STUDIES IN THE ANÆMIAS OF INFANCY AND EARLY CHILDHOOD

(From the Children's Hospital and the Department of Diseases of Children of the University, Birmingham).

Part IX.—Anæmia and reticulo-endotheliosis

BY

ROBERT GITTINS, M.D. M.R.C.P., D.T.M. & H.

In recent years the subjects of both anæmia and the reticulo-endothelial system have separately received much attention; they have offered interesting problems to the clinician and the pathologist, and great advance has been made in our knowledge of the causations of the one and the activities of the other. It is, therefore, somewhat surprising that more attention has not been given to the part played by the reticulo-endothelial system in the various forms of anæmia. To this system has been attributed the role of scavenger of cellular debris, chemical by-products and toxins of various kinds, and also a share, regarded by some as important, in hæmopoiesis. On a priori grounds it would seem probable that the reaction of the reticulo-endothelial system in the various anæmic states would be of some importance, and that its study might throw some light on the nature of the processes at work.

From time to time instances occur in children of both acute and chronic anæmia that do not correspond satisfactorily with hitherto recognized syndromes. Four such cases have recently been observed at the Birmingham Children's Hospital, and it is the object of this paper to record them in some detail with special reference to the changes found in the reticulo-endothelial system. It will be advantageous to anticipate the chief conclusions by stating here that of these four cases, two appeared clinically to be instances of acute erythronoclastic (hæmolytic) anæmia, and two have, subsequent to histological investigation, been regarded as examples of the same disease process in a chronic form. In all four cases the elements of the reticulo-endothelial system showed cutstanding activity. This, however, differed in form and degree not only in each case, but also from other forms of reticulo-endothelial activity, such as are seen, for example, in Gaucher's disease and other reticulo-endothelioses. This activity has been regarded as a response to damage to the hæmopoietic apparatus. Further, it is probable that similar findings may be taken as one of the chief forms of evidence of the existence of an erythronoclastic process.

Case 1.—J. W. The clinical features of this case were given in Part V of this series (p. 188), and only a brief summary is given here. This child, aged
21 months, had always been pale, and developed small scattered staphylococcal abscesses, following which the anaemia increased. The spleen and lymphatic glands were slightly enlarged; there was no icteric tinge, but the blood contained 4 units of bilirubin. The blood examination showed an aplastic picture: Hb. 26 per cent.; red cells 1,350,000 per c.mm., of which only 2 per cent were reticulocytes; white cells 950, of which only 8 per cent. were granulocytes; platelets 21,300 per c.mm. Although there was a slight improvement in the state of the blood, a temperature of 105° supervened and death occurred.

AUTOPSY. Nutrition fair, considerable pallor. Thymus, normal. Tonsils, normal appearance. Liver, some fatty change and enlargement. Spleen, somewhat enlarged. Lymphatic glands of mesentery, neck and groins not definitely enlarged. Marrow of left femur red throughout, but in one or two areas, there was a suggestion of a 'red currant jelly' appearance.

HISTOLOGICAL EXAMINATION: tissues placed in neutral formalin 15 hours post mortem in October, and stained with hæmatoxylin and eosin.

Fig. 1. Case 1.—Liver (× 700). Placed in neutral formalin 15 hours post mortem in October. Stain H.E. A histioyte (H), which has ingested a nucleus, and an erythrocyte, loosened Kupfer cells (K), and normoblasts (N) are seen in widened sinusoids.

Spleen. Lymph follicles small, pulp filled with large pink cells, no fibrosis, no congestion. Under high power (see Fig. 4) there was seen increase of reticulum fibres, which were thicker than normal. Numerous large pale cells were present; the cytoplasmic processes of some appeared to be in close relation with the reticulum, while other similar cells appeared to be lying free. The cytoplasm of these large cells was slightly granular, faintly eosinophilic and variously shaped; the longest diameter of these cells was often between 13 and 18 µ. Their nuclei, usually about 8 µ in diameter, were oval, bean-shaped, or sometimes bluntly lobulated and bounded by a delicate membrane; they stained rather faintly and the basi-chromatin was distributed in scattered small particles or finelythreaded, so that the appearance was often sponge-like; a nucleolus was sometimes discernible. The free cells frequently contained one or more ingested red cells. Their characters, therefore, were those of histiocytes, and owing to the close similarity of their features with those of the swollen reticulum cells, it appeared that the free and fixed cells were of the
same type and that the histiocytes were being produced from the reticulum cells. The cells lining the venous sinuses were not much enlarged nor phagocytic. Most of the remaining free cells were lymphocytes and a few myelocytes. In the centres of the follicles a few large pale cells were present. The Turnbull-Huecke preparation showed considerable quantities of haemosiderin, which was chiefly contained in reticulum cells and histiocytes. Bielchowsky’s silver stain revealed a slight increase in the condensed reticulum fibres. The striking feature was the large number of free phagocytic histiocytes.

Liver. There was oedema and the liver cell columns were broken up by wide sinuses which contained irregularly shaped large cells. Under higher magnification (Fig. 1), in the sinuses there was much amorphous eosinophilic material and many histiocytes, some of which were phagocytic. Many Kupffer cells, which were still lying against the wall of the sinuses, were swollen and partially free; their nuclear characteristics closely resembled those of the histiocytes. Turnbull-Huecke preparations showed slight haemosiderin deposit mainly in the Kupffer cells and histiocytes.

Lymph gland. There was widespread increase of reticulum tissue, in which the remains of follicles were discernible with difficulty; the germ centres were large. The characters of the reticulum and the reticulum cells were as described in the spleen. Lymphocytes were reduced. There was slight fibrosis of the capsule and around the vessels, all of which were congested. Some of the lymph sinuses stood out as columns of pink cells. Under the high power (Fig. 2) the germ centres consisted of cells with characters similar to the reticulum cells; their processes were branched to a certain degree. Free histiocytes were fairly numerous. There were also swelling, proliferation and liberation of the endothelial cells lining the lymph sinuses, which contained some histiocytes. By the Turnbull-Huecke method a fair proportion of histiocytes showed iron. The picture was that of considerable proliferation of reticulum, sinus endothelial and germ centre cells, together with an increase of histiocytes at the expense of the lymphatic tissue.

Bone marrow. Cellular; many of the cells appeared large and irregular, and the relatively regular shapes of the cells of normal marrow were missing. Under the high power (Fig. 3) the large cells were seen to be histiocytes, showing a remarkable
degree of phagocytosis of erythrocytes; some of them contained as many as 7 red cells, packed closely together in their cytoplasm. One histiocyte measured 230\mu and contained 2 polymorphonuclear cells and several red cells. Myelocytes, metamyelocytes, and polymorphonuclear cells were present but fewer in number than normal; some of the cells with nuclear polymorphism were somewhat large for granulocytes since they measured 10 or 11\mu, and their characters were rather histiocytes. Normoblasts were fairly plentiful. A slight hemosiderin deposit was demonstrated in the Turnbull-Hueckel preparation. The striking feature was the large number of intensely phagocytic histiocytes, though the fixed reticulum was not proliferated.

Kidney. Cloudy swelling of tubule cells and edema.

Tonsils. A good deal of proliferation of reticular cells of the germ centres, but not much in the pulp.

Lungs. Some bronchial catarrh; much patchy collapse and compensatory emphysema; congestion. Polymorphonuclear granulocytes and histiocytes present in capillaries.

Summary.—A case of subacute erythronoclastic anemia of aplastic type, showing on histological examination great activity of the reticulo-endothelial system, especially in the production of numerous phagocytic histiocytes.

Case 2.—B. M. Fuller clinical and hematological details of the first part of the illness in this case were given in Part IV of this series (p. 166).

The patient, a female child, who was aged 17 weeks on admission, had been pale at birth and slightly jaundiced a fortnight later. She had been fed on the breast for seven weeks and afterwards on Ostermilk.

On admission, nutrition was good, severe anemia with slight jaundice was present and the spleen was greatly, and the liver moderately, enlarged; a few shotty glands were found in the axillae. A blood examination showed: red blood cells 1,450,000
ANÆMIA AND RETICULO-ENDOTHELIOSIS

per c.mm., haemoglobin 21 per cent., colour index 72; the volume index was 86, and the saturation index 87; there were anisocytosis, poikilocytosis and polychromasia; the fragility of the red cells was slightly increased; a Price-Jones curve showed much anisocytosis and a mean diameter of 6·794μ; the white blood cells were 18,700 per c.mm. of which 63·5 per cent. were lymphocytes, 3 per cent. myelocytes, 5 per cent. myeloblasts and 11 per cent. monocytes; platelets were reduced; 1·5 normoblasts and 9·5 macro-normoblasts per 100 leucocytes were found (six days after transfusion of two ounces of blood). Urobilin was present in the urine and 1·0 units bilirubin were present in the blood. The Wassermann reactions of the patient and her parents were negative.

The child remained in hospital until her death nearly 4 months later. During this time eleven blood transfusions were given; in addition, ferrous sulphate (gr. 2 t.d.s.) in the early stages, and campolon (liver extract) injections towards the end, were administered. From time to time some petechiae and ecchymoses were seen. The spleen became smaller, though fluctuations in size were noted. The general condition and the state of the blood improved after two blood transfusions, to be followed by a definite fall in the haemoglobin and red cell content; after further blood transfusions improvement was maintained until about one week before death. Haemoglobin rose to 66 per cent. at its highest point; the colour index was always high after the first examination, sometimes over unity; the volume and the haemoglobin saturation indices of the red cells remained approximately at unity. The bleeding time was found to be prolonged and the clot retraction was poor; the clotting time was approximately normal. Although signs of regeneration were pronounced in the early stages, when there were also leucocytosis and some immaturity of the granulocytes, at the later blood examinations only 6 per cent. reticulocytes were present, anisocytosis and poikilocytosis were very much less than previously and a Price-Jones curve revealed a mean diameter of only 6·398μ. The monocytes varied in number but were usually slightly increased. A blood examination about one week before death showed that the white cells numbered only 9,500 per c.mm., and although the lymphocytes still accounted for 54·5 per cent., the immaturity of the granular series was much less.

Radiograms of the long bones showed some rarefaction and thinning of the cortex.

AUTOPSY. Development poor, nutrition fair, considerable pallor and a slight yellowish tinge. Pericardium contained a little yellowish fluid. Epicardium showed a few petechiae. Liver, rather pale, with early fatty change. Spleen, dark and enlarged to approximately four times normal size. Mesenteric and inguinal glands slightly enlarged. Frontal bones showed raised red areas (Fig. 18) and the left femur externally appeared dark red at both ends; on section the marrow was rich red in colour.

There were small extravasations of blood beneath the vertex of the skull and in the orbits.

HISTOLOGICAL EXAMINATION: tissues placed in neutral formalin nine hours post mortem in May.

Spleen. Lymph follicles small, composed of small dark and large pale cells. Reticulum cells in pulp prominent. High power:—‘Germ centre’ cells and reticulum in follicles proliferated. The small dark cells noted under the low power were lymphocytes, normoblasts and normoblastic nuclei. In the pulp the reticulum cells were enlarged and proliferated, and the appearance was similar to that in the first case, except that free histiocytes were few and phagocytosis was slight. The Turnbull-Huecke preparation showed a little scattered haeemosiderin. Silver stain did not reveal any gross increase in reticulum fibres.

Liver. Portal tracts normal. Many small cells scattered in sinusoids. High power (Fig. 5):—Liver cells contained some bile pigment. Most cells in sinusoids were erythroblasts: normoblasts with a few megaloblasts and pro-erythroblasts,
Histiocytes, containing erythroblastic nuclear fragments, bile pigment, etc., were fairly numerous. Kupffer cells were swollen and scarcely any normal forms were found. An extremely heavy deposit of hæmosiderin, chiefly in the peripheral areas of the lobules, was demonstrated by the Turnbull-Huecke method.

Lymph gland. Features similar to those described in the spleen. Free phagocytic histiocytes were present. Lymph sinuses were very wide and contained many histiocytes. The Turnbull-Huecke method showed a slight scattered deposit.

Bone marrow. Many normoblasts and pro-erythroblasts in all regions. Phagocytic histiocytes numerous.

Summary.—A case clinically resembling so-called von Jaksch’s anæmia in an infant aged 4 months; histological examination showed considerable abnormal erythropoiesis and widespread reticulo-endothelial activity.

Case 3.—J. B., male, 1 year old, one of twins, had been breast fed for 3 months. He had always been somewhat pale, but 1 week before admission the pallor had rapidly increased. Examination revealed considerable anæmia, purpura, rickets, the liver enlarged nearly to the umbilicus, considerable enlargement of the spleen, and a few enlarged lymph glands. The respiration rate after admission was 60 and over, and 4 days after admission signs of broncho-pneumonia were evident. Blood examination: Hæmoglobin 34 per cent., red blood cells 3,200,000, white blood cells 34,200 per c.mm., colour index 0-52, size of red cells (Eve’s halometer) 7-23μ. A differential count showed slight immaturity of the granular series with eosinopenia; the actual percentages were as follows: neutrophil polymorphonuclear cells, segmented, 40; neutrophil polymorphonuclear cells non-segmented 18; neutrophil metamyelocytes mature, 2; neutrophil metamyelocytes immature, 1; neutrophil myelocytes, 5; lymphocytes, 27-5; plasma cells, 5; monocytes, 10-5. There were 700 normoblasts, 350 macronormoblasts and 350 megaloblasts per c.mm. Poikilocytosis and anisocytosis were well marked, and there was some polychromasia. The platelets...
ANÆMIA AND RETICULO-ENDOTHELIOSIS

appeared normal in the film. The radiogram of forearm showed florid rickets. The child’s condition deteriorated and death took place 4 days after admission—11 days from the onset of acute illness.

Clinically it appeared that an acute respiratory infection had overwhelmed the child, who was already suffering from a chronic erythronoclastic anaemia and nutritional deficiency.

AUTOPSY. Bilateral empyemata and massive consolidation in lungs with some grey hepatization. Liver enlarged (410 grm.) showing some toxic pallor and early fatty change. Spleen grossly enlarged, slightly hard, and of a more or less normal colour. Inguinal lymph glands only were very slightly enlarged and congested. Bone marrow of femur a greyish-red colour. Costochondral junctions showed well marked rickets.

Histological Examination: tissues placed in formalin about 24 hours post mortem in August.

Spleen (stained with H.E.). Under the low power (Fig. 6), there was considerable increase of the pulp and the follicles were diminished; fibrous tissue was not obviously increased. Under the high power many of the cells were histiocytes and swollen fixed reticulum cells, as described in Case 1; the nuclei were often irregularly lobed and a few showed one or two nucleoli. The free histiocytes were fewer than in Case 1, and although there was some phagocytosis it also was very much less. Myelocytes, some of which showed granulation, and polymorphonuclear cells were found scattered in the reticulum. The outstanding feature was the increase in reticulum cells and fibres, which was well shown by Bieleowsky’s silver impregnation method. Much scattered hæmosiderin was found by the Turnbull-Huecke method.
Liver. The cell columns were broken up by oedema; there were some central fatty change and a slight increase of small round cells along the portal tracts. Under the high power (Fig. 7, 8 and 9) the widened sinusoids contained various cells, some of which appeared to be polymorphonuclear granulocytes and myelocytes, while the remainder were histiocytes, which had frequently ingested either lymphocytes or polymorphonuclear cells. No entirely normal Kupffer cells were found. One of several preparations by the Turnbull-Huecke method showed a very light irregular deposit of hemosiderin.

Lymph glands. Sections from several glands were examined, all of which showed congestion and oedema so that the cells were rather widely separated. One gland, probably from the hilum of the lung, showed much catarrh of the sinus endothelium, and many large pink cells were massed together in the sinuses. Under the high power (Fig. 10) these large free cells were often foamy in appearance, and displayed much phagocytosis. In only one section was there seen to be a slight swelling of the reticulum cells.

Bone marrow. Cellular, with small fat spaces. Under the high power (Fig. 11) most of the cells appeared to be either normoblasts, megaloblasts or pro-erythroblasts; myeloblasts and myelocytes were present in only moderate numbers. Mature granulocytes were diminished, and few reticular cells were distinguished.

Lung. There were much congestion and many small areas of collapse and compensatory emphysema. Many of the alveoli contained free mononuclear cells. The section was evidently not taken from a densely consolidated area.

Heart. The fibres were small and separated by oedema; many were broken and granular.

Kidneys. Slight catarrhal and toxic changes in the tubule cells.

Summary.—A case of chronic erythronoclastic anaemia of milder type associated with nutritional deficiency; in which pneumonia supervened and brought about a fatal termination. Histologically reticulo-endothelial activity appeared to be more limited than in the other cases, and was confined mainly to the splenic reticulum and liver sinusoids.
Case 4.—R. D., male, aged 1 year and 11 months when first seen. He was in hospital several times and many investigations were carried out before his death at an age of 3 years, 9 months. He was an only child, born at full term and weighing eight pounds. When first admitted on the 15th April, 1930, it was learned that he had been yellow at birth, but the jaundice soon cleared; he had always been pale. At the age of 15 months he bled profusely after circumcision; he had always bruised easily and some time before admission he had shown some melena. His maternal grandfather was said to be a bleeder.

Clinical examination revealed extreme pallor and a slight icteric tinge, but no other abnormal signs, except a spleen enlarged by three inches. The blood examination showed haemoglobin 37 per cent., red blood cells 2,500,000 and white blood cells 11,300 per c.mm. The percentage differential count showed neutrophil polymorphonuclear cells, 44; neutrophil myelocytes 2; eosinophil polymorphonuclear cells 1; lymphocytes 53; and a few normoblasts were present. There was slight increase of urobilin in the urine, the Wassermann reaction was negative and the fragility of the red cells was slightly increased (incomplete haemolysis in 0.5 per cent. saline, while the control showed it in 0.45 per cent.). Treatment comprised the administration of iron and copper, fresh lettuce, and a transfusion of 200 c.c.m. of blood. The child was discharged after 7 weeks improved, with a haemoglobin content of 40 per cent.

The child was re-admitted into hospital four times in the next twenty months, for fairly lengthy periods, and although at times he seemed slightly better, his condition slowly and insidiously deteriorated. Bleeding, especially from the nose and stomach, became more frequent and copious, and petechiae and ecchymoses were often observed; there was a gradual increase in the size of the spleen and liver, but glandular enlargement was never noticeable. Occasional slight rises in temperature
occurred with increasing frequency. The slight increase in the fragility was again found, and the van den Bergh test gave very slight positive direct and indirect reactions. In all, thirty-six blood counts were carried out, but none showed any important changes from the first; the reticulocyte response was usually low, but sometimes rose to 3 and even on one occasion to 6 per cent. The haemoglobin rose to 40 per cent. 3 weeks after the first estimation, but subsequently there was a fall with minor fluctuations to less than 15 per cent.; the colour index, never high, tended to decrease; nucleated red cells were found only occasionally; the platelets decreased ultimately to 10,000 per c.mm.; the white cells diminished to 4,000 per c.mm., and differentially the lymphocytes usually amounted to 50 per cent., one or two myelocytes and metamyelocytes were present, the monocytes were not increased, and the basophil cells disappeared.

A wide range of therapeutic agents used at various stages included a course of injections of healthy adult blood serum, X-ray applications to the bones and later to the spleen, dried yeast, vitamin D, histidine, suprarenal cortex (opocap) by mouth, adrenalin injections, when the bleeding was troublesome, and, of course, frequent blood transfusions. Nothing, however, appeared to have any definite effect on the course of the illness or the state of the blood. Towards the end efforts were chiefly directed towards staying the frequency and the amount of the hemorrhages; and finally the child died after further hematemesis and epistaxis.

As the illness progressed it was obvious that we were dealing with a most unusual form of anaemia; the failure of normoblasts to appear in any number and the relative maturity of the granulocytes did not lend support to a diagnosis of von Jaksch's anaemia. A diagnosis of splenic anaemia, of adult type, had some features in its favour; the age of the child at the onset was, however, against its being the correct diagnosis. A storage reticulo-endotheliosis such as Gaucher's disease, had to be considered, but was ruled out because of the progressive and severe character of the anaemia and lack of familial incidence. A diagnosis of aplastic anaemia, which may be a phase of erythronoclastic anaemia, accorded with the unusual blood picture and
was supported by the histological findings, which included the replacement of large portions of the marrow by reticular proliferation.

**Histological examination**: sections placed in neutral formalin or Zenker's solution 3 hours post mortem in February.

Spleen. Under the low power lymphocytes in follicles much diminished, but in the centre of thin rings of lymphocytes, were extensive closely packed collections of large pale cells; considerable increase in pulp, which appeared to consist mainly of of rather large pale cells, increased reticulum and a fair number of red cells; some perivascular fibrosis; in places the fine reticulum fibres were conglomerated into bundles or strands, which showed little structure and sometimes hyaline change; in others were strands of apparently fine fibrous tissue. Under high magnification (Fig. 12) the numerous and prominent reticulum cells were swollen and contained large pale nuclei; their characters were similar to those described in the previous cases. Free histiocytes and cells with definite ingested matter were not found. The venous sinuses were not generally dilated, but their characteristic lining cells (with fairly large slightly irregular nuclei and little cytoplasm) were somewhat prominent and easily distinguished, and were sometimes lying free in the lumina. In some areas the bundles of reticular tissue appeared to show partial necrosis. One section showed fairly numerous large dark cells, 10 to 11μ in diameter, with nuclei 8μ which contained rather large irregular masses of chromatin and one or two dark nucleoli; these cells resembled myelocytes, but were rather irregular in shape. The Turnbull-Huecke process revealed a slightly increased deposit of haemosiderin, irregularly scattered in the reticulum, and the silver stain showed gross increase in reticulum fibres (Fig. 13). The striking features were the great increase of reticulum fibres and large pale nuclei, the presence of small bundles and strands of reticulum fibres, and the occurrence of syncytial groups of pale cells.

**Liver.** Much fatty degeneration in the central areas of the lobules; slight periportal infiltration of lymphocytes and fibroblasts; many nuclei and cells of all shapes in the
widened sinusoids. Under high power liver cells contained groups of light yellow-brown granules. There were many free histiocytes in the sinusoids; their nuclei were often horseshoe-shaped, some were phagocytic and vacuolated. Other cells in the sinusoids were lymphocytes in moderate numbers and a few small (?) myelocytes. No absolutely normal Kupffer cells were found; those that were attached to the walls of the sinusoids were slightly swollen and possessed nuclei slightly darker than, but similar in texture and shape to, those of the histiocytes. The Turnbull-Huecke method showed some deposit of hemosiderin in the liver cells (Fig. 14).

Lymph glands. Lymph follicles were much diminished and often difficult to discover and identify. There was a striking increase of reticulum and reticulum cells throughout and lymphocytes were sparse, but the endothelial cells of the lymph sinuses were not proliferated nor prominent, nor were these sinuses packed with cells. Under the high power the proliferated reticulum cells appeared similar to those described in the other cases and possessed the same characteristic pale sponge-like nuclei; their cytoplasm was moderately eosinophilic, and on the whole their processes were bluntly contoured. In the meshes the free cells consisted of some lymphocytes, a few myelocytes and, in contrast to the spleen, some free histiocytes, which sometimes contained a rather foamy cytoplasm, vacuoles and a few ingested particles. The Turnbull-Huecke process showed some doubtful irregular deposits of hemosiderin. A gland from the meso-colon appeared more normal as regards the reticulum, but the lymph sinuses were dilated and packed with apparently normal lymphocytes and histiocytes.

Bone marrow. The sections from different portions of the marrow showed some differences: thus in some there was an increase of pale reticulum cells (Fig. 13), whereas in others there were numerous scattered bundles of fine reticular fibres, fibrous tissue or almost structureless eosinophilic material (Fig. 16). Under the high power the other cells were identified as some eosinophil leucocytes, and scattered mature red cells and normoblasts, which tended to be aggregated into small

---

**Fig. 16.** Case 4.—Bone marrow of femur (× 95). This section shows how the haemopoietic tissue was replaced by bundles and strands of reticular fibres; this is a later stage of the process seen in Fig. 15.

**Fig. 17.**—Splenic anaemia of adult type in a child aged 7 years. Spleen (× 230). Stain H.E. The cirrhosis between the dilated venous sinuses is well shown and is different from the reticulum cell proliferation shown in Fig. 12.
foci of erythropoiesis. Pro-erythroblasts were not numerous, and haemopoietic areas were severely diminished.

Kidney. All tubules showed advanced cellular degeneration and were dilated; there were no infiltrations and no increase in interstitial cells; the glomerular tufts were rather large.

Lungs. The bronchi contained masses of leucocytes; there were small areas of collapse and emphysema; some capillaries contained some large pigment carrying cells, 10 to 11 μ in diameter.

Summary.—A case of chronic fatal anaemia of aplastic type in a child aged 3½ years; a widespread reticulo-endotheliosis, which was of long duration and replaced areas of haemopoietic tissue was found on histological examination.

Comparison and interpretation of the cases.—The outstanding features common to these four cases were the presence of severe anaemia and activity of elements forming part of the reticulo-endothelial system. The cases, however, varied considerably in their duration, in clinical features, and also in the type of activity displayed by the reticulo-endothelial cells, but it is
believed that, different as many of the aspects were, the nature of the original morbid process and of the tissues’ reaction was fundamentally the same in all.

Reference is made later to the chief views held with regard to the function of the extensive reticulo-endothelial system, but for the moment, and for the purpose of correlating these cases, attention need be paid only to that principal function of the system, namely, phagocytosis and scavenging of waste material, the properties by which the components of the system were first recognized. The thesis is here put forward that the changes observed in the reticulo-endothelial system, though differing in form in the four cases, were reactive in nature; and further, that on the basis of the histological findings in this system cases differing widely in clinical characteristics can be correlated.

The first was the most acute case and clinically fitted into the subacute group of erythronoclastic (hæmolytic) anæmia, which has been described in Part V of this series. At the time of the first blood examination, so severe was the effect of the erythronoclastic process on the formative elements of the blood that an aplastic blood picture was presented. Later, during a remission, there appeared a somewhat regenerative picture, which could be accepted as one of a von Jaksch’s syndrome. This improvement was unfortunately not maintained and an aplastic state again supervened. Though there was definite proliferation of reticulum cells which appeared to be fixed in the tissues, the outstanding feature was the production of free wandering histiocytes, or macrophages, the appearances of which corresponded in almost every detail with those of certain fixed cells, namely, reticulum cells and cells lining the lymph sinuses, which also were increased in number. The conclusion could not be evaded that these prominent histiocytes were being actively produced from those fixed cells: a view which is in accordance with that usually accepted of the origin of histiocytes. Further, the striking phagocytosis of red cells which the histiocytes displayed, revealed their function: they were engaged in scavenging, and not in the production of blood cells. There remains the question whether this phagocytic activity was the cause of, or the response to, the red cell destruction and consequently the anæmia. At present the answer cannot be certain, but, since we know that hæmolysis of erythrocytes may occur so suddenly in some cases that only a direct injury of them seems conceivable, it is probable that in this case also, the primary damage was one of hæmolysis or erythronoclasia, and that the reticulo-endothelial activity was mainly reactive and consequent upon the original injury. It is probable that, as records of histological examinations on cases of relatively acute erythronoclasia accumulate, it will be found that activity of the reticulum cells and phagocytosis are outstanding features.

The second case clinically appeared similar, but the damage to the erythrocytes and their precursors was more chronic and regeneration was
ANÆMIA AND RETICULO-ENDOTHELIOSIS

more active than in Case 1: in other words, haemolysis of mature erythrocytes was relatively greater and erythronoclasia relatively less. The erythropoietic tissues, however, failed ultimately to meet the strain and a less regenerative blood-picture ensued. Histological examination revealed the existence of much abnormal erythropoiesis, for many nucleated red cells were found in the spleen and lymph glands, but again the outstanding features were the swelling and proliferation of reticulum and endothelial cells. Here, too, it is possible to consider that these were due to the activity of these cells in clearing up the debris of lysed red cells, and in phagocytosis of abnormal forms produced by a haemopoietic tissue, which was not only adversely affected by the erythronoclasia but was also attempting to make good a continuous and excessive loss of erythrocytes from haemolysis.

The third case showed a fairly typical von Jaksch's syndrome and, as regards the anaemia, the course had been longer than the first two. Acute pneumonia developed and the consequent strong myeloid reaction complicated the blood, and especially the histological, pictures. The latter, apart from myeloid reaction, displayed a considerable proliferation of the splenic reticulum, which accounted for most of the great increase in size of the organ. This proliferation showed throughout a greater proportion of fixed cells, and the production of free histiocytes was less than in the two preceding cases; there was also an increase in reticulum fibres, and elongated forms of cells preponderated. Similar but considerably smaller areas had been found in the second case. The features were that of an activity of longer standing, and the increase in spindle forms of cells and reticulum fibres was analogous to the increase of fibrocytes and collagenous fibrils as organizing inflammatory tissue grows older.

Again in this case evidence of abnormal erythropoiesis was found, especially in the presence of many normoblasts in the splenic pulp. Elsewhere, evidence of activity of the reticulo-endothelial system was confined to the hepatic sinusoids and lymph sinuses, in which phagocytic histiocytes were numerous. The stimulation to these cells lay, no doubt, partly in the intense terminal infection, but also may have been due to the erythronoclastic process. The changes in the spleen appeared to be of longer standing; they doubtless denoted a milder but more chronic form of blood destruction than in the first two cases.

The fourth case was clinically different from the others. At the time of the first examination a few normoblasts were found and this formed the chief evidence in favour of a diagnosis of von Jaksch's anæmia, tentatively held for some time until the aplastic blood condition developed. Ultimately, the prolonged course, the outstanding haemorrhagic tendency of the severe anæmia, the aplastic state of the blood and the absence of any definite increase in bilirubinæmia, seemed to exclude any connection with haemolytic anæmia. However, the subsequent histological examination revealed that, as in the other cases, the reticulo-endothelial system was grossly affected: there was enormous proliferation of reticular cells and fibrils not only in
the spleen and lymph glands, but in the bone marrow also. Now in such diseases as malaria and kala-azar the early activity of the reticulo-endothelial system is of a cellular type, and this proceeds to the development of dense reticular and fibrous tissue. It appears, then, highly probable that the state of affairs found in our fourth case represented the ultimate development of reticulum cell activity that had long passed through the stages observed in the other three cases: again it was analogous to the development of fibrous tissue from a fibroblastic tissue. The widespread replacement of hæmopoietic by reticular tissue explained the development of the aplastic state of the blood.

On the basis, therefore, that the outstanding morbid change found after death affected the reticulo-endothelial tissue, there seems justification for classifying this obscure case with others, in which there were good clinical and hæmatological reasons for the diagnosis of hæmolytic or erythronoclastic anæmia. Accepting this hypothesis we may regard this case as illustrating one mode of termination of erythronoclastic anæmia.

We are now in a position to consider the modes by which erythronoclastic anæmia may develop. The initial blow may fall most heavily on the mature erythrocyte, leaving the erythropietic tissue but little affected; in such a case the early blood picture will be regenerative. Should the bone marrow also suffer heavily, the blood picture will naturally be aplastic or anhæmopoietic. In either case there will be reticulo-endothelial activity, probably chiefly in the production of histiocytes, designed to clear up debris from the blood destruction, and also to destroy immature and unsuitable red cells produced by the affected marrow. If the erythronoclastic process continue, it is likely that it will affect the marrow to greater or less degree, and therefore the stimulation of the reticulo-endothelial system will be prolonged. There will be enlargement of the spleen, liver and lymph glands from the cellular proliferation, while the blood-picture will be regenerative or not according to the strength of the marrow’s response. Another factor which will affect the degree of response, is the existence or not of embryonic hæmopoietic foci, at the time of the commencement of the erythronoclasia. If these are present, for example, in the liver and spleen, they, along with the marrow, will attempt to make good the loss of blood cells and thus remain in activity instead of fading out of existence, as is the normal course in late ante-natal and early post-natal life. This aspect of the subject has been dealt with in Part IV of this series.

Finally, it appears that, if the erythronoclasia is relatively mild and yet prolonged in its action, the reticulo-endothelial system may maintain its reaction to the blood destruction and abnormal formation for so long, that it advances to extensive proliferation and the production of much reticular tissue; this may actually replace hæmopoietic tissue and so form a further contribution towards a state of anhæmopoiesis. Our fourth case is an example of this, and seems to represent the end result of a prolonged series of changes which began with erythronoclasia,
Owing to the confusion which has existed on the subject of von Jaksch’s syndrome, it is difficult to find a convincing description of its histological changes. The presence of numbers of nucleated red cells in the spleen is accepted widely, and some authors mention the occurrence of the embryonic erythropoietic foci in the liver. The reticulo-endothelial reaction has come in for little attention, but it is referred to by Aschoff and McNee. Doubtless the swollen reticular cells have often been regarded as erythrogonia or the most primitive progenitors of haemoglobiniferous cells, rather than the active participants in a reactive process. It is possible that some of the large cells, which Luzet described in the first adequate description of the disease, were actually histiocytes and not erythrogonia.

From the description given it is obvious that the histological features of the so-called von Jaksch’s anaemia, which we have regarded as a subchronic erythronoclastic anaemia, may be extremely varied and the changes will depend on: 1, the degree of response on the part of the marrow; 2, the existence or not of extramedullary embryonic centres of erythropoiesis; and 3, the reticulo-endothelial reaction, the type of which will largely depend on the duration of the morbid process.

In a recent annotation in the Lancet criticism is offered of the suggestion made in Part V of this series that von Jaksch’s anaemia should be regarded as a subchronic haemolytic anaemia, on the grounds that ‘conclusions were based upon an analysis of a small group of cases with no post-mortem reports.’ We regret that the number of cases of this syndrome available for study is so small, but we think that the pathological investigations contained in this paper afford strong evidence in support of our suggestion.

**Scheme of events in erythronoclastic anaemia.**

Erythronocasis

- Hæmolysis
- Injury to hæmopoietic tissue

Production of abnormal red cells

- Regeneration of blood by marrow (and any extant embryonic erythropoietic foci).

Production of histiocytes.

- Reticulum cell proliferation.

- Production of reticular fibrils.

**Histological features of the reticulo-endothelial activity.**—The features of the histological changes observed may be conveniently summarized here.
In the early stages of the reaction (e.g., Cases 1 and 2), there are swelling and proliferation of reticular cells of the spleen and lymph glands, and of the cells lining the hepatic capillaries and the lymph sinuses. In the sections of normal tissues stained with haematoxylin and eosin, these cells present an oval, triangular or even somewhat stellate nucleus, which stains rather darkly and uniformly, and which is of only moderate size, about 5μ in length. The cytoplasm is eosinophilic, and its tapered processes extend inconspicuously into the ground-work and often join the reticulum fibres. By suitable staining the ultimate union of these fibres with collagen bundles can be traced. The cell is generally not prominent. When such cells become active and proliferate they become much more conspicuous. The appearances of the nucleus are then characteristic: it is large, frequently 8μ in diameter, and often indented or even lobulated in shape; it stains rather faintly blue and the nuclear margin is delicately drawn; nucleoli are frequently not present and chromatin deposits are few, fine and irregularly scattered, and sometimes a network of slender threads can be made out. Large nuclei with an almost colourless interior are commonly found. Such characters can easily be made out in an active reticulum of a lymph gland or amongst active Kupffer cells, where normal individuals are still present with which comparison can be made. The size of the cytoplasm increases frequently up to a diameter of 10 and 12μ in sections, and forms over 20μ may be encountered; the cytoplasm is faintly eosinophilic and sometimes slightly granular. Large cells appearing free in the tissue spaces are seen to have features identical with the fixed ones; and, though phagocytosis varies from case to case, ingested inclusions, often lying in vacuoles, are found. The identification of these ingested cellular remnants, etc., is important, since it reveals the function of the free and fixed proliferated cells with certainty, and provides the weightiest reason for interpreting the reticulo-endothelial activity as reactive to a morbid process (such as abnormal blood formation and destruction) rather than as formative of different types of blood cells.

In the lumina of the lymph channels free cells similar to the above are often seen in large numbers, and cells partially attached to the walls. These cells may show degenerative changes, such as poor nuclear staining and a foamy cytoplasm. As far as the lymph channels are concerned the picture is similar to that so commonly seen in lymph glands draining an inflamed area. In these cases the cells lining the venous sinuses of the spleen have not been prominent or greatly increased in numbers, but proliferation and desquamation of this type of cell has been seen in myelosis (Part VIII), Banti's disease and acute infections. The numerous phagocytic histiocytes in the tissue spaces and sinuses, and the swollen lymphatic sinus and reticulum cells are characteristic and their features are easily recognizable. The only cell with which the last are likely to be confused is the fibroblast. Differentiation is usually possible on architectural grounds, but in individual cells there is often some difference in the appearances of the two types: the fibroblast usually shows a more regular contoured, but still lightly staining,
nucleus, often containing nucleoli; its basi-chromatin is in the form of a fine dust-like deposit\textsuperscript{37} and does not exhibit the tendency to net formation. It might be noted here that there is strong evidence for the contention, which Maximow has long supported, that the histiocyte or polyblast may develop as a fibrocyte and take part in the formation of fibrous tissue, but it is by no means certain that the converse is true: that fibroblasts or fibrocytes may produce histiocytes.

In the late stages of the process, as exemplified in Case 4, there is seen to be a great increase in the fixed proliferated reticulum cells, which have now produced many fine reticulum fibres. These may be condensed in scattered areas into the form of knots, which with ordinary staining may fail to reveal a reticular character but are shown by silver stains to be composed of closely packed reticular fibrils. Case 4 showed these clearly. Further features of this late stage are the increase of frank fibrous tissue, and the absence of a great number of free histiocytes.

In the early stages an increased deposit of hemosiderin, as revealed by the Turnbull-Huecke method is usually found, but this is not a feature later in the process. Along with this reticulo-endothelial activity various grades of erythropoiesis are found; the cytological features of the embryonic type have already been referred to in Parts IV and VIII and those of normoblastic type are too well known to require description. It may be noted, however, that normoblasts may be scattered widely in the tissues; large numbers were found in the lymph glands and even in the lymph follicles of the second case.

It is thus seen that in the development of the histological picture, a sequence of appearances from a cellular to a reticular fibril formation occurs, and this has many points of similarity to the sequence of changes in an inflammatory area proceeding to reparation.

The reticulo-endothelial system.—We owe our first and most valuable conceptions on the integrity and role of the widespread elements of the reticulo-endothelial system to Aschoff and his co-workers. The idea of the essential unity of the different components is largely based on the results of intra-vitam staining, and Aschoff\textsuperscript{3} gave the following as an ascending series of intensity of staining: 1, endothelial cells of blood and lymph vessels; 2, fibrocytes; 3, reticulum cells of splenic pulp, lymphatic cortical nodes and pulp; 4, reticulo-endothelial cells and sinuses of lymph nodes, blood sinuses of spleen, Kupffer cells of liver, capillaries of bone marrow, adrenal cortex and hypophysis; and 5, histiocytes. He considered that 1 and 2 may be excluded from the reticulo-endothelial system on account of their faintness of staining. Kiyono designated the reticulo-endothelial cells as histioblasts, because they gave rise to free cells, resembling histiocytes. The various cells of the system ingest foreign particles, such as colloids, bacteria, cellular remnants, and ‘fix’ toxins such as those of diphtheria and tetanus; on this account a large role in immunity reactions has been ascribed to them. Aschoff has referred to erythro-phagocytosis by the system in various conditions, but especially in experimental arsениретted hydrogen poisoning.
in birds. Much work has been devoted to following the fate of the non-
ferrous portion of the hemoglobin, and it is now accepted that the reticulo-
endothelial system plays an essential part in the production of jaundice.
The epithelioid cells of tubercle, lepra cells, characteristic cells in rhino-
scleroma, sporotrichosis, Gaucher's disease and other morbid processes, are
either histiocytes or other reticulo-endothelial cells.

It is to be expected that such an extensive combination of cells may
react strongly to certain stimuli; an example is found in typhoid fever, where
the endothelial cell activity has been noted by Mallory and more recently
has been studied by Schmidt and again by Graff. Their descriptions and
illustrations of cells correspond closely with those already given under the
case records. Goldzieher and Peck have shown how the reticulo-
endothelial cells of the spleen and liver react in infectious conditions in man
and experimental animals; the illustrations of their papers show cytological
features similar to those of the present cases. In typhoid fever and also in
ulcerative endocarditis there is an increase of monocytes in the peripheral
blood. This in itself is strong evidence for the origin of circulating
monocytes from the reticulo-endothelial system, an opinion held by many,
and supported by Garrod and Hadfield in their recent excellent review.
This rôle, however, is disputed by such an authority as Naegeli, who has
long contended that the monocyte is a variant of the myeloid series. It is
probable though, that some of the cells, placed in the group of monocytes,
are immature metamyelocytes, which have a similar shape but which contain
granules and are certainly myeloid cells. Aschoff and Kiyono found that
some, but not all monocytes, were stained intra-vitally and their opinion
appears to be that all blood monocytes have not the same origin, but that
many are histiocytic and derived from the reticulo-endothelial elements.

Dameshek has recently contributed a valuable review on the appearance
of histiocytes in the peripheral blood. He concluded that the blood
monocyte is a variant of the histiocyte which rarely circulates in the
peripheral blood, and both are direct derivatives of the reticulo-endothelial
system.

If blood monocytes are derived from the reticulo-endothelial system, the
question naturally arises why they are not increased in all conditions in
which the system is active. The answer is uncertain; but as the above
observations show, the reaction of the reticular tissue varies, sometimes
producing mobile histiocytes and at other times an increase of apparently
fixed cells and reticular fibrils. Moreover, the sphere of activity of
histiocytes is in the inner organs, where they may be seen assiduously
ingesting cells and debris as in Case 1. Kiyono traced the entrance of
reticulo-endothelial cells into the circulation and thence to the lungs, where
they were filtered off. It is thus possible that histiocytes entering the
circulation are soon removed, and that those seen in a film of the peripheral
blood have only just entered the stream and normally would have been
rapidly filtered off. The cytological appearances of many blood monocytes
are so similar to those of tissue histiocytes and sessile reticulo-endothelial cells, that it is difficult to escape the conclusion that they are the same type of cell. In addition to typhoid fever and ulcerative endocarditis, malaria and kala-azar, in which the reticulo-endothelial system is system, show a monocytois. Monocytic leukaemia, or leukämic reticulo-endotheliosis, is another condition in which large numbers of circulating monocytes are found. A case of this rare condition has recently been reported by us elsewhere, and its study supported the contention that circulating monocytic, or histiocytic, cells are derived from the reticulo-endothelial system and, if the system be affected by a leucotic type of process, may emigrate in large numbers.

There is thus some justification for concluding that the circulating monocyte is a direct derivative from certain elements of the reticulo-endothelial system.

The other rôle of the system, accepted by many, is that it may function, either obligatorily or vicariously, as a parent in post-natal life to all types of blood cells. This alleged and comprehensive rôle is one of the most vexed of haematological questions, and the evidence for it is much less certain than that for the scavenging and immunological functions. It is discussed in a later section of this paper.

Reticulo-endotheliosis.—Of recent years some cases, often under the above title, have been published mainly by German workers, and reference will now be made to some of these.

Letterer published one case which has points of similarity to the present cases. The age of the patient was 6 months; the degree of anæmia was only moderate: red blood cells 5·6 million, hæmoglobin 65 per cent., white blood cells 26,000, with neutrophil polymorphonuclear cells accounting for 65 and monocytes for 8 per cent. Areas of sepsis, gangrene and petechiae were present, and the duration of the illness before the fatal termination was 10 weeks. At autopsy an abscess of the axillary glands and small pea-like abscesses in the mediastinum were found, with enlargement of the spleen, liver and lymph glands. Histological examination revealed extensive proliferation of large pale histiocyte-like cells from the splenic and lymphatic reticulum and also from the Kupffer cells and marrow reticulum cells; small foci of necrosis in the midst of the cellular aggregations were found. Letterer compares his case with those of Pentmann, Borissowa, and Goldschmid and Isaac, which occurred in adults; and appears to favour an infective hypothesis of the origin of the disease. Letterer discusses Goldschmid's and Isaac's case and emphasizes the fact, in which it differed from his own, that there was hyperplasia of endothelial cells lining splenic sinuses and liver capillaries rather than of the reticular cells.

The case of Schultz, Wermber and Puhl was that of a child aged 2½ years, in which the diagnosis of von Jaksch's anæmia was suggested on clinical grounds; the objections to this diagnosis lay in a low white cell count of only 6,000, of which but 20 per cent. were lymphocytes, and normoblasts also were scanty. Petechiae were present and, with increasing anæmia, death occurred. Histological examination of the enlarged spleen revealed a proliferation of reticular cells, in which were knots of fine reticular fibrils, and necrosis had apparently supervened in the centres of the larger knots. The description of the proliferated reticular cells and an illustration of a section of the spleen reveal a great similarity between this and Case 4.

Akiba has reported the case of a female infant 10 months old, who was said to have been healthy until 1 week before admission, when fever, tonsillar sepsis, petechiae, some splenomegaly and increasing anæmia developed; death occurred after 5 weeks.
Histologically, many large proliferated cells were present in the splenic pulp and lymph glands; aggregations of these cells, in which were small necroses and clumps of streptococci, were found. Akiba concluded that these changes were reactive to sepsis, and that in rare instances a strong response of the reticular cells may take the place of the usual myeloid reaction; further, that there was no justification for regarding the reaction as leukemic in nature, and the title of aleukemic reticulosis, as suggested by Letterer, could not be applied to his case. Another case described by Podvinee and Terplan\(^8\) in a child of one year was similar in many respects to Akiba’s case and showed only moderate anæmia; it was considered to be due to some general infection of the blood stream and the reticulo-endothelial activity was regarded reactive. Krah\(^1\) published the case of a child aged 5 years, in which occurred fever, profound anæmia with leucopenia, and enlargement of the lymph glands in the presence of sepsis; great proliferation of reticulum and endothelial cells in lymph glands and spleen, and necroses and microbic emboli were found.

The only account in English of reticulo-endothelial activity in children that has come to our notice, is one by Sherman\(^1\), of an infant 11 days old, with erysipelas and jaundice. Blood culture yielded three hundred colonies of a haemolytic streptococcus in 1 c.cm. There were great swelling and proliferation of capillary endothelium of the suprarenal glands, and the reticulum cells of the spleen and marrow, with intense phagocytosis of the Küpffer cells. Guizetti\(^1\) has recorded a case of a child aged 3 months, in which there were bleeding and considerable enlargement of the spleen and liver. Histological examination showed well marked proliferation of reticulum and sinus endothelial cells similar to that of the present cases. There was also a large cyst, apparently formed in proliferated reticular tissue in the humerus. This condition was considered to have been caused by some infectious process.

There are more records of cases in adults, some of which may be mentioned briefly here in order to show that different kinds of lesions affecting the system may occur. Goldzieher and Hornick\(^2\) published two cases, one of which widely affected the bones, and the other was accompanied by pyrexia and anæmia; the authors review the subject. Wihnman’s\(^1\) recent case was somewhat similar to Goldzieher’s and Hornick’s second case. Brill, Baehr and Rosenthal\(^1\) reported three cases in adults showing marked generalized hyperplasia of the reticular cells of the lymphoid follicles, the illustrations are somewhat similar to those of glandular fever published by Pratt\(^2\) and Bland\(^2\).

While the present paper was in preparation a paper by Ross\(^2\) appeared, which reported three cases in adults under the title of reticulosis: the third case was typical of generalized lymphadenoma, and the second was a case of reticulosis resembling Goldzieher’s and Hornick’s second case and Tschistowitsh’s and Bykowa’s\(^2\) case. From the description of the first case, however, it appears very probable that it was a case of chronic aleukocytæmïc lymphadenosis accompanied by reticular reaction, and the photomicrographs show a type of lymphoblast, with somewhat large and irregular nuclei similar to those described in Part VIII (p. 303) as occurring in lymphadenosis in children. Ross favours Maximow’s views on the functions of reticular synctium, as giving origin either to cells which function as histiocytes or to cells which differentiate as parenchymatous myeloid or lymphoid cells. This view of the multipotent functions of the reticulo-endothelial system in post-natal life is discussed in another section.

Terplan and Mittelbach\(^2\) and Sachs and Wohlwill\(^2\) have published under the title of ‘lymphogranuloma,’ cases in adults, in which a general and diffuse proliferation of the reticular tissue, sometimes lacking the typical structure of Hodgkin’s disease, occurred; in some of these a tuberculous infection was present.

Roulet\(^2\) has recently put on record 10 cases of ‘retothelsarkom,’ in which invasive properties were marked, and Komocki\(^2\) has contributed similar cases to the literature. Roulet’s paper is beautifully illustrated and shows types and grades of reticular cell proliferation. Paine\(^2\) has recorded a case of hemendothelioma of the spleen. This type of case appears to exemplify a focal malignant neoplasm of the reticular cells.
ANÆMIA AND RETICULO-ENDOTHELIOSIS

Though many writers are as yet unwilling to accept the occurrence of leukæmic reticulo-endotheliosis, there is a good deal of evidence that it may occur. An example, together with a review of cases, was recorded by us recently. Further, aleukæmic types of reticulo-endotheliosis are claimed. It is not always clear what is meant by this qualification: whether simply an aleukæmic type or phase of a reticulo-endotheliosis that is essentially leukæmic (or leucotic) in type, or a reticulo-endotheliosis that is not essentially leukæmic or leucotic. Until the generalized reticulo-endotheliosis or reticuloses of obscure origin, for example, the cases of Tschistowitsch and Bykowa, have been further studied, it will be difficult to classify certain cases, just as it is still difficult always to separate cases of extreme leukocytic reaction from leucosis. Many workers, of course, would not attempt a differentiation, since they hold with Sternberg that acute leucosis is a form of reaction to severe infection. However, as suggested in our paper above mentioned, it is reasonably certain that cases of leukæmic reticulo-endotheliosis do occur and show leukæmic monocytes or histiocytes in the peripheral blood; and apart from this feature they may be identified by a widespread infiltration, as opposed to merely a proliferation, of similar cells in the tissues. It is reasonable to expect that aleukæmic forms or phases of this essentially leukæmic (or leucotic) type of reticulo-endotheliosis should occur. It appears that most of the cases in children to which reference has been made, e.g., Akiba's, are non-leucotic, but reactive in nature to some form of infection.

Classification and nomenclature.—It is thus evident that a variety of changes occur in the reticulo-endothelial system and sometimes these are more or less confined to one or more components. Some forms of activity appear to be reactive, while others are neoplastic. We may classify the morbid processes, affecting the system in the following way:

(A) Reactive.
   (i) To blood destruction.
   (ii) To sepsis and infection.
      (a) Glandular fever:—reticulo-endotheliosis of lymph glands, Pratt.
      (b) Typhoid fever.
      (c) Infection (Akiba, Sherman).
      (d) Granulomatosis:—e.g. Hodgkin's disease.
   (iii) To chemical abnormalities:—Gaucher's disease, etc.

(B) Focal neoplastic.
   Reticuloma (Roulet, Komocki).
   Hæmendothelioma (Paine).

(c) Leucotic.
   Reticulo-endothelial leucosis: leukæmic or aleukæmic reticulo-endotheliosis; or monocytic or histiocytic leukæmia.

The above sub-headings are intended to be only exemplary and not comprehensive.
The term reticulo-endotheliosis has then to serve for conditions which may differ in nature as widely as reactive hyperplasia and neoplasia. For this reason the qualification 'leucotic' is suggested for indicating a type of reticulo-endothelial activity which appears to be analogous to the leucoses. A further alternative in nomenclature for this leucotic type of reticulo-endotheliosis is the term 'reticulo-endothelial leucosis' to contrast with myeloid and lymphatic leucosis. Further, it is to be expected that leucotic reticulo-endotheliosis, or reticulo-endothelial leucosis, may be leukæmic or aleukæmic.

For certain cases the more restricted term 'reticulosis' seems more fitting (Ross, Letterer and others); but in most both types of components of the system, reticulum and sinus endothelial cells (littoral cells of Siegmund, Ross) are found to be active in greater or less degree, and, therefore, the more comprehensive term 'reticulo-endotheliosis' is convenient for general use and classification.

**Genealogy of the blood cells.**—Speculation on the origin of the blood cells is interesting and of some importance, for, if we can be certain of the source of the various types of cells we shall better interpret the changes in the peripheral blood, especially those noted by the differential count of the white cells. The present study, and those recorded in Parts IV and VIII of this series, have indicated that:

1. Immature leucotic cells usually display characters which are different in the two chief series of blood cells, i.e., myeloblasts are usually distinguishable from lymphoblasts.

2. Myelosis and lymphadenosis each present a distinctive histological structure.

3. A leucotic process is pure, i.e., histologically any given case of leucosis presents the architectural and cytological features only of its type. The cases recorded in Part VIII did not support the hypothesis of mixed types.

4. The reticulo-endothelial system shows activity in such widely different conditions as leucosis, erythroblastosis and erythronoclasia; and this can be better interpreted as reactive to, than as formative of, leucotic cells.

5. The reticulo-endothelial system when active produces histiocytes, and the blood monocytes are essentially the same type of cell.

Piney has given an excellent summary of the chief views held on the origin of the blood cells. The main contention lies between what has been called monophyletism and polyphyletism: supporters of the former creed hold that in post-natal life a cell which is multipotent in its genetic capabilities exists, and can therefore give rise to cells of different types, e.g., myeloid and lymphatic. This cell is called the lymphoidocyte or Ferrata's hämocytoblast. Naturally, in the embryo the different blood cells have a common ancestor at some period; although there is much discussion as to the relation of certain cells in the primitive blood islands, this aspect
of embryonic haemopoiesis need not detain us. The polyphyletic view holds that only unipotent stem cells are present in post-natal life, i.e., that myeloid cells are produced only from myeloid tissue, etc. Piney considers that the reticulo-endothelial tissue is multipotent but that its immediate offspring, as soon as produced, is endowed with fixed potentialities with regard to its future development, i.e., it is a myeloid, lymphatic, or other cell. Ferrata claims that tissue that is haemohistioblastic, probably the reticulo-endothelium, produces haemocytoblasts, which produce different types of blood cells and may circulate in the blood stream.

Now as regards the monophyletic view, a lymphoidocyte or haemocytoblast in an anaplastic leucosis should not show differentiation into either a myeloblast or a lymphoblast, but, if the view of its origin from reticulo-endothelium is correct, the characters would be histiocytic in type. Although the characters discerned over a range of leucotic cells have shown differences between myeloblasts and lymphoblasts, as recorded in Part VIII of this series (p. 308), it must be admitted that each and every cell did not show such distinctive features that it could be classified with certainty. But the most immature cells certainly did not display features resembling those of histiocytes or monocytes. The fact that myelosis and lymphadenosis each present a distinctive histological structure suggests that each type of leucotic cell is distinct from the other, and therefore probably unipotential in genetic capabilities. The third finding too, that mixed leucooses do not occur, though some observers, e.g., Downey, claim that they are rarely encountered, seems to have similar implication.

Of our results those which have most bearing on the subject of the genealogy of the blood cells relate to the activity of the reticulo-endothelial system (see paragraphs 4 and 5 on the previous page). In addition, we have recently recorded a case in a child, in which there appeared to be a leucosis of the reticulo-endothelial system, in which numbers of histiocytes or monocytes were produced. These cells showed no resemblance to myeloblasts or lymphoblasts, nor any tendency to develop in the direction of either. If monophyletism were true, it would be expected that such a leucosis would show cytological features less distinctive of histiocytes and a tendency to produce a histological structure of myelosis or lymphadenosis or both.

In the lymphatic follicle lymphocytes, which are one of the chief types of blood cells, are seen lying in close proximity to a component of the reticulo-endothelial system, e.g., the so-called germ centre. In such a region the study of the relationships of the two types is comparatively easy. Now a cogent argument against the formation of lymphocytes from reticulo-endothelium in post-natal life rests on the fact that the germ centres are not active in lymphadenosis, where there is a gross proliferation of lymphoblasts. Yet in conditions in which there is the greatest activity of the reticulo-endothelial, but not of lymphocytic, cells, as in erythroblastic anemia and chronic inflammation of lymphatic tissue, these germ centres also are actively proliferating.
Many of the views on the development of blood cells have been based on the alleged tracing of transition forms between recognized types of cell. This method has its uses, but is particularly open to fallacies, for in blood films or sections individual cells can usually be met that could be interpreted as transition forms between almost any types. For example, a series of cells might be chosen from most blood films or tissue sections showing 'transition' from lymphocyte to monocyte, and from monocyte to myelocyte, and thence to polymorphonuclear granulocytes. Now the appearances of the fixed reticulo-endothelial cells lend themselves readily to such interpretation: in myelosis or lymphadenosis, cells can be seen which taken individually appear to represent stages of transition from the active and swollen reticulo-endothelial cells to either myeloblasts or lymphoblasts. It is no doubt partly for this reason that active reticulo-endothelial cells in post-natal life have often been interpreted as forming the cells which lie in their neighbourhood. As has been emphasized already, the chief function of the reticulo-endothelial system seems to be somewhat different: it is that of a general scavenger, which can be expected to resent the intrusion of foreign cells and attempt to destroy them. It seems incongruous to suggest that the reticulo-endothelial system is at one and the same time both formative and destructive of immature or stem cells. An interpretation, therefore, which covers all our observations of the activity of the reticulo-endothelial system in post-natal life in the conditions of leucosis, erythroblastosis and erythronoclasis, is that this activity is reactive to the morbid process, abnormal blood cell formation or destruction. Thus the system in post-natal life cannot be regarded as a progenitor of the various types of blood cells.

In so far, therefore, as these studies bear on the subject, since we have found no evidence of an indifferent cell, the haemocytoblast, and the reticulo-endothelial system has not seemed to take part in the formation of myeloblasts, lymphoblasts, and erythroblasts, we are bound to accept a polyphyletic view of events in post-natal life, and conclude that myeloid cells are reproduced by myeloid tissue, lymphocytes by lymphatic tissue, erythrocytes from erythroblastic tissue, including normoblastic, and histiocytes and monocytes from reticulo-endothelial tissue. It may be added that the above scheme does not exclude the possibility of another line of development of the histiocyte, and fibroblasts, from the lymphocyte; this view has been put forward by Maximow, Bloom and others, and is based on careful and extensive experimental work. Evidence to suggest that the histiocyte may take part in the formation of fibrous tissue, i.e., become a fibrocyte, is not wanting in many common pathological processes, as in the resolution of inflammation, the fibrosis in a tuberculoma, etc., but, as mentioned previously, the converse change probably does not take place.

Summary of clinical features.—The four cases here presented varied considerably in their clinical features at the period of observation. It is believed that they represented different stages and grades of severity of
ere thromnoclastic (hæmolytic) anaemia. The clinical aspects of this disease have been dealt with in Parts IV and V of this series, and there remains only to consider what appears to be a chronic form, or rather end result exemplified in our fourth case. We may summarize this clinical picture by noting that the age was about two years at the time of the first observation, there was a history of prolonged anaemia, possibly from birth; there was splenomegaly with a few petechiae, and the blood examination revealed anaemia of moderate severity, with a somewhat high colour index and signs of slight regeneration on the part of the bone marrow. Thereafter the anaemia slowly increased, the haemorrhagic tendency developed so that alarming haemorrhages occurred, enlargement of the spleen and liver increased and the lymph glands became slightly palpable, and the blood-picture progressed to that of a severe asplenia of all the elements. A course such as this should at least raise suspicion that widespread reticulo-endotheliosis is supervening on chronic erythronoclastic anaemia.

Diagnosis.—This clinical picture is somewhat similar to that of Banti's disease or splenic anaemia of adult type. Clinically the age incidence is different, since Banti's disease is extremely rare in children under six or seven years of age. Hæmatemesis occurs in both conditions. In severe splenic anaemia the state of the blood is similar to that of our fourth case. Definite enlargement and hardness of the liver is somewhat in favour of splenic anaemia, whereas slight glandular involvement points towards a reticulo-endotheliosis. If splenectomy be carried out, histological examination should reveal points of difference. In three cases of splenic anaemia of adult type which we have examined pathologically there were dilated venous sinuses separated by thick well defined strands of fibrous, rather than reticular, tissue, and the cells lining the sinuses were somewhat prominent (see Fig. 17); there appeared to be some increase in reticulum cells also between the venous sinuses; Gandy-Gamma nodules were not present. Case 4 in our present series showed a proliferation which was much finer and produced separate strands and bundles of reticulum (see Fig. 12 and 18). The features of splenic anaemia correspond with those to be expected on the assumption that the cirrhotic process arises in some form of vascular disturbance especially operating in and through the venous sinuses.

The clinical course of familial hemolytic icterus (acholuric jaundice) is, of course, entirely different. Histologically there is found some proliferation of the splenic pulp cells, but our cases have shown neither the swelling nor the proliferation of reticular fibres seen in Case 4.

Lymphogranuloma (Hodgkin's disease) presents many points of resemblance even in the histological features. It may rarely be generalized, as in some cases of Terplan and Mittelbach24. Usually a pleomorphic picture is present, and some if not all of the characteristic features, giant cell formation, increase of eosinophil and plasma cells, and necrosis are found. These features, together with the usually focal nature of the disease, enable a differentiation from a case such as our fourth to be made.
In glandular fever proliferation of the cells of the reticulum and of the central follicular cells in the lymph glands is considerable and resembles that discussed above.\(^29,32\) Anaemia is, however, absent and there is no evidence of haemolysis or erythrophagocytosis; the spleen does not enlarge to any extent and the benign course assists in differentiation. The suggestion may be made, however, that cases of obscure reticulosis in adults, examples of which have been referred to, might conceivably commence with glandular fever which fails to resolve. So far as we are aware, no evidence for this has yet been produced.

The other types of reticulo-endotheliosis, e.g., storage and leucotic forms, have been mentioned elsewhere in this paper. The storage types present certain distinctive characteristics, into which there is not space to enter here. The leucotic type has been dealt with in another paper and is rare; our case showed a much more acute onset and shorter duration than our present Case 4.

Chronic or subacute myelosis and lymphadenosis may be accompanied by considerable splenomegaly and the clinical and histological features have been dealt with in Part VIII.

The above mentioned are, of course, only some of the many conditions which may be associated with considerable splenomegaly and a varying degree of anaemia, and especially diseases of parasitic origin should be considered before arriving at a diagnosis of reticulo-endotheliosis of the nature exhibited in Case 4.

Treatment.—The lines of treatment of the early and more acute stages have already been dealt with in the previous papers. The greatest hope lies in blood transfusion when anaemia is severe, though remission often sets in without obvious relation to any form of treatment, apart from general care and attention. With regard to the ultimate stage as seen in Case 4, the histological findings indicate that splenectomy might be beneficial, but this procedure might prove extremely hazardous and careful preparation of the patient would be essential.

Summary and conclusions.

1. Four fatal cases of severe anaemia in children are recorded. Clinically two were cases of acute or subacute erythronoclastic (haemolytic) anaemia; one of the chronic form of this anaemia; and one of obscure nature. All resembled in greater or less degree the so-called von Jaksch's anaemia.

2. Histological investigation after death showed widespread activity of the reticulo-endothelial system in all. This varied in type according to the duration of the anaemia. Details of the histological findings are given. In two cases abnormal erythropoiesis was present.

3. It is suggested that this reticulo-endothelial activity is reactive to erythronoclasia or blood destruction and abnormal erythropoiesis, the latter being a response to an erythronoclastic process of obscure origin.
ANEMIA AND RETICULO-ENDOTHELIOSIS

4. The syndrome known as von Jaksch's anaemia, is that of a regenerative phase, and but one of several phases, in the progress of erythronoelastic anaemia.

5. This phase may be followed by one in which the balance is upset, so that the reticulo-endothelial reaction outstrips the erythropoiesis and remains as the outstanding feature. This is accompanied chiefly by splenomegaly and an aplastic blood picture.

6. It is probable that some obscure and hitherto unclassified anæmias in children belong to this phase.

7. This and other histological studies in this series of papers suggest that reticulo-endothelial activity is reactive and not formative of blood cells. The bearing of this view on the question of the genealogy of the blood cells is briefly discussed.

9. Some recent cases of generalized reticulo-endotheliosis, chiefly recorded in the German literature, are briefly reviewed.

It is a pleasure to express my appreciation of the help given by my chief assistant, Mr. J. T. Hall, in the preparation of material, and by Mr. E. B. Brain in illustrating Parts VIII and IX; and to thank also the other members of the laboratory staff, on whom the burden of extra work has fallen.

REFERENCES.

(Articles marked * are accompanied by good illustrations.)

The above paper concludes the series of 'Studies in Anaemia' by Professor Leonard Parsons and his colleagues. The final Part on 'The haematocrit in clinical medicine' by Dr. R. Gittins has been unavoidably held over, and will appear as a separate paper next year. (Editors, A.D.C.)