending to the costal margin. The liver can be felt and seems to be somewhat firmer than normal. It is neither enlarged nor diminished in size.
9.11.23. Benzidene test positive in the faeces.
Operation: 4.12.23. Splenectomy.
The spleen was slightly enlarged (270 gm). The liver was not enlarged, but had a mottled appearance on the surface. The condition of the blood is shown in the appended table.
Spleen: Weight 270 grammes.
Vascular Lesions: Periarterial haemorrhage and fibrosis present. No perimalpighian change and no siderotic nodules.
Venous Sinuses: Dilated with increase of fibrous

tissue in their walls.

Malpighian Bodies: No germ centres seen.

Pulp Cells: No change in appearance.

Progress: March 1930 replied to questionaire that she was much improved and complained only of occasional indigestion and headache.

Facing p. 384.

David S. Case XXVIII

Blood

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
23.8.25	3,280,000	1,800	40	.63	34	62	2	2	0
24.8.25	Splenectomy								
6.9.25	4,200,000	6,400			50	37	7	6	0
15.10.25	4,730,000	10,000	75	.8					

C A S E XXVIII.

David S. aet 10.
Admitted to hospital 22.8.25.
History: A month before admission the patient had an attack of vomiting on rising from bed. No abnormal symptoms were noted apart from this and he seemed quite well until a fortnight later when the vomiting was repeated. The vomit contained no blood. Two years previously the child was run down and complained of headaches.
Family History: Nothing of importance.
On Examination: The physical development was good, but the child was pale and appeared to be definitely anaemic.
Abdomen: Showed a slight fulness, and the spleen was enlarged one and a half inches beyond the costal margin. The liver was also enlarged and its lower edge, which was firmer than normal, was felt two finger breadths beyond the rib margin.
Operation: 24.8.25. Splenectomy.
There were no adhesions. The liver had a somewhat mottled appearance. The patient made a good recovery from the operation apart from a slight temporary rise of temperature in the first twenty four hours.
Spleen:
Vascular Lesions: Perimalpighian haemorrhage and fibrosis. Periarterial haemorrhage and periarterial fibrosis. No siderotic nodules.
Venous Sinuses: Markedly dilated with increase of collagen in sinus walls.
Malpighian Bodies: Germ centres present.
Pulp Cells: Occasional giant cells seen: otherwise no abnormality in individual cells.

facing p. 347.

Isabella S. Case XXIX

Blood.

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
-.11.23	3,600,000	6,000	65	.9	65	27	7	0	1
-.2.26	3,530,000	6,600	73	1.0	76	18	4	2	0
8.12.26	2,800,000	7,500	55	.9					
28.12.26	2,900,000	4,000							
29.12.26	Splenectomy and Transfusion.								
2. 1.27	3,140,000								
24.1.27	4,040,000	7,160							

C A S E XXIX.

Isabella S. aet 49. Occupation: Housewife.
Admitted to hospital: 16.12.26.
History: Three years ago the patient knocked her side on a counter. Following this she had a pain which was worse on respiration and which radiated to the left shoulder. She felt a lump under the left rib-margin which was later found to be an enlarged spleen. She was in hospital at this time and the spleen was enlarged as far as the umbilicus. There was no glandular enlargement, and the condition of the blood is noted in the table. Radium was applied over the splenic area and after one month the splenic enlargement disappeared. Two years later she again became breathless and the spleen enlarged. The symptoms of anaemia, pallor, breathlessness, etc., again appeared. There was still considerable tenderness over the spleen. The patient was also definitely myxoedematous. No improvement of the anaemia resulted from the ordinary means of treatment, and she was ultimately recommended for operation. Wassermann reaction negative.
Operation: 29.12.26. Splenectomy.
There were a few adhesions to the diaphragm. The liver showed a slight degree of fibrosis which, however, was not very marked. At the operation 500 c.c. of blood were transfused. (Weight of spleen 890 gms.)
The blood findings are given in the appended table.
Spleen: Weight 890 grammes.
Vascular Lesions: Periarterial haemorrhage and fibrosis. No perimalpighian change and no siderotic nodules.
Venous Sinuses: Dilated with increase of collagen in their walls.
Malpighian Bodies: No germ centres seen.
Pulp Cells: No abnormality in appearance.

C A S E XXX.

Annie O. aet 44. Occupation: Housewife.
Admitted to hospital: 26.12.28.
History: For the past two or three years the patient has been easily tired and has sometimes suffered from giddy turns. She has also been troubled by a dull aching pain mostly on the right side of the abdomen. Sometimes she has had acute exacerbations of pain lasting about a day and felt across the upper abdomen. The pain is in no way related to food. She suffers from occasional flatulence and heart-burn. Her appetite is poor. She has never been jaundiced and has no urinary symptoms.
Three weeks before admission patient vomited bright red blood three times in one evening. Some of the blood was clotted. Since then the abdominal pain has been more severe. It was felt right across the upper abdomen and across the shoulders at the back. She had marked cutaneous hyperaesthesia and could not bear the weight of clothes on the abdomen. She has never before been troubled by vomiting. The abdomen has been somewhat fuller of late but there have been no other symptoms.
Previous Health: She has never been robust. Menstruation has been irregular, with scanty loss.
On Examination: The patient looks well, tongue is clean but there is slight pyorrhoea.
Abdomen: The liver is palpable just below the right costal margin. The spleen is felt in the left hypochondrium. There is slight tenderness above and to the left of the umbilicus but not over the spleen. There is no free fluid.
Blood: Details are given in the appended table.
Operation: 11.2.29. Splenectomy.

Spleen very adherent and a great deal of blood was lost during its removal. The patient's condition was fair for a few days. On 15.2.29. she suddenly collapsed with vomiting and a feeble pulse and died. Temperature was normal.

Abstract of post mortem notes: Death occurred from haemorrhage. The peritoneal cavity contained about a pint of fluid blood. The liver showed a slight cirrhotic change with slight thickening of the capsule. No portal thrombosis. Sections of liver showed central degeneration in the lobules. No change in portal vein.

Spleen:

Vascular Lesions: Perimalpighian haemorrhage and fibrosis. Periarterial haemorrhage: periarterial fibrosis. Siderotic nodules.

Venous Sinuses: Dilated with increase of collagen in their walls.

Malpighian Bodies: No germ centres seen.

Pulp Cells: No abnormality in appearance.

C A S E XXXI.

Helen C. aet 55. Occupation: Forewoman in rubber works.
Admitted to hospital: 30.1.29.
History: Four months ago patient began to suffer from weakness, lassitude and breathlessness especially on exertion. At the same time she noticed that she was becoming pale. For some time previously she had been feeling "run down", but it was only four months ago that she became unable to work. After treatment at home for eight weeks she improved and returned to work. Two weeks before admission she began to suffer from a constant epigastric pain. Her appetite has remained good and she has not lost weight. Her doctor thought that there was a slight tinge of jaundice along with the pallor.
Previous Health: Nil to note.
On Examination: The spleen was enlarged nearly to the umbilicus, was firm in consistence and not tender. The liver was enlarged to about four inches below the costal margin and was soft, smooth, regular and insensitive.

Blood:		
	R. B. C.	3,120,000
	W. B. C.	1,400
	Hb.	35%
	C. I.	0.56

Differential White Count:

Neutrophils	69%
Small Lymphocytes	24%
Large do	6%
Eosinophils	1%

Film: No nucleated red cells: a fair number of megalocytes: no poikilocytosis.
Fragility: Haemolysis begins in .45% saline and is complete in .35% saline (normal).

Van den Bergh: Direct reaction: positive delayed.
Indirect reaction: Positive.

Icteric index: 12.

Bleeding Time: 3 minutes (filter paper)

Coagulation Time: 3 minutes, 45 seconds (capillary tubes).

Respiratory System: On admission to hospital patient was suffering from a mild bronchitis with evening temperature up to 99.8. Apart from a few medium-pitched rhonci, there were no abnormal signs in the chest. The sputum was examined and contained pneumococci and mixed organisms. No tubercle bacilli were found.

Cardiovascular System: Nothing abnormal found.

Other Systems: Nothing abnormal.

Under treatment in a medical ward the liver and spleen both decreased in size especially the liver. At the end of February the liver was only one inch below the costal margin. The case was regarded as "Banti's disease" in the second stage with commencing liver involvement. Operation was advised.

Operation: 25.2.29. Splenectomy.

The spleen was considerably enlarged and free from adhesions. The liver appeared to be perfectly healthy without the least sign of cirrhosis. The gall bladder was free from any disease.

The patient stood the operation well and made a good recovery.

Spleen:

Vascular Lesions: Perimalpighian haemorrhage and fibrosis: periarterial haemorrhage: periarterial fibrosis. No siderotic nodules.

Venous Sinuses: Slightly dilated and very slight increase of collagen in the walls.

Malpighian Bodies: No germ centres seen. Hyaline deposits.

Pulp Cells: No abnormality in appearance.

Nellie L. Case XXXII

Blood

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
12.10.26	2,000,000	1,500	26	.65					
4.11.26	2,400,000	1,000	24	.5	56	38	4	2	0
	anisocytosis.								
16.11.26	Blood transfusion: 580ccs citrated blood.								
17.11.26	Splenectomy. Liver large and paler than normal : No ascites.								
25.11.26	3,490,000	6,300	44	.55	66	15	12	0	0
7.12.26	4,080,000	6,500	50	.62	41	27	22	0	0
7.1.27	3,800,000	9,000	58	.76	34	34	26	0	0

C A S E XXXII.

Nellie L. aet 44. Occupation: Housewife.
Admitted to hospital: 2.11.26.
History: For the past eighteen months the patient complained of shortness of breath on exertion and swelling and numbness of the hands and feet. During the past six months she has had noises in the head and epistaxis is said to occur and to bring about relief of the headaches. She has never been jaundiced. She states that two years ago she coughed up blood every morning for three months but she has never vomited blood. She has a scalding pain on micturition. During the last two years she has lost about two stones in weight.
Previous Health: Nil to note.
On Examination: The patient looks pale and anaemic. There is no jaundice. Slight oedema of the legs and over the dorsum of the feet was noticed. There is patchy pigmentation over the skin. The patient ran a slight temperature (B. Coli Bacilluria).
Abdomen: There is patchy pigmentation over the skin. The spleen reaches half way to the umbilicus. There is no ascites and the liver is not felt.
Cardiovascular System: There is a systolic murmur heard all over the precordium.
Van den Bergh: Negative.
Urinary System: Trace of albumen and B. Coli Bacilluria.
Respiratory System: Nil to note.
Central Nervous System: Nil to note.
The Blood Counts and the treatment are indicated in the table.
Spleen:
Vascular Lesions: Perimalpighian haemorrhage and fibrosis: periarterial haemorrhage: periarterial fibrosis

siderotic nodules.

Venous Sinuses: Dilated: no definite increase of collagen in their walls.

Malpighian Bodies: No germ centres seen.

Pulp Cells: No abnormality of individual cells.

C A S E XXXIII.

Mrs. D. aet 51. Occupation: Housewife.
Admitted to hospital: 16.1.33.

History: The patient states that she has noticed a swelling in the left side for many years. Soon after she noticed the swelling she began to have dragging pain which radiated to the umbilicus. Four months ago she had a severe attack of pain which was followed by vomiting. This attack only lasted a few hours. She has felt easily tired and gets short of breath on exertion. There is no history of melaena or haematemesis.

On Examination: Patient is somewhat pale and there is no jaundice. The teeth were all removed five years ago for pyorrhoea.

Abdomen: The spleen is enlarged as far as the midline and on respiration it reaches to the umbilicus. The liver is just palpable. There is no tenderness or enlargement of the other organs.

Blood Examination:

R. B. C.	3,700,000
W. B. C.	6,260

Differential Count:

Neutrophils	50%
Large Lymphocytes	20%
Small do	27%
Eosinophils	2%
Basophils	1%

Operation: Splenectomy.

The liver was not specially examined. The left lobe of the liver was densely adherent to the spleen. The veins in the hilum of the spleen were greatly enlarged. Weight of spleen 650 grammes.

Spleen: Weight 650 grammes.

Vascular Lesions: Perimalpighian haemorrhage and fibrosis.

periarterial haemorrhage : periarterial fibrosis: siderotic nodules.

Venous Sinuses: Dilated with increase of collagen in sinus walls.

Malpighian Bodies: No germ centres.

Pulp Cells: Nil to note.

Liver: Small portion adherent to spleen shows a regenerating nodule of liver tissue with degeneration of liver cells and focal round cell accumulations.

James P. Case XXXIV

Blood.

Bleeding Time 8 minutes.

Coagulation time: 2 minutes (Capillary tubes).

Fragility test No increase in fragility.

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
2.6.31	3,140,000	2,400	57	.9					
8.6.31	2,480,000	3,800	58	.8	64	29	4	3	0

Platelets. 97,800 Reticulocytes 2-3%

Arneth count: Slight shift to right.

16.6.31 Splenectomy.

27.6.31	4,530,000	16,300	70	.7	67	26	7	0	0

Platelets. 130,000 Reticulocytes. under 1%

C A S E XXXIV.

James P. aet 17.
Admitted to hospital: 25.5.31.
History: Patient was treated in another hospital for an enlarged spleen, for eight weeks, and was only discharged five weeks ago. He has had frequent epistaxis for six months. His nose bled about once a week. He was quite well otherwise. He had no melaena. No haematemesis. Appetite quite good. Bowels regular. He has always been pale.
Family History: Nil to note.
On Examination: Patient is definitely pale.
Abdomen: Feeling of fullness in the left hypochondrium. The spleen is found to extend downwards and forwards to the level of the umbilicus and within half an inch of the mid-line. The liver is one inch below the costal margin. There is no superficial or deep hyperaesthesia. No rigidity or tenderness. No evidence of free fluid.
Cardiovascular System: Nil to note.
Respiratory System: Breath sounds diminished over left upper lobe together with diminished vocal fremitus and resonance. He has a cough.
Blood Findings: indicated in the annexed table.
Operation: 16.6.31. Splenectomy.
No free fluid. Liver of normal size, slight fibrosis of capsule but not cirrhotic. Spleen very large, red in colour, capsule not thickened. No adhesions. Numerous large veins, in abdominal wall. The splenic vein was very large. There was practically no bleeding and transfusion was considered unnecessary. There was no thrombosis of the splenic vein. (Weight of spleen 1280 gms.).
7.7.31. Discharged. A good deal of pain at first and fairly high temperature. Fine crepitations at right

base. Temperature had settled on discharge and recovery was satisfactory.

Spleen: Weight 1280 grammes.

Vascular Lesions: Perimalpighian haemorrhage and fibrosis: periarterial haemorrhage and fibrosis. No siderotic nodules.

Venous Sinuses: Dilated. Very slight increase of collagen in the sinus walls.

Malpighian Bodies: Occasional germ centre seen.

Pulp Cells: No abnormality noted.

Progress: 21.4.33. Reported by request: very well.

R.B.C.	5,200,000
W.B.C.	8,200

Gerald G. Case XXXV

Blood

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
16.7.29	3,050,000	5,200	28	.5	64	28	5	2	1
23.7.29	3,000,000		26	.5					
28.7.29	2,780,000		27	.5					
9.8.29			34						
13.8.29	Splenectomy								
23.8.29	2,030,000	7,920	46	.86					

C A S E XXXV.

Gerald G. aet 19. Occupation: Van Driver.
Admitted to hospital: 10.8.29.

History: Patient was always delicate and very liable to get any illnesses that were going - measles, mumps, etc. He was, however, able to lead a fairly ordinary life, played games at school. and later was able to carry on his work until three months ago. During the last three years he was unable to take part with the boys of his own age as he was unable to keep up with them. He has noticed breathlessness on going uphill in the last three years, and he always gets tired quickly. He is not troubled by headaches. He notices palpitation on exertion.

Three months ago he noticed pains in the abdomen. These were present while walking about, but disappeared when resting in bed. He feels that there is something dragging in his left side. He has had occasional vomiting, usually brought on by foods which have disagreed with him. There has been no haematemesis. Bowels are constipated. Motions have never been black. No cough or pain in the chest. He is troubled occasionally by painful cramps in the legs.

Family History: Father and mother both dead: cause unknown.

On Examination: Patient is very pale and anaemic. He is undersized for his age. There is no growth of hair on the face; pubic hair has the feminine distribution.

Abdomen: Moved freely on respiration. There is no tenderness. Spleen is enlarged to 3 finger breadths below the costal margin: it is not tender. Liver is not enlarged. There is no free fluid.

Cardiovascular System: Pulse: soft and regular.

Heart: is enlarged, dilated and hypertrophied. Apex beat is ½" external to the nipple line in the 5th space. Impulse is heavy. There is dullness to the right of the sternum for ½". Systolic murmur conducted into the axilla, and a loud systolic murmur at the base.
Other Systems: Nil to note.
Van den Bergh: Direct negative: indirect faintly positive.
Icterus Index: 5.
Fragility Test: Haemolysis begins at .6% and is complete at .5%
Operation: 13.8.29. Splenectomy. (Weight of spleen 880 gms.). A large spleen with rounded edge and reddish-purple in colour was found. The liver appeared macroscopically normal.
29.8.29. Patient made an uninterrupted recovery. Wound healed. Discharged.
Spleen: Weight 880 grammes.
Vascular Lesions: Perimalpighian haemorrhage and fibrosis: periarterial haemorrhage: periarterial fibrosis. No siderotic nodules.
Venous Sinuses: Markedly dilated. Slight increase of collagen in sinus walls.
Malpighian Bodies: Germ centres marked.
Pulp Cells: No abnormality in appearance of cells.
Progress: Replied to a questionaire (March 1930) that shortly after operation he had had haematemesis and nose-bleeding, and felt only slightly improved otherwise. April 1933. Written to but letter returned through dead letter office. Last heard of in November 1931 when he was in good health but moving about in search of work. No breathlessness or bloodlessness, and had put on about 2 st. in weight. Had been playing football and cricket.

Ethel B. Case XXXVI

Blood

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
28.6.32	2,300,000	3,500	30	.65	63	28	7	1	0
	Platelets 250,000								
16.7.32	2,520,000	3,500	42	.84	66	28	4	1	1
16.7.32	Splenectomy: Blood transfusion. 700ccs.								
5.8.32	4,880,000	8,800	64	.66	77	18	4	0	1

C A S E XXXVI.

Ethel B. aet 22. Occupation: Housewife.
Admitted to hospital: 28.6.32.
History: The patient had three attacks of haematemesis during the three weeks prior to admission. All the attacks occurred within twenty four hours and there has been no recurrence since then. There was also maelena at the time but there has been none since then. The patient tends to bleed freely during her periods which last seven days, and she also bleeds freely from wounds.
On Examination: The patient is pale and there is no jaundice.
Abdomen: The spleen is enlarged to the umbilicus. The liver cannot be felt and there is no free fluid.
Urine: Contains no urobilin or urobilinogen.
Cardiovascular System: There is a mitral systolic murmur, otherwise nil to note.
Test Meal: Shows a normal curve.
Van den Bergh: Indirect positive, 0.7 units.
X-Ray: Shows no abnormality in the stomach or duodenum.
Blood Counts: shown in annexed table.
Operation: 16.7.32. Splenectomy. The spleen was large and pale. No adhesions. The liver appeared normal, there being no abnormality in its size or consistency. The splenic vein appeared quite normal. 700 c.c.'s blood transfused.
The patient made an uninterrupted recovery.
Spleen:
Vascular Lesions: Perimalpighian haemorrhage and fibrosis: periarterial haemorrhage: periarterial fibrosis. Siderotic nodules.
Venous Sinuses: Dilated. No special increase of collagen.
Malpighian Bodies: Germ centres present.
Pulp cells: No abnormality in appearance of individual Cells.

Nancy M. Case XXXVII

Blood.

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
31.5.29	1,650,000	12,400	21	.63	82	12	6	0	0
	Blood transfusion 700ccs.								
3.6.29	Haematemesis. Temp. 100.4. Spleen smaller.								
8.6.29	Transfusion of blood.470ccs.								
11.6.29	1,900,000	3,500	30	.78	68	28	2	0	2
15.6.29	Splenectomy. 370ccs Blood transfused. Adhesions round the spleen, Nonthrombosis. No ascites. Liver apparently normal.								
22.6.29	2,600,000	2,200	[illegible]		79	14	5	0	2
	Normoblasts. 555/c mm.								
8.7.29	3,300,000	9,500	50	.75	75	18	6	0	1
2.8.29	4,200,000	7,700	44	.5	55	31	13	0	1
1930	Readmitted with recurrent haematemesis.								
1.8.31	Again admitted to hospital with recurrent haematemesis.								
4.8.31	2,630,000	22,000	45	.8	72	22	4	2	0
2.9.31	3,880,000	10,000	64	.9	41	54	3	1	0

C A S E XXXVII.

Nancy M. aet 12.
Admitted to hospital: 31.5.29.
History: Patient was a normal healthy child until six weeks before admission when she had a feeling of sickness followed by the vomiting of blood. This was repeated a week or two later, and two weeks ago her doctor thought she had developed ascites. Two days ago haematemesis occurred and has recurred every few hours since then. Her digestion is generally good. She has no sickness and no colic. Flatulence is occasionally troublesome. Her bowels are regular and there has been nothing to note except malaena along with the haematemesis.
Four years ago the patient had a haematemesis similar to the present one. She was vomiting blood for a week. She has always been pale.
Family History: One sister was stillborn and one died aged five weeks. Eldest brother suffered from "fits".
Wassermann Reaction: On patient and father: both negative.
On Examination: The child is pale with a slight yellowish tinge in the skin.
Abdomen: The spleen has enlarged to a point midway between the costal margin and the umbilicus. The liver is just palpable below the costal margin. There are no signs of free fluid and there is no tenderness or enlargement of the other organs.
Cardiovascular System: A systolic murmur is heard at the apex. Otherwise nil to note.
Other Systems: Nil to note.
Blood findings: Indicated in the annexed table.
Operation: 15.6.29. Splenectomy.

There were some adhesions round the spleen. Neither thrombosis nor ascites were present. The liver was apparently normal.

Spleen:

Vascular Lesions: Periarterial haemorrhage: periarterial fibrosis: perimalpighian haemorrhage and fibrosis. No siderotic nodules.

Venous Sinuses: Dilated: slight increase of collagen in the sinus walls.

Malpighian Bodies: Germ centres seen.

Pulp Cells: No abnormality in appearance.

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Ian M. Case XXXVIII

Blood.

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
3.7.25	3,000,000	3,200	30	.5	64	31	1	4	0
	Film. Some anisocytosis and poikilocytosis. Mostured cells show central pallor.								
10.7.25	Splenectomy and transfusion.								
22.7.25	4,000,000	6,100							

C A S E XXXVIII.

Ian M. aet 11.
Admitted to hospital: 30.6.25.
History: Up to a year before admission, patient was perfectly healthy and well developed. In August 1924, patient suddenly vomited three pints of dark brown altered blood. This left him weak and anaemic, but after six weeks he had recovered. The haematemesis was not preceded by any pain but for an hour before he vomited he had a feeling of discomfort in the epigastrium with some nausea. Before this haemorrhage he had suffered from intermittent attacks of diarrhoea for several months. These attacks lasted several weeks at a time and in the intervals, bowels were quite normal. Six weeks before admission he had another gastric haemorrhage similar to the first. This left him very weak. For several months he has had occasional transient attacks of jaundice lasting a day or two but never very deep. His appetite is usually good and he has no other complaint.
Previous Health: Patient has never been very healthy. Whooping cough when aged one year has been the only definite illness, however.
Family History: Nil to note.
On Examination: The patient is well developed. Skin has a somewhat yellowish colour not sufficiently marked to be definite jaundice. Conjunctiva is pale and general appearance is that of well marked anaemia.
Abdomen: The spleen is enlarged to within an inch of the umbilicus. It is not tender. Liver is not enlarged.
Heart: Normal in size. A systolic pulmonary murmur was heard. The urine contains no bile constituents. Other systems normal.

Operation: 10.7.25. Splenectomy.
Transfusion was given at the operation: there were no adhesions. For a few days after the operation the patient ran a slight temperature, but made a good recovery and was discharged 31.7.25.
Blood condition is indicated in the annexed table.
Spleen:
Vascular Lesions: Periarterial haemorrhage: periarterial fibrosis: perimalpighian haemorrhage and fibrosis. Siderotic nodules.
Venous Sinuses: Dilated, with increase of collagen in their walls.
Malpighian Bodies: Germ centres present.
Pulp Cells: No abnormality in appearance.
Progress: March 1930. Replied to a questionaire that he was very well and had had no symptoms suggestive of hepatitis.

C A S E XXXIX.

Winifred M. aet 33. Occupation: Housewife.
Admitted to hospital: 25.5.27.
History: Patient was in her usual health until the beginning of 1927. She then began to feel tired and worn out and unable to do her usual amount of work. She complained of breathlessness on exertion and palpitation and states that she has always been pale. She is troubled with flatulence, but has no pain. Appetite has been good and bowels are regular. She has not been jaundiced, at any time. Menstruation ceased two months before admission. There is no history of haematemesis, or bleeding from the alimentary tract.
Previous Health: Apart from the pallor already mentioned she has been very healthy.
On Examination: The patient was pale and sallow with pallor of the lips and conjunctivae.
Abdomen: Slightly pigmented. Muscular tone was good. There was no pain or rigidity. The liver was not palpable but seemed slightly enlarged on percussion. The spleen was just palpable at the height of inspiration. The kidneys were not tender or palpable. No other abnormality could be detected.
Circulatory System: A faint systolic murmur (pulmonary) was heard. Nil else to note.
Other Systems: Nothing abnormal found.

Blood:		
	R.B.C.	4,450,000
	W.B.C.	3,800
	Hb.	68%
	C.I.	.76

Operation: 27.5.27. Splenectomy.
No adhesions were found. Patient had a slight temperature after the operation but otherwise made a good recovery.

Spleen:
Vascular Lesions: Perimalpighian haemorrhage and fibrosis: periarterial haemorrhage and fibrosis: No siderotic nodules.
Venous Sinuses: Dilated with slight increase of collagen in their walls.
Malpighian Bodies: No germ centres seen.

Progress: March 1920. Replied to questionaire that she suffered from breathlessness on exertion and was only fit for light work. She has occasional epistaxis. Operation has not restored her to normal health.

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Robert W. Case XL.

Blood

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
25.2.26	4,610,000	4,200	60	.66	64	36	0	0	0

1.3.26 Splenectomy. Omentum adherent with large veins coursing into the splenic capsule. Splenic veins very hard. Liver not inspected. Wt of spleen : 1500 grammes. Good recovery except that temperature rose to 103 on two occasions after operation. ?sepsis.

15.6.26 4,350,000 10,000 76 .9

C A S E XL.

Robert W. aet 19.
Admitted to hospital: 25.2.26.
History: Patient was quite well until a month before his admission to the hospital. He was then seized with pains in the back and loins, with shivering which lasted an hour and a half. He had four similar attacks at two day intervals. A swelling was found in the abdomen, and he was sent to hospital. Patient has not felt ill except during the shivering fits. He has never been abroad and has never had any malarial complaint.
Previous Health: Patient was always a weakly child. When aged 11 he had catarrh of stomach and bowels associated with a rash on the abdomen and legs ? Typhoid.
Family History: Nil to note.
On Examination: Patient is of medium development, mentally alert and rather pale and sallow. No glandular enlargement was found. The spleen was enlarged as far as the midline and below the umbilicus.
Blood findings and treatment are shown in the table.
Wassermann Reaction: Negative.
Operation: 1.3.26. Splenectomy.
Omentum adherent with large veins coursing into the splenic capsule. Splenic veins very hard. Liver not inspected. Weight of spleen 1500 grammes. Good recovery except that temperature rose to 103% on two occasions after operation. (Sepsis)
Progress: March 1930. Reported that he was well apart from slight flatulent indigestion.

20.6.30.	R.B.C.	5,080,000
	W.B.C.	5,000
	Hb.	70%
	C.I.	.7

Spleen:

Vascular Lesions: Perimalpighian haemorrhage and fibrosis: periarterial haemorrhage: periarterial fibrosis. No siderotic nodules.

Venous Sinuses: Dilated, with increase of collagen in their walls.

Malpighian Bodies: Occasional germ centre seen.

Pulp Cells: No special abnormality in appearance.

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Helen G. Case XLI.

Blood

Date	R.B.C.	W.B.C.	Hb	C.I.	N	Lym	M.	E.	B.
16.5.31	3,060,000	4,800	45	.75	54	43	2	0	1
	No nucleated red cells. Reticulocytes under 1%								
12.6.31	3,820,000	4,200	42	.6	64	22	12	0	2
	Arneth count: Slight shift to the left.								
19.6.31	Splenectomy.								
25.6.31	4,070,000	9,800	56	.6	64	28	8	0	0
	Platelets 210,000 No reticulocytes seen.								
3.7.31	3,880,000	7,600	50	.6	61	21	18	0	0
	Platelets 120,000								

C A S E XLI.

Helen G. aet 60. Occupation: Housewife.
Admitted to hospital: 6.5.31.
History: For ten years the patient has suffered from headaches which she ascribes to a minor injury. Three weeks before admission to hospital, patient felt very run down and was suffering from very severe headaches from which she could get no relief. She found it difficult to do her work and had to rest very often. She became very breathless on the least extra exertion. She was never jaundiced. Patient has had one or two attacks of epistaxis during the past year or so, the last occurring just prior to admission to hospital on 6.5.31. She lost a good deal of blood but cannot give any idea of the amount. She bruises very easily but has never noticed any haemorrhagic spots.
Patient has had no indigestion. Her appetite is good and her bowels are regular. She has never noticed any undue paleness or undue darkness in the colour of her motions. She has had no urinary trouble, her urine being clear and light in colour. No loss of weight.
Previous Health and Family History: Nil to note.
On Examination: Patient looks fairly well. Pale complexion with a slight yellow tinge.
Abdomen: No hyperaesthesia. No rigidity and no tenderness. On palpation there is a swelling which is fairly superficial, extending downwards and medially towards the umbilicus from the left hypochondrium. It is firm in consistence and the edge is easily palpable. It moves freely on respiration. It is notched on its medial border and extends down to about 1½" above the umbilicus and about a half to three quarters of an inch from the midline. There is a definite dull note on percussion. The liver is not enlarged. No other abnormal tumour palpable

Cardiovascular System: Soft blowing systolic murmur best heard in mitral area.
Blood Pressure: 118/65.
There is no enlargement of lymph glands.
Blood findings: indicated in the annexed table.
Other Systems: Nil to note.
Wassermann Reaction: Negative.
Fragility Test: Haemolysis begins at .45%, complete at .35% normal.
Bleeding Time: 6 minutes.
Coagulation Time: 2 minutes.
Operation: 19.6.31. Splenectomy.
The spleen was enlarged and had the appearance of having been dipped in brine. The upper pole was firmly adherent to the diaphragm and the liver. The artery was greatly thickened and brittle, due to atheromatous changes mainly at the splenic end. The splenic vein was then ligated and divided and the spleen removed. Patient's pulse was rather poor at the end of the operation.
7 p.m. Pulse had improved slightly. A blood transfusion was given (16 ounces of citrated blood). Condition improved perceptibly after this.
11 p.m. Pulse somewhat weak again. Patient good colour. No obvious signs of internal haemorrhage. Fairly comfortable.
Patient made a good recovery from the operation.
Spleen:
Vascular Lesions: Periarterial haemorrhage and fibrosis: No perimalpighian changes and no siderotic nodules.
Venous Sinuses: Dilated: no increase of collagen in their walls.
Malpighian Bodies: No germ centres seen.
Pulp Cells: No special abnormality.
Progress: 22.3.33. Reported. No obvious anaemia. Weight increased. Able for her work.

R.B.C. 3,680,000
Hb. 72%

Case XLIa

George S. aet 51. Occupation: Fruiterer.

Admitted to hospital: 13.3.33.

History: For the past eight months the patient has complained of general weakness and lassitude. The indisposition was first noticed after he had been kept in bed for a short time on account of a varicose ulcer. Three months before his admission he had some nose-bleeding. About this time his doctor found a lump in the left side of his abdomen. The patient himself has had no pain or discomfort whatsoever in the abdomen. During the past year he has lost about three stones in weight.

Previous health: Rheumatoid arthritis for 15 years, for which most of his teeth have been removed.
Syphilis acquired when aet 16, for which he has had Arsenical treatment up to the last year.
Patient has lived abroad, but there is no history of malaria, typhoid or other tropical illnesses.

On Examination: Patient is rather pale. Extensive rheumatoid arthritis gives him some discomfort.
Abdomen: The spleen is felt extending over the midline and down beyond the umbilicus. The liver edge is felt 2 inches beyond the right costal margin, and it has a "leathery" consistence. There is no free fluid. Enlarged veins are seen in the abd. wall.
Haematopoietic System A few enlarged glands can be felt in the groins.
Van den Bergh: Direct negative, Indirect, 0.5 units

Wassermann: Positive.

Blood 14.3.33.

R.B.C.	3, 410,000.	Neutrophils	5
W.B.C.	880	Lymphocytes	81
Hb	56%	Monocytes	13
C.I.	.82	Eosinophils	1

Red cells show anisocytosis.

Platelets: 153,000.

Cardiovascular System A blowing systolic murmur is heard over the precordium. No other abnormality detected.

Respiratory and Nervous systems: Nil to note

29.3.33 Splenectomy. There were no adhesions: The spleen weighed 2,700 grammes. The liver was finely cirrhotic, and the surface appeared red and inflamed.

The patient recovered from the operation, and the white cells on discharge had risen to 6,000 per c mm. Early in May, 1933, however the patient died at home.

Weight of spleen: 2,700 grammes.

Spleen: Vascular Lesions

Periarterial haemorrhages, with some iron deposits among the blood. Periarterial fibrosis.

Venous sinuses: Dilated and filled with active histiocytes.

Pulp Enormous proliferation of the pulp cells, giving a great increase of thickness of the intersinuous tissue.

Malpighian bodies: Germ-centres frequently seen.

Spleniculi at the hilum of the spleen are greatly enlarged. Histologically there is great proliferation of histiocytes into the sinuses.