

THE S I S O N ,
S P L E N I C A N A E M I A ,
WITH SPECIAL REFERENCE TO
H E P A T O L I E N A L F I B R O S I S .

by

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SPLENIC ANAEMIA

OTHER THAN

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"Facts are stubborn things, until
brought into connection with some
general law."

Louis Agassiz.

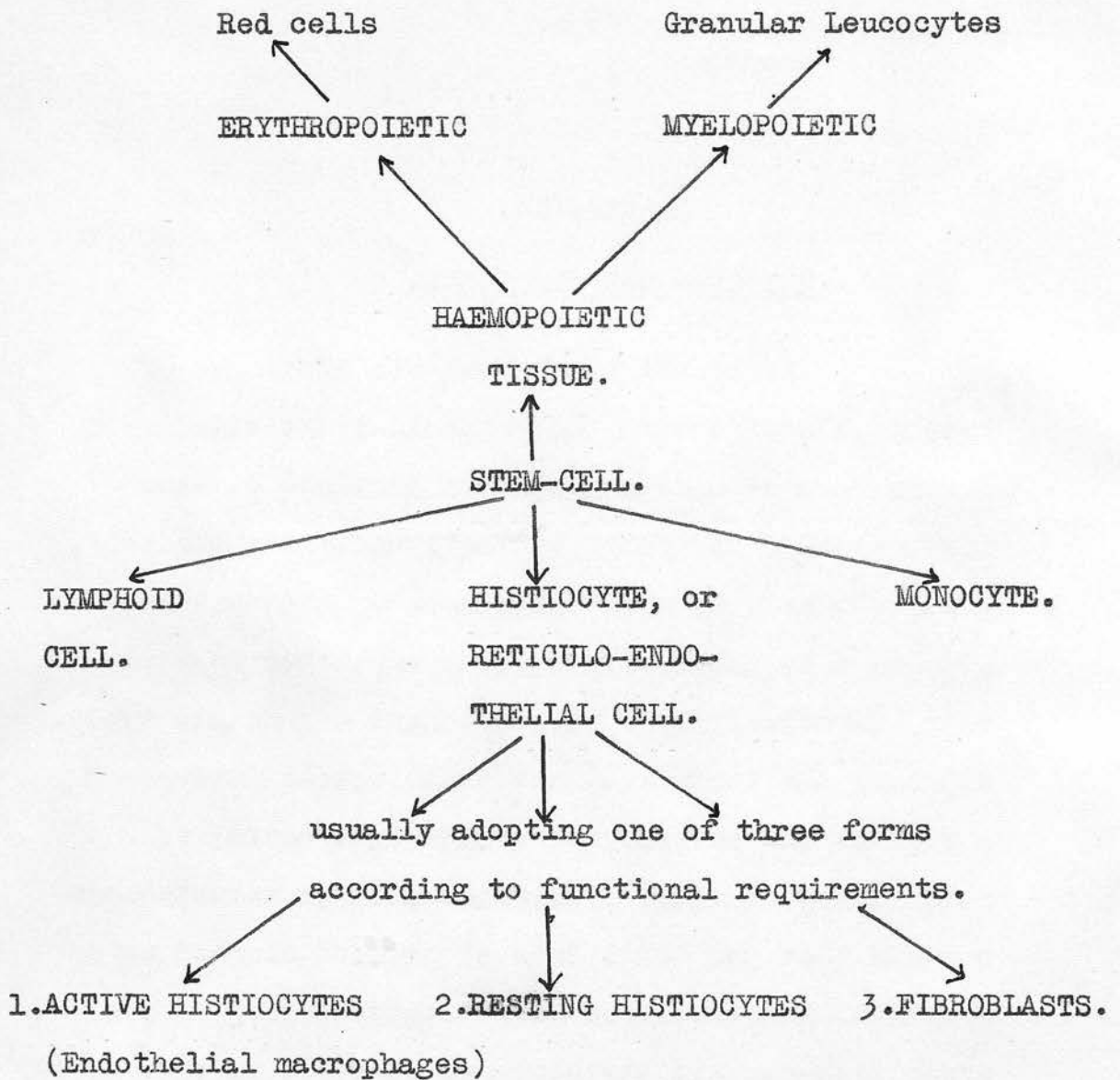
Chapter 14.

RETICULO-ENDOTHELIOSES.

In recent years numerous instances of hyperplasia affecting the reticulo-endothelial system have been described as a distinct disease picture under the names of "Reticulo-endothelioses", "Reticuloses", and "Endothelioses". Attempts have been made to subdivide these hyperplasias in various ways, especially into leukaemic and aleukaemic types. Although the anatomical and histological features may guide the pathologist to the "diagnosis" of reticulo-endothelial hyperplasia, it is nevertheless certain that the conditions at present classed as "Reticulo-endothelioses" constitute a group of diseases with certain histological features in common, but of varied etiology.

The reticulo-endothelial cells of the body form a tissue which is curiously fluid in its adaptability to the requirements of the moment. While the cells may have a more or less uniform appearance under resting conditions, they alter in size, shape and anatomical appearance as they

TABLE XI.



become active. In none of the parenchymal tissues of the body do such extreme anatomical changes occur in parallel with altering functional demands. In the liver, for example, with the single exception of glycogen storage, there are no anatomical changes to differentiate one type of metabolic activity from another.

Change in the functional activities of the reticulo-endothelial cells is associated with definite alterations in the histological appearances, leading to differentiation along the lines indicated in the adjoining diagram.

1. The resting histiocyte is characterised by a small amount of cytoplasm around a relatively large nucleus poor in chromatin, with branched processes linking it up with its neighbours. Histiocytes of this type constitute the great majority of the cells of the spleen pulp of the normal individual.

2. The histiocyte undergoes a remarkable metamorphosis when it becomes active. The cell separates completely from its neighbours and becomes rounded; the amount of cytoplasm around the nucleus increases while the nucleus becomes relatively small in proportion to the size of

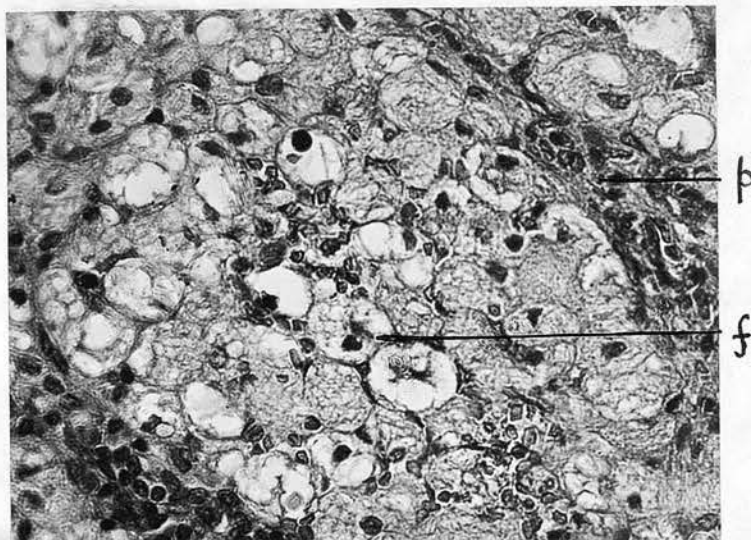


Fig. 106. Spleen from a case of Gaucher's Disease (x 400). Note the large 'foam' cells (f) with relatively small nuclei, which constitute the bulk of the splenic tissue. A small amount of normal pulp (p) is crushed into a strand of tissue

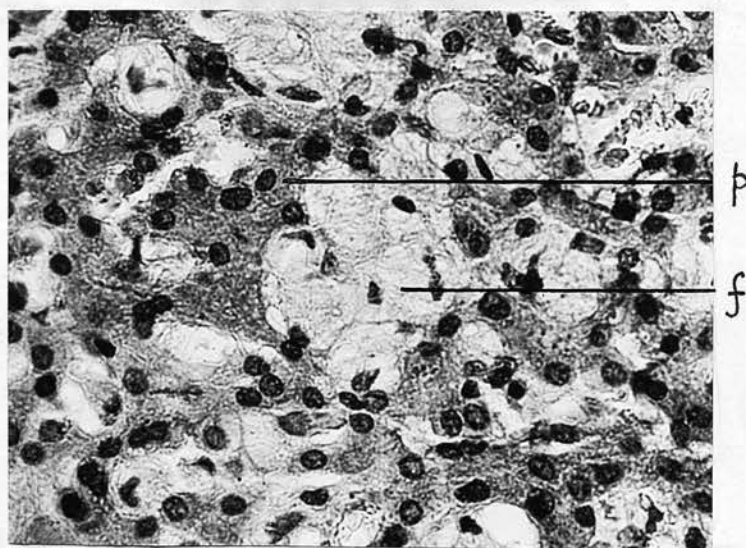


Fig. 107. Liver from the same case of Gaucher's disease (x400) . 'Foam'cells (f) constitute a large part of the organ crushing out the parenchyma cells (p).

the cell. Both the nuclear and cytoplasmic staining become denser. Such active histiocytes predominate in the spleen in acute infections where the increased functional demands may be made by circulating bacterial toxins, or the bacteria themselves. Enlargement and proliferation of the histiocytes may also occur in disturbances of lipoid metabolism, for example in Gaucher's disease (see Figs 106-7), Niemann-Pick's disease, and hypercholesterolaemic splenomegaly (Dyke, 1928). Increased histiocytic activity has been described in relation to hepatic disease in the first part of this work. Increase in the number of active histiocytes may thus occur in response to a variety of stimuli.

3. The resting histiocytes of the spleen are associated with the presence of a network of reticulin, which may be demonstrated by the use of Bielschowsky stains. The histiocytes possess the potentiality of transforming themselves into true connective tissue cells, which metamorphosis may be regarded as an exaggeration of the features which characterise the resting histiocyte. The cell tends to become elongated in one direction, and instead of linking up

with reticulin fibrils the cell processes appear to become continuous with collagen strands. The cell tends to become more and more flattened until the body of the cell is scarcely to be seen, except in the neighbourhood of the nucleus, which has now become a small hyperchromatic structure.

These changes have all been exemplified in the first part of this work. The transformation of the resting histiocytes into fibroblasts on the one hand and rounded macrophages on the other is well seen in figs. 16 and 51 .

While the relationship of the mature histiocyte to its "active" and fibroblastic derivatives is easy to follow, we are on less secure ground in the consideration of the inter-relationships of the histiocyte with the progenitors of the elements of the circulating blood.

All observers are agreed that the various forms of leucocytes have a common origin from cells of the embryonic mesenchyme, the latter simply constituting a primitive

type of reticulo-endothelium. It is also agreed that at birth these cells have been differentiated into the types of tissue seen in the adult: erythropoietic, myelopoietic, lymphopoietic, and reticulo-endothelial tissues, which give rise, respectively, to the red cells, the granular white cells, the lymphocytes, and the monocytes. Many authorities believe that even in the adult there are primitive reticulo-endothelial or "stem-cells" which, in case of need, can develop into any one of these types of blood cells according to the character and intensity of the exciting stimulus.

The fundamental point in dispute is at what stage this process of differentiation becomes irreversible.

The unitarians, led by Maximow, believe that irreversibility occurs very late in the development of the cell. They have described appearances which they interpret as evidence that lymphocytes are transformed into monocytes and vice versa. Members of the polyphyletic school are probably on somewhat firmer ground when they claim that the process becomes irreversible at a relatively early stage, and

deny the possibility of such a transformation, at least after the distinguishing characteristics of the cells have appeared.

We have made above a categorical statement that the monocyte is derived from the reticulo-endothelial tissues. This point is still debated. It is important, however, for our present purpose, to consider the problem of the origin of the monocyte, for some reticulo-endothelial hyperplasias are associated with monocytic leucocytosis.

The view held by Aschoff (1924), Kiyono (1914), Schilling (1926), Cunningham, Sabin and Doan (1925), Masugi (1927), Ferrata (1918) and Merklen and Wolff (1927) is that the monocyte is derived, like the histiocyte from a primitive reticulo-endothelial cell. This view is based on the following facts:

1. Morphological transitions can be seen between the monocyte and the histiocyte in normal and pathological conditions.

2. On culture both the monocyte and histiocyte are phagocytic (Maximow, 1927, Lewis, 1925).

3. Fluctuations in the number of monocytes may occur independently of variations in the

other types of leucocytes, and a specific monocyto-
sis may be induced by B. monocytogenes (Murray, Webb, and Swan, 1926).

While the above authorities agree in claiming a relationship between the monocyte and the histiocyte, they differ in their interpretation of the details. Some regard the histiocytes as progenitors of the monocytes (Damashek, 1930, Ferrata, 1918), while others believe that the monocytes may be the precursors of the histiocytes (Lewis and Lewis, 1925). Sabin and her co-workers went so far as to assert that the histiocytes rose from endothelium while monocytes were derived from reticulum cells. Maximow, however, regards reticulum and endothelial cells as essentially identical, and his view is generally accepted on this point. There is no convincing evidence of the origin of monocytes from mature histiocytes.

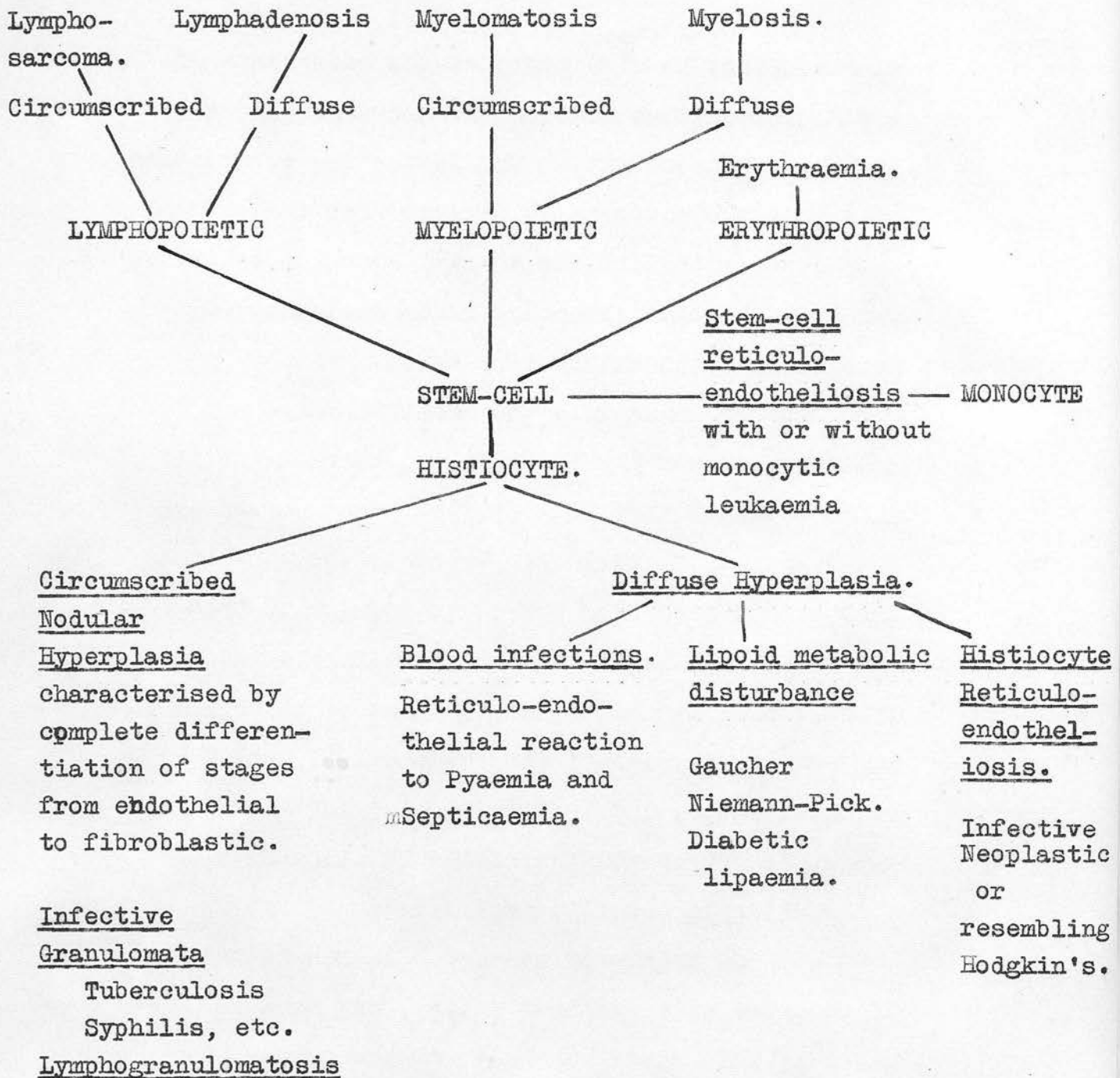
The other views of the origin of the monocyte are those held by Naegeli on the one hand, and by Maximow and Bloom (1928) on the other. The former holds that the monocyte is myeloid in origin, arising from myeloblasts. The evidence for this is mainly clinical, and

unconvincing. He also stresses the occurrence of a positive oxidase reaction in the monocyte: this however is inconstant. The latter two authorities hold that the monocyte is derived from the lymphocyte: they include however among "lymphocytes" cells which other observers might designate monoblasts or primitive stem cells.

To summarise, the monocytes have, anatomically and physiologically, characteristics which separate them sharply from granulocytes and lymphocytes. The evidence supports the view that they are derived from primitive stem-cells from which the histiocytes also take their origin. This view is in agreement with most of the observed anatomical, physiological, pathological, and clinical facts, and is incorporated in the schematic representation of the relationships of the histiocyte opposite page 374.

On this view monocytic leukaemia must be regarded as a distinct entity, and some 22 cases of this condition have now been reported by haematologists (See table, p397). Besides the increase of monocytes in the circulation there occurs a pathological hyperplasia of the primitive cells of the reticulo-endothelial system from

TABLE XII



which the monocytes are derived.

In cases otherwise resembling leukaemia but in which leucocytosis is absent, the term aleukaemic leukaemia is often applied. This designation, however, involves a contradiction in terms, and the better nomenclature is that based upon the underlying pathological condition. Hence the terms lymphadenosis and myelosis may be applied according to the type of cell involved — lymphoid or myeloid. We may thus speak of a leukaemic or an aleukaemic myelosis. In the same way we may meet with reticulo-endothelioses which are aleukaemic or leukaemic. In the latter instance the leucocytic increase involves the monocytes, and the hyperplastic process involves the parent cell of the monocyte, namely the reticulo-endothelial stem-cell.

The various hyperplasias which may result from overgrowth of the various derivatives of the stem-cell are shown schematically in Table XII. We see that we are on fairly clear and familiar ground in dealing with the erythro-, myelo-, and lymphopoietic tissues, but the way is more obscure in dealing with the reactions of the less defined histiocyte system. It has been shown by Sabin (1925) that the endothelioid cell

reaction which marks the beginning of the tuberculous process is entirely derived from local histiocytes. Thereafter the endothelioid cells become differentiated to fibroblasts in the further development of the tubercle. These reactions and also the development of the giant-cells can all be accounted for by the physiological potentialities of the mature histiocyte. Complete differentiation of the histiocyte takes place in various directions from the endothelial to the fibroblastic type.

The similarity of the lesions of Hodgkin's disease with those found in the infective granulomata has led to the adoption by many authors of the name "Lymphogranulomatosis". That the reaction in this disease involves essentially the reticulo-endothelial tissues is claimed by many writers (Piney, 1931, Boyd, 1931.). Giant-cells endothelial cells and fibroblasts may certainly all be derived from histiocytes (Maximow). If we accept that the cells of the infective granulomata are derived from histiocytes, then we have no need to postulate the primary involvement of any other cells in the lesion of chronic Hodgkin's disease. It has been shown by Brandt

(1929) that there is no cell concerned in the histology of the tubercle which may not be found in lymphogranulomatosis, and the converse also holds.

Passing from the granulomatous type of lesion which is characterised by its chronicity and its local nodular character, and the complete differentiation of its cells as far as the fibroblastic stage, we come to the hyperplasias of the reticulo-endothelial system in which the reaction is diffuse. Diffuse hyperplasia of the cells of the whole system may occur as a result of excessive lipid storage in Gaucher's disease, Niemann-Pick's disease, and in diabetic lipaemia (Dyke). As Sternberg (1933) points out these particular types are essentially symptomatic, being caused by some underlying disturbance of lipid metabolism. Those parts of the system which are in contact with the blood-stream in the liver, spleen and bone-marrow are mainly affected in Gaucher's and allied diseases. In blood infections, such as the various forms of septicaemia and pyaemia, the same parts of the reticulo-endothelial system undergo diffuse hyperplasia.

Apart from these well-defined types

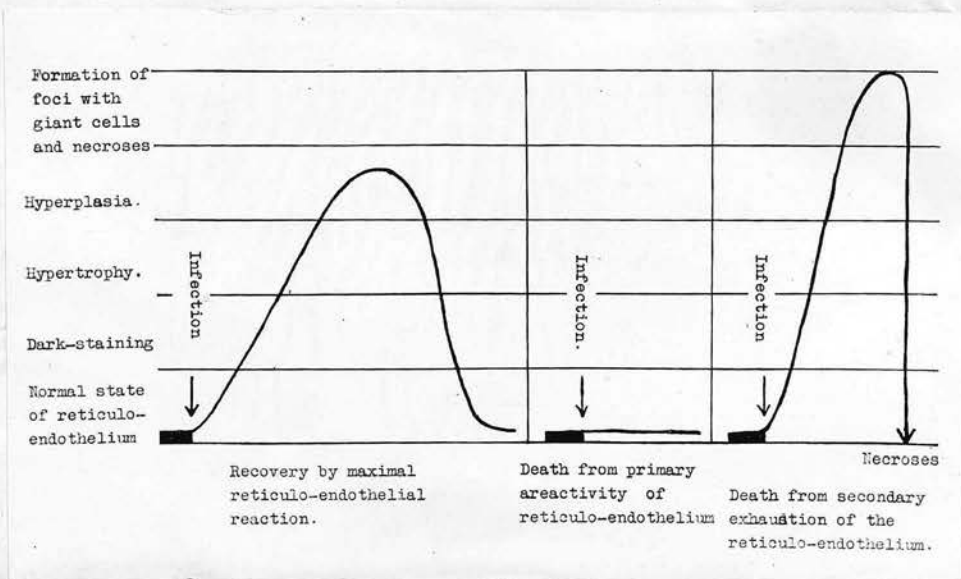


Fig. 108. (After Louros and Scheyer) showing the main types of reticulo-endothelial reaction to streptococcal sepsis.

of reticulo-endothelial hyperplasia of more or less known etiology, there still remains a group in which there has occurred a diffuse hyperplasia of reticulo-endothelial cells without relationship to any known cause. Theoretically we may meet with

1. A stem-cell hyperplasia,

aleukaemic or leukaemic
(monocytic).

2. A histiocyte hyperplasia.

The latter type affects a more mature type of cell than the stem cell, and is probably allied more closely to Hodgkin's disease than to monocytic leukaemia.

An interesting piece of experimental work is that of Louros and Scheyer (1928). These workers, experimenting with streptococcal infection in mice, found all varieties of reticulo-endothelial response from slight swelling of the reticulo-endothelial cells to the formation of foci with giant cells, and necroses. It is thus well to keep in mind that a single causal agent may, under slightly varying conditions, elicit a great variety of morbid histological appearances in the reticulo-endothelial system. It cannot be

over-emphasised that the reticulo-endothelioses do not constitute a single disease, and that the pathological subdivision adopted at present must be regarded as provisional only.

Group I

Histiocyte Reticulo-endothelioses.

The cases to be described in this group are characterised by a reticulo-endothelial hyperplasia in which all the cells present are of a type capable of derivation from mature histiocytes, and in which there are no evidences of major involvement of primitive stem-cells.

C A S E XLIII

Davina M. aet. 46. Occupation: Housewife.

Admitted to hospital: 6.4.29.

History: For the past six years the patient has suffered from mucous colitis, for which condition she was in hospital 5 years ago. The illness was associated with cramping pain in the abdomen, which was not related to mealtimes and was almost constantly present. She had frequent motions, the stool being stringy with mucus present. Sometimes the quantity of stool was large and sometimes only small in amount. After treatment in hospital the condition improved somewhat, but was nevertheless very troublesome.

Nine weeks before admission patient began to vomit whenever she took any food, either solid or fluid. She never vomited any blood. At the same time she noticed a gradual development of pallor, associated with exhaustion and breathlessness. The diarrhoea has become worse, and pain is felt in the left side of the abdomen.

Previous Health: Patient was never "strong". Mucous colitis as mentioned above; Suffers from attacks of bronchitis in winter. Six months ago she had an attack of pleurisy with stabbing pain in her right side.

Family History: Nil to note.

Home and Social conditions: good.

On Examination: The patient is very thin and there is marked pallor of the skin and mucous membranes with a slight icteric tinge of the skin and conjunctivae.

Abdomen: Liver and spleen are outlined through the thin abdominal wall. Palpation reveals marked splenic enlargement, the lower edge coming down a handsbreadth below the costal margin on inspiration. The spleen moves quite freely and is moved easily bimanually. There is therefore little evidence of perisplenitis. The liver is uniformly enlarged, the lower edge being felt two inches below the costal margin. There is some tenderness over the caecum and iliac colon.

Glands: There are no enlarged lymph-glands in the neck, axillae or groins.

Heart: Soft systolic murmurs are audible in the mitral and pulmonary areas, otherwise nil to note.

Respiratory, Urinary, and Nervous systems:

Nothing abnormal found.

Blood Examinations

	7.4.29	22.4.29
R.B.C.	1,990,000	1,610,000
W.B.C.	3,200	1,600
Hb	28	20
C.I.	.7	.6
Reticulocytes	2-3%	

Film shows a secondary anaemia: No nucleated red cells visible. There is no detectable abnormality in the proportions of the white cells.

Van den Bergh: Direct reaction negative.

Indirect reaction positive.

Wassermann: negative.

Barium meal: revealed no lesion of the alimentary tract.

Faeces: Benzidene test negative on three occasions.

Test meal: 8.4.29

Test meal (contd.)

Fasting juice:	Free HCl	0
	Total Acid	8
<u>Test meal</u>	Free HCl	0
	Total Acid	13
	No lactic acid.	

Operation: 25.4.29. Splenectomy.

The liver was uniformly enlarged and smooth, somewhat pale in colour, but there was no evidence of any cirrhosis or fatty degeneration. During the operation a blood transfusion was given from a suitable donor. Patient stood the operation well, colour and pulse being improved somewhat when she left the table.

- 26.4.29 A good deal of respiratory catarrh present.
- 27.4.29 Chest condition rather better and pulse not quite so rapid.
- 30.4.29 Rather weaker. Blood condition slightly improved, Hb 32%. W.B.C. 1,800.
- 2.5.29 Transfusion of 500cc citrated blood.
No resulting improvement. Died at 5 p.m.

Post-mortem. Broncho-pneumonia. Marrow shows a leucoblastic reaction.
No sections taken.

Spleen: Weight: 800 grammes approximately.

Dark and fleshy in colour.

Vascular lesions. There is a moderate amount of arterial congestion of the pulp. Apart from hyalinisation of the arterial walls, there is

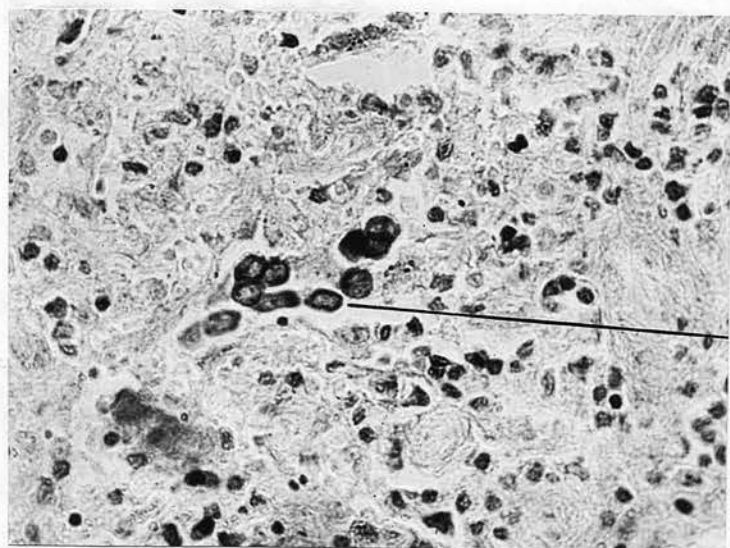


Fig. 109. Spleen from case XLIII (x 450). Large hyperchromatic cells (h) are seen in a venous sinus.

no other change. No haemorrhages visible.

Venous sinuses. Well seen, but not unduly dilated.

The cells of the sinus walls are frequently swollen, and lying in the lumina are large cells with darkly staining cytoplasm and large nuclei containing fairly dense chromatin masses.

Mitoses are frequently seen in these large endothelial cells. There is no evidence of phagocytic activity, and the iron reaction is negative. (See fig.109).

Malpighian bodies: are somewhat smaller than usual. No germ-centres seen.

Pulp-cells: slightly swollen. Nuclei frequently hyperchromatic.

Summary of Case XLIII.

A middle-aged female, who for some years had suffered from mucous colitis, developed a rapidly advancing severe anaemia of low colour index with a leucopenia. Liver and spleen were both enlarged. Medical treatment was unavailing and splenectomy was carried out. There was no response after the operation, and death occurred from bronchopneumonia. Sections of the spleen only were available for examination. These show a marked proliferation of large endothelial cells in the spleen sinuses.

Diagnosis: Reticulo-endotheliosis with
predominating endothelial reaction.

Case XLIV.

Blood counts

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B	Nuc.R.
12.1.33	3,700,000	2,000	76	1	23	67	8		2	
Reticulocytes 2.7% Platelets: 210,000										
27.1.33	4,500,000	2,000	72	.8	35	52	8	2	2	
Retic. 2.1%										
9.3.33	3,000,000	1,600	52	.87	6	84	10			
17.3.33	3,160,000	1,000	52	.8	11	76	10	2	1	
22 ~~3~~ .33		1,000			2	46	49	2	1	3%
Reticulocytes: 2.1% Price-Jones Curve: Normal.										
28.3.33	Splenectomy and transfusion.									
29.3.33	2,800,000	53,000	48	.9	89	7	4	.5		
Reticulocytes: 4.5%										
10.4.33	3,160,000	10,200		.8						
20.4.33	3,440,000	8,000			75	17	4	3		

C A S E XLIV

Mrs Annie S. aet 56 Occupation: Housewife
Admitted to hospital, Jan. 1933. Readmitted, Mar, 1933.

History: Patient was well until 2 years ago, when she had an attack of abdominal pain accompanied by jaundice. Cholecystectomy was carried out, the gall bladder containing many soft stones. In the autumn of the following year (1932) she did not feel well, and was thought to be slightly jaundiced. A barium meal revealed no lesion.

In January 1933 patient complained of colicky abdominal pain about two hours after food, accompanied by diarrhoea. The pain was relieved by passing faeces and flatus. While in hospital at this time the temperature was found to be normal in the morning and raised slightly in the evening. Since going home in January the evening temperature is said to have ranged from 100° to 105°. There has been no vomiting or nausea.

On Examination. Patient is pale, but there is no evidence of jaundice.

Heart is enlarged, the apex beat being $4\frac{1}{2}$ inches from the midline. Systolic murmurs heard in all areas.

Abdomen: Liver is felt two inches below the costal margin. The spleen is enlarged and reaches nearly to the umbilicus.

Blood counts (see table) show a progressive anaemia.

Fragility test: No increase in fragility.

Urine. Urobilin varied from +++ to nil.

Urobilinogen showed the same variation.

X-ray of bones negative.

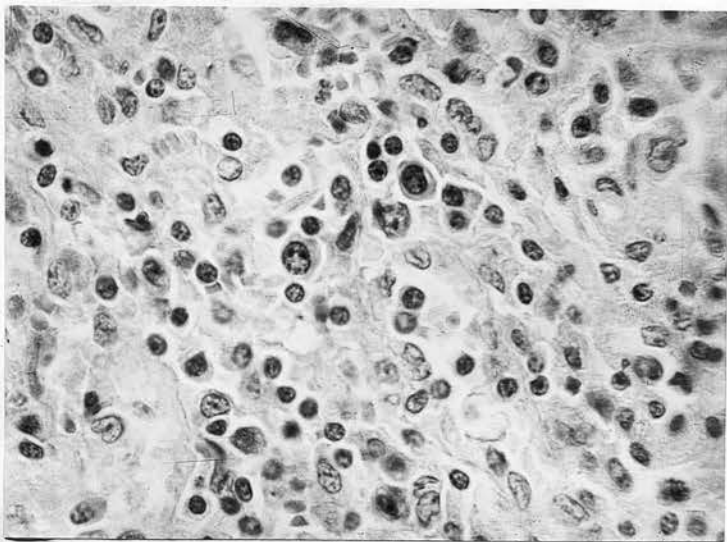


Fig. 110. Spleen from case XLIV. (x 450). The pulp contains large numbers of rounded active histiocytes with abundant cytoplasm.

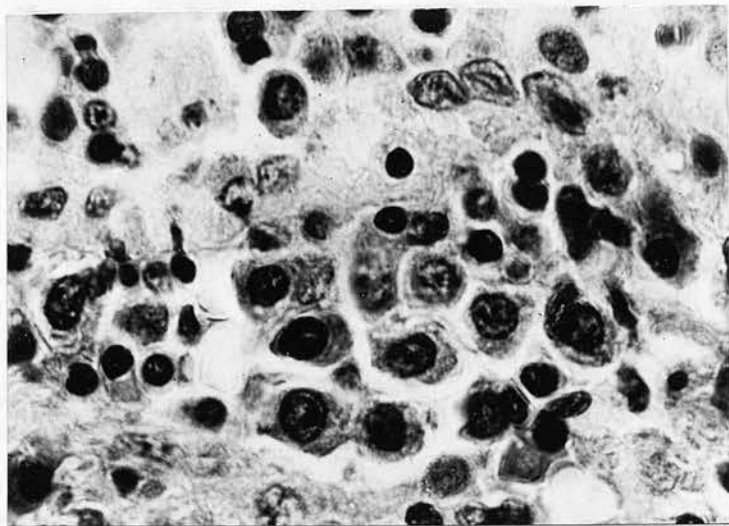


Fig. 111. Spleen from case XLIV (x 1020). A venous sinus occupies the lower part of the field: note the large cells filling its lumen.

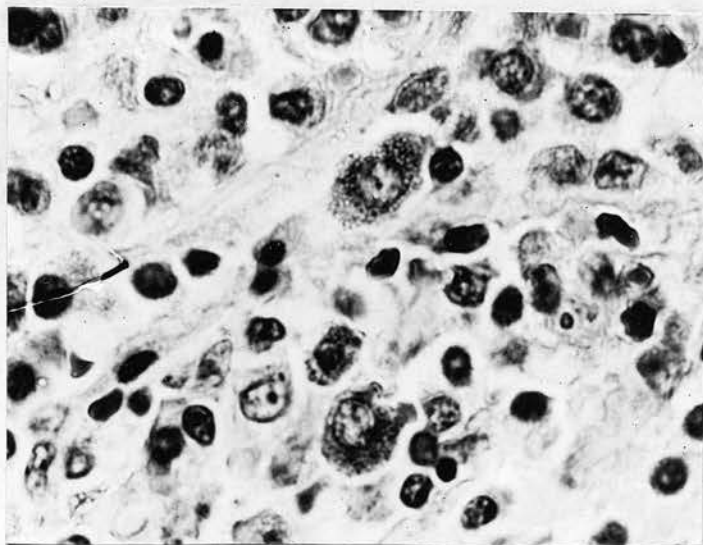


Fig. 112. Spleen from case XLIV (x 1020). Three cells are seen with granular (eosinophilic) cytoplasm.

Van den Bergh reaction: No increase in bile pigments (Indirect: .3-.8 units).

Price Jones Curve 22.3.33. normal (done by Dr Price Jones).

28.3.33 Splenectomy.

Liver apparently normal. Spleen weighed 1270 grammes. Transfusion given.

Spleen Weight 1270 grammes.

Red and fleshy in colour.

Vascular lesions An excessive amount of hyaline change in the splenic vessels, and large hyaline deposits present in the Malpighian bodies.

Venous sinuses: dilated and filled with large rounded or free cells, which are often large and one or two contain two nuclei. The following types of cell can be seen:

1. Large cells with vesicular nuclei, occupying nearly the whole cell, and with scanty dotted or lined chromatin.
2. Cells of similar size with smaller nuclei, and more densely arranged chromatin, and correspondingly more abundant cytoplasm.
3. Cells indistinguishable from lymphocytes.
4. Cells of varying types similar to the above but with eosinophilic granulations. These eosinophil cells are scanty.

The large round cells often occur in clumps in the sinuses, where mitoses and the development of eosinophilic granulations may occasionally be seen.

Malpighian bodies are small and inconspicuous.

Pulp cells: are often swollen and rounded and resemble those described in the sinuses.

Iron reaction: shows iron in many cells, but these are histologically normal spleen cells.

The large cells described above do not give
a positive iron reaction.

Summary of Case XLIV.

A middle-aged woman who had had gall-bladder disease two years previously, developed abdominal pain with diarrhoea. The spleen was markedly enlarged and the liver was also moderately enlarged. Patient ran a temperature for some weeks. There was a progressive anaemia with leucopenia, and marked diminution of the neutrophils with a relative monocytosis. Splenectomy was carried out, and the patient was discharged from hospital. The spleen showed a marked proliferation of large endothelial cells, some of which contained eosinophilic granulations.

It is of interest to note that the second case showed a definite preponderance (49%) of monocytes in the differential count made by Dr Price-Jones on 22.3.35. The absolute monocyte count of this date was 400 per c.mm., which is not appreciably raised as compared with the normal. The figures nevertheless indicate continued activity of the monocyte-forming tissues side by side with depression of the other leucopoietic tissues.

Discussion: The two cases described above show hyperplasia of the reticulo-endothelial elements of the spleen to different degrees. In the first case the hyperplasia is mainly confined to the sinus endothelium with the formation of large macrophage-like cells in the venous sinuses. The second case shows a much more diffuse type of hyperplasia affecting both pulp cells and endothelial cells. The absence of foci of myelopoietic tissue in the spleen and the absence of leukaemic changes in the blood may be taken as evidence against the primary involvement of primitive stem-cells in the hyperplastic process.

It is of interest to note that the second case showed a definite preponderance (49%) of monocytes in the differential count made by Dr Price-Jones on 22.3.33. The absolute monocyte count on this date was 480 per c.mm., which is not appreciably raised as compared with the normal. The figures nevertheless indicate continued activity of the monocyte-forming tissues side by side with depression of the other leucopoietic tissues.

Recorded cases of Reticulo-endotheliosis

Author	Age	Clinical Features	R.B.C. (mill)	C.I.	W.B.C.	Remarks	Pathological Features.
Borissowa (1903)	52	Enlarged liver & spleen: ascites.	1.9	.92	11,000	Many normo-blasts & megaloblasts.	Spleen filled with large cells like swollen endothelial cells. Liver sinusoids filled with cells like those in spleen.
Goldschmid & Isaac. (1922).	54	Enlarged spleen.	2.9	1.0	9,000	Polychromasia. 3% Myeloblasts. Normoblasts.	Swollen cells & giant-cells with large vesicular nuclei in liver spleen and bone-marrow.
Schultz, Wermbter & Puhl. (1924)	2	Enlarged lymph-gl. spleen & liver.	1.2	.71	17,800		Overgrowth of large giant-cells mixed with lymphocytes, plasma-cells & eosinophils. Often necroses in centres.
Tschistowitsch & Bykowa (1928)	63	Enlarged liver, spleen & lymph-glands	3.7	.9	6,000	Normal differential count.	Overgrowth of reticulum cells in spleen, liver & lymph-glands.
Bykowa (1929)	69	Enlarged spleen, oedema of legs.	2.0	1.2	1,800	Mono. 14% Lym. 70	Proliferation of large reticulum cells in spleen, and lymphglands.
Arinkin quoted by Bykowa	35	Enlarged liver, & spleen	4.0		11,000 to 1,200	Slight monocytosis	Hyperplasia of reticulum and endothelial cells

The records taken from the literature with which these two cases may be compared are tabulated on the opposite page. It is seen that there may be a certain amount of monocytic reaction in association with the reticulo-endothelial hyperplasia, as in the cases of Arinkin and Bykowa. Another feature seen in the cases of Borissowa, and of Goldschmid and Isaac, is the presence of numbers of nucleated red cells. A small number of erythroblasts was noted in our second case. The occurrence of primitive marrow cells in these cases is an unsolved problem, and we can only compare their appearance in this group of diseases with similar evidences of haematopoietic dysfunction recorded by Davidson (1932) in Hodgkin's disease.

One further point of resemblance to Hodgkin's disease may be mentioned: the presence of eosinophil granulation in some of the large cells in our second case. The occurrence of eosinophil granulation in Hodgkin's disease has been held by Pullinger (1932) as evidence of the involvement of a primitive stem-cell with local formation of myelocytes in the lesions.

Proof, however, is lacking that these cells are really myelocytes. Several authorities (Gutig, 1907, Downey, 1914, and Ringeon, 1915) hold that the eosinophils of the tissues differ from those of the blood. Weidenreich (1910) believes that the eosinophil granules are ingested particles of red cells. The local occurrence of eosinophil cells cannot be admitted as definite evidence of primitive stem-cell involvement.

Group 11.

Stem-cell Reticulo-endothelioses.

Into this group are admitted cases of reticulo-endothelial hyperplasia in which there is definite evidence of primitive stem-cell involvement. The latter often occurs in association with monocytic leukaemia. This type of leukaemia has not been seen by the writer, but the principal features of some of the accepted cases from the literature are summarised in the adjoining table. The clinical course of the disease is essentially that of an acute leukaemia, and only careful examination of a stained blood-film reveals the true nature of the cell type involved.

Recorded cases of Monocytic Leukaemia

with autopsy data.

Author	Age	Clinical Features	R.B.C. (mill)	W.B.C.	C.I.	Remarks	Pathological Features.
Reschad & Schilling (1913)	33	Gingivitis, enlarged spleen	2.2	15000		Mono.72%	Hyperplasia of reticulum cells of spleen & lymphglands.
Komiya & Hayashi (1921)	20	Stomatitis, enl. spleen & l.glands	.8	79000	.88	Mono.33%	Hyperplasia of reticulum cells
Ewald (1923)	60	Enlarged spleen & bleeding gums.	1.2	15000	.88	Mono.95%	Reticular and endothelial hyperplasia in liver, spleen & lymph-glands.
Schwirtschewskaja (1928)	27	Fever & weakness	4.7	416000	.5	Mono.96%	Reticulo-endothelial hyperplasia in spleen
Lawrence, Josey, & Young (1931)	13	Gingivitis, Angina.	1.1	180000	.9	Mono.83%	Hyperplasia of reticulo-endothelium of spleen
Gittins & Hawksley (1933)	1	bilateral ovarian tumours	1.2	124500	1	Mono.20% Assoc. ovarian tumours.	Spleen not much enlarged. Reticulo-endothelial reaction in liver.

Recorded cases of Monocytic Leukaemia

with autopsy data.

Author	Age	Clinical Features	R.B.C. (mill)	W.B.C.	C.I.	Remarks	Pathological Features.
Reschad & Schilling (1913)	33	Gingivitis enlarged spleen	2.2	15000		Mono.72%	Hyperplasia of reticulum cells of spleen & lymphglands.
Komiya & Hayashi (1921)	20	Stomatitis enl. spleen & l.glands	.8	79000	.88	Mono.33%	Hyperplasia of reticulum cells
Ewald (1923)	60	Enlarged spleen & bleeding gums.	1.2	15000	.88	Mono.95%	Reticular and endothelial hyperplasia in liver, spleen & lymph-glands.
Schwirtschewskaja (1928)	27	Fever & weakness	4.7	416000	.5	Mono.96%	Reticulo-endothelial hyperplasia in spleen
Lawrence, Josey, & Young (1931)	13	Gingivitis Angina.	1.1	180000	.9	Mono.83%	Hyperplasia of reticulo-endothelium of spleen
Gittins & Hawksley (1933)	1	bilateral ovarian tumours	1.2	124500	1	Mono.20% Assoc. tumours.	Spleen not much enlarged. Reticulo-endothelial reaction in liver.

One case however has been encountered in which there was considerable histological evidence of primitive stem-cell hyperplasia without any leukaemic changes in the blood-picture.

Case XLV

Blood Counts.

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.	Myc.	N.R.
19.4.23	4,200,000	28,000	68	.83	74	15	5	.5	.5	5	3%W

Polychromasia, anisocytosis, and punctate basophilia.

30.4.23	2,900,000	9,300	44	.77	66	17	9	2	0	6	1%W
14.5.23	2,500,000	4,660	44	.88	68	24	4	3			3%W

X-ray treatment.

6.6.23 Spleen smaller.

8.6.23	2,200,000	2,500	40	.9	77	16	4	1		2	.5%W
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3.8.23 Splenectomy.

9.8.23	1,600,000	15,000	32	1.0							
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16.8.23	2,160,000	26,500	37	.9							
---------	-----------	--------	----	----	--	--	--	--	--	--	--

31.8.23	3,040,000	14,200	61	1.05							
---------	-----------	--------	----	------	--	--	--	--	--	--	--

13.9.23	2,900,000	14,000	53	.9							
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11.10.23	4,200,000	25,000	67	.8							
----------	-----------	--------	----	----	--	--	--	--	--	--	--

20.3.24	4,880,000	36,000		.7							
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15.1.25	6,260,000	58,000	86	.71	65	1	15	7	3	8	265%W.
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C A S E XLV

Agnes H. aet. 30. Occupation: Clerk.

Admitted to hospital: 16.4.23.

Patient was first admitted to a gynecological ward and was operated upon for a large tumour which filled the whole abdomen and which was taken to be an ovarian cyst. The tumour was found to be an enormously enlarged spleen. She was then transferred to a medical ward. Fifteen months before admission the patient had an attack of "influenza", previous to which she had only noticed a little weakness and backache. There is no history of nose-bleeding, but she bleeds freely when her teeth are extracted or when she sustains a cut. Her periods were regular until four months before admission when they stopped. Bowels are regular.

On Examination: Cheeks are highly coloured, but conjunctivae are slightly pale.

Abdomen: is distended. A tense hard tumour can be felt extending from the rib-margin down into the pelvis. On vaginal examination the uterus is separable from the tumour. The lower pole of the tumour is felt in the left fornix. The liver at operation was smooth on the surface but slightly enlarged.

Cardio-vascular, Respiratory and Nervous systems:

Nil to note.

Blood counts: See table.

Van den Bergh: Indirect reaction positive.

Wassermann: negative.

Course: During her stay in hospital the anaemia became more severe, medical and X-ray treatment being unavailing. Splenectomy was decided upon.

3.8.23 Splenectomy.

After the operation the patient developed a leucocytosis which persisted for the remaining three years of the patient's life. The anaemia improved somewhat after splenectomy (see blood table). In 1924 the patient felt well and was back at work. Early in 1926 she was invalided with "phlebitis" of the leg and was unable to report.

15.7.26. Died.

Letter from her doctor stated that the outstanding feature of her final illness was extreme emaciation. She had occasional attacks of diarrhoea and the illness terminated with a severe haemorrhage from the bowel (the only one she had). She had occasional bleeding from the gums. Her liver was very large and occupied at least three quarters of the abdomen. Death was sudden.

Spleen:

Weight: 4,300 grammes.

Histology

Vascular lesions. Periarterial haemorrhages are present with pigment deposits. (This is a non-specific type of change which may occur in spleens congested from any cause.) The pulp spaces are moderately congested and there is no evidence of great dilatation of the venous sinuses. Such congestion as there is, probably results from active arterial congestion rather than from passive venous congestion.

Malpighian Bodies: small and inactive: no germ centres seen.

The pulp is very cellular and contains: -

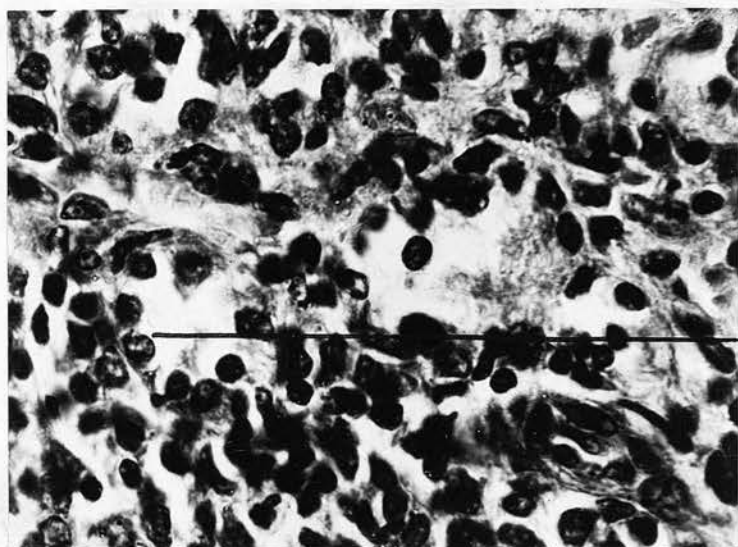


Fig. 113. Section of a normal spleen (x 800), for comparison with the succeeding three photographs. Note the size of the cells (c) lining the sinuses.

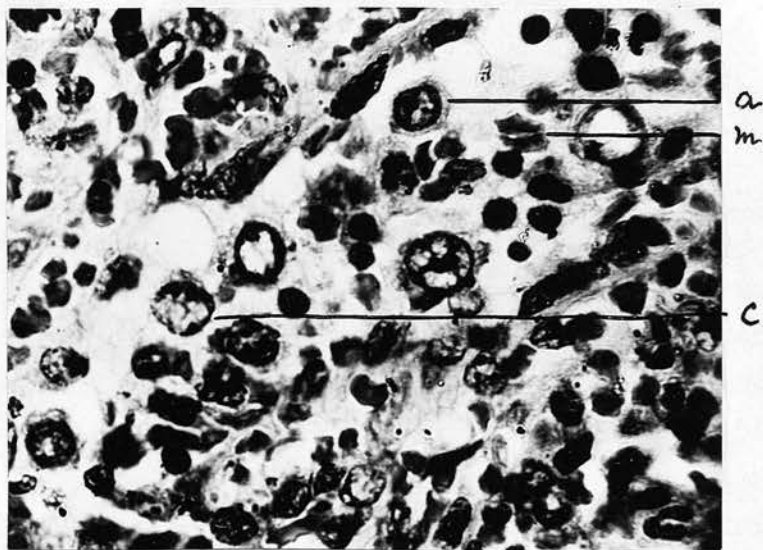


Fig. 114. Spleen from case XLV (x 800). Note the large cells (c) with vesicular nuclei, fully three times the size of the normal cells in Fig. 113. (a) shows a cell with more cytoplasm and denser chromatin. (m) indicates a mitotic figure.

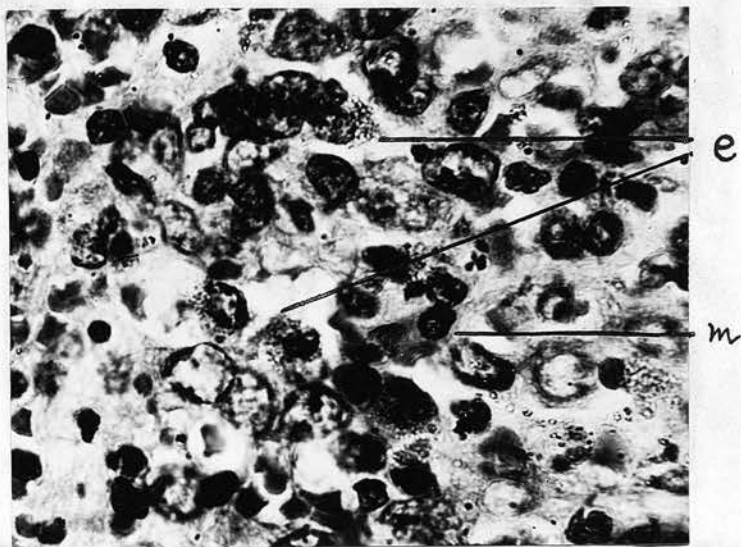


Fig. 115. Spleen from case XLV (x 800). One megakaryocyte (m) is seen and numerous eosinophilic cells (e).

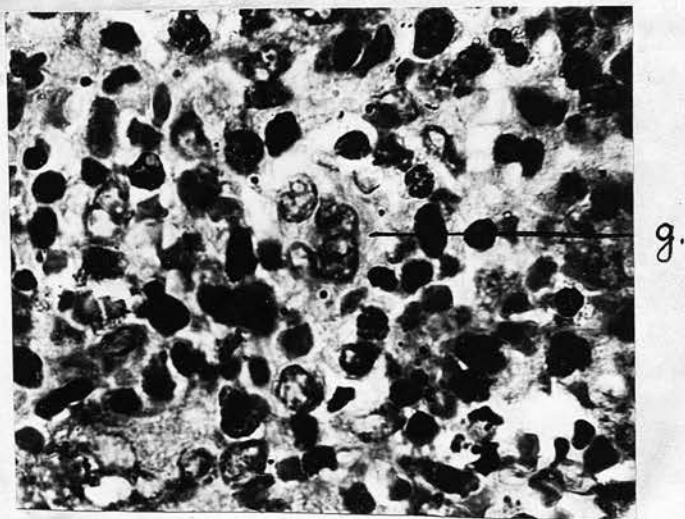


Fig. 116. Spleen from case XLV (x 800). A large giant-cell (g) is seen.

1. Numerous large cells with voluminous vesicular nuclei, and scanty basophil cytoplasm. These cells resemble closely in appearance the cells constituting the pulp of a normal spleen, but are approximately three times as large. The nuclei are poor in chromatin and contain no definite nucleoli.
2. Intermingled with the above are large cells richer in cytoplasm and with a smaller and more rounded nucleus richer in chromatin.
3. Very rarely a group of two or three cells is encountered similar to those of group (2), with mauve staining cytoplasm and nucleus with thick radiating chromatin rods — megaloblasts.
4. One or two cells occur in each field with eosinophil granulation: Some of these are polymorphs and others are myelocytes, the latter predominating.
5. Occasional giant-cells with multiple or convoluted nuclei, resembling the nuclei of cells of type (1).
6. Normoblasts were seen in the circulating blood: in one area only was there a suggestion of local formation of normoblasts. Mitotic figures are common throughout the spleen.

The hyperplasia in this case involves mainly a primitive "stem-cell" of the reticulo-endothelial type, and which may be a precursor of marrow tissue. This is evidenced by differentiation to megaloblasts and to myelocytes. The predominating cell however is the large parent "stem-cell".

This case can only be classified provisionally as a stem-cell reticulo-endotheliosis. The differentiation into mature marrow elements is too slight to allow emphasis on myeloid metaplasia.

Summary of Case XLV.

A woman aged 30 was admitted to hospital with swelling of the abdomen. The spleen was enormously enlarged and associated with a moderately severe anaemia, with leucocytosis at first and then a leucopenia. Nucleated red cells and myelocytes were constantly present. Following splenectomy a leucocytosis developed, and two years later 15 percent of 58,000 white cells were monocytes, myelocytes also being present. Enormous numbers of nucleated red cells were present, being actually more than twice as numerous as the white cells. Death occurred with haemorrhagic symptoms and enlargement of the liver three years after splenectomy. Histologically the spleen shows an enormous proliferation of its cellular content, affecting mainly large primitive "stem-cells" with differentiation to megaloblasts and myelocytes.

Discussion.

The evidence that a primitive stem-cell is involved in this case is based upon the histology of the spleen in association with the features of the circulating blood.

The principal cells encountered in the spleen are very large cells with vesicular nuclei resembling overgrown cells of the normal spleen. These cells have apparently been the precursors of megakaryoblasts and myelocytes. The circulating blood shows evidences of excessive formation of young red and white blood elements in the presence of nucleated red cells and myelocytes.

It must be emphasised that although a primitive stem-cell is involved in the hyperplasia in this case and in the monocytic leukaemias, there is no suggestion that these diseases are identical. We are dealing with a type of cellular reaction which may be elicited by a variety of different agents. The variation of the cellular response to a single cause has already been emphasised in quoting the work of Louros and Scheyer (see p. 384).

While some of these reticulo-

endothelioses are leukaemic, others are certainly infective in origin. As examples of the latter we may quote the cases of Akiba (1926) and Krahm (1926). In both these instances young children were affected by a febrile illness. At autopsy the liver, spleen and lymph-nodes showed marked reticulo-endothelial hyperplasia with necrotic areas containing streptococci. Other instances of reticulo-endotheliosis may be more closely allied with tumour formation. Here we may instance the case of Gittins and Hawksley (1933) where there were associated bilateral ovarian tumours, and that of Ungar (1932) where a reticulo-endothelial sarcoma developed in the humerus. Finally some instances of reticulo-endotheliosis may have affinities with Hodgkin's disease. A tentative classification of reticulo-endothelioses might be suggested on the following lines:-

I. Pathological Classification

based on the main type of cell involved.

	<u>Hyperplasia</u>	<u>Characteristics</u>
Stem-cell. ↓	Stem-cell reticulo-endotheliosis.	Evidences of erythro-, myelo- and monocytopoiesis.
Mature reticulo-endothelial cell.	Histiocyte reticulo-endotheliosis	No evidences of cell-formation other than those derived from the mature histiocyte.

II. Etiological Classification

1. Infective Reticulo-endotheliosis

Evidences of streptococcal or other infective agent causing the reticulo-endothelial hyperplasia.

2. Leukaemic Reticulo-endotheliosis.

Reticulo-endotheliosis with associated monocytic leukaemia.

3. Neoplastic Reticulo-endotheliosis.

With formation of reticulo-endothelial tumours in any site: ovaries, bones, etc.. Transitions between 2. and 3. common.

4. "Hodgkin's" Reticulo-endotheliosis.

Bearing clinical and pathological resemblances to Hodgkin's disease.

Chapter 15

MYELOID SPLENIC ANAEMIA.

(Vaquez--Aubertin's Disease)

The syndrome of splenic anaemia is usually held to include those cases of splenic enlargement associated with a secondary anaemia, without leucocytosis, in which well-known causes of splenic enlargement, e.g., leukaemia, Hodgkin's disease, and various infective conditions, may be excluded. Two distinct types of pathological lesion which may underly this disease picture have already been described, namely, hepato-lienal fibrosis and reticulo-endotheliosis. In subsequent chapters we shall also instance simple splenic hypertrophy, tuberculosis, and lymphosarcomatosis of the spleen as further pathological conditions forming a basis for this clinical syndrome.

The condition to be described in this chapter deviates somewhat from the definition of splenic anaemia given above, in that it is frequently associated with a leucocytosis. Leukaemia, however, can be definitely excluded,

and the pathological and haematological picture presents certain affinities with Addisonian anaemia. While leucocytosis is common, it is by no means constant, and a case which shows a high white count at one stage, may show a leucopenia at another. On this account the diagnosis of "splenic anaemia" is frequently made in this unusual type of case. The pathological picture of myeloid metaplasia in the spleen indicates however that this disease differs fundamentally from hepato-lienal fibrosis. The following cases are illustrative of the condition.

Apr 6-1908

Blood.

[illegible]

C A S E XLVI

Mrs L. aet 54.

Came under observation in 1927.

History: Patient was well until February 1924. During a visit to Italy she felt a swelling in her abdomen. On her return to this country X-ray treatment was carried out: 1924-1926. During this time the spleen diminished in size, but rapidly enlarged again on cessation of the treatment. There is no history of jaundice or haematemesis.

Family History: Nil to note.

On Examination: The patient is of poor physique. There is no jaundice. Colour is fairly good.

Abdomen: is largely filled by an enormous spleen which reaches down to the pubis and its right border extends to the right of the middle line. A notch can be felt to the right of the umbilicus. There is no friction. No distended veins are visible in the abdominal wall. There is no ascites and no history of haemorrhoids. The liver is enlarged to two inches below the costal margin and feels hard but is not nodular. There is no pain or tenderness anywhere in the abdomen.

Cardiovascular, Renal, Nervous, and Respiratory Systems show no abnormality.

Blood counts are indicated in the table.

Van den Bergh Indirect reaction: positive.

Fragility Test: Slight haemolysis at .5%,
definite at .45%

Wassermann Reaction: negative.

25.7.27. Splenectomy: The spleen was mobile and there were no adhesions. Weight of the spleen: 1950 grammes. There was considerable thickening

of the splenic veins at the hilum.

Progress: Patient got on quite well until three weeks after the operation. She then developed pain in the region of the left kidney with fever which lasted for five days, with albumen, blood and casts in the urine.(? renal embolism). She recovered from this and was discharged feeling quite well, with no albuminuria.

October, 1928. Patient is now tending to bleed easily from the gums, and recently on two occasions she has bled from the bowel. The liver is enlarged to below the umbilicus. Thrombosis of the veins of the right thigh and then of the left thigh developed recently.

February, 1929. Apart from the fact that she still tended to bleed easily, the patient was much better. The liver, though still greatly enlarged, had become smaller again. Patient suddenly developed a headache, became unconscious and died 48 hours after the onset of the headache. (?cerebral thrombosis).

Spleen

Weight: 1950 grammes

Histological features

Vascular lesions: Apart from some hyalinisation of the arterioles, there is no other lesion to note.

Venous Sinuses. These are filled with cells similar in appearance to those constituting the pulp.

App. p. 410
7

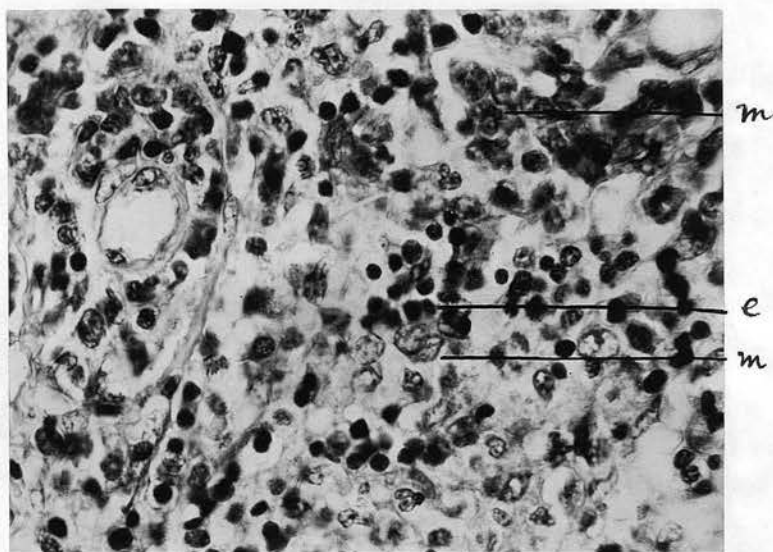


Fig. 117. Spleen from case XLVI (x 500).
Diffuse myeloid metaplasia is seen.
m -- areas of large myeloblasts (?).
e -- small pyknotic nuclei of erythroblasts.

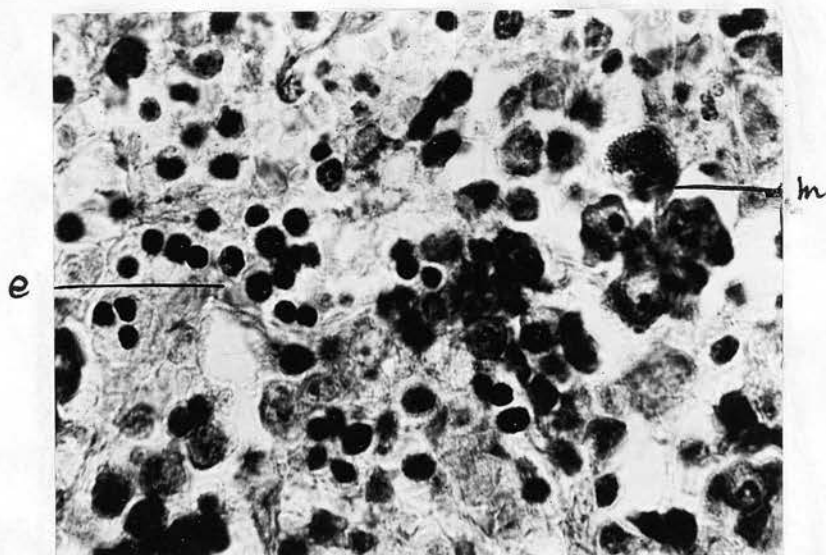


Fig. 118. Spleen from case XLVI (x 800).
 e -- erythroblastic area.
 m -- myeloblasts and one granular myelocyte.



Fig. 119. Spleen from case XLVI (x 800).
 g -- edge of a giant-cell.
 m -- myeloblast with nucleoli.
 e -- erythroblast.

Malpighian Bodies: are inconspicuous.

Pulp: Normal cells of the spleen pulp are scarcely recognisable. In every field a great variety of cells is seen, among which definite marrow elements are recognisable, and mitotic figures are exceptionally frequent.

1. Giant cells are seen occasionally with convoluted nuclei. These cells are oxidase negative.
2. Next in size are large cells with a slightly branched cell-body. There is a relatively small amount of basophilic, coarsely granular cytoplasm, round a large vesicular nucleus containing one to four nucleoli. These cells often appear in clumps containing up to twelve cells. Mitoses are common. These cells are oxidase negative. (? Primitive stem cells, or pro-myeloblasts).
3. Cells are present with rounded cell-body filled with neutrophil or eosinophilic granules. The nucleus is small and vesicular, containing one or two nucleoli. These appear to be myelocytes. They give a positive oxidase reaction.
4. Non granular cells are seen, otherwise exactly corresponding to group 3. ? myeloblasts or pro-myelocytes. These cells are oxidase negative.
5. Cells with diffuse, faintly eosinophil cytoplasm and small nuclei, with dense chromatin are present: These are normoblasts.
6. Large cells with mauve cytoplasm, and nuclei with thick chromatin rods, are seen. These are megaloblasts.

Summary of Case XLVI.

Female aged 54 complained of swelling in the abdomen. The spleen was enormously enlarged. A slight anaemia was present, with leucocytosis ranging from 10,000 to 36,000. Evidences of marked myeloid and erythroblastic activity were present in circulating erythroblasts and myelocytes. Splenectomy had little influence on the course of the disease. The liver became greatly enlarged, and a haemorrhagic diathesis was superadded. Death occurred 5 years after the onset of the illness. Histologically the spleen showed intense myeloid metaplasia.

7/15/12

Blood:

[illegible]

C A S E XLVII

Mary T. aet 55. Occupation: Stationer.

Admitted to hospital: 20.5.30.

History: For a few months the patient has been getting pale. She complains of being listless and short of breath, and is generally "run down". There has been no pain, and, during the past week or two, loss of appetite and vague gastro-intestinal disturbances have been present.

Previous Health: No illnesses of note.

Family History: No account of jaundice in any of the family.

On Examination: The patient has a slightly lemon-coloured skin like that seen in pernicious anaemia. Definite pallor was also present and the mucous membranes were definitely anaemic. Subcutaneous fat was plentiful, and there was no evidence of cachexia.

Abdomen: The spleen was enlarged to a point midway between the costal margin and the umbilicus. The liver could not be felt. There was no pain or tenderness elsewhere, and no enlarged glands were found.

Cardiovascular system: The pulse was rapid, over 100 per minute. Systolic haemic murmurs were heard especially at the base.

Respiratory and Nervous Systems: Nil to note.

Blood counts are given in the annexed table.

Van den Bergh: Indirect reaction: positive.

Icterus Index: 20.

Fragility Test: no abnormality.

Wassermann reaction: Anticomplementary: later negative.

Price-Jones Curve (Remarks by Prof. Davidson)

"Although there was a marked shift to the right in the peak, there was not the same degree of broadening of the base as is found in a case of pernicious anaemia of the same severity..... A marked macrocytic anaemia was present, but the coefficient of anisocytosis, i.e., the degree of variability was only moderate. In addition the cells were large and round, and not oval as is so typical of the genuine megalocyte of pernicious anaemia."

10.6.30 Splenectomy.

The spleen weighed 1,800 grammes. The liver was pale but showed no other abnormality. A small piece of the liver from the edge was taken for section. Transfusion given.

Progress: After the operation some upward fluctuation occurred in the blood count, but the improvement was not sufficiently immediate or striking to be ascribed to the operation. After four months the red cells reached 3 millions. In the following year, 10 months after the operation, the patient again became severely anaemic. The red cells fell rapidly to 700,000 without signs of bone-marrow reaction, and death took place.

Spleen Weight 1700 grammes.

The appearance was red and cellular with no evidence of increased connective tissue formation.

Histology.

Vascular lesions: Apart from hyalinisation of the arterioles there was no other vascular lesion.

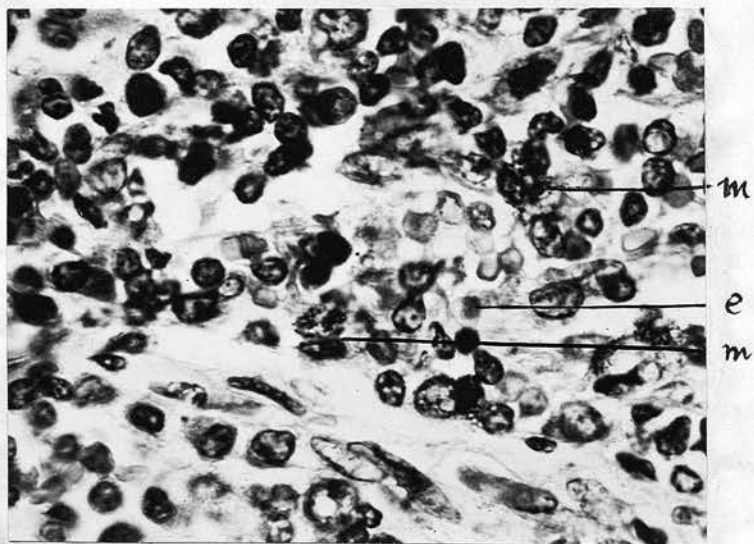


Fig. 120 Spleen from case XLVII. (x 900)
Note the granular myelocytes - (m), and the
nucleated red corpuscle - (e).

Venous sinuses: There is no marked dilatation of these, and such distension as exists is due to the increased cellularity of their content.

Malpighian bodies: are well-seen and present no abnormality.

Pulp : is very cellular, there being large numbers of large cells of the histiocyte type with pale vesicular nuclei. Well-defined areas are present in which nucleated red cells and myelocytes are present.

The Prussian-blue reaction is negative.

Liver. There was no evidence of cirrhosis or of fatty degeneration, and no sign of myeloid metaplasia. There was no pigment in the Kupffer cells, but the liver cells, especially near the centre of the lobule, frequently contained clumps of yellowish pigment which did not give a free iron reaction. It is probable that this was bile-pigment.

Summary of Case XLVII

A spinster aged 55 presented the symptoms of progressive anaemia for a few months. The spleen was greatly enlarged. Severe anaemia was present with a high colour index, and there was at first a leucopenia, and later a leucocytosis. Megaloblasts and normoblasts were present in the circulating blood. Reticulocytes varied from 1-12% before splenectomy. The latter operation had little influence on the course of the disease and the patient died a year later with signs of bone-marrow aplasia. The spleen showed pronounced myeloid metaplasia.

Oct-16-16

Case XLVIII.

Blood.

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.	Ret.	N.R.
13.9.28	1,000,000	10,000	22	1.1						30%	
16.9.28	1,000,000	7,200	22	1.1						15%	
22.10.28	650,000		15	1.1						70%	

C A S E XLVIII

Janet H, aet. 15.

Admitted to hospital, 12.9.28.

History: In April 1928 the patient noticed swelling of her feet, began to suffer from headaches and found that she was becoming pale and breathless on exertion. She became progressively weaker and paler. One week before admission she had a "rheumatic" pain in the right ankle. Apart from that the illness has been painless.

Family History and Previous Health: Nil to note.

On Examination: The patient was extremely anaemic with slight subcutaneous oedema. There was no loss of subcutaneous fat and no evidence of icterus. Tongue was clean and pale.

Cardiovascular System: Blood pressure: S.98..D.60.

Systolic murmurs were heard over the heart.

Blood culture was negative.

Abdomen: Liver just palpable. Spleen was felt one inch beyond the rib-margin.

Urine: Albumin and blood present. Some blood, granular, and hyaline casts were found in the deposit.

Blood Urea: 32 mg %

Respiratory and Nervous systems: Apparently normal.

Haemopoietic System: No enlargement of lymphatic glands was found.

Blood counts are indicated on the annexed table.

The patient did not respond to liver and liver extract by mouth. Blood-counts between 13.9.28 and 22.10.28 showed a steady fall in the red cell count, until on the latter date it had reached 650,000. The white count remained within normal limits: 6,000 -10,000, and the reticulocyte

477
percentage varied from 15 to 60. Nucleated red cells were present in considerable numbers.

Fragility test: No abnormality,

Van den Bergh: Delayed direct: Positive. Indirect: markedly positive.

While in hospital temperature varied from 97° to 100°.

In view of the complete failure of medical treatment, and the evidences of blood-destruction (icterus, reticulocytosis), splenectomy was recommended.

9.11.28. Splenectomy. Liver appeared normal. Transfusion of 22 ounces of citrated blood.

After the operation the white cell count rose to 74,000, 95% being polymorphs. The Arneth count showed a marked shift to the left. Death occurred from sepsis on 14.11.28.

Summary of post-mortem examination: Marked oedema of the subcutaneous tissues was present everywhere. Free fluid was present in excess in all the serous cavities.

Heart: Cavities dilated. Myocardium showed fatty changes. A small vegetation was present on the auricular surface of one of the cusps of the mitral valve. The pathologist was satisfied that this was of recent occurrence.

Abdominal cavity: Greenish-yellow pus was present underlying the lower end of the operation wound. The liver was large and showed fatty changes and chronic venous congestion. Prussian blue reaction moderate,

Kidneys: Large and exceedingly pale. Capsules

8p. 10. 118

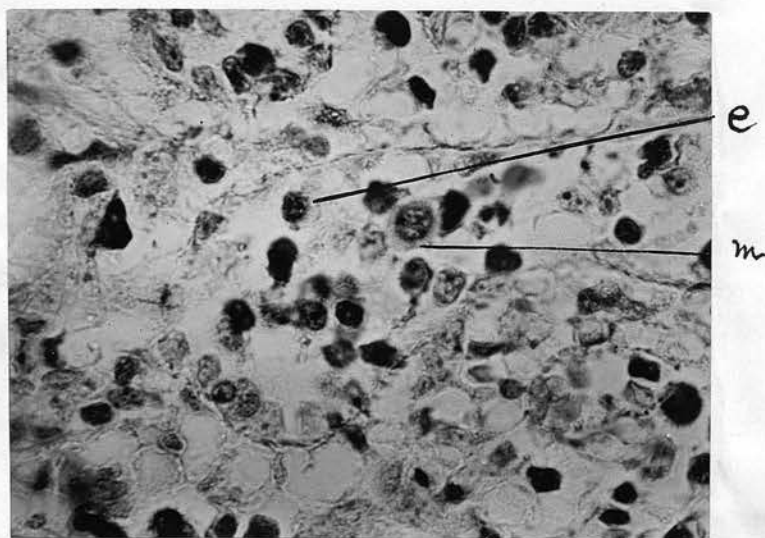


Fig. 121. Spleen of case XLVIII. (x 950).
A venous sinus occupies a great part of the
field. e denotes an erythroblast, and m, a myelo-
blast.

stripped easily, the subcapsular surface being smooth.

Bone-marrow: (shaft of femur) Showed a marked erythroblastic reaction.

Spleen Enlarged, soft in consistence, and dark red in colour.

Vascular lesions: Hyalinisation of the arterial walls. Apart from this, nothing to note.

Venous sinuses: are filled with cells similar to these of the pulp.

Malpighian bodies: are unchanged and there is no evidence of any increase of lymphoid tissue.

Pulp: The cells of the pulp are markedly altered from the normal. Instead of the usual histiocyte with clear open nuclei, the majority of the cells have denser nuclei with more abundant cytoplasm. Here and there, especially in the sinuses, primitive blood-cells are seen, nucleated red corpuscles and myelocytes being identified.

The whole picture suggests diffuse myeloid metaplasia, with a predominance of primitive cell-types.

Summary of Case XLVIII.

A girl aged 15 complained of increasing pallor. Definite evidences of nephritis were present with some temperature. The spleen was found to be enlarged. Anaemia was severe with a high colour index, and numerous nucleated red cells. The white count fluctuated from a normal level to 10,000. Large numbers of reticulocytes were present (up to 70%). Sepsis was superadded after splenectomy. Histologically the spleen showed myeloid metaplasia, and the bone marrow showed an intense erythroblastic reaction.

Discussion.

These three cases have a common pathological basis in the presence of myeloid metaplasia as the predominating feature of the splenic histology. Associated with this haematopoietic activity is the occurrence of erythroblasts, reticulocytes, and in one of the cases at least, myelocytes in the circulating blood.

This syndrome was first described clearly in 1904 by Vaquez and Aubertin. The following description was given by the latter author in 1928:

The syndrome is rare and mainly affects subjects between the ages of 40 and 60 years. There is nothing to suggest that syphilis, tuberculosis, malaria, or tropical diseases play any etiological role.

The onset is insidious and the first symptom may be a feeling of weight in the splenic region. The spleen is enlarged to a varying degree, while the liver is moderately enlarged.

Haemorrhagic phenomena may also occur, but haematemesis is as unusual as it is common in the "Banti type".

The blood shows the following features:

Red cells: may range from 850,000 to 3-4 millions.

Anisocytosis, poikilocytosis, and polychromasia are present, but the striking feature is the increased number of nucleated red cells which may reach 20-40 per 100 leucocytes. The nucleated red cells include both normoblasts and megaloblasts. Each red cell carries its full complement of haemoglobin, and the colour index is about unity or even above one.

The white cells number 12-20,000 on the average, and of these, myelocytes constitute from 1-10 per cent. Approximately 50 or 60 per cent are constituted by neutrophil polymorphs and a few eosinophils.

The course of the disease lasts about eighteen months or two years as a rule. Hitherto all the cases have been fatal.

Pathologically the bone marrow is found to be red and active, extending into the shafts of the long bones. The spleen is enlarged and weighs anything up to 3,000 grammes. The characteristic feature is myeloid transformation of the pulp, which contains myeloblasts, neutrophil and eosinophil myelocytes, and nucleated red blood corpuscles. The liver is enlarged and shows myeloid infiltration.

2. Atypia of the lines (Schack, 1913)

3. Haemolysis and haematuria, e.g.

The cases we have described correspond fairly closely to this description. Unfortunately a full pathological account cannot be given as material for histology is lacking. Nevertheless the available data present a sufficiently uniform picture to allow us to place the cases in the above group.

Before we can consider the nature of this pathological syndrome, it is necessary to devote some attention to myeloid metaplasia, its nature and significance, and the conditions of its occurrence.

Myeloid metaplasia is defined by Lang (1932) as extensive haematopoiesis in organs of the body which, under normal conditions form no myeloid tissue. It occurs most freely in organs which generated blood elements in the embryo, e.g. spleen, liver, lymph-glands, thymus, kidney, and suprarenal glands.

Experimentally myeloid metaplasia may be induced in animals by

1. Repeated haemorrhages, especially if combined with the injection of destroyed corpuscles (Itami, 1909).

2. Amputation of the limbs (Schaak, 1913)

3. Haemolysins and haemotoxins, e.g. phenylhydrazine.

Blood loss combined with the products of blood destruction may thus elicit myeloid metaplasia. The second method involves annihilation of a great part of the potential marrow-space, leading to compensatory development of myeloid tissue in embryonic sites.

In disease conditions, myeloid metaplasia tends to occur with greatest frequency in infancy and early childhood, this being the age least remote chronologically from embryonic blood-formation.

In early life myeloid metaplasia is a non-specific reaction which may occur in almost any form of anaemia. Luzet (1891), Weill and Clerc (1902), Fowler (1902), Lehndorff (1904) and Askanazy (1904) found myeloid metaplasia in the tissues of infants with von Jaksch's anaemia. The consensus of opinion indicates that this syndrome is an infantile reaction to anaemia induced by a variety of agencies.

In the adult, excessive granulo-poiesis in the spleen and in other sites occurs in myeloid

leukaemia, but myeloid transformation with formation of both red and white elements is rare. It occurs in osteosclerotic anaemia (Schmorl, 1904), Nauwerck and Moritz, 1905, Askanazy, 1904, and Assmann, 1907) where it may be a compensatory mechanism for the loss of marrow space. It is also said to occur in polycythaemia (Hirschfeld, 1925).

In pernicious anaemia, myeloid metaplasia is not as a rule a pronounced feature, (Ellerman and Bang, 1920, Piney, 1925, Sternberg, 1926.)

In the adult, therefore, this picture of considerable splenomegaly determined solely by myeloid metaplasia is rare.

In those cases of myeloid splenic anaemia which have been presented above, there are evidences of excessive blood formation (reticulocytosis, erythroblastosis, polychromasia, anisocytosis,) side by side with excessive blood destruction. The picture differs from ordinary congenital haemolytic jaundice and from pernicious anaemia in many respects. Acholuric jaundice does not show extramedullary haemato-poiesis, and nucleated red cells and myelocytes are unusual findings: the satisfactory response to splenectomy is absent in myeloid splenic anaemia.

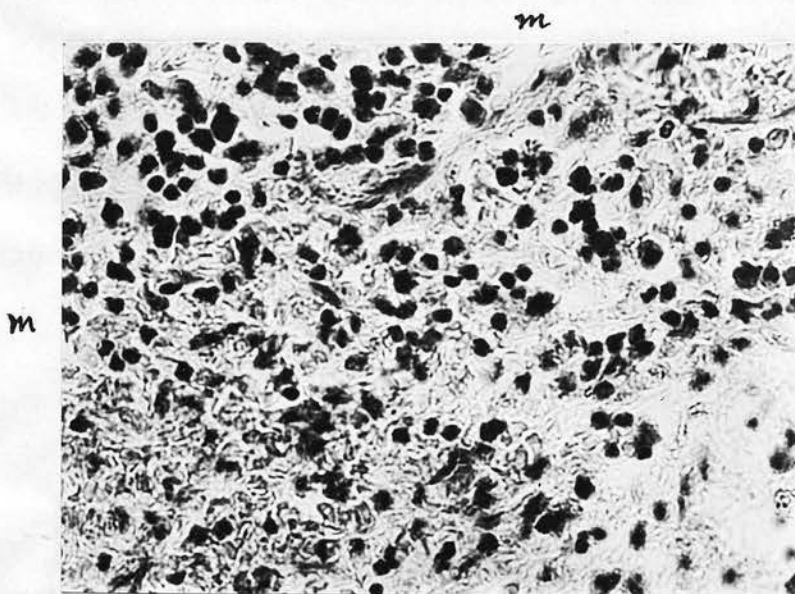


Fig. 122. Spleen from a case of von Jaksch's anaemia (x 680). Above and to the left of the line mm is an islet of myeloid metaplasia. The pulp tissue below and to the right of this line shows active congestion.

In pernicious anaemia, leucocytosis is absent, and pronounced evidences of blood regeneration are not seen apart from liver therapy. The latter form of treatment fails completely in myeloid splenic anaemia.

Pathologically and clinically myeloid splenic anaemia resembles most closely von Jaksch's disease, with one important difference: von Jaksch's disease tends to spontaneous recovery, while myeloid splenic anaemia is invariably fatal. Aubertin describes von Jaksch's disease as the "maximal plastic reaction to any form of anaemia" affecting the infant.

In myeloid splenic anaemia we are dealing with a systematised affection of the haematopoietic apparatus with excessive blood destruction (haemolytic jaundice). The spleen is not the "Angriffspunkt" of the haemolytic process as is the case in congenital haemolytic jaundice. In pernicious anaemia the haemolytic process can be arrested by the restoration of marrow function as a result of liver therapy, while splenectomy is valueless. The haemolytic process is therefore secondary. In this disease haematopoietic function is upset and is unable to keep pace with the excessive blood destruction which is probably secondary.

No known method (liver, etc.) can correct the haematopoietic dysfunction in these cases and the disease is ultimately fatal.

There can be little doubt that myeloid splenic anaemia is identical in every respect with the condition described by Leube and Arneth (1901) as "leukanaemia". Their case occurred in a boy aged 10 who had a febrile illness with anaemia, and moderate enlargement of the liver and spleen. The red cells fell to below one million, with a high colour index, and numerous nucleated red cells were present in the circulating blood. The white count was 10,600, of which 13% were myelocytes, 44% polymorphs, and 40% lymphocytes. At autopsy, there was red metaplasia of the bone marrow, and myeloid transformation of the spleen. The liver showed no siderosis. Leube indicated the apparent combination of the pictures of leukaemia and pernicious anaemia, and suggested the name "leukanaemia".

A similar clinical picture is said to occur in malignant disease with bone-marrow metastases, and a series of such cases have been summarised by Levy (1910). Clinical and autopsy examinations in such cases reveal the causal lesions. In osteosclerotic anaemia, the blood

picture resembles that in myeloid splenic anaemia, but radiological and autopsy examinations show the primary cause.

A clinical picture closely resembling that of myeloid splenic anaemia has been described as "Acute infectious haemolytic anaemia" (Lederer, 1930). This condition runs an acute course with fever, extreme anaemia with normoblasts, high reticulocytosis and leucocytosis with myelocytes. The disease is self-limited and tends to undergo spontaneous cure, with or without transfusion. Splenic enlargement is occasionally seen but is not a pronounced feature of this disease.

Clinically, then, there are several distinct conditions which may resemble haematologically myeloid splenic anaemia. After excluding malignant disease, osteosclerosis, and Lederer's anaemia, a clinical diagnosis may be made with reasonable certainty.

Aubertin regarded the morbid process in myeloid splenic anaemia as resembling leukaemia. The hyperplasia affects both red and white cells in the marrow. While there is a moderate leucocytosis, there is no erythraemia at any stage. Blumenthal (1907) has described a form of erythr-

aemia accompanied by leucocytosis with a high percentage of myelocytes which runs a more prolonged course than the disease under discussion and is not associated with splenic enlargement. The leucocytosis in myeloid splenic anaemia is always moderate compared with the high figures so common in the leukaemias. Blumenthal's disease is probably more closely allied to leukaemia. In our present state of knowledge, it can only be stated that myeloid splenic anaemia is a dyscrasia of the haematopoietic system of unknown etiology.

The new cases recorded here allow us to add but little to the account of Aubertin. In our third case the syndrome appeared in a girl aged 15, suffering simultaneously from nephritis. It is impossible to say what etiological relationship the latter condition had to the morbid process in the haematopoietic system.

Pathologically, biopsy sections from the liver of the second case showed no myeloid metaplasia in this organ. It is possible that the liver might be involved in blood formation at a later stage.

It is to be noted that two of the cases showed a variable degree of leucopenia at one stage or another. Leucocytosis may only be detected by repeated blood examinations.

Chapter 16.SIMPLE SPLENIC HYPERTROPHY.

From time to time clinicians have encountered cases of so-called "splenic anaemia" conforming to the usual definition of this syndrome, but in which the spleen presented no definite histological abnormality. Cases of this type have been described by Kidd (1913) and by McNee(1929). The latter writer describes the condition briefly as follows:

In this group "the writer would include a few patients in whom secondary anaemia was present and the spleen moderately enlarged, but no increase of bilirubin in the blood was noted, so that a diagnosis of haemolytic jaundice could be ruled out. On histological examination of these enlarged spleens no real abnormalities could be made out, and the condition can best be described as a pure splenic hypertrophy or hypersplenism....."

The occurrence of this syndrome has undoubtedly led to much confusion, for clinically it has been diagnosed as the "first stage of Banti's disease", and pathologically nothing has been found to correspond to the histological

picture described by Banti. The advisability of describing simple splenic hypertrophy as a separate syndrome was debated until McNee recognised its frequent occurrence in 1929 and recommended its relegation to a special group on pathological grounds alone. The rapid strides made in clinical haematology in the last few years have justified his judgment.

In 1930 Witts, for the first time in this country, called attention to chronic microcytic anaemia. This syndrome is now too well-known to require elaboration here. A chronic microcytic, hypochromic anaemia associated with achlorhydria or hypochlorhydria occurs mostly in women of early middle age. In this type of anaemia the spleen is not infrequently enlarged (Witts, van Leeuwen, 1933). Witts was able to retrieve a section of an enlarged spleen, from a case of this disease, which had been removed at operation before the syndrome became generally recognised. On examination it was found to show no histological abnormality. To this key observation we are now able to add a second case.

044-1-431.
Daniel L.

Blood.

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
25.3.29	2,270,000	7,000	20	.4	81	16	3	0	0
29.3.29	2,390,000	6,000	20	.4					
4.4.29	3,340,000	2,400	30	.4	64	36	0	0	0
16.4.29	3,620,000	3,600	37	.5					
28.3.30	4,920,000	5,200	53	.5					

C A S E XLIX

Daniel L. aet 24: Occupation: Miner.

Admitted to hospital: 26.3.30.

History: Patient was in hospital in March 1929 complaining of general weakness and exhaustion during the past six months. He had had frequent severe headaches lasting the whole day. He also suffered from breathlessness and palpitation, but there was no swelling of the ankles or pre-cordial pain. He had become very pale. His appetite was fair, but he was troubled with heartburn, and three weeks before his admission he had vomited a small quantity of bright red blood.

Patient was readmitted on 26.3.30 with a history that he had kept fairly well until two weeks prior to his admission, when he developed a slight cough, and in his sputum there have been tinges of blood. He has had giddy turns in the mornings. The giddiness is accompanied by blurring of vision. No nausea. The patient has been taking a mixture containing iron during the past year.

Previous health and Family History. Nil to note.

On Examination: Patient is a pale undersized man, fairly well nourished.

Abdomen: The upper abdomen looks rather tumescent, and moves freely on respiration. There is no hyperaesthesia or rigidity. Liver dulness is level with the costal margin. The spleen is palpable just below the rib-margin and the surface is smooth.

Cardiovascular, Respiratory, Nervous, and Urinary Systems: show nothing abnormal.

Blood Findings: see adjoining table.

Sept. 6. 1932

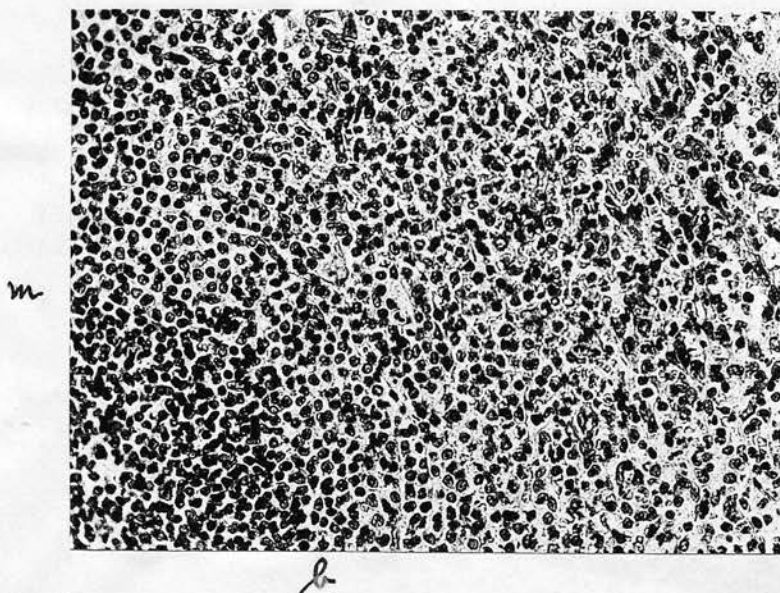


Fig. 123. Spleen from case XLIX. (x 330). In the lower left corner m-b denotes a malpighian body. Note the even distribution of cells in the pulp and the absence of either arterial or venous congestion.

Wassermann Reaction: Negative

Van den Bergh Reaction: Negative

Test Meal:

Fasting Juice.	Free HCl	0.
	Total Acid	16
Test Meal	Free HCl	0
	Total Acid	8.

8.4.30 Splenectomy. The spleen was about three times the normal size. There were no adhesions. The liver appeared normal. The gall-bladder was normal, and there was no evidence of disease in the stomach or duodenum. There was no disease in the splenic artery or vein and there was no thrombosis. There were fewer enlarged glands in the splenic pedicle than is usual in a case of splenic anaemia.

Spleen: Weight (Approx.) 400 grammes.

Histology.

Vascular lesions: Apart from some hyalinisation of the arterioles there is no vascular lesion.

Venous sinuses: show no dilatation.

Malpighian Bodies: Occasional Germ-centre seen.

Pulp: Shows no congestion and no cellular abnormality.

Summary of Case XLIX.

A male aged 24 complained of the general symptoms of anaemia — pallor, headache, and breathlessness. Some vague digestive trouble was present and on one occasion he vomited a small quantity of blood. On examination there was a severe anaemia with leucopenia and low colour index. In the course of one year on small doses of iron the haemoglobin value had risen from 20 to 53 per cent. There was also an achlorhydria. Splenectomy was carried out and histologically the spleen showed no abnormality.

DISCUSSION:

The intense hypochromic anaemia, the response to iron, even in the small doses given before 1930, and the achlorhydria put the matter beyond doubt that the case was one of achlorhydric microcytic anaemia. Slight haematemesis has been noted by Witts. In most of these cases the tongue is smooth and dysphagia is a common feature. These symptoms are referable to a definite leukoplakia-like lesion of the mucosa of the tongue, pharynx, and oesophagus (Suzman, 1933). It is quite possible that the slight bleeding may result from trauma to the diseased mucosa.

Since the introduction of massive iron dosage for these cases, the operation of splenectomy is no longer justifiable. Before the clinical syndrome was fully recognised, however, splenectomy must have been carried out frequently in this disease. The introduction of successful therapy has also brought with it a lack of pathological material. Before this advance was made, full data were seldom available, as the cases were relegated to the group of splenic anaemias on the evidence of blood counts alone. The above case is a fortunate

instance in which test meals had been carried out.

In the others to be described in this chapter

the diagnosis of microcytic anaemia is a probability rather than a certainty.

C A S E L.

Elizabeth K. aet.41. Occupation:Housewife

Admitted to hospital: 29.7.30

History: Patient enjoyed good health until three months before admission, and her bowels moved regularly daily. She had a transient attack of diarrhoea a year ago, lasting a few days, but it cleared up, and otherwise there had been no history of previous diarrhoea. Diarrhoea began abruptly for no apparent cause three months ago. On the first day she passed five or six motions, the first one or two being of loose consistence, and the subsequent ones watery. The diarrhoea was associated with colicky pains in the abdomen. Under treatment the diarrhoea disappeared and she passed normal motions once or twice a day until three weeks later when the diarrhoea returned and again responded to treatment. She then had a third attack about six weeks ago which did not react to treatment, and for the past four weeks she has usually had two motions a day, the first shortly after rising, fairly well-formed, and the next about an hour later and loose.

Patients' appetite has been good.

Sometimes she was troubled with flatulence and a feeling of fulness in the stomach. Patient was able to continue her household duties until six weeks ago, when increasing weakness caused her to rest. For the past six weeks she has had an occasional dragging sensation in the left side of the abdomen.

Previous health and Family History: Nil to note.

8pp-6-437
Elizabeth K.

Blood.

Date	R ~~B~~ B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.	Ret.
7.8.30	4,960,000	4,400	55	.55	82	12	4	2	0	.5%
22.8.30	Splenectomy.									
23.8.30	5,420,000	12,200	62	.6						
3.9.30	4,070,000	14,900	72	.8						

On Examination: The patient has flushed cheeks, but otherwise the skin is rather sallow. There is no evidence of jaundice in the conjunctivae.

Abdomen: Moves freely on respiration. There is slight fulness in the left hypochondrium. There is no hyperaesthesia and no rigidity. The spleen is enlarged three inches below the costal margin. The left kidney is also palpable through the thin abdominal wall. The liver is not enlarged. There is no evidence of any free fluid and there is no other palpable tumour.

Fragility Test: haemolysis begins at .4% saline.

Blood counts are indicated in the table

Cardiovascular, Renal, Respiratory, and Nervous Systems: Nil to note.

Rectal Examination: Negative.

Barium Series: Examination does not reveal any lesion of the intestinal tract.

Barium Enema: The enema ran freely round to the caecum. There was no delay at any point and no abnormality was outlined.

Bacteriological Examination of the Stool.

No amoebae or cysts.

No Tubercle bacilli,

No organisms of dysentery or typhoid.

Benzidene: Negative.

Stool 13.8.30

Total fats: 12.4%

Split fats	27%	} of total.
Neutral fats	73%	

22.8.30: Splenectomy.

The consistence of the spleen was soft and the lower pole reached $1\frac{1}{2}$ to 2 inches below the costal margin. The left kidney was mobile.

8pp-1-4-38

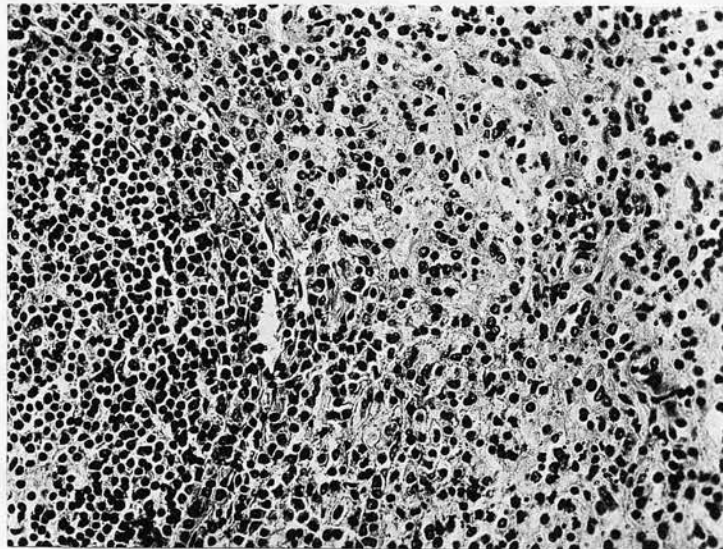


Fig. 124. Spleen from case L. (x 330). A Malpighian body is seen on the left. The pulp on the right shows no cellular change and although the content of blood is greater than that in Fig. 123, this cannot be regarded as abnormal.

The liver was healthy in appearance and not enlarged. The gall-bladder was healthy and contained no stones. There was no evidence of gastric or duodenal ulcer. A degree of visceroptosis was present. There was no phlebitis of the splenic vein.

Progress: Husband wrote on 17.3.33 that she died very suddenly on 15.1.33 in her sleep, death being ascribed to "heart-failure". She had had no breathlessness or bloodlessness to any marked extent and her colour was good. Appetite was good and she was able to perform all her usual household duties with a little help. She remarked shortly before her death that she had not felt so well for a long time.

Spleen: Weight (approx.) 500 grammes.

Histology: Apart from hyalinisation of the arterioles there was no histological abnormality. There was no undue congestion of the pulp spaces or of the sinuses; there was no cellular abnormality.

Summary of Case L.

A woman aged 41 complained of diarrhoea and vague digestive disorders. The spleen was found to be enlarged and there was an anaemia of low colour index with leucopenia. Reticulocytes were under 1%. Splenectomy was carried out. The spleen showed no histological abnormality. The patient seemed to make good progress until she died suddenly in her sleep 3 years later, possibly from some unrelated cause.

Ref. 10.440

Blood.

Date	R.B.C.	W.B.C.	Hb	C.I.	N.	Lym.	M.	E.	B.
14.4.30	2,510,000	1,250	15	.6	64	30	3	2	0

No nucleated red cells.

19.4.30 2,640,000 1,800 18 .7

22.4.30 Splenectomy: Blood transfusion.

29.4.30 3,500,000 31,000 23 .3

7.5.30 3,600,000 9,000 35 .5

29.5.30 2,820,000 7,100 30 .5

30.5.30 Operation: Inoperable cancer of stomach.

C A S E LI.

Kate P. aet.52. Occupation: Housewife.

Admitted to hospital: 12.4.30

History: Two years before admission the patient had a prolonged attack of ulcerative colitis. At that time she was troubled with breathlessness, and she had palpitation on exertion which soon passed off. She had a little pain in the abdomen on defaecation and blood always appeared before the faecal matter. After two months in hospital she was discharged very much improved.

For the next eighteen months the patient was able to undertake her household duties. Then she began to feel weak and unable for her work. In January 1930 she became ill with "influenza" and has been under treatment since then.

Patient has been much troubled with haemorrhoids for twenty years but of late they have been bleeding more frequently.

Previous health: Diphtheria aged 5 years.

Family history: Nil to note.

On Examination: The patient's skin is sallow and the mucous membranes are pale.

Abdomen: There is some loss of subcutaneous fat. The liver is not enlarged and the spleen is palpable at the costal margin. There is no tenderness or palpable mass elsewhere.

Per rectum: Visible haemorrhoids.

Cardiovascular System: On auscultation there is a systolic murmur heard over the heart in all areas, being loudest at the base and blowing in character. Otherwise nothing of importance was found.

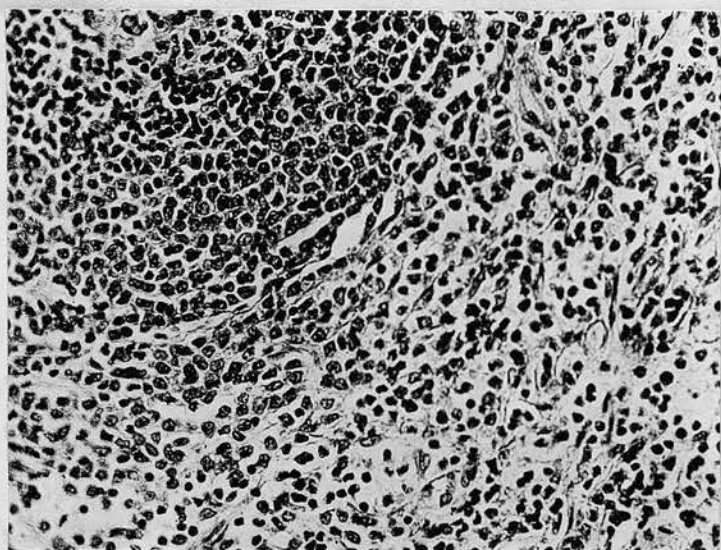


Fig. 125. Spleen of case LI. (x 330). A Malpighian body occupies the upper left corner of the field. The pulp cells show no abnormality and there is no undue congestion.

Respiratory, Renal and Central Nervous Systems.

Nothing abnormal found.

Blood Findings are shown in the appended table

22.4.30 Splenectomy: At operation the liver appeared to be normal. Carcinoma of the stomach, unsuspected clinically, was found. There were no secondary growths. The spleen was enlarged beyond the costal margin. Blood transfusion given.

Progress: Haemoglobin level improved very slightly in the five weeks after the spleen had been removed. The patient was then admitted for a second operation.

30.5.30 Operation: The gastric tumour was found to be inoperable on account of free fluid in the abdomen and metastases.

Spleen: Approximately three times the normal size.

Histologically: There was no abnormality to be detected either in the cells or in their anatomical arrangement.

Summary of Case LI.

A female aged 52 had a prolonged attack of "ulcerative colitis" two years before admission to hospital. The spleen was found to be slightly enlarged and there was a hypochromic **anaemia**. Splenectomy was carried out, and at operation a carcinoma of the stomach was found which had given rise to no symptoms to excite suspicion clinically.

Discussion.

Cases I and II show a hypochromic anaemia together with a splenomegaly of a type exactly similar to that in case XLIX, i.e. moderately enlarged but showing no histological abnormality. In both, the clinical, haematological and pathological pictures are compatible with the diagnosis of chronic microcytic anaemia. One further feature which they present in common is the occurrence of diarrhoea.

Diarrhoea is frequently a symptom in chronic microcytic anaemia (Witts, Davies, van Leeuwen). Often the patients complain of alternating constipation and diarrhoea, and more rarely of frequent watery motions. Loose stools occur and are frequently ascribed to some dietetic indiscretion. In two cases van Leeuwen describes proctitis with blood in the stools.

In chronic microcytic anaemia the primary cause appears to be defective absorption of iron, which may be only partially dependent on the absence of hydrochloric acid from the gastric secretion. Cases are recorded which present

the complete picture of the disease with an apparently normal acid content in the stomach. (Witts, van Leeuwen). Evidences of defective absorption from the small intestine were present in the form of fatty diarrhoea with excess of split fat in the faeces (van Leeuwen). In these cases at least, defective absorption of iron is a factor, and it is quite possible that this defect may also be present in the cases showing achlorhydria. There is thus suggestive evidence of an extensive disorder throughout the whole alimentary tract — mouth, oesophagus, stomach, small intestine, and (?) large intestine also.

The relationship of so-called ulcerative colitis to hypochromic anaemia with splenomegaly can thus be viewed from a new angle. Bargen and Giffin (1930) noted the association of ulcerative colitis with splenomegaly and anaemia. It is possible that the rapid movements through the intestine in this disease lead to defective absorption of iron resulting in chronic hypochromic anaemia. On the other hand the diarrhoea itself may merely be the expression of some primary affection which extends throughout the alimentary tract leading to changes in the tongue, pharynx, oesophagus, stomach and small intestine. The actual occurrence

of carcinoma of the stomach in case LI, (as well as in one other similar case of the writer's, not recorded here) may possibly be related to this anatomical lesion of the alimentary tract.

With regard to the actual cause of the splenic enlargement in such cases little can be said. The function of the spleen as a storehouse of iron is only brought into prominence in the presence of an excess of iron in the body, a condition which is the exact reverse of the disease under consideration. Chronic infection was cited as a possible cause in those cases associated with ulcerative colitis (Bargen and Giffin). This may possibly play a part although the histological appearances are not suggestive of this cause. Experimentally splenic enlargement, with a somewhat oedematous state of the organ, has been produced by severe haemorrhage (Roessle, 1928). The writer has seen such enlarged oedematous spleens at autopsy, in patients dying of severe haemorrhage. In one instance the spleen weighed 290 grammes in a woman dying as a result of a ruptured tubal pregnancy. So far as the writer is aware no further investigations have been made into the

cause of this type of splenic enlargement,
and its possible relationship to haemoglobin or
iron deficiency.

While it may be said that the spleen
is commonly involved in tuberculosis, especially
if the terminal stages are characterized by
dissemination of the organism by the blood-stream,
nevertheless predominant splenic tuberculosis
is a rarity. The statement by Gruvelhier that
"with the exception of the lymphatic glands the
spleen is the abdominal organ most frequently
attacked by tuberculosis" is an assertion which
can only be based on the frequency of secondary
involvement of the spleen.

With regard to the actual frequency
of lesions of the spleen in tuberculosis, the
autopsy observations of Reinhold (1899) showed
splenic involvement in
280 out of 428 cases of infantile tuberculosis, and
166 out of 456 cases of adult tuberculosis.
The frequency in early life is undoubtedly related
to the greater incidence of miliary dissemination
at this age.

Chapter 17.

TUBERCULOSIS OF THE SPLEEN.

While it may be said that the spleen is commonly involved in tuberculosis, especially if the terminal stages are characterised by dissemination of the organism by the blood-stream, nevertheless predominating splenic tuberculosis is a rarity. The statement by Cruveilhier that "with the exception of the lymphatic glands the spleen is the abdominal organ most frequently attacked by tuberculosis" is an assertion which can only be based on the frequency of secondary involvement of the spleen.

With regard to the actual frequency of lesions of the spleen in tuberculosis, the autopsy observations of Reinhold (1899) showed splenic involvement in 280 out of 428 cases of infantile tuberculosis, and 166 out of 836 cases of adult tuberculosis. The frequency in early life is undoubtedly related to the greater incidence of miliary dissemination at this age.

Even at autopsy the development of splenic tubercles may pass unnoticed without microscopic examination, and the condition may be unaccompanied by any enlargement of the organ. In miliary tuberculosis there is nearly always some degree of splenic enlargement, up to two or three times the normal size. If the course of the disease is acute the histological appearance may be dominated by the presence of active histiocytes, and the picture resembles that of the "typhoid spleen". If the course is more prolonged definite tubercles develop, especially in the Malpighian bodies, and by replacing these nodes, may bring about their apparent obliteration.

In chronic tuberculosis, the spleen may be involved by miliary or caseous nodules, but often it may be found to be atrophied or indurated.

When the splenic involvement appears to be the outstanding manifestation of tuberculosis some writers have suggested the term "primary tuberculosis of the spleen". The term "primary" however is not absolute, as the spleen is never involved primarily. Quenu and Baudet (1898)

suggested the term "localised tuberculosis", but this is also unsuitable, as the spleen is never involved alone. The best term is "predominating splenic tuberculosis" (Roch, 1923).

With regard to the path of infection, the etiological agent is almost invariably carried to the spleen by the blood-stream. The spleen has no lymphatics and no ducts, and the only other possible mode of infection would be spread by contiguity from perisplenitis, e.g. in tuberculous peritonitis. The latter path of infection must be very rare. The focus of origin may be the lymph-glandular, osseous or respiratory systems in which "primary" lesions occur.

Clinically the disease is manifested by splenomegaly. The size of the spleen is variable, and it may be very large as in the case recorded by Bruns (1905) where the weight was over 3 kilogrammes. The spleen is often embedded in a vague mass of adhesions, rendering its recognition difficult. Subjectively such a splenic enlargement may pass unnoticed for years or it may give rise to a feeling of heaviness or a dragging sensation in the side. Pain may occur locally or be referred to the left shoulder as a result of contiguous diaphragmatic peritonitis.

Temperature and signs of tuberculosis elsewhere may arouse suspicion of the exact nature of the lesion.

Haematologically, stress has been laid upon the association of splenic tuberculosis with polycythaemia. In Winternitz's (1912) review red cell counts varying from 6 to 8 millions were found in 23 per cent of cases. Askanazy (1921) suggests that this may be an effect of simultaneous involvement of the bone-marrow by tuberculosis. His case showed extensive erythroblastic reaction of the marrow in association with local tuberculosis.

The degree of polycythaemia is, as a rule, mild, and much more commonly anaemia is encountered. The red cells range from 3 to 4 millions and a leucopenia is frequent with 4-6,000 cells per c.mm. Where the liver is simultaneously involved the differential diagnosis from hepato-lienal fibrosis may be exceedingly difficult.

Pathologically, numerous classifications have been suggested in an attempt to include all types of lesion:

- | | | |
|--|---|--|
| 1. Topographical classification | { | Splenic
Hepato-lienal.
Lieno-hepato-glandular.
Lieno-glandular medullary. |
| 2. Classification based on anatomical appearance of the spleen | { | Nodular-infiltrative.
Caseous sclerotic.
Haemorrhagic necrotic. |

Such terms are purely descriptive and an enormous number of permutations and combinations would require to be arranged for such classifications to be comprehensive, and it is difficult to see what useful purpose they would serve.

The enlargement of the spleen is usually uniform but nodular and sclero-caseous masses may distort the outline. Histological evidences of tuberculosis are present but several authors have noted the difficulty of culturing tubercle bacilli from the lesions of splenic tuberculosis (Askanazy).



C A S E LII.

Mrs La. aet 44. Occupation: Housewife.

Admitted to hospital: 12.6.25.

History: Patient was in good health until six months prior to her admission. Since that time she has gradually become weak with marked breathlessness on exertion. Her ankles began to swell at nights, and for a month before her admission she had noted swelling of the abdomen.

Previous Health: Ten years ago the patient had medical treatment for swelling of the abdomen, but no further information is available.

On Examination: The patient is pale, anaemic, and thin, and the ankles are slightly swollen and oedematous. Temperature, during the two days before operation, rose in the evenings to 100° and 100.4° .

Abdomen: Was somewhat protuberant, and shifting dulness was found in the flanks, with a fluid thrill. The spleen could be felt extending almost to the midline above the umbilicus. The swelling had a definite edge, but no notch was palpable, and its consistence was firm. The liver could not be felt, and percussion indicated that it was somewhat smaller than usual.

Other Systems: Nothing abnormal found.

Blood

Wassermann: negative

R.B.C.	3,740,000
W.B.C.	2,000
Hb	30%
C.I.	.4

Differential Count.

Neutrophil polymorphs.	60
Lymphocytes	34
Monocytes	5
Eosinophils	1

Operation: Splenectomy 19.6.25. The spleen had descended into the lesser sac posterior to the stomach, and was very adherent. There were general peritoneal adhesions and free fluid. Much bleeding took place from the splenic bed after removal of the organ. 500 ccs blood were transfused after the operation.

20.6.25 Death.

Abstract from Post-mortem report.

Permission was granted for an examination of the abdomen only.

The abdominal cavity contained a very large quantity of free blood under the left half of the diaphragm. All the abdominal contents were matted together by very firm adhesions. The mesentery contained enlarged lymph-glands but no calcification was present in these. Small nodules were present in the liver tissue suggesting partial necrosis. Gall-bladder, kidneys, and pancreas normal.

Spleen

Histology.

Vascular lesions: Periarterial haemorrhages present with the formation, in one area, of a fully-developed siderotic nodule.

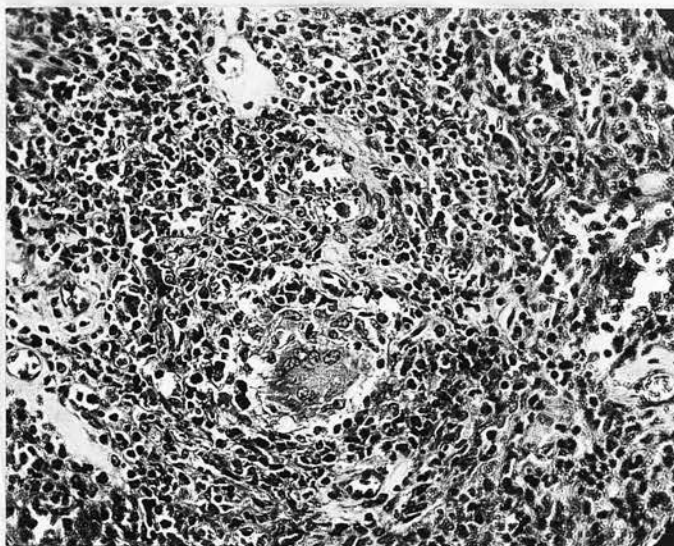


Fig. 126. Spleen from case LII. (x 250).
A giant cells is seen with endothelioid cells
in its immediate neighbourhood.

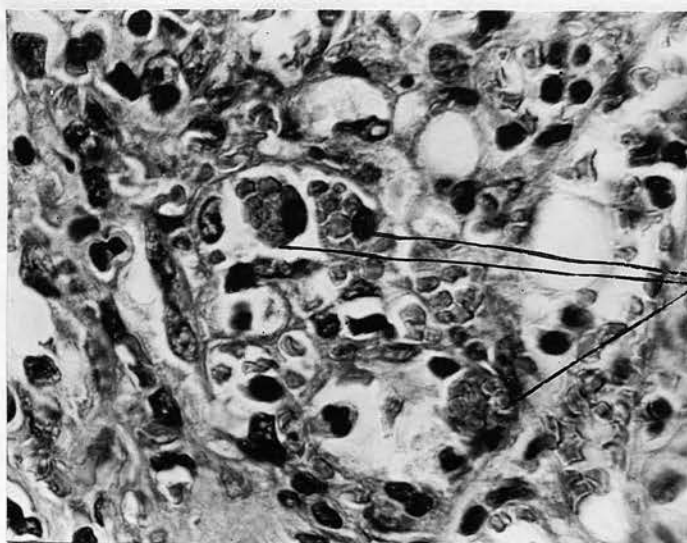


Fig. 127 Spleen of case LII (oil immersion). Three
large macrophages (m) are seen in the sinuses, each
containing a number of ingested red blood corpuscles.

Venous Sinuses: No marked dilatation. The cells of the sinus walls are active, numerous macrophages being present, some of which show erythrophagocytosis.

Malpighian Bodies: No special change seen .

Pulp. There is some congestion of the pulp spaces with activity of the pulp cells evidenced by the frequent formation of free macrophages. Here and there at the periphery of the Malpighian bodies there is a tubercle with endothelioid and giant cells. Evidences of necrosis are not seen.

Summary of Case LII.

A woman aged 44 complained of symptoms referable to anaemia, with the addition of swelling of the abdomen and oedema of the ankles. The former symptom had been present ten years before. There was slight nocturnal temperature, the spleen was enlarged and the abdomen contained free fluid. There was also a secondary anaemia with leucopenia. The case was considered to be one of "Banti's disease" and splenectomy was carried out. There was an old-standing chronic peritonitis and death occurred from haemorrhage due to breaking-down of adhesions.

Examination of the spleen showed tubercles and autopsy showed lesions in the mesenteric glands and liver which were probably tuberculous.

DISCUSSION.

The histological evidences of tuberculosis in the spleen in this case render it probable that the enlargement of the mesenteric glands, the chronic peritonitis, and the small nodules in the liver were also tuberculous although these lesions were not examined histologically.

If an attempt were made to give a descriptive name to the lesions in this case, the term "Lieno-hepato-glandular tuberculosis" would be used.

It is of some interest to discuss the histological appearances of the spleen under three headings — the vascular lesions, the tuberculous lesions, and the appearances of local reaction.

1. The vascular lesions. Periarterial haemorrhages were noted in this case with ensuing changes exactly similar to those described in Part I of this work, i.e. the development of siderotic nodules. These changes must have resulted from increased local vascularity due to passive or active congestion. There is no feature present to suggest passive venous congestion of the spleen (no dilatation of the venous

sinuses, etc.) and it is most probable that local haemorrhages occurred during a stage of active congestion. Askanazy noted marked extravasation of blood in the spleen in his case. Numerous experimenters have shown that the vascular reactions in tuberculosis are much more marked when fresh infection is superadded to pre-existing tuberculosis. Whether these haemorrhages are evidences of a focal "von Pirquet" reaction it is difficult to say, but the intensity of the vascular reaction renders such an explanation quite probable.

2. The Tubercles. These lesions show the ordinary histological characters of tuberculosis elsewhere, except in the complete absence of necrosis and caseation. This latter feature led Askanazy to style his case "lupus of the spleen". The paucity of tubercle bacilli in the splenic lesions (p.451), together with the evidences of intense vascular inflammatory reaction would lead us to suspect a superadded tuberculous infection in an immunised subject.

3. The appearance of reaction. The occurrence of large macrophages in the pulp and sinuses outside the tubercles indicates a local reaction to the tuberculous infection, and the

appearances can all be related to increased activity of the histiocytes. As has already been emphasised (p.109), erythrophagocytosis does not indicate increased destruction of red blood corpuscles. The appearances, though limited and localised, resemble those which occur when the spleen reacts to any infection, e.g. typhoid fever.

The focus of origin of the disease in this case was probably tuberculosis of the abdominal glands and tuberculous peritonitis.

Chapter 18.

TUMOURS OF THE SPLEEN.

The resistance of the spleen to tumour growth has long been recognised. In those malignant tumours which are spread by the blood-stream, neoplastic cells are filtered off by the capillaries of the lungs and of the liver, thus accounting for the frequency of secondary growths in these organs. A similar filtration of tumour cells from the blood stream must take place in the spleen pulp, and yet secondary growths in the spleen are of extreme rarity. The spleen seems in some way to be definitely inimical to tumour growth. This resistance is not a property common to reticulo-endothelial tissues, as evidenced by the frequency of tumour growth in lymph-glands and in the bone-marrow.

It is suggested that the resistance of the spleen to tumour growth may be due to the local formation of antibodies. Braunstein (1911) showed that splenectomised mice were less resistant to

tumour transplantation than normal animals. These experiments have been confirmed by Lewin and Meidner, (1912) and Oser and Pribram (1913).

Primary growths in the spleen are also exceedingly rare. From the capsule, trabeculae, pulp, and blood-vessels; fibromata, sarcomata, and angiomata may arise. A case of arterial haemangioma has been described briefly on p. 34.

Primary malignant tumours have usually been recorded either as sarcomata or lymphosarcomata. As there is often some difficulty in distinguishing a small round celled sarcoma from a lymphosarcoma, it is not easy to be certain of the type in some instances. The tumour may form a single large mass in the spleen.

The two cases to be mentioned here showed a nodular lymphosarcomatosis beginning apparently simultaneously in all the Malpighian bodies. Only one similar case has been found in the literature. In the first case full notes are not available, but a certain amount of information is given together with an account of the pathological appearances.

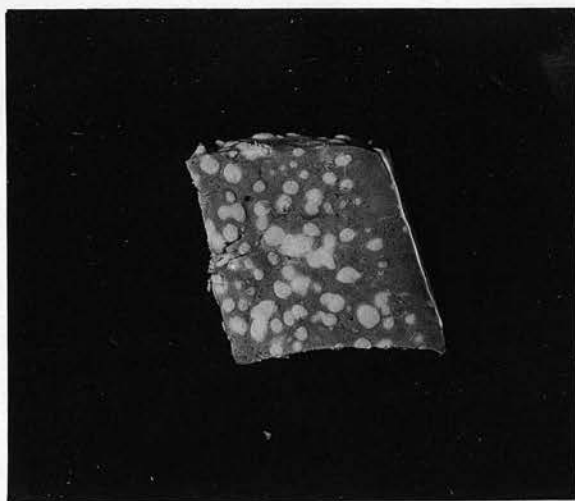


Fig. 128. Portion of the spleen of case LIII ($\times 1\frac{1}{2}$). Note the white areas of growth like greatly enlarged Malpighian bodies.



Fig. 129. Section of the spleen of case LIII. ($\times 27$). The central arteries (a) of the Malpighian bodies are seen in the growths. Between the avascular new growths of lymphocytes are bands of vascular pulp tissue.

Summary of Case LIII.

A female patient aged 58 years was admitted to hospital with an enlarged spleen. The blood picture showed a moderate secondary anaemia with leucopenia, and a diagnosis of "splenic anaemia" was made. Splenectomy was carried out and the patient recovered from the operation. (No further details are available as to the patient's subsequent progress.)

The spleen weighed approximately 1,200 grammes. On section the cut surface was studded with nodules, white in colour, and varying in diameter from $\frac{1}{2}$ to 3 mm.. The nodules were perfectly round in contour except where they had become confluent. The intervening pulp tissue was normal in appearance.

Histology.

The tumour masses consist of cells indistinguishable from the lymphocytes of the Malpighian bodies. Among these cells are a few larger cells with more vesicular nuclei, like pulp-cells. Mitotic figures are common, and there are only a very few blood corpuscles visible in the tumours. The central arteries of the Malpighian bodies are often seen in the tumour masses. The edge of the new growth is well-defined, and abuts on pulp tissue which has a normal appearance, although somewhat crushed by the growth.



Case LIV.

Blood.

Date.	R.B.C.	W.B.C.	Hb	C.I.	N. Lym. M. E. B.
-.10.29	3,540,000	1,800	60	.8	
4.12.29	3,460,000	3,200	60	.8	
	No nucleated reds. Anisocytosis and poikilocytosis.				
12.6.30	2,480,000	2,700	28	.6	
1.7.30	Blood transfusion: 600 ccs.				
2.7.30	1,850,000	9,600	28	.7	
3.7.30	1,940,000	6,200	27	.7	
11.7.30	1,480,000	4,800	24	.6	

C A S E L I V .

Mr A. aet. 70. Occupation: Brewer.

Came under Observation: October, 1929.

History: Until the present illness the patient has been healthy all his life. There is no history of syphilis. In May 1929 he fell off a step-ladder and developed a severe pain in the left side. The doctor, on examination, heard a friction rub and diagnosed a broken rib. On the following day however it was found that the friction was taking place over an enlarged spleen. The patient has never been abroad.

On Examination: The patient was pale and old-looking. There was no lemon-yellow tint.

Abdomen: An enlarged hard spleen could be felt reaching as far as the umbilicus. Hepatic dulness was normal. In the groin there were some definitely enlarged glands the largest of which was about the size of a walnut. These had been noted by the patient during the past year.

Other Systems: Nothing abnormal found.

The blood counts are indicated in the table.

4.12.29 The spleen is still enlarged to the umbilicus. The glands in the groin continue slowly to enlarge. One of these glands was removed for examination. The pathologist reported that the gland showed an overgrowth of the lymphoid elements. Hodgkin's disease could be definitely excluded and the diagnosis lay between lymphosarcoma and lymphoma. The latter condition is benign and tends to progress more slowly.

X ray treatment to the spleen and glands was carried out.

12.6.30 The patient is definitely very pale, and

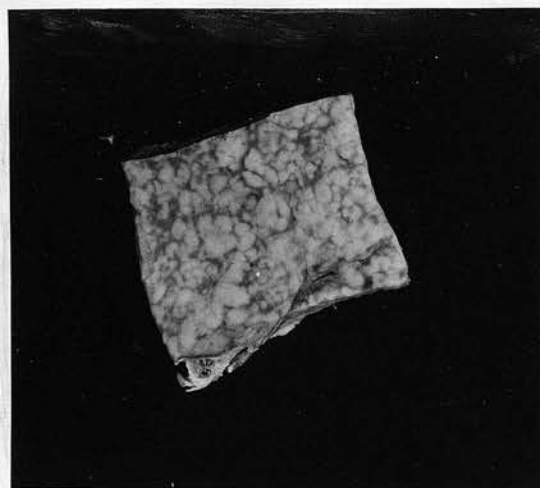


Fig. 130. Portion of the spleen of case LIV. ($\times 1\frac{1}{2}$). Note the whitish areas of growth becoming confluent in many places.

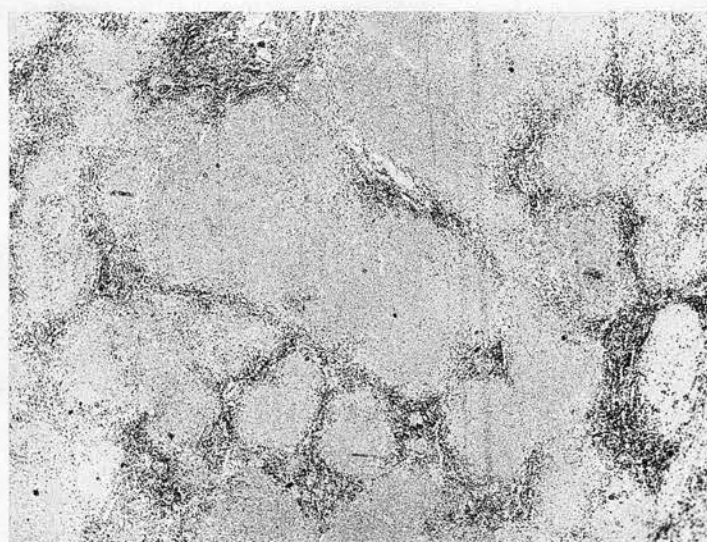


Fig. 131. Section of the spleen of case LIV. ($\times 21$). The avascular lymphoid tumour tissue has crushed the pulp into thin strips.

the splenic enlargement has increased. The spleen is now enlarged to two inches below the umbilicus. The inguinal and axillary glands are unchanged.

In spite of a very large transfusion there was no improvement in the anaemia. In view of the possibility that there might be a primary sarcoma in the spleen, it was decided to remove this organ.

17.7.30 Splenectomy. The spleen was adherent to the liver and to the diaphragm. On breaking down the adhesions, considerable oozing of blood took place, and owing to the patient's already feeble condition such loss of blood could not be borne. The patient died after the operation.

Spleen. Greatly enlarged. The cut surface showed extremely numerous whitish nodules varying in diameter from less than $\frac{1}{2}$ to nearly 5 mm.. These nodules were frequently confluent, and less clearly defined from the surrounding pulp than in the previous case. The pulp tissue was markedly diminished in amount being limited to thin layers between the tumours.

Histology: The spleen presented no vascular lesions apart from hyalinisation of the arteries. The tumour masses consist of large avascular clumps of cells indistinguishable from the lymphocytes of the Malpighian bodies. The cells have a small amount of protoplasm with vesicular nuclei and granular and lined nuclear chromatin. There are no large cells like pulpecells. Mitotic figures are common.

Summary of Case LIV.

A man aged 70 complained of pain due to a traumatic peritonitis over an enlarged spleen. This was found to be associated with enlarged glands in the groin, and both the spleen and the glands continued slowly to enlarge. The blood showed a progressive anaemia usually with leucopenia. Splenectomy was carried out on the possibility that there might be a primary sarcomatous growth in this organ, but death ensued.

The spleen showed lymphosarcomatous nodules throughout the organ.

DISCUSSION.

In these two cases we have examples of tumour growth apparently taking origin from the Malpighian bodies of the spleen, as shown by: -

1. the lymphocyte-like cells, and
2. the persistence of the central arterioles of the Malpighian bodies in the growths.

In the first instance there was no evidence of any other growths, while in the second there was a simultaneous growth in the inguinal glands.

Lymphosarcoma is a curious type of growth in that it arises from a group of lymph-nodes or a tract of lymphoid tissue: it does not invade in the ordinary sense, but crushes the adjoining tissue and keeps strictly to lymphatic paths in its extension. Blood-borne metastases are late in appearing. The tumour differs from lymphadenos~~is~~ (lymphatic leukaemia) not only in the absence of leukaemic changes in the blood, but in the absence of lymphadenoid~~a~~ growth throughout the whole system. When the spleen is involved a diffuse lymphoid infiltration of the whole

spleen does not occur as in lymphadenosis.

There appears to be little doubt that the two cases are instances of lymphosarcomatosis arising simultaneously throughout the lymphatic tissue of the spleen — diffuse nodular lymphosarcomatosis of the spleen.

The only similar case which has been found in the literature is that recorded by Foix and Roemmele (1912).

A female patient aged 45 with a rapidly growing spleen, died from cachexia after a few months. The red cell count was 3.8 millions, with 12,500 leucocytes, 89 per cent of which were neutrophil polymorphs. At autopsy the spleen was found to weigh 1,400 grammes with nodules on the cut surface from the size of a millet seed to a lentil. In some places the nodules had become fused. Malpighian bodies were not recognisable as they were replaced by the tumours which were white and avascular. The central artery was often seen in the tumour masses indicating an origin from the Malpighian body. The cells of the tumour were somewhat larger than the small lymphocytes which occur at the periphery of the Malpighian bodies, and Foix and Roemmele therefore suggested that the tumour probably took origin from the larger cells in the centre of the Malpighian body. One small metastasis was found in the peri-suprarenal tissue.

In both our cases the cells constituting the tumours resembled exactly in size and appearance the lymphocytes which form the outer zone of cells of the Malpighian body.

Clinically, one or two points are of interest. The rapid growth of the tumour may be the only index of its exact nature, Rapid growth was noted in the case of Foix and Roemmele, and in our second case to a less degree. It is of some interest also that although Foix and Roemmele's patient died of malignant cachexia, there was only one small metastasis present. The absence of lymphatics in the spleen may act as a remarkable check to the spread of lymphosarcoma, and it is theoretically possible that early surgical removal may allow a good prognosis.

Chapter 19.

S U M M A R Y.

Splenic anaemia, as originally defined, is the syndrome of splenic enlargement with anaemia and without leucocytosis, in which the better known causes of splenic enlargement, such as leukaemia and Hodgkin's disease, can be definitely excluded.

The pathological basis of this syndrome has for long been obscure, but the advance of pathological and clinical knowledge has separated off, as distinct entities, Gaucher's disease and congenital acholuric jaundice, which have very characteristic pathological and clinical pictures. There still remains, however, a large residue of clinical material to which the name "splenic anaemia" is applied, although the pathologist is often at a loss to confirm this clinical diagnosis, on account of difficulties in the interpretation of the pathological histology of the spleen. The pathological pictures in splenic anaemia are far from uniform and the present study has been

carried out to clarify, if possible, the complex pathological substratum underlying the clinical syndrome. Details, pathological and clinical, are given of 54 cases of "splenic anaemia", although the pathological material at the writer's disposal was drawn from 90 cases.

Pathologically, the cases fall into several distinct groups, although the clinical features present an approximate similarity. The following pathological groups have been recognised:

1. Hepato-lienal fibrosis.
2. Reticulo-endotheliosis.
3. Myeloid splenic anaemia.
4. Simple splenic hypertrophy.
5. Tuberculosis of the spleen.
6. Tumours of the spleen.

1. Hepato-lienal fibrosis.

Pathologically the spleen is enlarged and averages about 900 grammes in weight, although it may range from 500 to over 2,000 grammes. The histology is characterised by:-

1. Periarterial haemorrhages. These may develop into areas of periarterial fibrosis, or siderotic nodules. In the latter condition,

crystalline and amorphous pigments are deposited on the fibrotic tissue around the arteries.

These pigments have been subjected to a detailed chemical analysis, and have been found to consist of phosphate, carbonate and probably also oxide and hydroxide of iron.

2. Dilated venous sinuses. Thickening of the reticulin of the sinus walls occurs until it shows the staining reactions of collagen.

The splenic and portal veins are frequently affected by endophlebitis, which may be the starting point of thrombosis. The histological appearances of the endophlebitis suggest that it is caused, at least in part, by increased pressure in the portal venous system. Such raised pressure would also account for the vascular changes in the spleen.

The evidence of concomitant hepatitis is considered fully, and it is shown that hepatitis cannot be excluded, even when the liver appears to be normal to the naked eye. Microscopic and clinical evidence of hepatitis is presented in one or two instances in which there was no "cirrhosis".

The splenic enlargement cannot be wholly accounted for by venous congestion of the spleen; experimental evidence is adduced to show that, when the liver cells are damaged by hepatitis there ensues a proliferative change of the reticulo-endothelial cells in the peri-sinusoidal lymph-spaces of the liver. A similar proliferative change is seen along the lymphatics of the portal spaces. The lymph-flow from the liver, even at rest, is far greater than that from any other organ in the body, and passes, via the thoracic duct, directly into the blood-stream. It is surmised that, in hepatic inflammations, the flow of lymph is enormously increased, carrying with it some inflammatory products which stimulate the reticulo-endothelial cells of the spleen to proliferation.

Portal hypertension, which has been postulated to account for the vascular pathology of the disease, is not always caused by scar contraction in the liver. The physiology of the portal circulation and of the circulation through the liver is fully considered and summarised at the ends of chapters 7 and 8. Either vascular spasm of the portal venules within the liver, or the local arterial dilatation of hepatic inflammation would lead to a rise of portal

pressure. If one or both of these vascular changes occurs in hepatitis, then both the vascular and proliferative factors would be brought to bear on the spleen at a relatively early stage of liver inflammation, leading to "pre-cirrhotic" splenomegaly of an anatomical type identical with that seen in the later stages of cirrhosis.

The conditions described as "Banti's disease", Egyptian Splenomegaly and Bastai's Familial Splenomegaly, are essentially identical in their pathogenesis with the other types of hepatolienal fibrosis. The clinical picture is fully considered, and the results of splenectomy are discussed. There is no proof that splenectomy either arrests the hepatitis or cures the anaemia. Many patients remain anaemic years after the operation. The bulk of the evidence here presented shows that the splenic involvement is secondary, and Banti's hypothesis, that the hepatitis is splenogenic in origin, is refuted.

An account is given of certain experimental and clinical observations on the absorption and excretion of water in conditions of portal congestion, with a view to using the

water absorption rate as an index of the latter condition in man. The preliminary experimental work yielded promising results, but, clinically, the exchange of water was found to be influenced by various conditions of disease and debility, in a manner too complex to allow the test to be applied for this purpose in its present form.

2. Reticulo-endotheliosis. A small number of cases of splenic anaemia are found to be associated pathologically with the proliferation of large histiocytic cells in the spleen. This proliferation may affect mature histiocytes or immature "stem-cells". Such histiocytic proliferation may result from infection, or it may be associated with a leukaemic process (usually monocytic). On the other hand, the condition may be closely allied to Hodgkin's disease or to tumour growth. The numerous instances of this group of diseases now recorded have invariably run a fatal course; as the condition is diffused throughout the haemopoietic system, splenectomy does not appear to be a rational procedure.

Clinically, the anaemia varies in

degree, but is often extreme, and frequently there are primitive marrow cells in the circulating blood, especially nucleated red cells and monocytes. Leucopenia is inconstant.

3. Myeloid Splenic Anaemia. In this condition, the spleen is characterised by intense myeloid metaplasia, and is enlarged to over 1,000 grammes as a rule. Clinically, there is an anaemia usually with leucocytosis, but sometimes with leucopenia. The characteristic features are:-

1. High colour index.
2. Nucleated red cells in the blood.
3. Myelocytes up to 40 per cent.
4. Failure to react to liver therapy.

The condition is identical with the "leukanaemia" of Leube. A somewhat similar syndrome may be caused by osteo-sclerosis, malignant disease with bone-marrow metastases, Lederer's acute haemolytic anaemia, and von Jaksch's anaemia. It is only when these conditions have been excluded with certainty that the diagnosis of myeloid splenic anaemia should be made.

4. Simple Splenic hypertrophy. In this condition the spleen is enlarged but usually remains under 600 grammes. Histologically it shows no definite abnormality of anatomical structure or of cellular detail. The anaemia is of the hypochromic type and one case was definitely shown to be identical with the microcytic hypochromic anaemia of Witts. It is probable that the latter condition, which is not infrequently associated with a moderate degree of splenomegaly, accounts for all the cases in this group. No satisfactory hypothesis is forthcoming to account for the splenic enlargement. With the modern intensive iron therapy there is no further need to submit these patients to splenectomy.

5. Tuberculosis of the Spleen. This condition may resemble very closely hepato-lienal fibrosis, in that it may produce splenomegaly of considerable proportions, secondary anaemia with leucopenia, and associated ascites, as in the case recorded in this work. Pathologically, tubercles are found in the spleen, associated with vascular lesions (haemorrhages) and the appearances of general histiocytic reaction to infection.

6. Tumours of the Spleen. These are rare. The instances include one of arterial angioma, and two of lymphosarcomatosis. The latter condition was diffused throughout the Malpighian bodies leading to growth of the lymphoid tissue of these throughout the whole spleen, the pulp being crushed between the nodules of growth. In one instance the tumour was diagnosed from the rapid growth of the spleen, and from examination of a gland taken from the groin. In the other, the enlarged spleen was apparently the only tumour and a diagnosis of "splenic anaemia" was made.

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