THE EARLY STAGES OF LEUKAEMIA.

by

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Thesis for the Degree of M.D.

Of recent years there has been a growing literature on the subject of leukaemia in its earlier stages, and it is becoming apparent that conditions formerly thought to be separate entities, are actually unusual manifestations of a well recognised type. Thus the classification and nomenclature tends to become simplified, and terms such as "leucanaemia" and "mixed leucaemia" are passing into disuse, although such a horror as "aleukaemic leukaemia" still survives to offend the aesthetic sense. The difficulty remains that apparently the marrow may be the seat of a leukaemic process before the blood is affected.

But although more attention is being paid to these early cases, the literature available is still very small as compared with that on fully established leukaemia, partly because the early condition may pass unrecognised as such, and partly because the onset is so insidious that patients do not seek advice until an advanced stage is reached.

Six cases in all are reported herein, three acute, and three chronic. These were all admitted to the Royal Infirmary of Edinburgh under the charge of Dr Goodall to whom I am indebted for facilities to study them. Of the acute cases, two are lymphatic leukaemia, and one chloroma, the others are chronic lymphatic leukaemia, one of them occurring some years after the successful treatment of Banti's disease.

CASE I.

M.M., female, Age 26.

Occupation - Shop assistant.

Admitted, 5.11.35.

Died, 2. 1.36.

Complaint Pain in the back and abdomen, and tiredness.

History. On September 17th, 1935, the patient came home from the theatre and was seized with a pain in the back, which was diagnosed as muscular rheumatism.

She was in bed for a fortnight and thereafter never regained her former strength, being always tired and very easily fatigued. About this time the menstrual period occurred as expected, but accompanied by a dull aching pain in the right side, which she had never felt before, while the menstrual blood clotted, and was more scanty than usual. Shortly before coming to hospital, she had a sore throat, with spitting of blood, and so painful that she could hardly swallow. Since then, spitting of blood and nose bleeding occurred frequently.

The appetite remained good, but she was more thirsty than usual, and often had attacks of vomiting in/

in the morning without bringing up a great deal. There was frequency of micturition without any pain or sensation of burning, accompanied by a dull pain in the lower abdomen, which was relieved by passing water, sometimes necessary every ten minutes.

She noticed no swelling in the abdomen, and thought that she had lost weight.

Previous illnesses. Influenza two years before admission. One year later she had an abscess at the right corner of the mouth, and another over the right cheek.

There was nothing of note in the family history.

State on admission. The patient was an intelligent woman with a pale, freckled face, thin but not cachectic in appearance.

Alimentary System. The teeth were good, the tongue moist and clean, and the fauces healthy. On the soft palate, just above the uvula, there was a small haemorrhagic spot.

In the abdomen there was no abnormal swelling or pulsation, but movement was poor on respiration, especially in the upper part. The liver was greatly enlarged, extending downwards below the level of the iliac crest, and the spleen was enlarged downwards almost to the umbilicus.

Haemopoietic/

Haemopoietic System. There were no palpable lymph glands. The haemoglobin percentage was low, and the colour index above unity. The blood film showed a macrocytic type of anaemia with nucleated red cells, while the white cells were noticeably few, with an undue proportion of lymphocytes.

Urinary System. The kidneys were not palpable. There was a trace of albumin, and a few epithelial cells in the urine. No growth was found on culture.

Circulatory, Respiratory, and Nervous Systems. Nothing abnormal was found.

Radiological Examination. After Uroselectan nothing of interest was noted. The Xray film showed some calcified glands in the left side, and enlargement of the liver with displacement downwards of the bowel on the right side.

Chest: Nothing abnormal. No bone changes were seen in the lower ends of the femora.

Further Investigations.

Wassermann Reaction: negative.

Test meal: no free HCl. Otherwise not abnormal.

Venous blood - Fat: normal 340 mgs per 100 cc.

Calcium: 10.2 mgs " " "

Sugar: 94 mgs " " "

Cholesterol: 190 mgs " " "

Icteric Index: 12

Urine: No fat.

Progress Notes. In view of the severe macrocytic anaemia, the patient was treated with liver extract, but no reticulocyte response, and no improvement followed. One week after admission, she developed bronchopneumonia, with coughing of blood and mucus and a swinging temperature reaching a maximum of 103°. There was dullness on percussion over the apex and middle portion of the right lung. A report on the sputum stated that there was a scanty growth of haemolytic and non haemolytic streptococci, staphylococcus aureus and albus, and micrococcus catarrhalis. No pneumococci were found. She was given 10 cc. of 0.4 Collosol iodine intravenously every four hours, and on the ninth day after the beginning of the attack, the temperature had returned to normal. She then made satisfactory progress for a fortnight, the spleen being much reduced in size, and the haemoglobin rising steadily, but this improved state of affairs was of short duration. By 11.12.35 the spleen was again easily palpable, petechial haemorrhages had appeared on the soft palate, and the patient complained of malaise and abdominal discomfort. Petechial haemorrhages were then seen on the flexor aspects of both arms, and large patches of bruising on both wrists, while the haemoglobin percentage fell rapidly. From then onwards, fresh petechiae and ecchymoses continued/

continued to appear in the same situations, the spleen remained enlarged, palpable and tender, and the patient became weaker and cachectic. The haemoglobin continued on the downward grade and the liver remained enlarged. During this period there were several pyrexial attacks, the temperature rising to 100° or 102° without any special symptoms, except once, when the rise was accompanied by signs of perisplenitis. She gradually became weaker and died eight weeks after admission.

BLOOD CHART.

Date	R.B.C. millions	Hb%	C.I.	Reticulocytes.	W.B.C.	Lympho %	Poly %	Mono %	Myelocytes	Primitives	Megaloblasts	Normoblasts	
6.11.35	2.1	50	1.1	Very few	1400	33	41	13	0	13	2 seen	12 seen	42 white cells seen.
11.11.35	2.3	50	1	5%	1200	35	53	7	0	5	22 seen	19 seen	40 white cells seen.
15.11.35	2.88	52	.95		2400	40	54	0	0	6	20 seen	10 seen	30 white cells seen.
22.11.35	2.1	45	1		2100	36	56	2	1	5	5 seen	12 seen	58 white cells seen.
26.11.35	1.98	40	1	Very few	2200	28	60	9	0	3	2 seen	3 seen	48 white cells seen
1.12.35	2.98	60	1		2200	52	31	5	5	7	1 seen	0	62 white cells seen
5.12.35	2.8	65	1.1		3100	50	42	1	3	4	2 seen	2 seen	200 white cells seen
13.12.35	2.7	65	1.2		3000	50	42	1	2	5	2 seen	3 seen	170 cells seen
19.12.35	1.4	32	1.1	Very few	2200	Bleeding time 10 minutes.							
24.12.35	1.7	38	1.1		2600	48	44	2	1	5	12 seen	4 seen	78 white cells seen.
28.12.35	1.7	32	1.0		2800	75	15	3	0	7	3 seen	6 seen	112 white cells seen.
1.1.36	1.3	28	1.0		2100	78	12	1	0	9	1 seen	6 seen	247 cells seen

Fragility of red cells normal.
Platelet count about 70,000 throughout.

Notes on the blood chart.

The white cell counts showed that there was a relative lymphocytosis and an absolute leucopenia affecting all types of white cells.

The blood film at first sight resembled that of a severe case of pernicious anaemia. (See Appendix p.10) There were many megalocytes some extremely large, and well marked anisocytosis and poikilocytosis. Nucleated red cells were present in all stages of development, from large basophilic megaloblasts, to pyknotic normoblasts; many cells were polychromasic, and some contained Howell-Jolly bodies. Punctate basophilia was seen in a few macrocytes, and in two or three haemoglobinised megaloblasts.

White cells were very scarce. The granular cells were neutrophil mostly "stab cells" or "band cells", and bilobed polymorphs. Very few eosinophils were seen, and no basophils. In some of the films there were myelocytes in small numbers.

The lymphocytes were nearly all large, and the majority of these had rather deeply basophil cytoplasm, the chromatin in the nucleus too finely arranged for normal cells.

These primitive cells were very large, the nucleus oval, finely reticulated, with three or four nucleoli, and the cytoplasm scanty, forming a deeply basophilic/

basophilic ring. A few of these cells had a slightly paler stained cytoplasm, with a finely granular or foamy appearance.

Unfortunately the relations would not allow a necropsy to be performed, and would only assent to a puncture of the liver and spleen. The specimens were inadequate for the purpose of forming an accurate histological report, but it was possible to make out that both the liver and spleen were heavily infiltrated by lymphocytes. Little more could be ascertained from the spleen sections, but the liver showed a definite interlobular rather than an intralobular lymphocyte invasion, and no doubt was entertained about the diagnosis of lymphatic leukaemia. Before death the proportion of granular and fully developed cells was falling, and the blood picture was assuming a lymphoblastic character.

COMMENTS.

This is a case of lymphatic leukaemia, where the illness is of sudden onset, and rapid course, the main features being - tiredness, occasional small haemoptyses, intermittent pyrexial attacks, gross enlargement of the liver and spleen, macrocytic anaemia accompanied by leucopenia, thrombocytopenia, and the presence of primitive white and red blood cells/

cells in the circulation. The information derived from clinical and biochemical investigation was mostly negative, and was of little help in making a satisfactory diagnosis, at which it was impossible to arrive during the patient's life. Pernicious anaemia was at once suggested by the blood picture, and the absence of free HCl in the stomach contents, but there was only a small and transient response to liver therapy, if one may use this as a diagnostic point. No infective process could be found, and Gaucher's disease, thought to be a possibility, was excluded because there was no evidence of derangement of fat storage.

An ultimate diagnosis of acute lymphatic leukaemia was made on discovering that the liver and spleen were invaded by cells of lymphocytic type.

A case very similar both in regard to the duration and manifestations of the illness, but with an even lower leucocyte count, was reported by White and Davey[2], who identified the condition at necropsy, when they found infiltration of the viscera with lymphocytes, and regarded the appearance of the liver as characteristic of lymphatic leukaemia.

Another, published in 1894, is very fully reported, and the names "oligo-splenomegaly" and "splenic subleukaemia" are suggested as being descriptive of the/

the condition[3].

While not running the very rapid course of some of the frankly myeloblastic or lymphoblastic leukaemias, the condition proved fatal three months after the onset, and may therefore be described as acute.

CASE II.

E.B. Female, aged 72.

Housewife.

Admitted to hospital, 18.1.36.

Died, 11.3.36.

Complaint: Pain in the stomach, and tiredness.

History. About three months before admission, the patient began to notice a dull pain in the pit of the stomach, and felt that she was growing stouter. The pain increased in severity, and remained constant and gnawing, always in the same place, and never radiating, but sometimes flaring up and becoming acute for a short time. The abdomen continued to swell, and she could not endure any tight clothes round the waist because of the discomfort and tenderness, and could not lie on her left side in bed. At the same time her appetite diminished, she became breathless on very little exertion, and felt weak and tired. There were occasional attacks of nausea, but no vomiting, and the pain was not influenced either way when she took food. Her health previously had been good.

State on Admission. The patient was an elderly woman of short, stout build, with slightly cyanosed cheeks and lips.

Abdomen./

Abdomen. The spleen was enlarged to such an extent, that it filled the left hypochondrium, and made the left side of the abdomen noticeably more prominent than the right. The inferior angle of the spleen extended well beyond the umbilicus, and the anterior border and notch were easily palpable. The liver was not demonstrably enlarged.

Alimentary System. The mouth was edentulous, the tongue clean and moist, and the fauces and tonsils healthy.

Haemopoietic System. There were no palpable lymph glands.

Integumentary System. The skin was healthy, and there were no ecchymoses.

Circulatory System. The radial vessels showed signs of arteriosclerosis, the pulse was regular in time and force. The heart was not enlarged, and the sounds were healthy.

Urinary System. A trace of albumin was present in the urine.

The Respiratory and Nervous Systems were normal.

The Blood, of which the findings are recorded separately, showed an anaemia of microcytic type, and a moderate leucocytosis in which the predominating cells were/

were small lymphocytes. There were a few primitive leucocytes.

Progress Notes. The abdominal pain continued unabated, with occasional exacerbations, sometimes accompanied by a rise of temperature to 100° or 101°. In spite of iron therapy, the haemoglobin percentage fell, and she became steadily weaker. X-ray therapy was attempted, to reduce the size of the spleen, but the deterioration of her general health made it impossible to give her more than two exposures. After the first exposure she had a pyrexial attack lasting for three days, during which the temperature rose to 104°, and which was explained at the time as being due to influenza. After both exposures there was a fall in count of white cells. She gradually became weaker, and more anaemic, and signs of pneumonia appeared, the temperature fluctuating between normal and 100°, with rusty sputum, and dulness and crepitations over the base of the left lung. At this stage there was an increased leucocytosis, and a rise in the percentage of polymorphs, while primitive white cells appeared for the first time in considerable numbers. She gradually sank and died, nine days after the onset of the pneumonia.

BLOOD CHART.

Date	R.B.C. Millions	Hb	C.I.	Reticulo	W.B.C.	Lympho	Poly	Mono	Lympho-blasts.	
18.1.36	4.72	52	0.6	2%	13,600	90	8	2	One seen.	
24.1.36	4.70	51	0.5		15,400	90	9	1	0	
27.1.36	4.3	50	0.6		14,800	92	5	3	0	
31.1.36	4.2	50	.6		14,600	93	4	3	0	X-ray to Spleen
2.2.36	3.5	45	.6		11,200	90	5	3	2	
5.2.36	3.2	42	.6	5%	9,800	91	4	4	1	
10.2.36	3.5	44	.6		12,000	90	6	2	2	X-ray to Spleen
16.2.36	3.32	45	.7		5,000	90	8	1	1	
28.2.36	3.2	45	.7	2%	9,200	92	6	1	1	
3.3.36	3.1	45	.7		9,200	90	5	1	4	
6.3.36	3.15	45	.7		20,300	75	20	1	4	
9.3.36	2.8	40	.7		16,100	77	15	2	6	
10.3.36	2.8	40	.7		14,200	65	15	2	18	

Blood platelets were approximately normal in number throughout.

Notes on the cell count. During the course of the illness the leucocyte count was above normal except on one occasion, but high figures were never reached. On both occasions when the spleen was exposed to X-rays, there was a subsequent fall in the count, the first time from 14,600 to 9,800, the second from 12,000 to 5,000. During the terminal bronchopneumonia the figures were again higher. The differential counts showed a great preponderance of lymphocytes throughout, and except in the last few days, when there was a feeble attempt at a polymorphonuclear leucocytosis, a scarcity of granular cells, both relative and absolute. Primitive cells were not present in any numbers until the day before the patient died.

The Blood Picture. Of the white cells, small lymphocytes were by far the most common. They showed little deviation from the normal, with the usual darkly staining nucleus of coarse chromatin masses, and rather deep blue scanty cytoplasm, sometimes with a few azurophil granules. (See Appendix p. 11)

The large lymphocytes had a bigger nucleus than the small lymphocytes, staining more lightly, and with less coarse arrangement of chromatin. Some of them had one or two pale, ill-defined nucleoli. A few had plentiful cytoplasm, but in the majority it was more sparse/

sparse than usual. Primitive cells comprised 20% in the late films. Judging by their appearance, by the large number of lymphocytes accompanying them, and by the fact that the peroxidase reaction (Beacon and Goodpasture) was negative, they were lymphoblasts.

The lymphoblasts were not remarkable for their size, few being any larger than the large lymphocytes. The nucleus was round or oval, of fine reticular structure and velvety appearance, and staining a light purplish blue. Most of them had two or three pale, well defined nucleoli, while a few had as many as six. There was often a distinct non-staining perinuclear ring. They had no azurophil granules. A few were vacuolated.

Polymorphs were very scarce until the last films were made. Many of them were strikingly small, some very little bigger than red cells. These miniatures showed no abnormality, except in regard to their size, were two or three lobed, and all had neutrophil granules. (see Appendix p. 12) Only two myelocytes were seen, eosinophils were very rare, and no basophils at all were seen.

The red cells varied in size, and to a lesser extent in shape, and were small, and poorly filled. Very few normoblasts were seen, and no megaloblasts.

Diagnosis. Acute lymphatic Leukaemia.

POST MORTEM REPORT.

Haemopoietic System. The Spleen was very much enlarged, weighing 1,700 gms. as against the normal 150.

The capsule was slightly thickened and there were a few patches of perisplenitis on the surface with fibrous adhesions.

On section the spleen was seen to be of a bright pink colour, and there was no enlargement of the Malpighian bodies. A few infarcts of varying age could be seen, particularly under the surface of the organ.

The spleen did not give a Prussian blue reaction.

Para-aortic glands were all enlarged. On section these glands were seen to be pale pink in colour.

Bone Marrow The marrow from the middle of the shaft of the femur showed a pinkish colour.

Alimentary System. No abnormality was detected in the alimentary tract.

The Liver was slightly enlarged, and on section was seen to be much paler than usual. It was pink in colour and showed a mottled white appearance, there being many small white areas throughout its substance. In the middle of these areas there was a reddish dot, and/

and these were taken to be portal tracts, with peri-portal infiltration of leukaemic tissue. The liver did not give a Prussian blue reaction.

Genito-Urinary System. Both kidneys were of normal size and shape. On section it was appreciated that there was a marked increase in the peripelvic fat, with decrease in the renal parenchyma. The usual demarcation between cortex and medulla was not present.

The capsule stripped with difficulty, leaving a finely granular surface, with a few depressions, due to arteriosclerotic changes. The kidneys did not give a Prussian blue reaction.

Circulatory System.

The Heart was somewhat smaller than normal. The pericardium was smooth and glistening. The subepicardial fat was normal in amount. The myocardium was of a brownish colour, showing some degree of brown atrophy, and the endocardial surface showed some whitish areas, there being a typical thrush breast appearance.

The coronary vessels showed a slight degree of atheroma. The endocardium also showed some atheroma.

All the valve cusps were healthy. The mitral valve admitted three fingers. The tricuspid valve four/

four fingers. The aortic and pulmonary valves were competent.

The Aorta showed slight atheroma at its commencement, and marked atheroma at its lower end, where there was some ulceration of atheromatous patches with calcification.

Respiratory System.

The Larynx and Trachea were somewhat congested.

Lungs. The pleural surface of the upper part of the left lung was smooth and glistening. The pleural surface of the lower part of the lung was covered with fibrinous exudate. This lung was markedly collapsed.

On section both lungs were seen to be congested, particularly towards the bases, and there was a patchy bronchopneumonia at the base of the left lung. The left pleural sac was ¾ full of serous fluid.

HISTOLOGY.

Spleen. The Malpighian bodies were small. The pulp was packed with lymphocytes, in some areas so dense that little of the reticulum could be seen. (See Appendix p.4)

Lymph Glands. No interference with the usual structure and no undue packing of the lymph paths was noticed/

noticed. There was gross infiltration of the capsule, and surrounding fibrous and adipose tissue (See Appendix p.4).

Bone Marrow. Sections of femur marrow showed great encroachment on the fat. Throughout the section, fat cells were to be seen, but every here and there were areas barely discernible to the naked eye, but easily seen with a hand lens, where no fat cells could be seen. They were found to consist of densely packed lymphocytes, and no other cells were noticed. The transition to ordinary bone marrow was abrupt, but there was no evidence of fibrous tissue or any other structural demarcation. Surrounding the area was very active marrow, showing the ordinary mixture of cells, but the proportion of eosinophils was greater than might have been expected, and red cell activity was very slight. (See Appendix p.2)

Liver. The cells were atrophic with many areas of dilated capillaries, and some areas showing fatty degeneration. Along most of the portal tracts was a lymphocytic infiltration, and there was an excess of lymphocytes in the capillaries of the outer zone of the lobules. Nowhere could the infiltration be described as massive. There was no haemosiderin. (See Appendix p.3)

Lungs/

Lungs. Patchy bronchopneumonia in the left lower lobe, but no excess of lymphoid tissue.

Kidneys. There were some catarrhal changes in the tubes. There were some scattered areas of lymphatic infiltration between the tubes, more numerous in the cortex. No subcapsular infiltration was seen.
(See Appendix p.3)

Diagnosis. Lymphatic leukaemia.

COMMENTS.

This was an obvious case of lymphatic leukaemia, but it had several unusual features which might give rise to the question as to whether it was a really short and always acute illness, or a fatal exacerbation of a chronic leukaemia. Suggestive of a condition of long standing were the enormous size of the spleen, the absence of any haemorrhagic symptoms, and the small number of primitive cells seen in the circulation. On the other hand, the history of recent onset with previous good health, the rapid growth of the spleen, the relatively small leucocytosis, the absence of any obvious lymph node enlargement, and the swift decline in health despite energetic therapy, all point to an acute leukaemia. The history given of recent/

recent onset is not, in itself, convincing enough, for chronic leukaemia might begin insidiously without noticeable disturbance of the general health, and the spleen might already be considerably enlarged before it made itself felt, but taken with the clinical observations, and the post-mortem findings, the patient's version seems more likely to be true, than not. In the haemopoietic system the only organ in which there was gross infiltration was the spleen. The packing of the lymph glands with lymphocytes sufficiently to obscure their structure, so often found in lymphatic leukaemia of long standing, was notably absent.

There was no massive lymphoid invasion of the viscera and in the bone marrow was the remarkable picture of islands of densely packed lymphocytes surrounded by active marrow tissue, and normal fat spaces.

The pathology tends to substantiate the patient's own story, that she was in good health until three months before entering hospital, and as in the previous case the rapid downward progress to a fatal issue justifies one in calling it an acute leukaemia.

CASE III.

J.S., male, aged 34.

Butcher.

Admitted to hospital, 6.9.33.

Died, 2.11.33.

Complaint. Swellings on the back.

History. Some nine months before admission to hospital the patient on going to bed noticed by chance a painless swelling about the size of a shilling on his back. Other similar swellings appeared until about twenty were present on the abdomen and back, and in addition one on each cheek, and one on each upper eyelid, which were of later development. The swellings gave rise to no pain, unless firmly pressed upon. (See Appendix pp. 5, 6)

During this time he had lost about a stone in weight, and his appetite, previously good, had grown less.

Immediately prior to admission he had a severe attack of pain in the lower abdomen, constant and gnawing, which lasted for twenty-four hours and was not relieved by vomiting or by the bicarbonate of soda to which he resorted.

Previous/

Previous illnesses. He had neuritis of the right elbow fifteen days before admission to hospital, but otherwise could not remember anything of importance.

Habits. His habits were always temperate. He smoked ten to fifteen cigarettes a day, and took little or no alcohol.

The family history was devoid of interest.

State on admission. The patient was a man of average build, of fresh complexion, well nourished, and in fairly good general health.

Integumentary system. On the trunk, in front and behind, were twenty raised purple firm swellings, rounded or oval in shape, varying in size from half an inch to two and a half inches in diameter. Similar swellings of more recent appearance were present on each cheek and upper eyelid. On firm pressure these spots did not disappear, and slight pain was elicited.

Alimentary System. The tongue was furred; he had no upper teeth, and the teeth in the lower jaw were in poor condition.

Abdomen. The respiratory movements were diminished. There was tenderness in the upper half of the abdomen, especially in the left hypochondrium, where the enlarged spleen could be felt extending two fingers' breadth below the left costal margin. The liver was not enlarged.

Circulatory System. The heart was normal in size, and the sounds closed and pure in all areas.

The pulse was regular in time and force, of good amplitude, and well sustained. The arterial wall was palpable. Blood pressure 114/60 mm. of mercury.

Genital System. Both testicles were swollen and tender to the touch, giving him a dragging sensation in the groins.

Haemopoietic System. When the patient was first seen, examination of the blood revealed nothing pathological.

Nervous System. The knee jerks were slightly exaggerated, but otherwise nothing abnormal was found. There was no muscular wasting and no sensory impairment.

Respiratory and Urinary Systems. Nothing abnormal was found.

Further Investigations:-

The Wassermann Reaction was negative.

Blood cholesterol:- 160 mgs.%

Radiological Report. "Neither humeri nor femora give any evidence of bone lesion."

Skull: "In the left parieto-occipital region there is a small circular density, which may be, but is/

is not definitely a bony deposit. In lateral view, a tiny translucent area is noticed in the parietal region."

The examination of the blood is recorded separately.

Progress. There was gradual enlargement of the patches on the face, and the patient was most insistent that X-ray treatment be tried for the skin and testicles. It was agreed to do this, after the dangers of such treatment had been fully explained to him. Exposure to X-rays was accordingly begun on September 23rd, and the patches on the skin disappeared with dramatic speed, while the testicular swelling became much less. Six days after treatment was begun, disturbing changes in the blood were noticed. The white cell count had fallen by half, primitive cells appeared in the circulation, and a granular leucopenia was apparent. The agranulocytosis became more marked and the patient gradually sank and died five weeks after the commencement of the X-ray treatment. During these last five weeks the haemoglobin percentage and red cell count fell rapidly, and the leucopenia became extreme, the white count being only 400 per cmm. on the day of the patient's death. The last fortnight of his illness was marked by orchitis, with a raised temperature, which climbed day by day till it finally reached 106°.

Biopsy/

Biopsy Report. The section of skin showed a fairly dense infiltration of the cutis vera, immediately below the epithelium, by large mononucleated cells. In places the invasion continued downwards into the deeper layers of the skin, but not upwards into the epithelium to any extent, where only a few cells lay round the deeper papillae.

Throughout the deeper layers of the cutis vera there was a general invasion of primitive leucocytes, mostly in scanty numbers, forming a "spider's web" pattern, but here and there massed together forming discrete but not encapsulated nodules. Round the sweat glands the infiltration was more intense. In the subcutaneous tissue there were also some small areas of infiltration. The invading cells appeared to be all of mononuclear type. (See Appendix p.7)

BLOOD CHART.

Date	R.B.C. millions	Hb	C.I.	W.B.C.	Poly.	Eosin	Baso	Lympho	Mono	Myelo-blasts	Myelo-cytes	Megalo-blasts	Normo-blasts	
17.7.33	5	100	1	6.600	55.7	1.2	.8	36.8	5		.5			
21.8.33	5	100	1	7.200	53	5	0	23	18		0			
8.9.33	5.2	95	.9	5.300	57	2	0	27	14		0			Spleen two fingers breadth below costal margin
13.9.33	5.18	95	.9	6.200	62.5	0	.5	20	16		1.5			
17.9.33	5.2	98	.9	6.200	63	0	0	29	7		1.0			
19.9.33	5.1	100	1	6.800	59	3	1	26	10		1.0			
23.9.33	5.3	97	.9	6.800	61	X-ray treatment begun. A few myelocytes seen.								
29.9.33	5.29	88	.8	3.400	15.8	1.6	0	35.4	2.6	26.8	18	7	12	per 100 white cells
15.10.33	4.1	68	.8	600	16.5	2	0	74	3.5	1.5	2.5	5	22	per 100 white cells
17.10.33	3.8	64	.8	800	12	1	0	65	4	8	10	2	17	per 100 white cells
18.10.33	3.6	58	.8	950	21	2	0	67	1	5	4.0	4	20	per 100 white cells
25.10.33	3.0	55	.9	1000	18	1	.5	61	0	4	15.5	8	15	per 100 white cells
27.10.33	2.72	51	.9	1000	22	0	0	58	1.5	10	8.5	4	15	per 100 white cells
30.10.33	2.5	42	.8	500	27.7	0	0	53	.8	7.7	10.8	5	22	per 100 white cells
2.11.33	2.4	40	.8	400	5	0	0	63.3	0	10	21.7	7	15	per 100 white cells

POST MORTEM EXAMINATION.

Respiratory System. Small pin point subpleural haemorrhages were present in both lungs. On section the lobes showed marked congestion and oedema.

The Heart was of average size. The pericardial surface was smooth and glistening. Numbers of subepicardial haemorrhages were present on both anterior and posterior aspects of the auricles and ventricles. The right auricle and ventricle were about average in size. The left ventricle was slightly dilated. Numbers of subendocardial haemorrhages were present, and haemorrhages were seen to extend right through the myocardium as far as the epicardium. There was no naked eye evidence of thrush breast appearance or fatty degeneration. The valves were healthy.

The Aorta showed very early atheromatous change.

Stomach and Small Bowel. There was no evidence of haemorrhage or ulceration in the stomach, pylorus or duodenum, or in the remainder of the alimentary tract. The Peyer's patches did not show any hypertrophy. The tissue in the vicinity of these patches showed a black pigmented discolouration.

Large Bowel. No evidence of ulceration was seen in the large bowel. Some slight congestion of the mucosa was present.

The Liver weighed 2035 grms. It was of a pale reddish brown colour, and gave a positive Prussian blue reaction.

The Gall Bladder was filled with thick dark green bile.

The Spleen was considerably enlarged. Weight - 450 gms. (Normal 150 gms.) On section it was almost black in colour owing to certain amount of post mortem change. A positive Prussian blue reaction was present. The pulp was semi-diffluent in consistence.

The Kidneys were of average size. The capsule stripped leaving a smooth surface, but scattered over the surface were patches of greenish black discolouration. These varied in size from $\frac{1}{8}$ cm. to 2 cm. in diameter. On section they were seen to penetrate into the cortex in wedge-shaped areas.

The cortex was well defined from the medulla.

Testes. The left testicle was slightly enlarged. The sac of both testes was obliterated. On section the body of the left testis showed a semi-translucent appearance of the tissue. The appearances were those of oedema, congestion and haemorrhage. The tissue was more or less structureless in appearance. The right testicle did not show any abnormal appearance of the tissue.

Bone/

Bone Marrow. The marrow in the ribs appeared to be reduced in amount, and was of a dark brown colour.

The fatty marrow of the femur was partially replaced by a red erythroblastic-looking tissue, but this erythroblastic reaction did not appear to be extensive, and there was still a certain amount of fat left.

Lymphatic System. There was slight enlargement of a few cervical glands on either side of the neck. The axillary glands showed slight enlargement. On section they were of a dark brown colour, and to the naked eye appeared fibrotic. They were very firm in consistence. There was no enlargement of the mediastinal or paraaortic glands.

BACTERIOLOGICAL REPORT.

Culture from the spleen: a good growth of Bacillus Coli was obtained.

HISTOLOGY.

Bone Marrow, Femur. The greater bulk of the bone marrow was occupied by haemopoietic cells, and in some of the fields very few fat cells were to be seen. There was a marked erythroblastic reaction, and the majority of the cells were normoblasts and fully formed/

formed red cells, but a few erythroblasts were also present. There was also a well marked leucoblastic reaction, and most of the invading cells were large leucocytes of primitive type. There was a fair proportion of eosinophils. Giant cells were scanty and small.

Lymph Glands. The usual structure was almost entirely lost. The cortical follicles were scanty and very small. The bulk of the section showed uniform infiltration with primitive leucocytes, including a small proportion of eosinophils. The fibrous trabeculae at parts seemed normal, at others they were so infiltrated with red and white corpuscles as to resemble bone marrow.

The capsule and surrounding fat showed similar appearances. Parts appeared normal, others showed a dense leukaemic infiltration.

The Spleen showed a few haemorrhages into the pulp which was also the seat of leukaemic infiltration. The Malpighian bodies were small and ill-defined. There was no fibrous tissue overgrowth. There was no evidence of abnormal pigmentation.

Skin. The section showed several areas of lymphoid cell infiltration in the cutis vera, just subjacent to the epithelium. There was also some infiltration round/

round the deeper parts of the epithelial papillae by primitive leucocytes, and a few cells in the deeper layers (See Appendix p.7) of the skin in the neighbourhood of the sweat glands, but not specially associated with them. There was also a leukaemic infiltration of parts of the subcutaneous tissue. The infiltration was by no means so extensive as that shown in the tissue removed previously at biopsy.

Right Testis. The section showed an area of massive leukaemic infiltration, also active phagocytosis of red cells, and much intracellular golden brown pigment in rounded and granular masses. There were necrotic areas with large numbers of cocci. There was a marked increase in the fibrous tissue stroma.

Left Testis. These changes had advanced to a stage where the organ could hardly be recognized. The spermatogenetic cells could not be defined. There was enormous leukaemic infiltration and phagocytic activity with intercellular pigment. In the portions examined there was a moderate leukaemic infiltration throughout the capsule.

The Liver showed throughout a moderate invasion of the portal areas by large lymphoid cells. Here and there, was also some invasion of the sinusoids. The sinusoids tended to be dilated. The liver cells showed/

showed fatty degeneration which appeared to be capriciously distributed. The liver cells round the portal tracts were compressed by the infiltration. There was a moderate quantity of golden yellow pigment, some of which gave the Prussian blue reaction.

The Kidney. In the cortex there were areas of haemorrhages between the tissues, and areas where the interstitial tissue appeared to be invaded by large lymphoid cells. The kidney epithelium showed a considerable amount of post-mortem change. The medulla showed comparatively little change. There was a little brown pigment in some of the tubule cells, but no Prussian blue reaction. (See Appendix p.8)

The Lungs showed marked catarrhal and post-mortem changes, but nothing of haematological interest.

The Heart showed some haemorrhages, but no definite leukaemic infiltration was seen.

Peyer's Patches. The mucous coat appeared to be mainly necrotic due to post mortem change, and the section was chiefly remarkable for the scantiness of lymphoid tissue.

Invading Cells. The majority of the cells were large and mononucleated with slightly basophil granular cytoplasm. The shape and size of the nuclei varied, and/

and most showed a diffuse localisation of chromatin. There were also numbers of cells of the same type, but containing no granules in the cytoplasm.

In many of the sections it was difficult to make out detail, owing to necrotic changes in the organs.

Diagnosis - Chloroma.

COMMENTS.

Three phases may be observed in the course of the illness: the first lasting about eleven months, during which the blood showed no abnormality, and the patient was in fair health, but had swelling of the testes, and definite skin tumours increasing in number: the second of some seven days duration beginning after irradiation, when there was leucopenia, with many myeloblasts and myelocytes in the circulation: the third, the terminal three weeks of the patient's life, a stage of intense leucopenia, fewer primitive cells in the blood stream, and a rapidly developing anaemia.

The cause of death was an acute infection of B. Coli, responsible for the necrotic changes found throughout the body, and the intense degree of the infection was probably due to the almost total disappearance/

disappearance of polymorphonuclear cells.

Splenic enlargement was moderate, the liver was unchanged, and the lymph nodes were impalpable, but slight enlargement confined to the neck and axilla was found post mortem.

The effect of irradiation on the skin tumours was striking and is well illustrated by the photographs of sections taken at biopsy, and post-mortem. The effect on the blood stream was unfortunately equally striking, and amounted to no less than a sudden collapse of the white cell forming elements.

This case may be fairly classified as chloroma, inasmuch as there was myelocythaemia, with tumour formation. The most characteristic form is usually associated with tumours of greenish hue affecting the bones, most frequently the skull in the orbital region, and with a moderately high leucocytosis, in which primitive granular cells are numerous. In the present case, therefore, the several unusual features are, formation of new growths in the skin only, early infiltration of the testes, and leucopenia, the latter being rare judging by the few records in the literature on the subject.

According to the purists, by however much the disease may otherwise run true to type, the term chloroma cannot be correctly used, unless green pigment is present in the tumour[4], so this case would seem to find its place midway between chloroma and true myeloid leukaemia.[5]

CASE IV.

R.S. Male, aged 48.

Rabbit Catcher.

Admitted, 3.10.31.

Complaint. Swollen glands.

History. Two or three months ago, the patient noticed a lump in the right armpit, while he was pumping up a bicycle tyre, and later on found others in the left armpit, the left groin, and neck. At first hard and painless, they became softer a few weeks before his admission to hospital.

Previous History. At the age of twenty he had rheumatic fever, and at thirty-four was rejected by the Army, on account of stiffness of the right arm. He was, however, later accepted, and from 1918 until 1925 was almost continuously undergoing treatment in military hospitals for a tuberculous abscess involving the right elbow joint and causing sequestration of bone, for which he had several operations before the wound was permanently healed. He never regained his former strength, and in 1929 had pneumonia, which left him still less robust. He had always led a healthy open-air life.

Family/

Family History. His father and mother both died of cancer: his brothers and sisters are alive and well.

State on examination. The patient was an intelligent healthy man, very thin, of good complexion, and with no pallor of the lips and conjunctivae.

Haemopoietic System. Glands varying in size from an inch and a half long, to small shot-like swellings, soft, painless and discrete, were felt in both axillae, the subclavicular region on the right side, the anterior angle of the neck on both sides, and in both groins.

The spleen was not enlarged.

Blood examination.

Red blood cells 5.34 million per cmm., Hb 92%, C.I. 0.9

Reticulocytes 2.5%.

White blood cells 12,400.

The film showed a polymorphleucocytosis.

Wassermann reaction negative.

Alimentary System. Tongue and fauces healthy, no teeth except for rather carious lower incisors.

Otherwise nothing abnormal was found.

Respiratory System. On auscultation bronchial breathing with fine crepitations was heard over the upper two lobes of the right lung, and at the apex of the left lung.

The/

The percussion note was resonant and vocal resonance normal.

There was no cough or sputum.

The Circulatory, Urinary and Nervous Systems were healthy.

Biopsy of an enlarged gland suggested lymphadenoma, although a biological test made by Dr Van Rooyen was negative.

Progress Notes. An experimental application of X-rays was followed by improvement. On 19.11.31 he stated that he felt better, and the glands were smaller and softer. The leucocyte count was 13,500 per cmm., with large lymphocytes now the most numerous cells.

On readmission, 13.1.32, the glands were hardly palpable, but the spleen was enlarged to the anterior axillary line. A further course of X-ray treatment was given.

On readmission, 26.4.33, since the last course of treatment he had an attack of shingles, and several influenzal colds, but was otherwise in moderately good health, although he became tired easily. There was no change in the glands until two months ago, when he noticed that the glands on the right side of the neck, and in both axillae were increasing in size, without any/

any associated pain. At the same time there was some shortness of breath, palpitation, and dizziness. The digestion and appetite remained good, and the weight unaltered.

On examination the upper deep cervical glands on both sides of the neck were found to be enlarged, more so on the right side, where they appeared to be adherent, but not hard. They were slightly tender on palpation. The suboccipital and supraclavicular glands on each side were swollen and hard, the axillary glands, particularly the central groups, were enlarged, hard and discrete, and the sublingual glands were similarly affected. An excised gland now showed leukaemia with infiltration of the capsule. (See Appendix p.9)

The spleen was enlarged, the lower edge being about one inch below the left costal margin.

On readmission, 3.10.34. The condition of the glands had remained very much the same during the past eighteen months. The patient was suffering from a vesicular rash, later becoming pustular, on the face, arms and legs, and a large boil with associated lymphangitis on the left leg. In the early stage of the eruption, eosinophil polymorphonuclear leucocytes were found in the vesicular fluid. The condition soon cleared up, and the patient received a further course of X-ray therapy.

On/

On readmission, 15.6.36. He had been continuing fairly satisfactorily, but within the last five months had noticed that the abdomen had become swollen, that he felt increasing tiredness, and had a bad cough. More recently he had caught a severe chill, and was confined to bed for a few weeks, after which he improved greatly and felt better than for some time previously.

The liver was enlarged four inches below the ninth rib, the spleen was palpable at the costal margin, and enlarged mesenteric glands could be felt in the abdomen.

The condition of the peripheral lymph nodes was unaltered.

The patient was discharged with the cough much alleviated.

On readmission, 4.2.37. His general health had deteriorated, and he felt constantly unwell, with heaviness and distension of the stomach, but had no pain, or vomiting. He was very easily tired, exertion made his breathless, and a walk of a hundred yards was enough to make his exhausted for the rest of the day. He thought that the glands had grown bigger.

On examination, the patient was a very thin man, rather pale, with a resigned expression and weary manner/

manner, disheartened by ever recurring ill-health.

The skin was healthy, and there were no ecchymoses.

The weight had remained much the same since the beginning of the illness over five years ago.

Haemopoietic System. There were enlarged glands in the axillae, groins and neck, in the supraclavicular and sternomastoid regions. They varied from the size of a pea, to that of a walnut, were discrete, firm, and not hard.

Blood Examination.

Red blood cells, 4 million per ccm., Hb. 64% C.I. 0.8

White blood cells, 40,600.

Over 90% of the white cells were large lymphocytes.

The blood picture was one of lymphatic leukaemia.

Alimentary System. The mucous surfaces were healthy, the teeth artificial, the tongue moist with a thin white fur.

The Abdomen was uniformly distended, moving freely on respiration, and the veins on the flanks were prominent. On palpation, a doughy resistance was felt all over, without any clearly defined mass being outlined.

The liver and spleen could not be palpated.

Respiratory/

Respiratory System. The musculature was poor, emaciation contrasting strongly with the tumid abdomen. Bronchial breathing, dulness on percussion, and increased vocal resonance were heard posteriorly, just below the apex of the right lung, otherwise no abnormalities could be detected.

Circulatory and cardiovascular systems. Nothing to note.

Central Nervous System. The knee jerks were very sluggish, and only obvious on reinforcement. No other abnormalities were found.

Date	R.B.C. millions	Hb%	C.I.	Retic.	W.B.C.	Lympho	Poly N	Poly Eosin	Poly Baso	Mono	Myelocytes.	
23.9.31	5.34	92	.9	2.5	12,400	52	30	5	1	2	0	Large lymphocytes predominating.
20.11.31	5.22	92	.9		13,500	64.6	32.4	3	0	0	0	Large lymphocytes predominating.
13.1.32	5.40	86	.85		16,800	51	35	8	0	0	6	Large lymphocytes predominating.
26.5.32	5.40	100	1		11,000	58	35	6	0	1	0	Large lymphocytes predominating.
26.4.33	4.59	90	1		13,000	64	29	5	2	0	0	Large lymphocytes predominating.
30.5.34	4.32	90	1		15,200	60	30	8	0	2	0	Large lymphocytes predominating
18.6.36	4.20	80	.9	2.5	16,200	71	26	1	0	2	0	Large lymphocytes predominating.
6.2.37	4.00	64	.8	1.5	40,000	93	6	0	0	1	0	Large lymphocytes predominating.
15.2.37	3.38	61	.9		21,000	86	8	0	0	6	0	Large lymphocytes predominating.
6.3.37	3.32	62	.9		38,000	90	7	0	0	3	0	Large lymphocytes predominating.
8.3.37	3.40	62	.9		56,000	84	11	0	0	5	0	Large lymphocytes predominating.
16.3.37	3.34	62	.9	.5	47,800	95	5	0	0	0	0	Large lymphocytes predominating.

Notes on the Blood Chart. It is convenient to consider the blood chart in two parts: in the first the counts from 1931 to 1936, in the second, the counts made in 1937.

For the five years from 1931 until 1936, the blood counts show remarkably little variation, except for a slight fall in the number of red blood corpuscles, towards the end of the period. The actual figures for polymorphonuclear cells are within normal limits, and the leucocytosis is caused by lymphocytes, which form roughly 60% of the white cells. Quite a pronounced eosinophilia is shown by the actual figures.

In 1937 the leucocytosis has reached a much higher level, still due to a preponderance of lymphocytes, and by this time the actual figures for polymorphonuclear cells are reduced, though not by very much. The red cell count and haemoglobin percentage have fallen appreciably.

Notes on the Blood Picture. There was a slight secondary anaemia, the red cells were fairly well filled, and showed little variation in size and shape. No nucleated red cells were seen.

The vast majority of the leucocytes were large lymphocytes; in the earlier films of 1937, they were fairly/

fairly mature cells, with coarse chromatin masses in the nucleus, and faintly basophil cytoplasm sometimes containing a few azure granules.

As the condition progressed, the cells became much more primitive in type. They were larger, with round or oval nuclei in which the chromatin was arranged in a fine reticulum of purplish colour, against which two or three rather ill-defined white nucleoli stood out. The cytoplasm was very scanty and of a moderately deep blue colour, but in a few of the larger cells it was abundant. Probably a high percentage of these cells were lymphoblasts, but it was impossible to distinguish them accurately enough to make a differential count. They were peroxidase negative. (See Appendix p.13)

The polymorphonuclear cells were mostly two or three lobed, and of mature type. Very few eosinophils and basophils were seen. In the film a few very large polymorphs with seven or eight lobed nuclei were seen, resembling the "Type II macropolycyte" described by Cooke.[1] (See Appendix p.14) The monocytes were very large cells with plentiful cytoplasm and deeply indented nucleus. (See Appendix p.15)

Radiological Report on the Chest, 1936. "Gross tuberculosis in the apices of both lungs, but such a degree of fibrosis, that the lesion in the left lung can be taken/

taken as healed. In the right apex there is fine cavitation, so the condition cannot be considered as completely cured."

Report on Lymphatic Gland from the neck, 1937.
"The gland shows infiltration of its sinuses by cells of lymphatic type. The findings are indicative of leukaemia." The gland was packed with lymphocytes to such an extent that the normal features were unrecognisable, the infiltration extending right through the capsule into the periglandular tissue.

As an illustration of the difficulty of making a diagnosis the following two reports are included.

Gland from Axilla, 1931. "In the tissue examined no evidence of tuberculosis was seen. The normal architecture of the gland is altered, there being no evidence of germinal follicles.

"There is uniform proliferation of lymphoid tissue, but otherwise none of the typical cellular changes found in Hodgkins disease are present. There is certainly a diffuse structureless groundwork which is suggestive of lymphadenoma. Lymphosarcoma must be considered, but no evidence of invasion can be seen. "On the whole, the condition is rather more suggestive of an early lymphadenomatous condition."

Gland/

Gland from Axilla, 1933. "In the tissue examined, the normal architecture of a lymph gland has entirely disappeared. It is composed entirely of a solid mass of small round mononucleated cells. In one area, these cells can be seen to have burst through the gland capsule, and to be lying in the surrounding fatty tissue.

The appearances are much more those of a lympho-sarcoma, than those of a lymphadenoma."

COMMENTS.

The chief feature has been glandular enlargement, beginning with the accidental discovery of a swollen gland in the armpit, and increasing year by year in spite of constant treatment directed against it.

Tiredness, found so often as an early symptom of leukaemia, did not occur until the condition had been established for almost two years, at the same time that enlargement of the spleen first became obvious.

Enlargement of the liver and spleen has never been great, and when the patient was last examined they appeared to be of normal size.

In the first stage of the illness, it is extra-ordinary how little alteration there was in the con-dition of the blood, either by way of leucocytosis or by decline in the red cell count and haemoglobin percentage/

percentage. In five years, during which there was progressive glandular enlargement, and the patient's health was steadily growing worse, the red cell count only fell by one million.

Although under observation for an unusually long time, it has not been possible to identify the condition until a fatal issue is within measurable distance, and the case now presents itself as a chronic lymphatic leukaemia in the terminal stages, a diagnosis which is put beyond any doubt by the blood picture, the white cell count, and the corroborative evidence of the latest examination of an excised gland.

CASE V.

Mrs S. Female, age 62.

Housewife.

Admitted, 17.4.36. Discharged, 16.5.36.

Readmitted, 27.6.36 and transferred to a Gynaecological Ward.

Complaint. Listlessness and difficulty in swallowing, and slight shortness of breath.

History. All her life she had been bloodless, and ever since she grew up, had suffered from constant tiredness, and was very easily fatigued. This condition continued unchanged until seven years ago, when she began to have attacks of vomiting blood, and noticed that the abdomen was becoming swollen. The abdomen was tapped several times, but although this gave her temporary relief, fluid soon gathered again, and the abdomen continued to increase in size, while the haematemesis continued unabated.

She then entered hospital, where Banti's disease was diagnosed, and splenectomy performed. She made a successful recovery, and there was no return of either the haematemesis or ascites, but she found that the lassitude was worse than before the operation, and fatigue came more readily. The tiredness grew worse, and she had attacks of giddiness and was always a little short of breath on exertion, but she never fell/

fell, nor fainted. More recently she noticed that she had slight difficulty in swallowing solid food, although her appetite remained good. The complaint which worried her more than anything else, since her operation, was the constant feeling of tiredness.

Past History. She had been bloodless all her life, but otherwise had no illnesses of importance, until haematemesis began seven years ago. She had four children, of whom two died, one at two years of age from kidney disease, and the other at ten months from an unknown cause. The others were alive and well.

State on Admission. The patient was an intelligent, elderly woman of small build, fairly well nourished, and with a yellowish complexion. She was completely edentulous, the tongue was clean, moist, and atrophic, and the fauces healthy. The abdomen was flaccid, with a firm scar under the left costal margin, and no splenic dulness could be elicited. No abnormal mass or tenderness could be found, and the liver was not enlarged.

The pulse was regular in time and force, and of poor volume, and the artery wall was palpable but not tortuous.

The heart was not enlarged, and a soft blowing systolic murmur could be heard in the mitral area, not propagated in any direction.

There was well marked koilonychia.

No abnormality could be found in the respiratory, urinary, or nervous systems.

The blood findings were: a microcytic type of anaemia, with a low haemoglobin percentage, and low colour index, and a moderate leucocytosis with a preponderance of lymphocytes in the majority of counts. Primitive leucocytes were present in small numbers.

BLOOD CHART.

Date	R.B.C. millions	Hb %	C.I.	W.B.C.	Poly. Neutro	Eosin.	Baso	Lympho	Mono	Myelo-cytes	Primitive cells	Normoblasts.
19.4.36	3.7	44	.6	8,000	28	9	0	52	8	0	4	One seen
28.4.36	3.58	35	.5	8,400	40	3	0	48	7	0	3	Two seen
4.5.36	3.64	47	.6	10,200	42	0	0	55	1	1	2	0
7.5.36	3.5	45	.6	13,700	43	3	0	51	2	0	1	One seen
11.5.36	3.5	49	.7	17,200	30	3	3	49	12	0	3	0
14.5.36	3.8	52	.7	15,000	44	8	0	36	14	2	7	0
16.5.35	3.7	52	.7	12,300	49	2	0	38	10	0	2	0
23.5.36	4.4	58	.6	8,400	48	6	2	34	8	1	1	Patient discharged from Hospital.
						On readmission						
29.6.36	4.5	85	.9	5,600	52	4	1	27	15	1	0	

Blood platelets 600,000.

Notes on the Blood Chart. It will be seen that when the blood was first examined, the white cell count was but little above normal, and that during the patient's stay in hospital, a moderate leucocytosis developed, the most numerous cells being lymphocytes, which outnumbered the polymorphs by two to one in the first count. It is of interest to compare the actual numbers of these cells per cmm.

Date	Polymorphs per cmm.	Lymphocytes per cmm.
19.4.36	2240	4160
28.4.36	3360	4032
7.5.36	5891	6987
11.5.36	5160	8428
14.5.36	6600	5420

There was thus an absolute and relative lymphocytosis, while the polymorph count lay more or less within the normal range. Primitive cells, though constantly present during the patient's first stay in hospital, were never numerous. When she was discharged the blood condition had obviously improved, the haemoglobin percentage had risen, and there was less disproportion between the figures for granular cells and lymphocytes.

On/

On readmission six weeks later, there was a marked improvement, the haemoglobin having risen to 85%, the proportion of polymorphs to lymphocytes being 52% to 27%, in actual numbers, 2,912 per cmm. to 1512 per cmm., and primitive cells were absent from the blood stream.

There was a slight increase in the number of monocytes during the patient's last ten days in hospital, and also when examined on readmission.

Eosinophil polymorphs were present to the extent of 9% in the first count, and except for one other occasion their numbers were not excessive. Basophils were only found once and numbered 3%

Notes on the Blood Film. The first thing to catch the eye was the number of platelets, clumped together in large masses here and there over the film. The red cells were mainly microcytic, showing marked variation in size, and to a lesser extent in shape, and there were occasional large well filled macrocytes. Nucleated red cells were very rare, and those seen were all normoblasts. (See Appendix p.16)

An unusually large number of the polymorphs were vacuolated, mostly in the cytoplasm, occasionally in the chromatin, but they showed no other abnormality, and were in the main of mature type, with two or more lobes in the nucleus.

Large/

Large and small lymphocytes were present in about equal numbers, in all the films examined. The large lymphocytes had plentiful pale clear blue cytoplasm, with a few large azure granules, and a nucleus of masses of darkly staining chromatin.

About one cell in three was of more primitive type than the last, with scanty, darker cytoplasm, and a rather lightly stained round nucleus of finer chromatin arrangement, containing two or three well defined pale nucleoli. It was sometimes difficult to differentiate between some of these, and the frankly primitive pathological cells, than which they were usually smaller, the nucleus of coarser construction, and the cytoplasm less basophilic.

The primitive cells were large, and had a fairly copious cytoplasm of finely granular appearance, but none were noted which contained azure granules. The nucleus was round or oval, sometimes slightly indented, stained evenly a medium purple colour, with no massing of the chromatin, and with two or three clearly defined whitish round nucleoli. The chromatin was slightly condensed round the periphery of the nucleus, and there was in many a silvery perinuclear ring. No peroxidase granules could be demonstrated. They were considered to be lymphoblasts.

Progress/

Progress. During the patient's stay in hospital, there were occasional slight evening rises of temperature up to 101°, for no obvious reason. On discharge, she felt slightly less tired, had gained a few pounds in weight, and with full doses of iron had become less anaemic, but it could not be said, that she was markedly improved.

Six weeks later, she was readmitted, with vaginal bleeding, but in spite of this, she felt much better, and there was a substantial increase in the haemoglobin percentage; the difficulty in swallowing, however, still remained.

Carcinoma of the cervix of the uterus was diagnosed, and she was transferred to a gynaecological ward.

Report on Splenectomy in 1931. It is unfortunate that no clinical account of her condition six years ago could be traced, when she was in hospital suffering from ascites and haematemesis, for in view of the later condition of the blood, it must have been of great interest. A histological report on the spleen was available, however, and stated as follows:

"The/

"The sections show:

1. A thickened capsule and trabeculae.
2. Disappearance of Malpighian bodies.
3. Reticulum cell (endothelial) hyperplasia throughout the pulp.

"This is considered to be a case of Banti's disease, and the occurrence of a hepatic cirrhosis is in accordance with this view. The term splenic anaemia covers the condition."

Diagnosis. Lymphatic leukaemia.

CASE V.

The classification of this case presents difficulties owing to the previous diagnosis of Banti's disease, but looking at it as it stands, there are good reasons for calling it lymphatic leukaemia. There was a long history of tiredness, and a definitely pathological blood picture. A slight leucocytosis, on occasion reasching moderate dimensions, was present during the whole time the patient was under observation, and for this, an increase in the number of lymphocytes was almost entirely responsible. Primitive white cells resembling lymphoblasts were always present, and at their maximum of 7%, numbered 1050 p.cmm. Eosinophil polymorphonuclears were sometimes seen in increased numbers, and on two occasions, a few myelocytes.

There was also anaemia, with a reduction of the haemoglobin percentage roughly by half, the red cells being small and poorly filled, and showing much diversity in shape.

In spite of a leukaemic condition, platelets were abnormally numerous, possibly due to removal of the spleen, although no literature on the subject could be found giving an account of the blood condition so long as six years after the operation.

The history of difficulty in swallowing is hard to/

to assess, and although the association with microcytic anaemia, glossitis and koilonychia suggests the Plummer Vinson syndrome[6], it is not convincing in this case.

On admission to hospital for the second time, a month later, the patient had greatly improved, and without the first series of observations one would have hesitated to make a diagnosis of leukaemia.

CASE VI.

B.R. Female, aged 11 years.

Admitted to Hospital 19.1.37.

Discharged 18.3.37.

Complaint, Shivering and frequent sickness.

History. About eight months before admission to hospital the patient began to complain of cold, and shivering. Her mother noticed that she had become paler than usual, and as the shivering was no better, the family doctor was summoned, and she was put to bed for three weeks. When she got up again, there was some little improvement, but the shivering still persisted, and in addition she began to have attacks of pain in the right side of the abdomen. From then onwards her health steadily deteriorated; she lost her appetite, had frequent attacks of sickness and vomiting, and became listless and easily fatigued. A few bright red spots of blood were noticed on one occasion after she had vomited, but apart from this there was no sign of any tendency to bleeding.

Previous Illnesses - Measles. When five years of age she was very pale for about two months, and complained of sickness and pain above the eyes.

Family History. Father and mother alive and well.

One/

One sister, aged fifteen, in good health. One brother, aged five, in good health, but always pale. The paternal grandmother had rather a yellow complexion. Three paternal aunts were very pale, but never jaundiced.

State on admission. The patient was a well developed girl, tall for her age, rather thin, very pale and highly emotional.

Alimentary System. There was extreme pallor of the mucous surfaces. The tongue was moist, with a thin white fur. The teeth were good.

The Abdomen was of normal contour, and moved freely and evenly on respiration.

There was no tenderness, and no rigidity of the muscles, through which the spleen was easily palpable, the lower border half way between the costal margin and the umbilicus, and the anterior border almost in the mid line. The liver was not enlarged.

Cardio Vascular System. The pulse was 120 to the minute, soft and of poor volume, and regular in time and force, except for occasional sinus arrythmia.

Heart was not enlarged. A soft blowing systolic murmur was heard in the mitral and pulmonary areas. The second sound was closed in all areas.

Respiratory/

Respiratory System. Myotatic irritability was present, and the vocal resonance was increased on the left side posteriorly below the apex. Nothing else abnormal was found.

Urinary System. An increase ofurobilin was proved with diazo reagent. Otherwise there was nothing abnormal.

Central Nervous System. The patient was intelligent, and very emotional, with quickly changing moods of elation and depression.

Further Investigations:-

Van den Bergh Test: Direct Test - negative

Indirect Test - positive.

Bacteriological Report. The Widal reaction was negative. There was no agglutination of B. Typhosus, B. Paratyphosus A or B, or B. Abortus in serum dilutions of $\frac{1}{32}$ upwards.

Haemopoietic System. Red blood cells, 1.14 millions per cmm. Haemoglobin 20%. Colour Index 1. Reticulocytes 15%. Leucocyte count 2000 per cmm. The blood film showed anaemia of macrocytic type, with much variation in size and shape of the red cells, some of which were well filled, while in others there was only a small ring of colour round the margin of the/

the cell.

Leucocytes were abnormally few, and the majority were polymorphonuclears. The number of platelets was reduced. The appearance of the film suggested severe pernicious anaemia. The fragility of the red cells was found to be approximately normal.

Treatment. On admission the patient was immediately transfused with half a pint of Group IV citrated blood.

Progress Notes. After the blood transfusion the haemoglobin percentage was a little higher, but the arm used for the operation became swollen and tender, and what was probably a venous thrombosis went on to pus formation, with cellulitis of the upper arm. The arm was incised, pus evacuated, and the wounds later healed without any trouble. This attack of cellulitis caused a high temperature and rapid pulse for seven days, during which the anaemia became very severe, the red cell count dropping to 630,000 per cmm. and the haemoglobin to 18%.

Treatment by liver extract intramuscularly, and iron by mouth was then given, and the patient steadily improved, for the space of three weeks. When the haemoglobin had reached 45% the response ceased, and she began to go downhill; the spleen gradually enlarged until its lower border reached the level of the umbilicus, and the anaemia became worse. A

second/

second blood transfusion made a slight improvement lasting for a few days, but she continued to grow weaker and more bloodless, and a large number of primitive leucocytes were seen in the blood film, the white count having risen to 20,000. Her condition by now appeared to be without hope, all treatment had proved fruitless, and as she was very restless and irritable her parents were allowed to take her home, where she died three days later.

BLOOD CHART.

Date	R.B.Cs. Millions	Hb%	C.I.	Reticulocytes %	W.B.Cs Thousands	Lymphocytes	Polymorphs Neutrophil
19.1.37	1.14	20	1	15	2000	46	46
21.1.37	1.4	26	.9	7	3100	44	51
23.1.37	1.09	22	1.1	10	3500	38	59
25.1.37	.630	18	1.5	1	3350	27	67
29.1.37	.720	18	1.3	8	3400	32	63
2.2.37	1.01	23	1.1	12	3100	27	65
6.2.37	1.07	24	1.2	6	3000	28	63
8.2.37	1.4	25	.9	6	3400	21	73
12.2.37	1.45	26	.9	10	3000	15	77
14.2.37	2.04	32	.8	5	3000	29	62
16.2.37	2.31	45	.9	8	2900	34	55
23.2.37	1.78	40	1.1	4	3180	37	55
26.2.37	2.0	40	1	1	5000	71	19
28.2.37	1.98	32	.8	2	7200	51	34
4.3.37	1.80	30	.8	3	15100	47	27
7.3.37	1.15	26	1.1	1	20400	41	22
10.3.37	1.01	20	1	1	14900	42	20
11.3.37	.890	16	.9	1	4000	56	16
12.3.37							
13.3.37	1.1	18	.9	$\frac{1}{2}$	4200	51	23
17.3.37	.610	15	1.2	$\frac{1}{2}$	4800	45	20

Polymorphs Eosinophil	Polymorphs Basophil	Mono-cytes	Myelo-cytes	Primi-tives	Megalo-blasts	Normo-blasts	
1	0	2	2	3	1 seen	2 seen	Transfusion
0	1	3	1	0	0	2 seen	
1	0	1	1	0	1 seen	1 seen	
2	1	0	3	0	0	2 seen	
2	0	1	1	1	1 seen	1 seen	
0	0	4	0	4	1 seen	1 seen	
2	0	5	1	1	0	0	
1	1	4	0	0	0	1 seen	
2	1	4	0	1	0	0	
1	0	3	1	4	1 seen	1 seen	
1	1	6	0	3	1 seen	1 seen	
1	0	2	1	4	2 seen	2 seen	
0	0	2	1	7	2 seen	1 seen	
0	0	4	0	11	0	2 seen	
0	0	5	1	20	0	0	Two plasma cells seen
0	0	8	1	28	0	0	
0	0	2	0	26	0	0	One plasma cell seen
0	0	14	2	12	0	1 seen	
							Transfusion
1		6	2	17	1 seen	0	
0	1	4	2	28	1 seen	0	

Notes on the Blood Chart.

When the patient was first seen, there was leucopenia, and a relative lymphocytosis, the actual figures being 960 lymphocytes per cmm. and 960 polymorphonuclears per cmm. In response to the cellulitis there was an increase in the number of polymorphonuclears which reached a peak of 77% three weeks after the beginning of the attack, but although the relative proportion of granular cells to lymphocytes was approximately normal at this time, the total count was still leucopenic. This stage was of short duration, and the lymphocytic predominance became re-established, the leucocyte count began to rise, and primitive cells were found in increasing numbers, reaching a maximum of 28% of a total count of 20,400. In four days' time the patient was again leucopenic, and on the day of discharge the figures had fallen to 4,800 of which 28% were primitive.

Reticulocytes were fairly numerous when the patient was first admitted, and for about five weeks afterwards, but when the anaemia again became pronounced they were fewer, and for the last ten days were never more than 1%. The number of nucleated red cells seen was remarkably small considering the severity of the anaemia.

The blood film resembled a severe pernicious anaemia/

anaemia (see Appendix p.17). The cells varied greatly in size and shape, the majority being well filled, and larger than normal, contrasting strongly with smaller cells, containing so little haemoglobin that they gave the impression of being merely empty shells. Many showed polychromasia and a few were seen with punctate basophilia. Nucleated red cells were very scarce, surprisingly so in such a severe anaemia, and those seen were either normoblasts or haemoglobinised megaloblasts.

The number of platelets was reduced.

In the early films the majority of the white cells were large lymphocytes of mature type, with abundant cytoplasm, and nucleus consisting of masses of darkly stained chromatin. Later, polymorphonuclear cells temporarily predominated, and they were mostly bilobed, or band cells. Eosinophils and basophils were infrequent. A few myelocytes were seen.

Primitive cells were present in most of the films, latterly in comparatively large numbers. They varied considerably in size, a few being little larger than small lymphocytes, from which they were fairly easily distinguished by the appearance of the nucleus. Most of them were large cells with a thin ring of deeply basophilic cytoplasm, sometimes containing a few azurophil granules. The nucleus was large, round/

round or oval, sometimes slightly notched, and the chromatin was arranged in a fine network containing several pale nucleoli. They were considered to be lymphoblasts, a view supported by the fact that the majority of them were peroxidase negative; the few exceptions were in all probability stray myeloblasts appearing in the midst of a lymphoblastic reaction.
Diagnosis - Lymphatic Leukaemia.

COMMENTS.

In this case the onset was insidious with weakness and increasing pallor, later accompanied by sickness and vomiting, but with no haemorrhagic symptoms either in the skin or mucous surfaces. When the patient was first brought under observation there was profound anaemia of macrocytic type with leucopenia and relative lymphocytosis, and a few primitive leucocytes in the blood stream. The spleen was moderately enlarged, the liver of normal size, and the peripheral glands were impalpable, remaining so throughout the course of the illness. The result of liver therapy was disappointing, and the patient gradually became weaker and more anaemic, a second blood transfusion making no appreciable difference. A leucocytosis of short duration, accompanied by the appearance of numerous lymphoblasts, was followed by a terminal leucopenia.

The scarcity of nucleated red cells throughout and the steady diminution of reticulocytes almost to vanishing point, showed that the marrow was already in a severe state of exhaustion when the patient was admitted, and later became quite aplastic.

When first seen the diagnosis of this case was difficult. The appearance of the blood film suggested severe pernicious anaemia, but strong evidence to the contrary was the poor and temporary nature of the response to liver therapy. Acholuric jaundice was also considered, and careful inquiry was made into the family history, without eliciting any helpful information, however; the normal fragility of the red cells, absence of temperature, and steady decline in the number of reticulocytes were also against this diagnosis. The ultimate appearance of a definitely leukaemic blood picture solved the problem.

The general features are very similar to Case I; in both there was severe anaemia of macrocytic type at first responding a little to treatment and then becoming steadily worse, leucopenia, primitive cells in the blood stream, enlarged spleen, and absence of lymph gland enlargement. The chief differences are of degree. In this case the process was much slower, the illness lasting for fully ten months, so that it cannot be called an acute condition, and must be classified as chronic lymphatic leukaemia.

Discussion./

Discussion.

Gulland states that the starting point of the leukaemic process may be either outside the bone marrow, or in the marrow itself[7]. If outside the marrow, the acuteness or chronicity of the case depends on the time when the marrow is involved, and the speed with which the marrow space is filled by invading cells; if inside the marrow the course is rapid, and the disease of acute myeloblastic or lymphoblastic type. It is not intended to discuss the pathology of leukaemia to any extent, or the various theories as to its etiology, but this simple explanation of the mode of onset accounts for the variations which may occur in the early manifestations of leukaemia, better than any other.

The haematology and histology of the infiltrated organs show that Case II was a lymphatic leukaemia, and a point of great interest is that the only lymph glands which were invaded were in the paraaortic group. The structure of the glands was not altered, (see Appendix p.4), the lymph paths were clear, and the infiltration not intense, in fact the microscopical appearance did not suggest that this small group of glands could be the starting point of the process.

In the marrow there was great encroachment on the fat spaces, caused by densely packed lymphocytes which formed/

formed islands, separated by areas of clear fat spaces, and relatively healthy tissue, where the chief activity was in the production of granular cells, red cell formation being slight. These findings suggest that the focus of origin was more likely to be in the bone marrow than in the lymph nodes (see Appendix p.2). The bone marrow was not so heavily invaded that there was much disorder in red cell production, and the number of nucleated red cells seen in the circulation was never large, nor was it sufficient to inhibit entirely the granulocyte forming tissue, which, though functioning in a feeble manner, still had enough reserve of energy to show a reaction when pneumonia set in. The patient was an old lady without much resistance to infection, and died before the condition progressed further, but had she survived long enough, it is probable that more intense irritation of the red cell forming tissue would have resulted in a megalocytic anaemia, with a colour index above unity, greater diminution in the number of granular cells, and haemorrhagic symptoms due to thrombocytopenia.

Case I was a similar type of lymphatic leukaemia, and though the histology is a matter for conjecture, the general course of the illness, and the absence of general lymph gland enlargement, suggest that it was much the same as in Case I, but that the bone marrow infiltration/

infiltration was more acute. This is shown clinically by the marked irritative reaction of the red cell forming elements, and the early disappearance of granular cells and thrombocytes from the circulation. Cases I and II may be regarded as lymphatic leukaemia, where the proliferative process has begun in the marrow, the red cell and granular cell forming tissue has become speedily encroached upon, and the disease has therefore run an acute course.

Tiredness and giddiness, common early symptoms of leukaemia, are produced by the rapidly increasing anaemia, spitting of blood and ecchymoses by reduction in the quantity of thrombocytes, sore throat and susceptibility to bacterial infection is due to agranulocytosis, and these symptoms will appear early or late according to the order and rate at which the cell forming elements are damaged by the invading cells in the marrow.

Crawford and Weiss[8] report six early cases, under the name of subacute leukaemia, which all resemble cases I and II closely in their mode of onset, general symptoms, and course. In only one was there enlargement of lymph glands when first examined, and in another they became palpable towards the end of the illness.

In passing it may be remarked that reticuloendotheliosis,/

endotheliosis, described by Dameshek,[9] probably a closely related condition, produces almost identical symptoms and runs a similar course. The difference lies in constant general glandular enlargement, and the post mortem finding of proliferation of much more primitive cellular elements.

The centre for the production of granulocytes being the bone marrow, one would not expect to find enlargement of the lymph glands in Case III, which is of myeloid type. Here, although the proliferation in the marrow is the same as in lymphatic leukaemia, a different type of cell is involved, giving a different blood picture. In the lymphatic type, the granular cells are crowded out by invading lymphocytes, in the acute myeloid, the granular cell forming tissue is destroyed by the weight of its own excess of primitive and effete cells, some of which overflow into the blood stream along with whatever more or less mature cells the exhausted tissue can produce. The result is the same in either case, the patient suffers from agranulocytosis. This description does not, of course, apply to the chronic form, where the hyperplastic tissue still has elbow room, so to speak, and can produce vast numbers of fairly mature cells.

The result of x-ray irradiation produced most dramatic results in this case. The skin tumours disappeared/

disappeared very rapidly, (see Appendix p.7) and, at the same time, there began a leucopenia, in a few days becoming intense. The irradiation was over the skin growths, and not the bones, so it is unlikely that sufficient injury could be done to the marrow to produce such a great effect. One is tempted to wonder if the explanation may not be that the bone marrow was packed with primitive cells, and that the neoplasms were extra medullary centres of leucopoiesis. If they were just sufficient to provide the circulation with a normal quantity of polymorphonuclears, their sudden destruction would throw the burden on the bone marrow, the seat of a useless hyperplasia, unable to produce mature cells which would pass into the circulation, and yet not so crowded that the primitive cells overflowed. The possibility of extra medullary haemopoiesis is further supported by the microscopic appearance of a lymph gland, the report stating: "The fibrous trabeculae at parts seemed normal, at others they were so infiltrated with red and white corpuscles as to resemble bone marrow".

A similar theory has been mentioned by Pinkerton[10] in regard to leukaemia with leucopenia, where it is suggested that the viscera may possibly be the seat of abnormal regenerative activity of the blood forming organs.

Chloroma/

Chloroma with leucopenia is a most unusual condition, and few cases have been published recently. One, however, by Swanson,[11] reports a child with orbital tumours, and no primitive cells in the blood, but there was not a true leucopenia, as the white cell count was always a little above normal.

Case IV is of quite unusual interest, in that the blood picture did not become openly leucopenic until five years after the development of glandular symptoms. A chronic lymphatic leukaemia, it illustrates the invasion of the bone marrow from an external source, and as the process is different from that in the first three cases, so are the symptoms. Lymphatic proliferation began in the peripheral lymph nodes, which were found to be enlarged at about the same time in the groins, axillae, and neck; the first symptom, and for quite a long time, the only one. That the bone marrow was practically unaffected for five years is indicated by the blood examination over this period, showing no anaemia, and no reduction in the number of polymorphonuclear cells, the only pathological feature being a slight leucocytosis due to an overflow of lymphocytes. When the signs of frank leukaemia did at last appear, the invasion of the bone marrow was evidently rapid, judging by the definite anaemia, and the falling off in numbers of granulocytes; and that the lymphoid hyperplasia/

hyperplasia is becoming still more pronounced is shown by the increasing number of primitive lymphocytes in the blood stream. Here again, the ultimate result is the same as in the acute leukaemias, anaemia, with disappearance of granular cells and platelets. The only difference is in the site of onset, and the time at which the main blood forming organs are affected.

The unusual train of events in Case V make it rather a problem in diagnosis, which is obvious enough however if too much stress is not laid on the patient's previous chequered haematological career. After a long history and clinical manifestations of Banti's disease, splenectomy was performed with very satisfactory results as regards the relief of the symptoms, in fact the operation definitely cured the most distressing complaints, ascites and haematemesis. The pathologist who examined the spleen had evidently no doubt whatever as to the correctness of the diagnosis, which he substantiated in his report. Six years later the patient was found to be suffering from a condition of the blood, which can only be described as leukaemic, and no pathological process could be discovered to which such a state might be secondary. Admittedly she developed carcinoma of the uterus, but it was in the early stages when its effects were purely local, and there was no question of metastatic growths. It would/

would seem therefore that she had a true leukaemia, and the point which at once arises is: what bearing, if any, had Banti's disease on the subsequent leukaemia? Not much help could be got from the literature on splenectomy, which does not deal fully with the effect of operation at such a remote period as six years afterwards, though an immediate leucocytosis sometimes persisting for several months, and a lymphocytosis which may possibly be permanent are described.

A case is reported by Krumbhaar[12] bearing a resemblance to this one, and it is interesting to quote the main features. A man of 49 years had slight leucopenia verified on several occasions over two and a half months. For three years previously the spleen had been much enlarged. Splenectomy was performed, and at the operation the liver was found to be much enlarged. Histological examination of the spleen was considered by the author to have confirmed the diagnosis of rather early Banti's disease, and the picture certainly did not bear any resemblance to a leukaemic spleen. After a few months of improvement weakness returned and the leucocyte count rose to 21,000, with a preponderance of mononucleated cells of different kinds. The count rose to 40,000 at the patient's death a few months later. Histologically there was a picture of myeloid leukaemia, with myelocytic infiltration/

infiltration of different organs.

While not committing himself to a definite diagnosis Krumbhaar states that either leukaemia in a leucopenic stage may simulate Banti's disease even to the gross and histological appearance of the spleen, or Banti's disease may be followed by leukaemia, or it may terminate in an indistinguishable leukaemoid picture. More succintly,

"Was it always leukaemia simulating Banti's disease in an aleukaemic early stage, or Banti's with a terminal leukaemoid picture, or true Banti's merging into a true leukaemia at the end?"

The last question seems to supply the answer to the case under discussion, in view of the absence of any evidence to the contrary.

Another case of splenectomy for Banti's disease followed by leukaemia two and a half years later, is reported by Pinkerton,[10] but the author states that the original diagnosis was in some doubt after examining the spleen microscopically, and it is not unlikely that myeloid leukaemia with leucopenia was present all along.

If it be admitted then that the fifth case is a true leukaemia, it must be chronic lymphatic type, for it is obviously not acute, and lymphocytes are present in excess. Possibly it is in an even earlier/

earlier stage than Case IV, when first observed, seen before glandular enlargement has become palpable, and before the leucocytosis has risen much above normal.

Case VI is an example of lymphatic leukaemia, originating in the bone marrow, and running a slow course, and therefore comes in between Case I, an acute condition beginning in the bone marrow, and Case IV, a chronic condition affecting the lymph glands first, and the marrow later.

Beginning as it did in the marrow like Case I, the symptoms and general features are somewhat similar, with the difference that they appeared more slowly, because the encroachment of the invading cells on the marrow space was much slower. In both cases there was absence of enlargement of the lymph glands, macrocytic anaemia, and leucopenia. In Case I the spleen and liver were enormously enlarged, in this case splenomegaly was moderate, and the liver was unaffected. In Case I the granular cell forming tissue was damaged early, and the patient suffered from agranulocytosis, and died before the blood picture had become leukaemic, and while there was still some regeneration of red cells. In this case the formation of granular cells was still sufficient to give the patient some resistance to infection, and she survived long enough for leukaemia to become apparent in the blood picture, and/

and for the haemopoietic tissue to be so badly invaded that so far as red cell formation was concerned the marrow was aplastic.

The mode of onset precluded the same chronicity as in Case IV, but when the latter entered its second stage of bone marrow invasion, the two cases are comparable.

Some recent reports on early leukaemia running an acute course, by White and Davey, Crawford and Weiss, and Gordon[13], along with the three described here, give eleven cases in which the chief points of interest may be compared.

Age incidence. The youngest was 13 years, the oldest 72. Seven were in or near the decade 25 - 35.

Onset. Gradual in seven, sudden in four.

Pyrexia. Intermittent up to 103° in ten, absent in one.

Haemorrhagic Symptoms. Five had various degrees from petechiae to haemoptysis and melaena. In the other six none were evinced.

Sore Throat. Present in six.

Anaemia. More or less severe in all cases. In the present six cases, three were macrocytic, and three microcytic.

Enlargement of Spleen. Palpable in nine.

Enlargement of Liver. Present in six. In no case was the liver enlarged without splenomegaly.

Lymph gland enlargement. Palpable in two. In one in the neck, in the other in the neck and groin. In all eleven cases there was either leucopenia, or at the most a small leucocytosis, and the differential count showed granular leucopenia, the predominating cell type being mononuclear.

In the two cases with obvious glandular enlargement there was a septic condition of the throat and mouth, whether elsewhere is not stated, and it is probably that there was adenitis secondary to an infection permitted by agranulocytosis. The assumption is that in none of these eleven patients when first observed, were the lymph nodes infiltrated by leukaemic cells to any extent.

Satisfactory records of early chronic leukaemia are difficult to find, because the condition does not as a rule cause any symptoms until well established. In the lymphatic variety, by the time the patient's attention is called to glandular enlargement, or he realises the stealthy arrival of tiredness, there is nearly/

nearly always a fully fledged blood picture. Case IV is quite unusual in that the typical blood changes were delayed for such a long time, and remained in an early phase long after the glandular proliferation was well advanced. Such conditions are recognised by Vines[14] who says of them "It is probable that the lymphatic hyperplasia is a phase in the leukaemic syndrome, and that changes in the white cell count will eventually appear. The only recent record at all comparable is that of Hyland[15] of lymphatic leukaemia occurring in three children. In all three cases there was generalised glandular enlargement and marked leucopenia.

From the cases discussed it can be seen that the diagnosis may be a matter of great difficulty, and in Pinkerton's series for instance, none were diagnosed with certainty during life, although leukaemia was regarded as a possibility. In early leukaemia the leucocyte count is not of much value, because it is little more than normal, and often considerably less. The point of primary importance is the examination of stained blood films, and the recognition of primitive leucocytes, the constant presence of which indicates leukaemia. The majority of the white cells seen are mononuclear cells, more or less mature according to the acuteness of the case, and the observer must acquire/

acquire sufficient experience to recognise the characteristic appearance of immaturity. The primitive type of cell is usually large, with basophilic cytoplasm, usually not very abundant, and often containing a few azurophil granules. The nucleus is round or oval with a fine reticulum of chromatin containing several pale nucleoli. The attention must be directed to the appearance of the nucleus by which the cell is recognised, and not to the size which is no criterion of immaturity,[16] (see Appendix p.13).

It is of no practical importance to distinguish whether the cell be myeloblast or lymphoblast, for if the condition be acute, the outlook will be the same in either case, and if chronic, it can be more correctly differentiated by means of the company in which it later appears than by the unreliable and tricky peroxidase stain, or by the supravital method on the interpretation of which there is not full agreement at present. In any case some of these cells may be stem cells, an even less mature type than either myeloblasts, or lymphoblasts.

Radiological examination, the blood chemistry, and biopsy examinations do not seem to give any assistance. In Case IV, for instance, the examination of excised glands merely seemed to obscure the issue, for, although progressive stages of leukaemic infiltration/

infiltration were seen in the series, the nature of the changes was not appreciated in the absence of the typical blood picture, an essential piece of evidence without which a diagnosis of leukaemia would have been quite unjustified.

On the other hand post mortem findings are sometimes the conclusive proof of the real nature of the disease, especially microscopic examination of the marrow and spleen, or often better still, the liver, and this suggests that in these doubtful early cases with a normal or leucopenic white count, and an indefinite blood picture, sternal and splenic puncture might be of great assistance in establishing a diagnosis.

The post mortem finding of iron pigment in the tissues, which occurs in some cases and not in others, is a point of minor importance, depending on the type of anaemia present, and is specially prevalent in the megalocytic type, when many of the cells are immature, and possibly too large to pass through the capillaries easily, and so are caught and destroyed by the reticulo-endothelium.

In conclusion, it would seem that enlargement of the peripheral lymph nodes does not occur in the early acute cases, except in response to a secondary infection, but in the chronic condition on the other hand/

hand, it may be the main symptom before suspicious changes appear in the blood.

Great enlargement of the spleen is usually associated with a chronic condition, but two examples have been demonstrated here, where the spleen was large enough to fill up most of the abdomen, and had reached this immense size in about two months' time. Gross splenomegaly, therefore, does not rule out an early condition. One of the main functions of the spleen is to destroy effete cells in the circulation, so a great increase in size in a short time indicates the rapid production of immature or otherwise faulty cells, and it may be that the leucopenia seen in the first case was, to a certain extent, a testimonial to the efficiency of that organ. As the spleen is the first line of defence, the liver is not affected until extra aid is required, and so therefore does not become enlarged unless there is previous splenomegaly.

SUMMARY.

The early manifestations of leukaemia differ in acute and chronic types. If acute, the chief features are leucopenia or count near the normal range, primitive cells in the circulation, more or less anaemia, and commonly haemorrhages. There are intermittent pyrexial attacks and enlargement of the spleen, sometimes gross, while the liver may also be palpable. The lymph glands are not enlarged. The symptoms include tiredness, weakness, petechiae and bruising, epistaxis and haemoptysis.

As to the chronic forms, sufficient data were not produced on which to base conclusions, but on the evidence available, they would seem to include in one type early enlargement of the peripheral lymph nodes, mild leucocytosis or leucopenia, with lymphocytic preponderance, slight or no anaemia, and absence of pyrexia and general symptoms. In another type there may be slowly progressing macrocytic anaemia, leucopenia, and enlargement of the spleen, the general appearance of the case resembling an acute leukaemia with leucopenia, but of more gradual development.

A full description of six cases was given, of which the main features, when they first came under observation, are set out in tabular form.

Some of the cases reported emphasise the great danger/

danger of x-ray treatment:-

(a) When leucocyte counts are not well above normal.

(b) When early primitive cells (myeloblasts or lymphoblasts) are present.

Illustrations are submitted from a case in which the leukaemic process in the marrow appeared to have begun in small scattered islands, and not as a diffuse process.

	Age	Onset	Tiredness.	Haemorrhagic symptoms	Lymph gland Enlargement.	Spleen Enlargement.	Liver Enlargement.	Red cells per ccm. per million	Hb	C.I	White Cells per ccm.	Primitive white cells %.
No. I. Acute lymphatic leukaemia	26	Sudden	+	+	-	+++	+++	2.1	50	1.2	1400	13
Case II. Acute Lymphatic leukaemia	72	Gradual	+	-	-	+++	-	4.72	52	.5	13600	Very few.
Case III. Chloroma	34	Gradual	-	-	-	+	-	5	100	1.0	6600	None.
Case IV. Chronic lymphatic leukaemia	48	Gradual	-	-	++	-	-	5.22	92	.9	12400	None
Case V. Chronic lymphatic leukaemia	62	Gradual	+	-	-	Splenectomy.	-	3.7	44	.6	8000	4
Case VI.	11	Gradual	+	-	-	+	-	1.14	20	.9	2000	3

CONCLUSIONS.

Leucopenia is a fairly frequent indication of a leukaemic process in the haemopoietic organs. In such cases the leukaemic process is one involving primitive cells, or cells of the lymphocyte series, and not of the granular series.

Anaemia, commonly macrocytic, is a frequent feature of such cases, and may lead to a diagnosis of pernicious anaemia or haemolytic jaundice.

Death may result from anaemia before the leucocyte content of the peripheral blood has risen, but life may be slightly prolonged by the use of transfusion.

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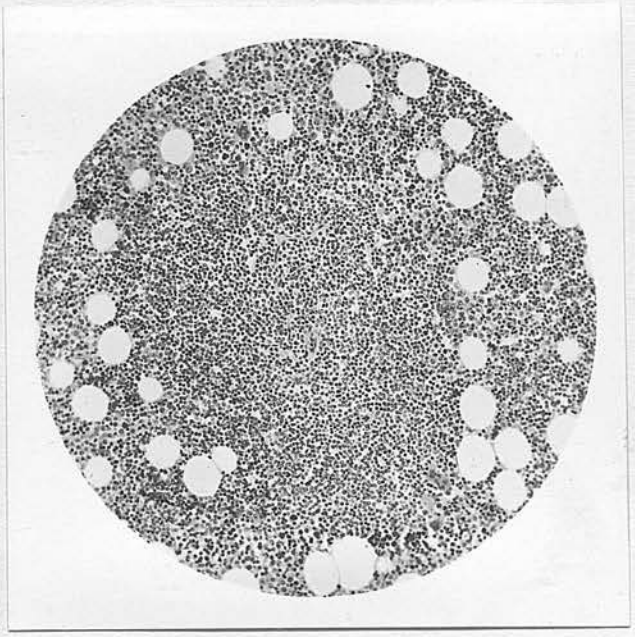
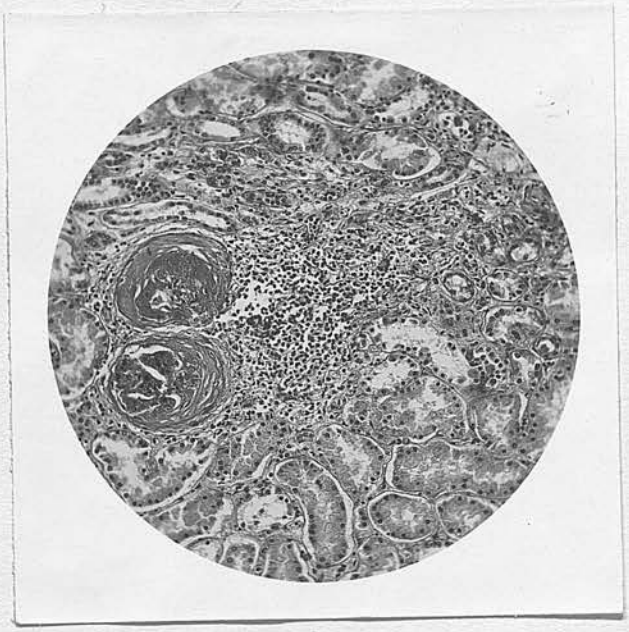
APPENDIX.

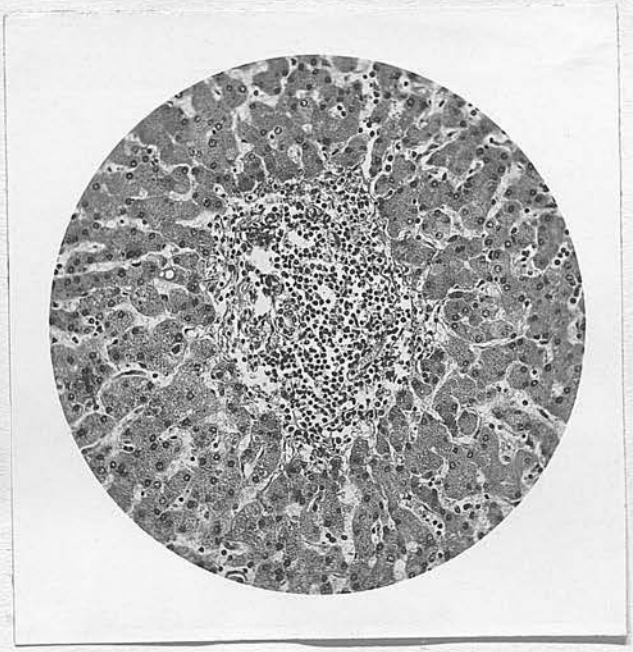
1.



CASE 11. Microphotograph of a section of bone marrow. This picture shows a zone of invading lymphocytes surrounded by relatively healthy tissue and normal fat spaces. These nodules of lymphocytes were scattered throughout the bone marrow, showing that the process was patchy, and not a diffuse infiltration.

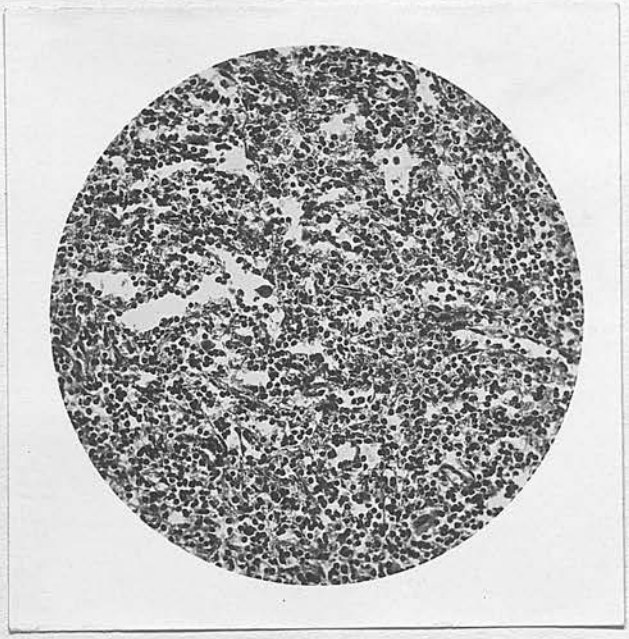


A.

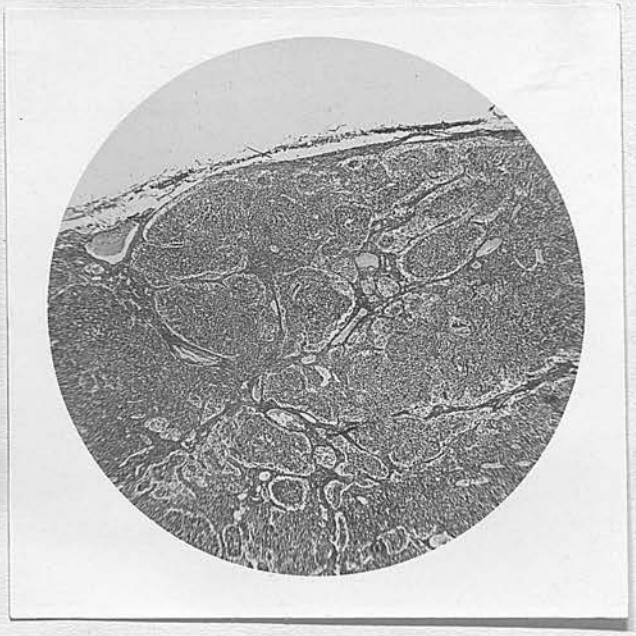


B.

CASE II. Microphotographs showing small patches of early lymphocytic infiltration in A the kidney, in B the liver, where it was of interlobular character. The leucocyte count was only 14,200 per c.m.m.

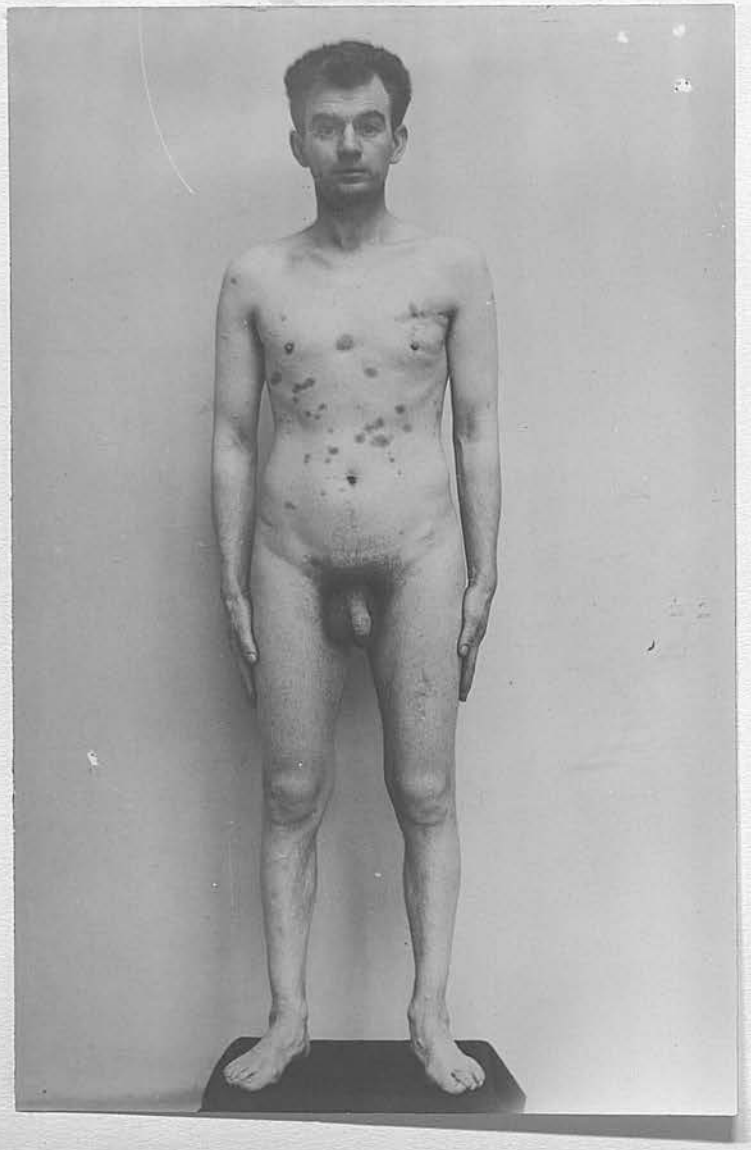


A.

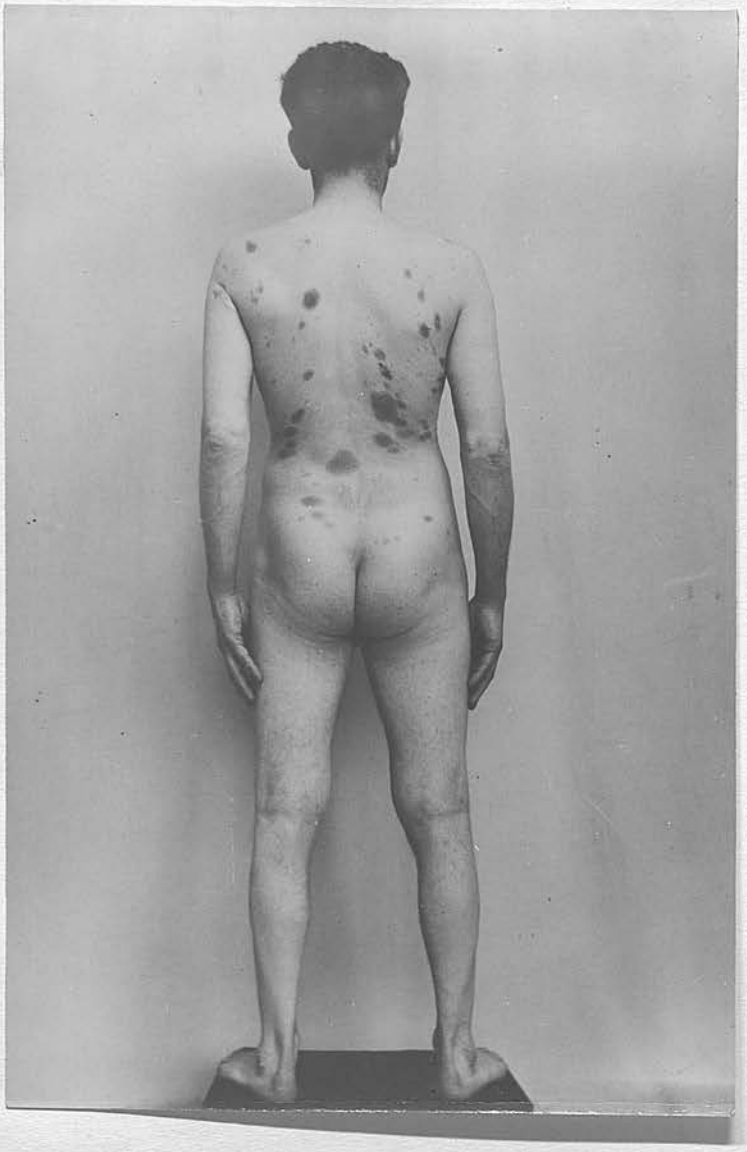


B.

Case II. Microphotographs of sections of A the spleen, showing lymphoid infiltration, and B a lymph gland, showing that the normal structure of the gland was unaltered.



CASE III. Photograph showing chloromatous skin tumours on the front of the chest and abdomen.

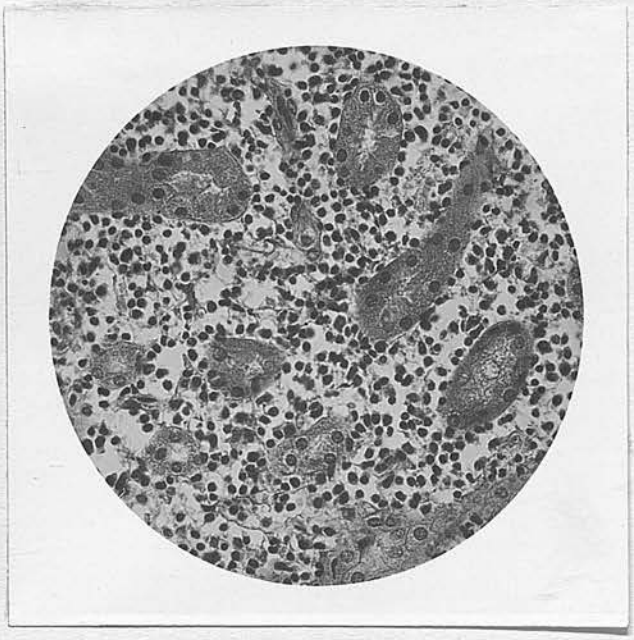


CASE III. Photograph showing skin tumours on the back of the trunk.

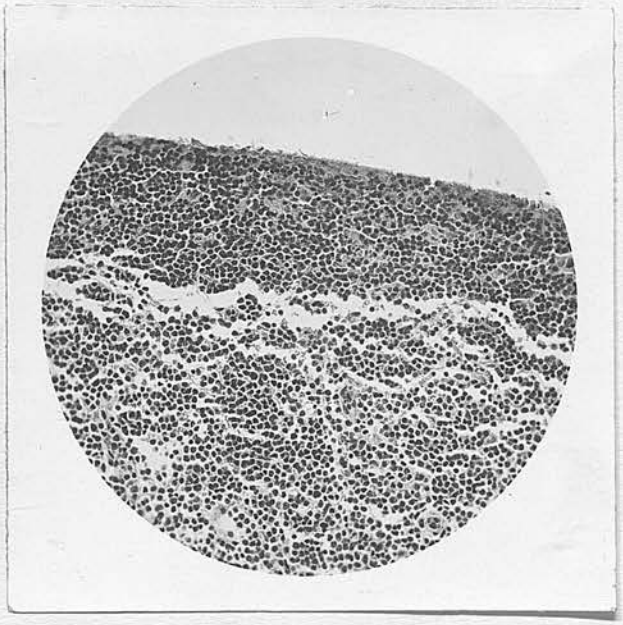
A.

B.

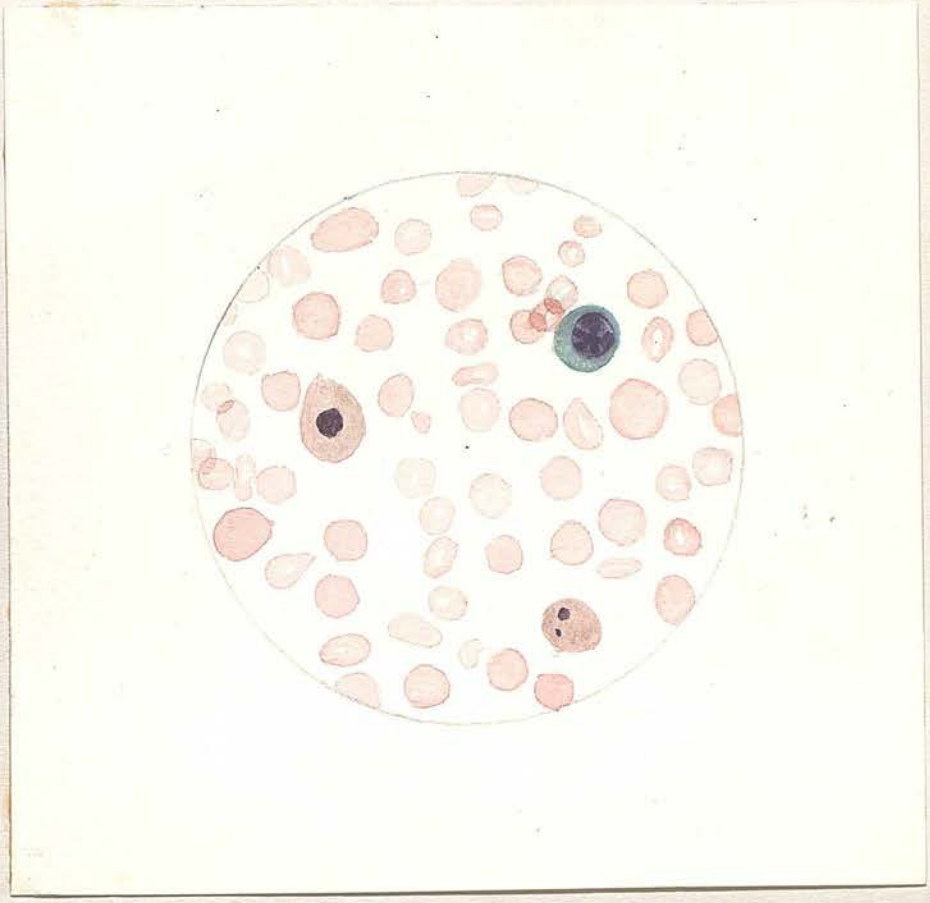
Case III. Microphotographs of sections of skin, A removed at biopsy, showing infiltration of the deeper layers of the cutis vera by mononucleated cells before X-ray therapy: B post mortem, demonstrating how the infiltration had largely disappeared after X-ray therapy.



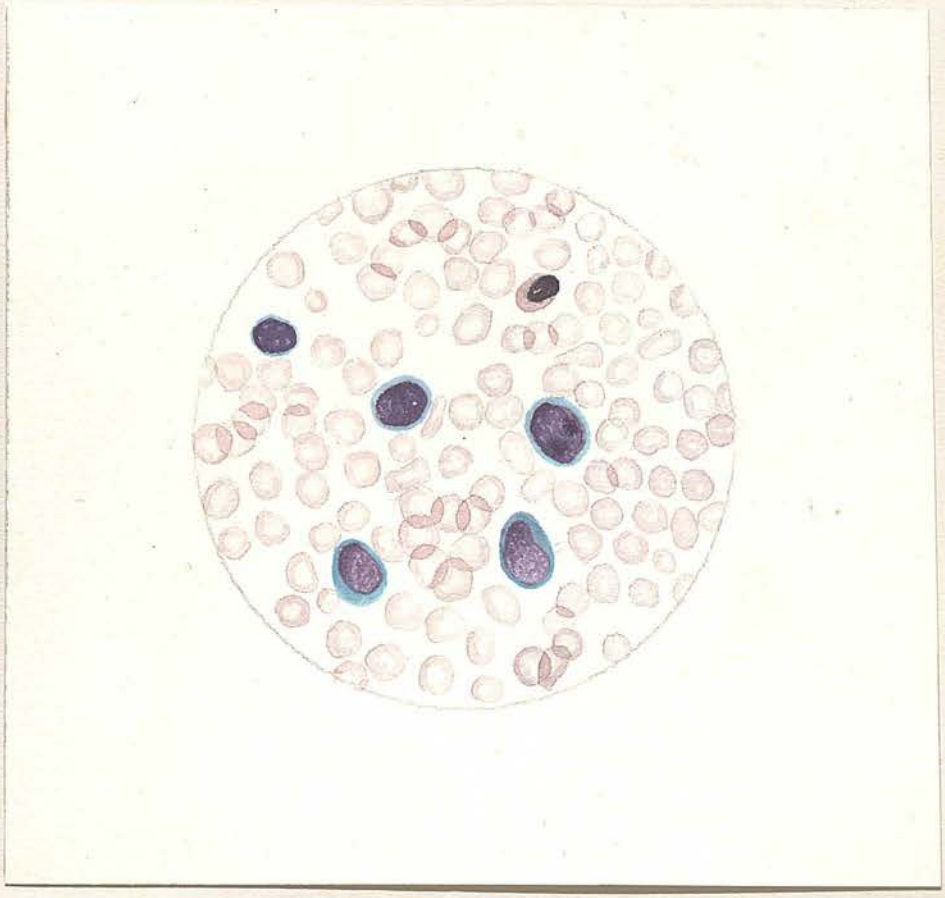
CASE III. Microphotograph of a section of the kidney, in which great intertubular invasion by mononucleated cells is seen, in spite of the fact that the patient was leucopenic, the last white cell count being only 400 per c.m.m. This was the only clear photograph that could be made, as the other organs were rendered almost unrecognisable by the action of B.Coli.



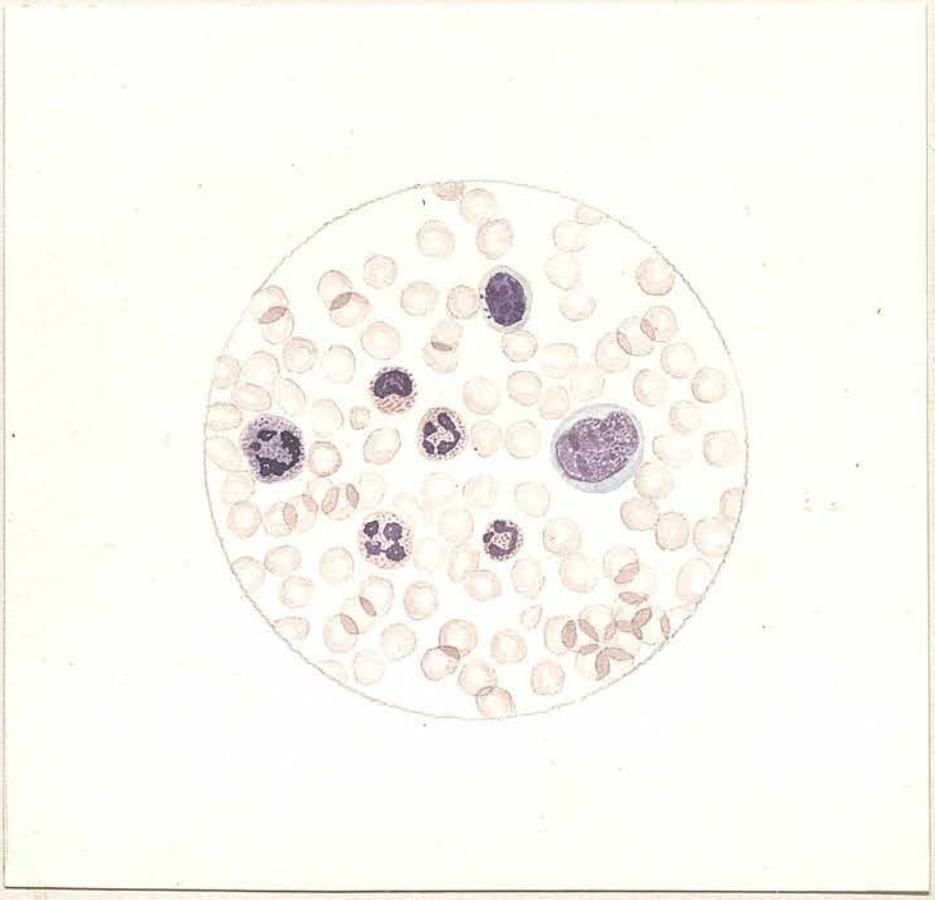
CASE IV. Microphotograph of a section of lymph gland removed at biopsy, showing great infiltration of the gland capsule by lymphocytes.



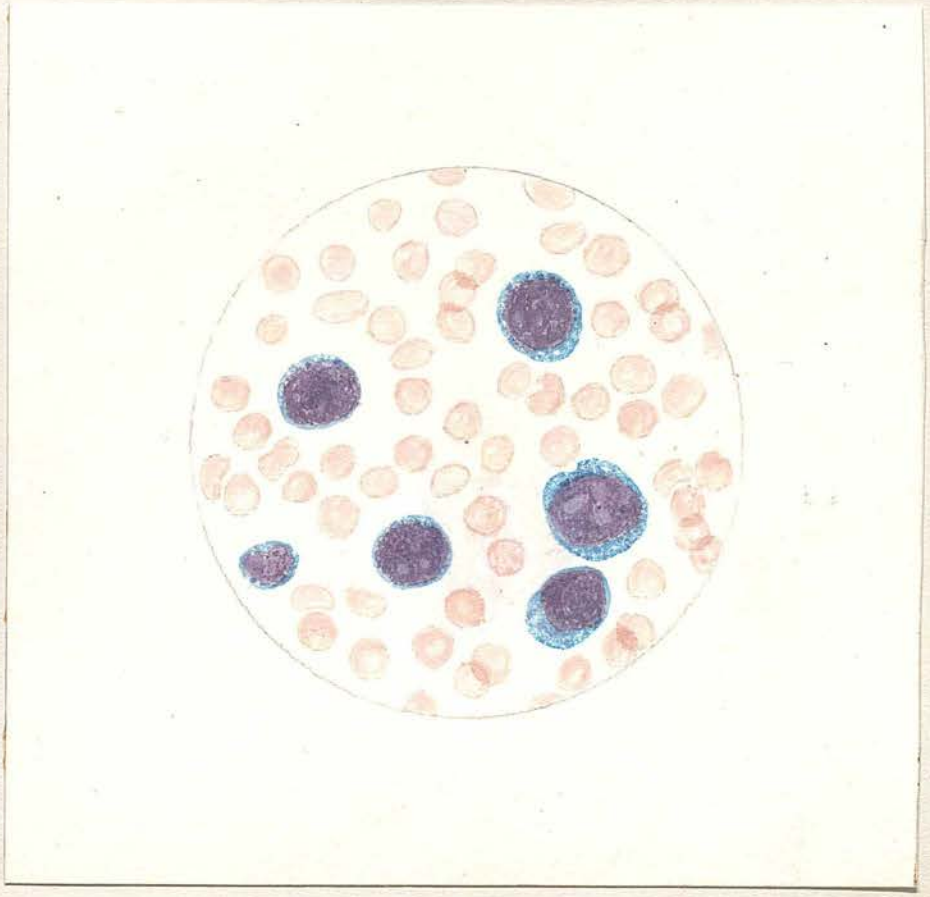
CASE I. Blood film Leishman's stain showing anisocytosis, poikilocytosis and macrocytes. A megaloblast, a normoblast, and a cell containing Howell-Jolly bodies are illustrated. The resemblance to severe pernicious anaemia can be seen.



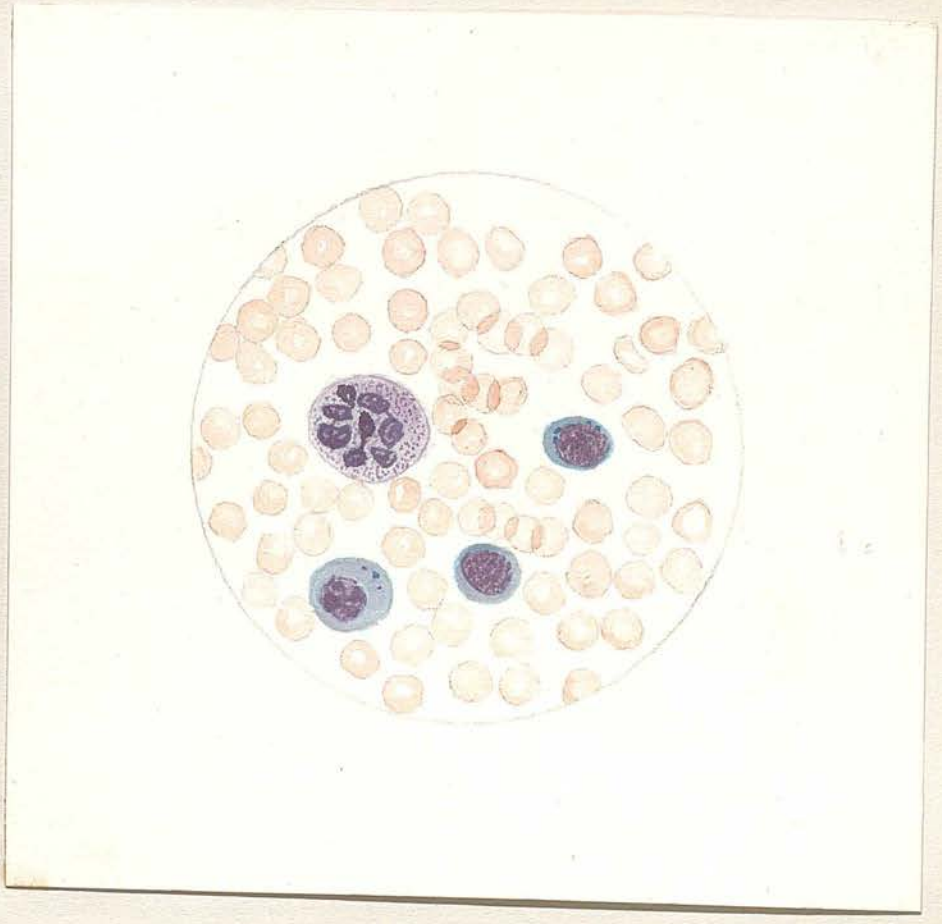
CASE II. Blood film, stained by Jenner Giemsa method. The illustration shows microcytic anaemia. The red cells are poorly filled, and show some variation in size and shape. One normoblast can be seen. The small lymphocytes are of mature type.



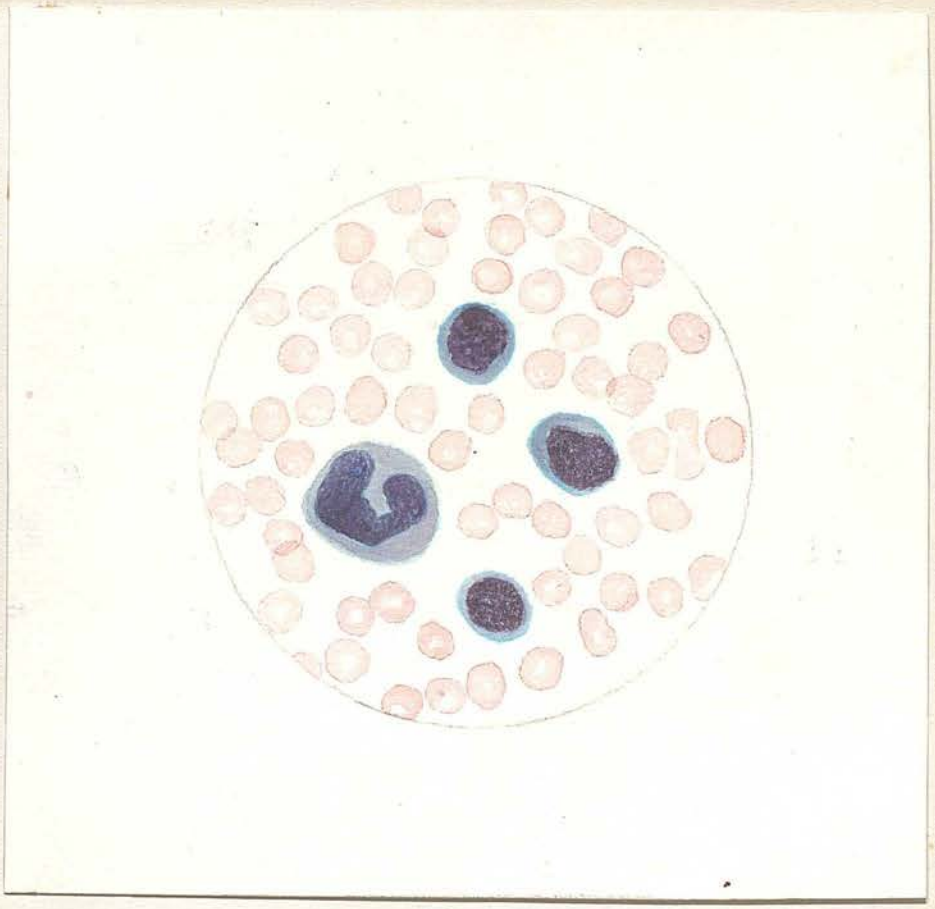
CASE II. Blood film stained by the Jenner Giemsa method, showing a small lymphocyte, and a large lymphoid cell of immature type. The polymorphonuclear cells are remarkable for their small size.



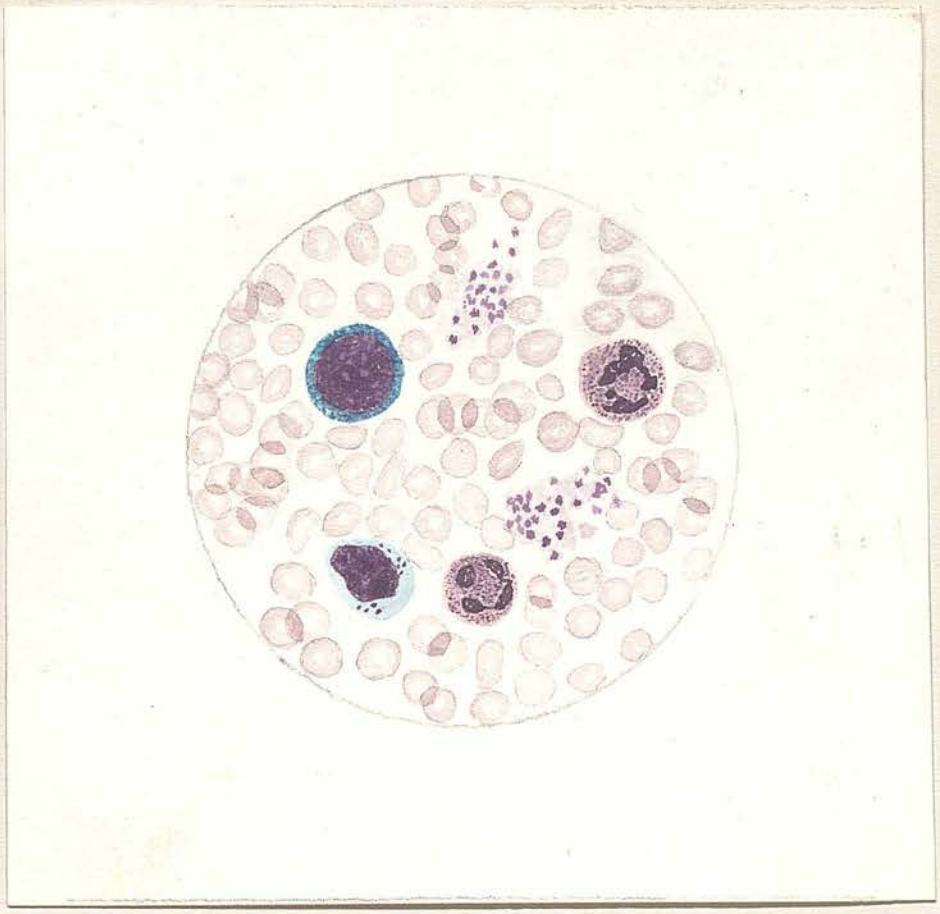
CASE IV. Blood film, Leishman's stain. In this illustration six lymphoblasts are seen, of which the main features are: finely arranged chromatin in the nucleus, with several small light coloured nucleoli: basophil cytoplasm sometimes containing azurophil granules, and sometimes vacuolated. The variations in size which may occur are demonstrated.



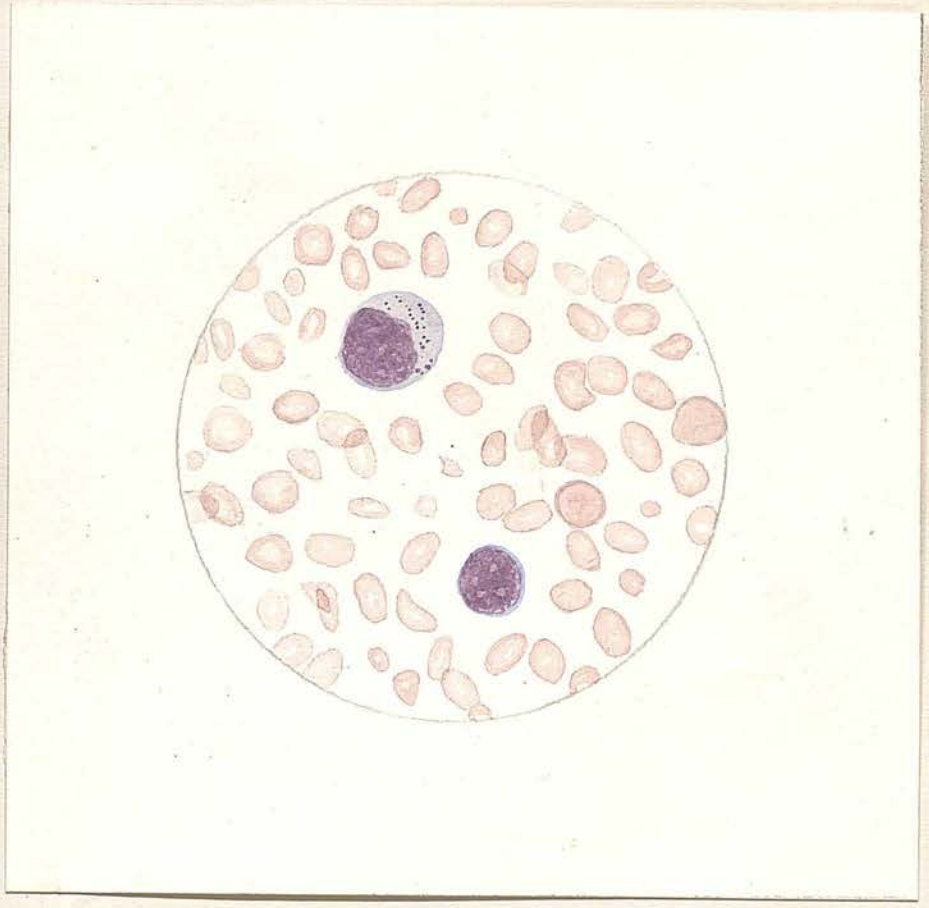
CASE IV. Blood film, Leishman's stain. Three large lymphocytes are shown, one with abundant cytoplasm, containing azurophil granules. The polymorphonuclear cell is of the type described by Cooke as a macropolycyte.



CASE IV. Blood film, Leishman's stain. A slight secondary anaemia is shown, three large lymphocytes, and a monocyte. At a certain stage monocytes of exceptional size, similar to the one illustrated, were commonly seen in the blood films of this case.



CASE V. Blood film, stained by the Jenner Giemsa method. The illustration shows anaemia of microcytic type. Two polymorphonuclears of mature type are shown, one large lymphocyte, blood platelets, and one lymphoblast.



CASE VI. Blood film stained Jenner Giemsa method. The picture shows macrocytic anaemia, with great variation in the size of the red cells, and two lymphoblasts. The smaller is a common type, with scanty cytoplasm, the larger is more unusual, with abundant cytoplasm containing many azurophil granules.