OBSERVATIONS ON THE MORBID HISTOLOGY AND BLOOD CHANGES IN MYELOCYTHÆMIA.¹

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I. PRELIMINARY.

IN a recent paper (1906) we discussed the pathology of lymphatic leukaemia and chloroma.

We now propose to give an account of the histological changes found in seven cases, with brief notes of the clinical features of the first case.

We have also tabulated the results of enumeration and differential counts of the leucocytes in twenty-four cases.

The methods employed were similar to those used in our research on lymphæmia.

II. CASES.

CASE 1.

CLINICAL NOTES.—Man, æt. 40, unmarried, a boatman, began to suffer from breathlessness, and ten months before coming under observation noticed an abdominal tumour. On two occasions within six weeks of admission he suddenly developed a large hæmatoma in the back. Family history negative. No history of syphilis or alcoholism. On examination the liver and spleen were found to be greatly enlarged, the latter reaching Poupart's ligament. The cervical, axillary, and inguinal glands were slightly enlarged. There was oedema of the feet and legs. Under X-ray treatment some improvement occurred. The blood condition improved and the spleen diminished in size. The liver remained as large as ever. Patient was able to leave hospital, but returned worse in a few weeks and died.

In making differential counts some peculiar cells in addition to those corresponding to the ordinary types were noticed.

(a) Many of the myelocytes had very scanty granulation.

(b) A very large cell closely resembling the large lymphocyte, showing a large pale nucleus and deeply stained finely granular protoplasm, was present in large numbers in the later counts.

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(c) In a few instances the latter cells showed a scanty basophile (azure) granulation. Such cells could be distinguished from the myelocytes by the more basophile reaction of the granules and the deep basophile staining of the cytoplasm. Mitosis was noticed in some of these cells.

Blood Examination.

	Red Blood Corpuscles.	White Blood Corpuscles.	Hæmoglobin.
August 20, 1905. . .	2,670,000	451,875	40 per cent.
September 24, 1905 . .	2,720,000	285,625	40 ,,

(d) In many of the forms the centrosomes were large and prominent. While in the following table these cells have been separately classed (lymphoid cells), there were gradations between the basophile "lymphoid" cell, with or without granules, and the typical large lymphocytes. We therefore regard them as merely slight departures from the ordinary form of the typical large lymphocyte.

Date.	Polymorphs.	Myelocytes.	Eosinophiles.	Eosinophile Myelocytes.	Small Lymphocytes.	Lymphoid Cells.	Large Lymphocytes.	Basophiles.	Per 1000 Leucocytes.	
									Megaloblasts.	Normoblasts.
Aug. 22 . .	18	68	2	1	1	2	2	7	0	0
Sept. 24 . .	19.6	44	3	1	0.4	3	22	7	0	64
„ 28 . .	31	46	1	0.4	1	1	18	1.6	0	12
Oct. 11 . .	7	58	0.2	0	0.2	0.6	34	0.6	16	16
Marrow . .	2	47	1	4	0	0.5	45	0.5	0	15

The section revealed great enlargement of the lymph glands and spleen. The glands were firm, and felt almost gritty on cutting.

HISTOLOGY.—*Stomach.*—A good deal of post-mortem digestion. No gross leucocyte infiltration. Epithelium shed, except at bottom of crypts. Leucocytes not more numerous than normal in the mucous membrane. Those present were mainly lymphocytes and a fair number of eosinophiles. Other coats normal. No pigmentary changes. A piece of adhering omentum showed great infiltration, with leucocytes between the fat cells. The varieties present were lymphocytes, eosinophiles, basophiles, and eosinophile myelocytes. The great bulk was composed of lymphocytes.

Small intestine.—Post-mortem digestion. Much of epithelium shed. Very few leucocytes in coats. Cells in Peyer's patch comparatively scanty. The cells there were ordinary lymphocytes. In the submucosa, especially under the Peyer's patches, were numerous cells rather irregular in shape, with a small darkly stained round nucleus and large rather darkly stained eosinophile granules. The bowel content consisted mainly of shed epithelium, leucocytes,

and some organisms, with granular detritus. Many of the leucocytes were eosinophiles similar to those seen in the submucosa. No pigment was seen.

Pancreas.—A few leucocytes, mainly polymorphs, were scattered between the acini. No special aggregations.

Liver.—The whole of the lobules were broken up, and the columns of cells were squeezed into thin strands or had altogether disappeared. In a few lobules there were a few comparatively unaltered cells round the intralobular vein, which was packed with leucocytes, while the portal veins were comparatively empty. In some parts the destruction of liver cells had given rise to a fibrous change. Where the infiltration was massive there were very large blood spaces and round them masses of leucocytes, separated by strands of fibrous tissue, recalling the structure of an alveolar sarcoma. In some of these blood spaces were large giant cells with basket-shaped nuclei, and with the differentiation of the protoplasm into an outer and inner zone which is found in the giant cells of bone marrow. The portal spaces were practically free from leucocyte invasion. In the blood spaces and surrounding liver tissue the cells were mainly lymphocytes and neutrophile myelocytes with some nucleated red cells. A considerable number of cells showed mitotic figures. Passing away from these blood spaces among the liver cells more eosinophiles of both types appeared. Some of the polymorphs had markedly branched nuclei (karyorrhexis). There were very numerous phagocytes in these spaces; in some parts six or eight in one field of a $\frac{1}{2}$ oil immersion lens. In the liver cells was a fair amount of pigment. In some parts a considerable amount of this gave the iron reaction, but the incidence of this change was very partial. Among the leucocytes were masses of pigment in leucocytes and endothelium. A curious appearance noted was the presence of pigment in a cell showing a monster mitotic figure. Here and there this pigment gave the iron reaction.

Spleen.—Malpighian bodies small and indefinite. The great mass of the pulp is taken up with red blood corpuscles. Leucocytes are scanty, even as compared with a normal spleen. Eosinophiles of both varieties were present in islands around the remains of the Malpighian corpuscles. A few basophiles were seen. There were some myelocytes and a good many nucleated red cells. Polymorphs were scanty. Phagocytes were seen in fair numbers. Mitotic figures were fairly common. There was a great deal of golden brown pigment both free and in cells, leucocytes, and endothelium. This gave the iron reaction in scattered areas, notably in cells along the trabeculae and along the connective tissue fibrils. The iron pigment was often in large masses.

Kidneys.—Comparatively little affected. Infiltration principally situated round the interlobular arteries and round some of the glomeruli. There was a less amount in the medulla. Cells of the convoluted tubules and the glomeruli were normal. No pigment was seen. Parts of the organs were very vascular.

Suprarenals.—Vessels distended, but no infiltration between the gland cells. Here and there in the fat outside was some leucocyte infiltration, as seen in the omentum. No pigmentary changes.

Heart.—Vessels distended with leucocytes.

Lungs.—Vessels distended with leucocytes. Masses of black pigment and a few small granules of iron pigment were seen.

Thyroid.—Practically normal. No pigment was found.

Lymphatic glands.—Structure lost. Here and there were islands of small lymphocytes which had no resemblance to germ centres. Between these islands were cell areas composed of eosinophiles, eosinophile and neutrophile myelocytes, and in some cases these were inextricably mixed up with small lymphocytes. The subcapsular sinus was normal. No iron. In different glands the proportion of lymphocyte to granular areas differed, but there was no essential difference. A few lymphocytes showed karyorrhexis.

Hæmolymph glands.—These were unusually large, and showed the same general arrangement as the lymph glands, with the addition of red cells strewn

through the spaces. Few phagocytes ingesting cells. Some mitotic figures. A few "mulberry" cells. There was a great deal of pigment, often in large masses, lying both in cells and free. A large proportion of this gave the free iron reaction.

Thymus.—Only a few lymphocytes in fat and fibrous tissue remained.

Bone marrow.—Fat had entirely disappeared. The density of the cellular arrangement differed from place to place. There were more white cells and fewer red cells than normal. Many of the red cells were nucleated, and most of the nuclei showed curiously branched processes (karyorrhexis). Some showed polychromasia. The bulk of the white cells were myelocytes, but all other varieties were represented; many of the polymorphs showing the branching nuclear change already referred to. Giant cells were few, small, and degenerated. Phagocytes ingesting cells were present in fair numbers. Very little pigment was seen. It was mostly contained in the endothelium of the blood spaces, and did not give the iron reaction. A differential count of the marrow cells is given along with the blood counts.

CASE 2.—A Man, æt. 31 (Case 15 on p. 224).

HISTOLOGY.—*Stomach*.—Mucous membrane congested. In deeper coats were a few collections of lymphocytes.

Small intestine.—Villi digested. Epithelium well preserved in Lieberkühn's follicles. There was an excess of leucocytes in the submucosa, and there were scattered white cells in the muscular coat. The cells were lymphocytes and eosinophiles.

Pancreas.—Much digested. Vessels packed with leucocytes.

Liver.—There was fatty degeneration, especially at the periphery of the lobules. There were deposits of leucocytes in the portal spaces, and the capillaries were dilated and engorged with leucocytes, in some cases right up to the centre of the lobule. In addition to polymorphs, eosinophile and neutrophile myelocytes, eosinophiles and large lymphocytes, there were numerous large phagocytes enclosing leucocytes and red cells. A few nucleated red cells were noted. Some of the endothelium of the capillaries was greatly swollen at certain points, and contained a large amount of pigment, which gave the iron reaction. In the liver cells there was also iron pigment in very large amount at parts, but very irregularly distributed.

Spleen.—Malpighian bodies small. Pulp very congested, and contained leucocytes corresponding to those found in the blood, and some normoblasts.

Kidneys.—Congested. There were slight catarrhal changes and casts in some of the collecting tubules. There were islands of leucocytes between the medullary tubules, and in the cortex leucocyte infiltration had destroyed some of the tubules.

Suprarenals.—There were a few islands of leucocytes in the medulla, and extending along the capillaries in the cortex.

Heart muscle.—There were numerous small collections of white cells in the connective tissue between the fibres. These consisted of lymphocytes, polymorphs, and eosinophiles.

Lung.—There was fibrinous pneumonia. The cells in the exudation were polymorphs.

Cerebrum.—Normal. Vessels packed with myelocytes.

Tonsils.—Normal. Germ centres few. Lingual tonsils.—There were some germ centres in the cortex.

Lymphatic glands.—A large axillary gland showed lost structure and great vascularity. Only lymphocytes were seen. A mesenteric gland showed the usual structure with defined lymph paths. The cells were large and small lymphocytes, some eosinophiles, a few giant cells of bone-marrow type, and a few phagocytes in the lymph paths ingesting lymphocytes.

Bone marrow.—The fat had all disappeared. There were numerous neutrophile and eosinophile polymorphs and myelocytes. Red cells and lymphocytes were scanty. No giant cells were seen.

CASE 3.—A Man, æt. 40.

HISTOLOGY.—Liver.—There was great infiltration by leucocytes in the portal spaces and between the rows of liver cells. The majority of the cells were myelocytes—some in mitosis. There were some basophile myelocytes. The liver cells were pressed upon, and in many cases shrunken. There was a large amount of pigment in the liver cells and in the capillary endothelium. The endothelial cells were prominent, and projected into the blood stream. In the liver cells there was most pigment at the edge of the portal spaces, but it extended a considerable distance into the lobules. All the pigment gave the iron reaction.

Spleen.—There were no definite Malpighian corpuscles. The pulp was fibrous and the cells shrunken. There were numerous giant cells; as many as in normal marrow. Some showed degenerative changes. There was some iron pigment.

Kidneys.—There was very great leucocyte infiltration in rather discrete patches. In these patches kidney structure was destroyed. Where the tubules were present they were catarrhal and degenerated, and showed polymorph invasion. The Malpighian bodies were very fibrous. Between the layers of Bowman's capsule were numerous leucocytes. The collecting tubes were crowded together by masses of cells. There were casts consisting of granular débris. There were a fair number of giant cells in the connective tissue in the medulla. There was a fair amount of pigment in the endothelium.

Heart.—Marked brown atrophy. On the mitral valve was a fibrinous vegetation containing leucocytes and organisms.

Lung.—There were patches of catarrhal pneumonia with ordinary neutrophiles in the exudation. The capillaries were filled with leucocytes.

Lymph glands.—Distinction between cortex and medulla quite definite. Mitoses were numerous. There were many giant cells with basket nuclei lying among the lymphocytes with no red cells near. There were also large cells ingesting red corpuscles. There was some pigment here and there in the endothelium and in free cells, but none in very large masses.

Brain.—The vessels were distended with leucocytes. The lymphatic spaces seemed to contain more leucocytes than the veins, and the veins more than the arteries.

CASE 4.—Man, æt. 50.

Small intestine.—There were some large lymphocytes and some large cells containing pigment in the fibrous tissue between the gland tubules, and also in the submucosa. The pigment did not give the iron reaction. The lymph follicles showed no enlargement. There were very numerous basophiles in the muscular coat.

Tongue and lingual tonsil.—Large number of basophiles in the lymphoid tissue and submucosa.

Pancreas.—There was no infiltration. The vessels and lymphatics were full of leucocytes.

Liver.—Numerous accumulations of leucocytes were seen in scattered areas. These were very extensive in the region of the portal spaces. There were some collections in the capillaries large enough to compress the liver cells. Many of the portal veins showed thrombosis. The cell infiltrations consisted mainly of myelocytes, but there were also numerous large lymphocytes, which in some instances preponderated. These latter were always found in clumps.

There were a few basophiles and some nucleated red cells. There were a few phagocytes ingesting leucocytes. No giant cells were seen. Many of the lymphocytes had peculiar branching nuclei. Many of the endothelial cells of the capillaries were swollen and prominent, and contained large masses of iron pigment. Iron was also present in free cells in the capillaries. There was very little pigment in the liver cells, and none of it gave the iron reaction.

Spleen.—Malpighian bodies not distinguishable. Trabeculæ obscured. Pulp was very cellular. There were areas where the red cells preponderated, but the great majority of the cells were leucocytes, mainly myelocytes and polymorphs. Lymphocytes were not so numerous as in the liver. There was a fair number of normoblasts and a few phagocytes. There were granules of iron pigment in large cells along the trabeculæ, and also in the pulp in the neighbourhood of trabeculæ. The endothelial cells of the sinuses were swollen and prominent, and also contained iron pigment.

Kidneys.—There were enormous deposits of white cells scattered irregularly. There were masses under the cortex displacing and destroying the convoluted tubules, and running down the pyramids of Ferrein. The tubules were catarrhal, and many of the convoluted and collecting tubules contained casts. Many of the Malpighian bodies were almost entirely converted into fibrous tissue. The infiltrating cells were myelocytes and polymorphs, a few eosinophiles and large lymphocytes. In a few isolated areas there were masses in the kidney tubules which stained a diffuse blue with the ferrocyanide and hydrochloric acid. There were also granules of iron along the fibrils of connective tissue.

Lymph glands.—The mesenteric glands showed thickening of the capsule and septa. The gland tissue consisted of discrete nodules. Germ centres were few. The cells in the glands were mainly small lymphocytes with an occasional large one, a few polymorphs, and eosinophiles. No myelocytes. There were a few cells with dendritic nuclei. The vessels were filled with white cells. The connective tissue contained many basophiles.

Thyroid.—On one part there was an aggregation of thyroid cells full of iron pigment. Throughout the gland were large cells in the intervesicular connective tissue containing iron pigment in large granules.

Cerebrum and cerebellum.—Vessels engorged with white cells. Nerve tissue was normal.

Marrow.—The fat had disappeared. The great bulk was composed of myelocytes. The capillaries were densely packed with these cells. Among the myelocytes were islands of red cells in which some megaloblasts showing marked polychromasia were seen. There were very few normoblasts. There were a few basophiles. Large phagocytes were numerous. Giant cells were few and degenerated. There was no pigment.

CASE 5.—A Man, æt. 44, who had an enormously enlarged spleen. No enlargement of lymphatic glands.

Blood Condition.

	Red Cells.	Hæmo- globin per Cent.	Leuco- cytes.	Poly- morphs.	Myelocytes.	Lympho- cytes.	Eosino- philes.
Sept. 28 .	2,184,000	50	130,000	69	26·5	3·5	1
Oct. 9 .	2,000,000	50	81,450	70	25	4	1
„ 15 .	2,070,000	54	36,000	91	3	5	1
„ 20 .	2,300,000	60	6,200	75	5	20	0
Nov. 3 .	2,100,000	40	2,400	62	7	31	0

In a long series of differential counts only one nucleated red cell, a normoblast, was ever seen.

HISTOLOGY.—*Small intestine.*—Epithelium largely shed. Villi short. Lieberkühn's glands well preserved. Eosinophiles were numerous in the mucosa and submucosa, but there was no crowding with leucocytes.

Vermiform appendix.—The interior was completely converted into fibrous tissue, in which were a few collections of myelocytes, eosinophiles, and lymphocytes.

Pancreas.—Healthy, except for some leucocyte infiltration round the larger veins.

Liver.—Leucocyte infiltration round the portal spaces, and to a less extent between the rows of liver cells. The liver cells were healthy, except for a great inequality in the size of their nuclei. There was a large quantity of iron pigment in the capillary endothelium, and in the liver cells towards the periphery of the lobules.

Spleen.—Malpighian bodies indistinct. There were some old infarcts. Many leucocytes in the pulp. There were several giant cells much degenerated. There was a considerable amount of iron pigment in large cells and lying free in the pulp.

Kidneys.—Kidney substance was healthy. Leucocyte infiltrations were noticed in the connective tissue under the capsule, along the vessels, and also scattered indiscriminately. Myelocytes, lymphocytes, polymorphs, and eosinophiles were present.

Suprarenal.—A few small groups of leucocytes were seen in the cortex.

Lymph glands.—A small inguinal gland showed normal structure. A large axillary gland showed lost structure, and in certain parts groups of myelocytes and eosinophiles, as well as lymphocytes. A mesenteric gland showed structure obliterated by crowded lymph paths. The blood vessels were congested. The capsule was invaded with myelocytes and eosinophiles. In a hæmolymp gland there was a great deal of pigment among the lymphocytes, not in the lymph paths. There were numerous large phagocytes in the lymph paths and under the capsule.

Cerebrum.—Healthy; no infiltrations.

Bone marrow.—Very little fat. The great majority of the cells were myelocytes. Eosinophiles were not very numerous. Red cells few, but a large percentage were normoblasts and megaloblasts. Giant cells were few and degenerated. There was some golden brown pigment here and there.

CASE 6.—Male, æt. 42.

HISTOLOGY.—*Stomach.*—There was some post-mortem shedding of the epithelium. Throughout the coats was an excess of polymorphs, lymphocytes, eosinophiles, and myelocytes. In the submucosa eosinophile myelocytes were numerous, and there were some basophiles with large dropsical-looking granules. There was no iron reaction.

Pancreas.—Healthy.

Liver.—There was slight leucocyte infiltration along the portal tracts. The leucocytes were of all varieties, including some very large lymphocytes. There were no giant cells and no phagocytes. At the periphery of the lobules the liver cells were rather atrophic, and contained a large amount of iron pigment.

Spleen.—Malpighian corpuscles were indefinite and small. Pulp was not very cellular, but all varieties of leucocytes were represented. Many normoblasts were seen at parts. Areas along the capsule and trabeculæ showed granular and rod-shaped masses of iron pigment. There were also areas

showing a network-like deposition of iron pigment in the pulp, possibly due to deposition along fibrin threads in old hæmorrhages.

Kidneys.—There was a fine infiltration of cells along the tubules, and some catarrh and congestion. There was no iron reaction.

Suprarenals.—There were a few scattered collections of leucocytes in the medulla.

Heart.—Healthy.

Lungs.—There were patches of catarrhal pneumonia. Only polymorphs occurred in the exudation.

Tonsils.—These were practically normal. There were no germ centres.

Lymph glands.—There was no definite gland structure. A few myelocytes and eosinophiles were seen among the lymphocytes. No iron. A mesenteric gland showed an old caseous nodule.

Bone marrow.—The fat had all gone. Except for an increase of eosinophiles, the leucocytes seemed in normal proportions. There were no phagocytes. Giant cells were much degenerated. There was no iron.

CASE 7.—Man, æt. 60.

HISTOLOGY.—Tongue.—Healthy.

Intestine.—Mucous membrane rather atrophic. Peyer's patches small, and composed entirely of lymphocytes.

Pancreas.—Healthy.

Liver.—There were a few myelocytes and other granular cells between the rows of liver cells, and a small number of polymorphs and myelocytes in some of the portal spaces. The liver cells were healthy. Here and there they contained iron pigment in small quantity.

Spleen.—Malpighian bodies indistinct. Some infiltration of pulp, with myelocytes and other granular cells. There were some granules of pigment which did not give the iron reaction.

Kidneys.—Practically healthy. Excess of leucocytes in the vessels.

Heart muscle.—Healthy.

Lungs.—Patches of catarrhal pneumonia and emphysema. Cells in exudation were polymorphs and catarrhal cells.

Medulla oblongata.—Increase of granular cells in the vessels.

Lymph glands.—There were very large phagocytes ingesting lymphocytes in all the lymph paths. There were a few basophiles and eosinophiles.

Bone marrow.—Fat had practically all disappeared. The most numerous cells were myelocytes and coarsely granular cells. Polymorphs were numerous. Lymphocytes were few. Nucleated red cells were numerous. No giant cells were seen. Phagocytes and pigmentary changes were not found.

III. SUMMARY OF CHANGES FOUND.

Alimentary canal.—In none of the six cases in which sections were examined were there accumulations of white cells sufficiently large to affect the structural arrangement. In only two cases was there any excess of cells, and these were mainly found in the sub-mucosa.

Liver.—A prominent feature was the invasion of the portal spaces and hepatic capillaries with leucocytes. The packing of the portal spaces with blood cells was considerable in all the cases, with one exception; but the cellular excess in the capillaries varied very greatly in degree. In Case 1, while the portal spaces were not invaded, large

areas of liver tissue were rendered unrecognisable by the capillary engorgement. Myelocytes and other granular cells usually preponderated, but large lymphocytes were also present in large numbers in Cases 1, 2, 4, and 6. The liver cells were compressed, and atrophied wherever the capillary engorgement was great; but definite fatty degeneration was only found in one case. In only one case (1), that in which the capillary engorgement with white cells was most massive, were giant cells found. Normoblasts were numerous in the capillaries in three cases. Large phagocytes, ingesting red and white cells, or containing pigment, were found in the first four cases. Pigment in varying amount was present in the liver cells in all the cases, and gave the free iron reaction in six cases, but in none to so great an extent as in pernicious anæmia or acute lymphatic leukæmia.

Spleen.—In every case the Malpighian corpuscles were small. The pulp in six cases was packed with leucocytes as an outstanding feature. In Case 1 leucocytes were scanty, the pulp being congested; and in Case 3 it was fibrous. Nucleated red cells were present in fair numbers in five of the cases. Giant cells were numerous in two cases. Phagocytes ingesting red cells were found in three cases in varying numbers. Pigment was found in seven cases, and in six of these gave the free iron reaction.

Kidneys.—Catarrhal changes were present in four cases. In six cases there were white cell infiltrations, in some instances destroying the tubular structure. Giant cells were associated with these in one case. The epithelium of the tubules contained pigment in two cases. In one of these the iron reaction was present.

Lymphatic glands.—In four cases there was infiltration of the glands examined to such an extent as to obliterate their structure. Although a larger number of granular cells than normal was present, the bulk of the cellular excess was lymphocytic. An old caseous nodule was found in Case 6.

Hæmolymph glands.—In only two cases were these structures recognisable as such. Both showed lost structure and pigmentary changes. One case showed the free iron reaction.

Bone marrow was examined in six of the cases, having been lost in Case 3. In all it was definitely myelocytic, but eosinophiles were also a striking feature in Case 6. In two cases the proportion of cells other than myelocytes was insignificant. In the remaining four cases the bulk of cells other than myelocytes consisted of red cells. Normoblasts were present in all of the cases; megaloblasts in two of them. Phagocytes were seen in two cases. Pigment was present in two cases, and gave the iron reaction in one of them.

The main features of the cases are summarised in the following schedule:—

Number.	Sex.	Age.	Alimentary Canal Cellular Excess.	Liver.					Spleen.					Kidneys.				Glands.			Hæmolympth Glands.			Marrow.									
				Infiltration.	Fatty.	Normoblasts.	Giant Cells.	Phagocytes.	Pigment.	Malpighian Corpuscles.	Pulp.	Normoblasts.	Giant Cells.	Phagocytes.	Pigment.	Catarrh.	Infiltration.	Giant Cells.	Pigment.	Structure lost.	Giant Cells.	Pigment.	Structure lost.	Phagocytes.	Pigment.	Type.	Second Type.	Megaloblasts.	Normoblasts.	Giant Cells.	Phagocytes.	Pigment.	
1	M.	40	0	++	0	+	+	++	I	Small Red	+	0	+	I	0	+	0	+	0	0	I	+	I	Mye- locyte	Red	0	+	Few	+	+	I		
2	M.	31	+	++	+	+	0	+	I	Leu- cocytic	+	0	0	+	+	0	0	+	+	+	+	+	+	Mye- locyte	Red	0	+	0	0	+	+	0	
3	M.	40	-	+	0	0	0	+	I	Red	+	+	+	I	+	+	+	0	+	+	+	+	+	Red	Red	+	+	+	+	+	+	+	
4	M.	37	0	+	0	+	0	+	+	Red	+	+	+	I	+	0	I	0	0	0	+	+	+	Red	Red	+	Few	+	+	+	+	+	
5	M.	44	0	+	0	-	0	0	I	Red	+	+	+	I	+	0	0	+	+	0	+	+	+	Mye- locyte	Mye- locyte	+	+	+	0	+	+	+	+
6	M.	42	+	+	0	0	0	0	I	Red	+	+	+	I	+	0	0	+	+	0	+	+	Mye- locyte and Eo- sino- phile	Red	0	+	+	+	0	0	0	0	
7	M.	60	0	+	0	+	+	+	...	Red	+	+	+	I	+	0	0	+	+	+	+	+	Mye- locyte	Mye- locyte	0	+	+	0	+	+	+	+	

IV. BLOOD COUNTS.

The following table shows the result of enumeration and differential counts of the leucocytes in twenty-four cases made when the patient first came under observation :—

No.	Sex.	Age.		Polymorphs.	Large Lymphocytes.	Large Mononuclears.	Small Lymphocytes.	Eosinophiles.	Neutrophile Myelocytes.	Eosinophile Myelocytes.	Basophiles.	Per 300 Leucocytes.	
												Normoblasts.	Megaloblasts.
1	M.	43	...	37	3	7	0·3	5·6	34	4	9	0	1
2	F.	28	350,000	48	4·6	2·4	1·2	0·9	32	3·2	6	1	0
3	F.	21	412,000	24	3	6	1	8	53·7	3	1	0	0
4	M.	45	210,000	26	7	4	0	7	53	2	1	6	3
5	M.	50	...	58	0·5	1·5	0·5	0·5	36	2·5	0·5	3	1
6	F.	47	170,000	10	15	1	0·5	5	65	3	0·5	0	0
7	F.	39	470,000	61	0	0	0·5	0·5	37	0·5	0·5	22	10
8	F.	32	500,000	53	3·5	1·5	1	4	24	0·5	12·5	2	2
9	F.	37	400,000	64	1·5	1	1·5	6	15	4	7	5	0
10	F.	23	8,000	42	19	3	6	4	13	1	12	6	12
11	M.	33	116,562	50	4	0	1	1·5	41	2	0·5	7	7
12	F.	35	380,000	66	4	8	1·5	0·5	18	1	1	3	0
13	M.	40	451,875	18	2	2	1	2	68	1	7	0	0
14	M.	42	238,000	41	23	4	4	6	11	2	9	6	6
15	M.	31	320,000	66	4	3	1	1	20	5	0	2	4
16	M.	51	136,000	77	3	6	3	2	2	1	6	2	0
17	M.	50	640,000	37	3	3	1	1	47	8	0	6	3
18	M.	37	580,000	33	12	4	4	2	26	5	14	18	12
19	M.	29	450,000	60	3	2	4	3	24	2	2	9	9
20	M.	13	212,000	49	15	5	2	3	15	5	6	0	0
21	F.	9	130,000	32	15	7	3	5	22	3	13	6	33
22	M.	60	...	64	2	1	0	5	27	1	0	6	18
23	F.	7	59,000	53	13	3	3	3	22	2	1	9	14
24	F.	42	420,000	48	10	3	1	3	16	4	15	0	0

As will be seen, the numbers of the total counts of leucocytes in the twenty-four cases cited are generally within the usual limits of from 200,000 to 500,000. The one case which has a really low count was in complete remission at the time. The striking point which comes out in the study of the percentages is their extreme variability in different cases, and, though this does not appear in the table, in the same case at different dates. Thus we find the following variations :—

Polymorphs	10	to	77	per cent.
Neutrophile myelocytes	2	„	65	„
Lymphocytes (all sorts)	3	„	13	„
Eosinophile polymorphs	0·5	„	8	„
„ myelocytes	0·5	„	8	„
Basophiles	0·5	„	15	„

This marked variability was pointed out by Ehrlich long ago, and, like him, we do not find that the alteration of percentages corresponds to any noticeable clinical differences or pathological variations. The difference in the individual case may be illustrated by taking the first one, in which, on four separate occasions, the percentages were as follows :—

Polymorphs	18	19	31	7
Myelocytes	68	44	46	58
Lymphocytes	2	30	18	34
Basophiles	7	7	1·6	6

The striking point that comes out in all the counts is the number of nucleated reds, and especially of megaloblasts, which were present. The normoblasts run from 0 to 22 per 300 leucocytes; the megaloblasts from 0 to 33. Both were absent from five cases on the first examination, and in one only were no nucleated reds ever found—a chronic relapsing case which has had several remissions. This patient is now very ill indeed, and very anæmic, but in spite of that fact there are no nucleated reds to be found in the films. We did not expect to find so many megaloblasts, and they were not by any means found mainly in late cases. A count of 12 per 300 whites was found in one case where the leucocytes were only 8000, and the case was symptomatically well with a decrease in the size of the spleen. Another count of 7 per 300 whites was found in a man doing full work, whose leukæmia was discovered accidentally. In cases which we followed out, however, they seemed to increase towards the end, and curiously enough in one, at least, where this was the case, they were not found in the marrow, all the nucleated reds there being normoblasts. The highest count of megaloblasts was in a case from the Sick Children's Hospital—an instance of the well-known fact that the anæmias of childhood are specially prone to assume the megaloblastic type. It seems to us that the presence of so many nucleated reds in the blood, especially when the anæmia is not very

marked, is a strong argument against the theory of an infectious origin for the disease, and in favour of that of a bone-marrow disturbance from other causes.

We thought that it would be of interest in view of the discussions which have recently taken place as to the place of origin of lymphocytes to find what the total number of these cells per c.c. of blood was. We are, of course, strongly of opinion that most, if not all, of the lymphocytes circulating in the blood are derived from the bone marrow, and in practically all the cases which we have cited the total number of lymphocytes was enormously increased. The numbers, indeed, were so great that one could not possibly imagine them coming from elsewhere than the marrow. If we take half a dozen cases at random the totals work out in this way—

Total counts—412,000, 400,000, 8,000, 116,500, 136,000, 451,800
Total Lymphocytes—41,200, 16,200, 2,240, 5,825, 14,820, 22,590
Lymphocyte percentage—10, 4, 28, 5, 12, 5.

V. PATHOGENESIS.

Löwit's view that leukæmia is due to a *hæmamœba* is now generally discredited, though he continues to publish observations. There is no other very definite theory as to causation. Ehrlich, we presume, adheres to his theory of mixed-cell leucocytosis. A fair number of experimental observations which have been undertaken with the view of throwing light on causation have been published within recent years. Schupfer (1905) injected leukæmic blood into rabbits, guinea-pigs, and bats. The rabbits showed a leucocytosis not leukæmic in type; the guinea-pigs died, probably because the injected blood was toxic or hæmolytic; the blood of the bats showed no change, though they are sensitive to organisms of the same type as the presumed *hæmamœba*. He also injected leukæmic blood into four patients suffering from carcinoma. The results should, of course, have been positive if the disease were due to an infection with organisms circulating in the blood. The patients lived varying times after the injections. The first showed a leucopenia; the second an ordinary leucocytosis as before the injection; the third a leucocytosis with an increase of lymphocytes, as before the injection; while the fourth received blood from an acute lymphatic leukæmia, and the pre-existing leucocytosis diminished. Löwit's bodies were never found in the blood of these patients. Masetti and Rubinato (1905), working along somewhat similar lines, injected leukæmic blood intravenously into rabbits in doses of from 10 to 15 drops, and placed portions of leukæmic spleen and marrow in the peritoneum. All the rabbits died after a few days, when the tissue was used; after one or two months, when blood had been injected. The authors state that a temporary leucocytosis was produced, generally running about 10,000, once up to 50,000. Mast

cells were increased, myelocytes appeared, and sometimes normoblasts, and there was a neoplastic hyperplasia of lymphatic tissue and marrow. Marrow from these animals carried on into others caused the same appearances. No organisms were found in the blood or organs of the human leukæmics, but in the organs of the rabbits staphylococci, bacilli, and diplococci were found. They regarded the lesions produced as being due to some toxic agency which escapes bacterial and microscopical investigation. It is curious, moreover, that leukæmia is not known to occur in these animals. Weil and Clerc (1905) find that it is common in the dog, horse, cattle, and pig; rarer in the cat; still rarer in the goat, sheep, and rat; unknown in the guinea-pig and rabbit. They found that intravenous injection of the blood of a leukæmic dog into another dog was fruitless. It was also unsuccessful when the blood was injected into the peritoneum, when the leukæmic tissues were transplanted under the skin, and when blood was injected into the veins of rabbits.

For very much the same reasons as those given in our recent paper on lymphatic leukæmia we regard myelocythæmia as a useless overgrowth of marrow cells, possibly due to the disturbance of the mechanism governing cell production—something akin to sarcomatosis. The origin of the conditions may differ, since a sarcoma always begins locally, while leukæmia is probably not a localised process in the same strict sense in the beginning, though possibly the great mobility of the tissue involved may account for the early diffusion of the process. As the elements involved are mainly granular cells in myelocythæmia, and as these are more highly differentiated than the lymphocytes, the disease is less malignant, and therefore in the great majority of cases runs a more chronic course than lymphatic leukæmia.

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