lymphæmia with typical medium-sized or small lymphocytes, to a benign or histioid tumour—the lymphocytes being fully developed; whilst the present acute case would resemble a tumour process of sarcomatous nature affecting the lymphoid tissue throughout the body.

5. As regards the seat of origin of the disease: looking at the remarkable condition of the marrow alone, one might be inclined, with Benda, to regard the large lymphocytic cells, of which it was almost exclusively composed, as primitive marrow cells, his myelogonia, the "indifferent lymphoid cells" of A. Wolff,³ and to regard the disease as one primarily affecting the bone marrow. Morphology alone can hardly help us here, for it is not possible to distinguish undifferentiated embryonic cells of one kind of tissue (myeloid) from those of another kind (lymphoid). The objection to Benda's view is that it leaves the intensely active participation of the lymph-glands unexplained. It seems more natural to regard acute leukaemia as a primary disease of lymphoid tissue wherever situated—a disease with distinct affinities to the malignant tumours.

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ACUTE LYMPHATIC LEUKAEMIA,

WITH THE REPORT OF FIVE CASES.

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[From the Clinic of Professor Osler.]

In the fifteen years since the opening of the Johns Hopkins Hospital, among 17,100 medical admissions there were 37 cases of leukaemia. Of these, 24 were of the spleno-myelogenous type and all chronic. Among the 13 cases of lymphatic leukaemia 5 were acute. The histories of these cases are as follows:

1. A. H., male, white, tailor, aged 15 years, was admitted on November 28th, 1897, complaining of headache and weakness. The family history was negative. From the age of 2 to 4 years he was sickly, but since then strong and well. He had measles at 5, but no other infectious disease. He had not had tonsillitis, but had been subject to attacks of epistaxis.

The present illness began on November 18th, 1897, with headache and general malaise. He kept at work until November 23rd, when, on account of weakness, he had to go to bed. His throat was sore and he had some difficulty in swallowing. He felt feverish. The next day there was nose-bleed, which was severe and lasted for four hours. He grew progressively weaker and had severe headache.

On admission the patient looked very ill. There was dyspnoea and cyanosis. Pallor was marked. The tongue was brown and dry. The throat was injected. The tonsils were enlarged; on the right there were several white points and on the left a patch of membrane 3 cm. in diameter. Large numbers of cocci and bacilli, but no diphtheria bacilli, were found. There was an abundant herpetic eruption on the lips. The lungs were clear. The heart was not enlarged. There was a soft systolic murmur at the apex and over the body. The pulse was 120, of small volume and collapsing. The abdomen was enlarged, tense and tympanitic. The edge of the liver could be felt 7 cm. below the costal margin. The spleen was readily palpable. There was general glandular enlargement. The glands of the neck were enlarged, discrete, but not specially tender. The epitrochlears were very large and tender. There was a petechial eruption on the neck and arms.

The blood showed haemoglobin 45 per cent., red cells 2,445,000, and leucocytes 326,000 per c.mm. The red cells showed some poikilocytosis. An accurately-classified differential count of the leucocytes was impossible, as there were a large number of mononuclear cells difficult to classify. They varied from small lymphocytes to large cells with a pale-staining nucleus with homogeneous protoplasm for the most part, although a few were more or less granular. The predominant mononuclear was small, probably about 90 per cent. In some the granules were distinct, taking a slight purplish tint with the Ehrlich stain. Many of the nuclei of the mononuclears took a greenish stain. The count of 1,000 leucocytes showed: Lymphocytes, 94.2 per cent.; polymorphonuclears, 4.0 per cent.; eosinophiles, 0.8 per cent. In counting

these two nucleated reds were seen, both normoblasts. The coagulation time was ten minutes.

The temperature averaged 104° to 105°; the pulse was 120. Blood cultures showed a very abundant growth of streptococci. There was no Widal reaction. The urine had a specific gravity of about 1020, contained a very faint trace of albumen, but no casts were found. The diazo reaction was given. There was a marked acetone reaction. An enormous quantity of leucin spherules, and tyrosin crystals was obtained from the urine passed shortly before death. In the last eight hours of life 1,900 c.cm. of urine were passed, which contained 1.7 grams of uric acid.

On November 29th there was severe epistaxis, partially controlled by plugging the posterior nares. The patient died the following day, November 30th. The temperature continued elevated, averaging 105°. An autopsy was not obtained.

In this case the whole course was thirteen days. The rapid course and repeated severe haemorrhages were the principal features. The presence of acetone and leucin and tyrosin crystals in the urine is to be noted. In regard to the blood condition, it is of interest that although this was a rapid course with haemorrhages, the large majority of the lymphocytes were of the small type.

2. J. L., male, aged 3 years. Anaemia; fever; purpuric rash; blood picture of leukaemia; haemorrhages; convulsions; death; duration about one month. (This case was reported in full in the *Johns Hopkins Bulletin*, No. 110, May, 1900, p. 102. Only a short summary is given here.)

J. L. was admitted on May 11th, 1898. There is nothing of moment in his history, and he did not complain of any serious symptoms. He had been troubled with adenoids, and for a few days had seemed rather easily tired. On examination he was found to be very pale; there was marked swelling of the tonsils and large adenoids. The thorax was clear; liver and spleen were enlarged; there was no glandular enlargement. He had slight irregular fever; the pulse and respirations were rapid. The blood examination showed 35 per cent. of haemoglobin, 1,680,000 red cells and 26,000 white cells per c.mm. The differential count of 1,000 leucocytes showed 13 per cent. of polymorphonuclears, 86.5 per cent. of lymphocytes (of which 45 per cent. were large, 41.5 per cent. small). The red cells showed no special changes; no nucleated reds were found. The lymphocytes showed all variations in size, from the smallest to some which were 15 microns in diameter. The general staining was pale. There were, however, a few small lymphocytes with a typical deeply-staining nucleus. Subsequent counts showed an increasing percentage of small lymphocytes. On May 19th the lymphocytes were 99.2 per cent., of which 96.6 per cent. were small, and only 2.6 per cent. large. Death occurred on May 30th, following convulsions. The duration of the attack was probably about four weeks.

3. J. A., male, white, farmer, aged 20 years, was admitted on August 2nd, 1899, complaining of weakness. A point of interest in the family history was that his father and his three brothers are all subject to frequent attacks of bleeding from the nose. He had been very healthy. Measles was the only infectious disease he had.

Two months before admission his nose began to bleed spontaneously and he lost a great deal of blood. There was much difficulty in stopping the haemorrhage. He bled frequently after this, but for a week before admission there had not been any bleeding. He has gradually become weak and lost some weight. Otherwise he has no special complaint.

The patient was very anaemic. The skin had a yellow tint. There were some petechiae on the thorax. The lungs were clear throughout. Over the upper sternum the percussion note was dull; this was most marked opposite the second interspace. The heart was not enlarged. There was a soft systolic murmur heard everywhere over the heart and over the carotid and subclavian arteries. There was a venous hum over the neck. The pulse was soft and of low tension. It could be well felt in the tips of the fingers and there was a slight visible capillary pulse. The liver was enlarged, the edge being felt 5 cm. below the costal margin in the nipple line. The spleen was large and easily felt. Its edge was 5 cm. below the costal margin. There was general glandular enlargement.

The blood showed: Haemoglobin, 35 per cent.; red cells, 1,230,000; and leucocytes, 12,000 per c.mm. The differential count showed: Lymphocytes, small, 93.3 per cent.; lymphocytes, large, 0.9 per cent.; polymorphonuclears, 4.9 per cent.; eosinophiles, 0.9 per cent. The great majority of the mono-

nuclears were of the small type. In counting 500 leucocytes 155 nucleated reds were seen; of these, 70 were normoblasts, 75 intermediate forms, and 10 megaloblasts.

The urine had a specific gravity of 1012, contained a small amount of albumen, but no casts were found. The course was rapid; the temperature varied from 100° to 104°. He grew rapidly weaker, and died on August 5th, 1899.

Autopsy (Dr. W. G. MacCallum).—Anatomical diagnosis: Lymphatic leukaemia; general glandular enlargement; splenic tumour; anaemic infarction of spleen; lymphoid nodules in the kidneys; anaemia of all the viscera, with fatty and parenchymatous degeneration; lymphoid bone marrow; enlarged persistent thymus. There was general enlargement of the glands; the lymph glands of the omentum were large and firm. The abdomen was clear. On opening the thorax the thymus was found to measure 13 cm. vertically and 4 cm. transversely. On section it was oedematous and very pale. Its upper margin was just above the sternal notch. The pericardium was clear; there were a few ecchymoses on the right ventricle. No thrombi were found in the heart. The endocardium and muscle were very pale; the heart weighed 370 grams. The valves were normal; there were a few small areas of fatty degeneration in the aortic and coronary arteries. The lungs on section were clear. The spleen, weighing 320 grams, measured 17 × 11 × 6 cm., and was soft and flabby. The veins were very apparent on the surface. Over the upper and lower surfaces there were fine, translucent nodules to be seen which were apparently in the lymphatics. These were about the size of a pin-point. At the lower end there was a small anaemic infarct. On section the trabeculae stood out prominently; the pulp seemed increased in amount. The Malpighian bodies were irregular in size and shape, but not excessively enlarged. The liver weighed 1,900 grams, and measured 25 × 19 × 11 cm. On section the lobes were rather indistinctly marked; the general colour was rather greyish, the surface homogeneous. The gall bladder and gall ducts were normal; the periportal lymph glands were enlarged. The stomach and pancreas were normal. The mesenteric and retroperitoneal lymph glands were considerably enlarged. The kidneys were exceedingly pale and showed numerous small ecchymoses over the surface. On section the kidney was very pale; there were a number of irregular white areas which seemed to be somewhat elevated from the surface. These extended a short distance into the cortex. The axillary glands were much enlarged, and on section presented a mottled, whitish-pink colour. The thyroid was somewhat enlarged and seemed normal on section. The intestines showed general hyperplasia of the lymphoid tissue, especially in the ileum just above the ileo-sacral valve. In the upper part of the ileum there were a few small superficial ulcers which were apparently undergoing healing and for the most part covered in.

Histological Report.—The heart muscle seemed normal. The small vessels with a single line of endothelial cells were often accompanied by a heading of small rounded cells on either side. These seemed to be in the lymphatic sheath if so small a vessel could be said to have one. The epicardium was densely infiltrated with such cells. The pancreas was normal. The capillaries of the liver contained abundant cells with large round vesicular nuclei, somewhat larger than those described in the lymph glands, but the differences were slight and they are probably the same cells. The tissues about the vessels were thickly infiltrated with these cells. In the spleen the Malpighian bodies were not enlarged; the splenic pulp was somewhat oedematous and there were definitely-walled tubercles throughout it which resemble what are generally called blood spaces. These were filled with large lymphoid cells and between them was the blood. In the intestines the Peyer's patches were much enlarged and presented the same histological features as the lymph glands. The adrenal glands showed no special change. The adjacent fat seemed to contain many small rounded cells with relatively large vesicular nuclei. These were also seen in the blood in the vessels. The kidney showed extensive infiltration with cells lying about the tubules. They were apparently in the small lymphatics which accompany the lymphatics between the tubules and which were thus so distended as to compress the capillaries. The testicles showed much the same condition. The tubules were widely separated. The blood vessels were compressed and empty of cells except a few red-blood corpuscles, but the lymphatic tissue about was widely distended with cells. The thyroid was normal except that the sheaths of the vessels were filled with the previously described cells. The protoplasm of these was in

very small amount and took but a feeble stain. The structure of the inguinal lymph gland was altogether destroyed. There did not seem to be any nodules in the lymph sinuses. The whole was a mass of rounded cells of the type described but without any definite arrangement. Through these ran delicate endothelial vessels and also fibrils of substance resembling fibrin (stained by Weigert). The blood vessels contained these same cells.

Bone Marrow.—This was extremely rich in cells, chiefly of small size. The crowding of the blood vessels with small nucleated cells was a particularly striking feature. There were many megalocaryocytes; there were relatively few myelocytes. Typical myelocytes did occur in groups, but they were greatly outnumbered by the other cells. Eosinophilic myelocytes occurred in typical form, but were even less numerous. Polymorphonuclear leucocytes were only rarely found. There were a few large lymphocytes with large pale-staining nuclei. On the other hand, there were enormous numbers of small cells about the size of a red corpuscle or slightly larger, with relatively large round vesicular, deeply-staining nuclei, sometimes appearing almost solid, surrounded by scanty protoplasm, which was clear or very faintly granular. In some of these the nuclei were nicked. These cells formed the great bulk of the cells seen in the blood vessels. The marrow was not especially rich in red corpuscles, but normoblasts and megaloblasts, as in normal marrow, were found here and there. The predominant cells were evidently the forming and well-formed lymphoid cells of the marrow, and suggested a proliferative change in that particular sort of lymphoid tissue which one finds in the bone marrow. The bacteriological examination was negative.

It is difficult to determine the duration of this case. If the severe haemorrhage be considered as the onset the course was eight weeks. A striking feature in the blood picture is the large number of nucleated red cells. There were 3,720 per c.mm., of which 45 per cent. were normoblasts, 48 per cent. intermediate forms, and 7 per cent. megaloblasts.

4. T. W., male, white, clerk, aged 21 years, was admitted on April 25th, 1903, complaining of sore throat and bleeding from the nose. His family history was negative. There was a history of an attack of gonorrhoea three years before, otherwise he had been healthy. He had been in the Philippine Islands for three years previous to October, 1902. There he had suffered from a severe attack of tonsillitis for which he was admitted to the hospital.

The present illness began in the middle of March, 1903, when he had a severe attack of tonsillitis. With this there was fever and *malaise*. The throat condition persisted and he lost strength. On April 18th he had a severe haemorrhage from the nose which lasted for several hours. There was bleeding at intervals up to admission. He had lost 30 lb.

On admission he looked ill; his colour was sallow. The mucous membranes were very pale. There was no jaundice. The teeth were in good condition. The gums were not spongy. Both tonsils were enlarged. There was an area of ulceration on the left. There were areas of haemorrhage over the soft palate. The neck was swollen, due principally to the enlarged glands. Over the trunk, arms, and legs was an abundant purpuric eruption. Many of the areas were fresh, others were old. There was general glandular enlargement. The lungs were clear. The heart was not enlarged. There was a soft systolic murmur at the base. The pulse was 96 and slightly dicrotic. No pulsation was made out in the veins. The abdomen was natural. The liver was not felt. The spleen was just palpable. The temperature varied from 101° to 103.5°. The urine contained a trace of albumen with some granular casts.

Blood.—The haemoglobin was 45 per cent., red cells, 3,000,000 and white cells 133,000 per c.mm. The coagulation time was five minutes. In the fresh blood there were many large mononuclear cells, which showed fairly active motility. There were clear areas in these cells, which showed rapid variation in size and number. The differential count showed: Polymorphonuclears, 5.8 per cent.; small lymphocytes, 10.8 per cent.; large lymphocytes, 70 per cent.; medium lymphocytes, 13 per cent.; large mononuclears and transitionals, 0.4 per cent. The red cells showed little change. There were some small cells, and a few larger than the average. There was very slight poikilocytosis. In counting 1,000 leucocytes two normoblasts were seen. The specimens were stained with difficulty. There were all gradations in the size of the lymphocytes. The prevailing form was large. The rim of protoplasm sometimes took a faint granular stain. No definite granules could be seen in the large mononuclears, whose

nuclei took a pale-blue stain. The neutrophilic granules also stained very faintly and irregularly. Many of the granules were very small.

At times, with both the Ehrlich and Wright stains, some of the large mononuclears showed red-staining bodies in the cytoplasm. These were at times rodlike, again broken up into smaller fragments, with rounded ends, and some formed only a red granular mass.

The differential counts for several days showed little alteration. On May 7th the haemoglobin was 35 per cent., red cells 1,850,000, and leucocytes 118,000. The mononuclear cells showed some amoeboid movements which were very sluggish. The same red-staining bodies were found in various shapes.

Nosebleed occurred often. During this time there were frequent fresh areas of purpura. There were large retinal haemorrhages. The temperature was irregular, varying from 99° to 103°.

The course was progressively downward. The blood showed on May 13th the small red-staining rods in nearly every large mononuclear and in some of the small mononuclears. The differential count showed much the same percentages as noted before. There were all sizes of mononuclears. On May 14th 6 nucleated reds were found in counting 1,000 leucocytes. They were normoblasts.

Haemorrhages and fresh petechiae were frequent. Oedema appeared. Several times the nose was plugged to stop the bleeding. There was haematemesis. No blood was found in the urine. Cultures from the tonsils gave streptococci and staphylococci. Blood cultures were negative. Fever was constant. The patient died on May 16th. An autopsy was not obtained.

A point of special interest in this case is the occurrence of amoeboid movements in the large lymphocytes. These were quite active at times. The duration of the disease was about eight weeks.

5. S. J., male, white, schoolboy, aged 16 years, was admitted in coma on September 21st, 1903. The history was obtained from his mother. His family history was negative. As a young child he had been fat and apparently robust, but never very strong. His testicles did not descend until the 10th year. He had at times suffered from boils. The last time was four months before admission. He had been at school and working on the farm until the present illness.

In July, 1903, he had a shaking chill followed by a sweat. After this he was apparently not very well. He seemed to lose strength and weight, and it was noticed that he passed large amounts of urine. This was examined and found to contain sugar. He was not put on any special diet, but gradually improved until the latter part of August, when the sugar was found to have decreased in amount. There was never any excessive thirst. During the latter part of August he was much better and gained strength. It was noted that he was often very drowsy, and would fall asleep even when driving. About this time he cut his face while shaving, and following this there was quite an extensive abscess which required lancing. In the early part of September he had severe diarrhoea. There was never any blood in the stools. On September 16th he complained of severe pain in the lower jaw, while the gums became swollen and bled when touched. Fever also was noted of an intermittent type, the temperature rising in the evening. He became weaker, and on September 20th he brought up blood thought to come from the lungs. There was some numbness of the hands and feet. There had been some dyspnoea and palpitation of the heart.

On examination there was an extensive pallor. The lips were dry. The gums were dry and bled readily. The respirations were 60 and very shallow. The breath had a sweetish odour. The breath sounds were everywhere harsh and accompanied by many *râles*. The heart was not enlarged; there was a soft systolic murmur at the base. The pulse was 140 and of fairly good volume. The abdomen was full; the walls were held rigidly. Neither the liver nor the spleen could be felt. The glands generally were enlarged, but not tender. No urine could be obtained. The temperature was 106° on admission.

The patient's condition was desperate; he improved for a time with stimulation, but soon became worse and died nine hours after admission. An autopsy was not obtained.

The blood showed haemoglobin 16 per cent., red cells 748,000, and leucocytes 57,800 per c.mm. The differential count of 1,000 leucocytes was: Polymorphonuclears, 0.3 per cent.; small lymphocytes, 88.2 per cent.; medium lymphocytes, 5.3 per cent.; large lymphocytes, 6.2 per cent. No large mononuclears, eosinophiles, or myelocytes were seen in

counting these or in subsequent search. In counting 1,000 leucocytes two nucleated red cells were seen, one a normoblast and one an intermediate.

SUMMARY.

All the patients were white males, their ages varying from 3 to 21 years. The only point of interest in the family history was in Case III. There was a history of several of the family having been subject to attacks of haemorrhage. There was no tuberculous family history in any case. The previous history was rather unimportant. One patient had adenoids, and then had been subject to attacks of tonsillitis, while a third gave a history of attacks of epistaxis for some years.

Onset.—In studying the reported cases of leukaemia one is impressed by a group in which the onset is rather difficult to determine. Of this series, in three the onset was abrupt, in two more gradual. The prominent symptom at onset was weakness in two; haemorrhages, tonsillitis, and abscesses in one each.

Symptoms.—The symptoms during the course showed much similarity. There was fever, weakness, haemorrhages, either externally or into the skin, and a rapidly progressive downward course. Loss of weight was a marked feature in three, and throat symptoms were present in two. Marked changes in the gums were only seen in one case. Glycosuria was present once.

The main conditions found on physical examination was as follows: Pallor was a striking feature in all, and with this marked weakness. The tonsils were swollen and covered by a membrane in one, a tonsillar ulcer was present in one, and in a third the tonsils were only slightly enlarged. Herpes of the lips occurred once. Purpura was seen in three cases and bleeding in four, in three from the nose and in one from the gums. Haemorrhages into the retina were noted once. General glandular enlargement was noted in four, but was not present in the fifth. The spleen was enlarged in four and the liver in three cases. Dullness over the sternum was noted once, and found at autopsy to be due to a persistent thymus. A systolic murmur over the heart was heard in all but one.

The urine was clear in two cases. Albumen was present in three, and sugar in one. The diazo reaction was given in one, and in the same case acetone and large numbers of leucin spherules and tyrosin crystals were present.

In all there was fever reaching above 103° F. In two the temperature rose to 106° F. The course was usually irregular. The pulse was rapid, varying from 120 to 140.

Blood cultures were positive in two instances (Cases I and III). In one streptococci and in the other streptococci and staphylococci were found.

Course.—The average duration was six weeks. The most rapid course was twelve days; one was four weeks and three eight weeks. Treatment did not seem to have any influence. Large doses of arsenic were given, but otherwise the only treatment was symptomatic.

Blood.—The average count of the five cases on admission was haemoglobin 35.4 per cent., red cells 1,822,000, and leucocytes 104,000 per c.cm. If, however, Case I with the high white count of 326,000 be omitted, the average leucocyte count for the others is 48,500. The highest count was in Case IV, with haemoglobin 45 per cent. and red cells 3,000,000. The lowest was in Case V, in which before death the haemoglobin was 16 per cent., and the red cells 748,000. The most rapid fall in the count was in Case IV, where in fifteen days the haemoglobin fell from 45 to 20 per cent., and the red cells from 3,000,000 to 1,450,000. A point to which special attention is directed is the high colour index in the average of the counts. It equals 0.97. The colour index in the cases is 0.93, 1, 1.4, 0.75, and 1.1. In only one is the colour index below 0.9, and in three it is 1 or over. This seems of some importance, and reference will be made to it again.

It will be noted that in every case the lymphocytes were over 90 per cent. of the total leucocytes. The highest percentage was 99.4, in Case II, the lowest 94.2, in Cases I and III. In three the prevailing cell was the small lymphocyte. This is unusual, for taking the cases in the literature, only in about 20 per cent. of the acute cases is the small lymphocyte the prevailing cell. Of special interest is the fact that in Case I, with profuse haemorrhages and a course of less than two weeks, 90 per cent. of the lymphocytes were of the small type. As a rule the rapid cases with haemorrhages show a predominating lymphocyte of the large type. In Case IV there were many of the large lymphocytes which showed active motility in the fresh specimen. There were also various

rod-shaped bodies in the leucocytes and red cells which took a deep-red stain with eosin. These were probably the same bodies which Dorothy Reed¹ describes in the case reported by her as being found in the lymphoid cells of the bone marrow. They will be dealt with more fully in an article by Dr. John Auer. In the later cases frequent examinations were made for parasites after the methods described by Löwit, but none were found.

The differential counts showed :

Case.	Leucocytes.	Polymorpho- nuclears.	Lymphocytes.		Eosinophiles.	Large Mono- nuclears and Transitionals.	Myelocytes.	Nucleated Reds per 1,000 Leucocytes.
			Small.	Large.				
I	326,000	4.0	90.0	2.2	0.8	0.2	0.0	2
II	26,000	13.2	41.5	45.0	0.0	0.2	0.1	0
	60,800	0.3	96.6	2.2	0.1	0.2	0.0	0
III	12,000	5.0	93.3	0.9	0.9	0.0	0.0	310
IV	133,000	5.8	10.8	70.0	0.0	0.4	0.0	2
V	57,800	0.3	88.2	6.2	0.0	0.0	0.0	2

There is no necessity for any discussion of the general problems connected with acute leukaemia. There have been a number of recent articles² which have taken up the whole question of our present knowledge of the disease.

While our clinical knowledge of acute leukaemia is fairly definite we are still far from any exact explanation of its etiology. Recent work has continued to prove the truth of Neumann's contention that the bone marrow is always involved, and the study of acute cases without glandular enlargement has thrown some light on the disease. It seems well established that the primary condition is one affecting bone marrow and other lymphatic structures are involved secondarily. The normal formation is disturbed and we find cells in the peripheral blood which are usually only present in the bone marrow. Are these cells attracted into the blood stream by chemiotactic agency or are they "pushed out" from the bone marrow? As Dorothy Reed³ points out, there are two important types of cells: (1) Smaller than a red cell and with a densely-staining protoplasm, and (2) small and large lymphocytes with a proportionately large nucleus. Both types proliferate rapidly by direct division, but only in the bone marrow.

Parkes Weber⁴ has suggested that acute leukaemia is probably a "more primitive or less differentiated type of disease than the more chronic forms of lymphatic leukaemia." As he points out, there may be intermediate types, and this it is well to keep in mind. In going over the cases in the literature one is impressed by the various differences in details.

While the attention of students of the disease has been specially directed to the condition of the leucocytes, it may be that there is another factor perhaps equally important, namely, the condition of the red blood cells. In noting the blood counts of these five cases it was pointed out that the average colour index was 0.97, and that in only one did it fall below 0.9. For purposes of comparison the blood counts of 40 cases⁵ from the literature were gone over, and the average colour index for the series was found to be 0.94. In 15 of these the colour index was over 1, in 20 under 1, and in 5 approximately 1. In these 40 cases the red count was over 2,500,000 in 8, from 1,500,000 to 2,500,000 in 11, from 1,000,000 to 1,500,000 in 11, and below 1,000,000 in 9. Adding the cases of the present series, we have in 24 out of 45 cases a red count below 1,500,000, and in 38 out of 45 cases below 2,500,000. Such a proportion of low counts with a high colour index we find in only one other disease, namely, pernicious anaemia. Does such a finding not suggest that we have with the special leukaemic features also a very rapid severe anaemia of the primary type? Further, does not such a condition strengthen the view that certainly a very essential part of the process is situated in the bone marrow? The cases of acute myelogenous leukaemia reported by Billings and Capps⁶ give an average colour index of 0.82 for 7 cases with full counts.

Regarding the condition of the red cells, the usual report is that they showed little change. There is generally no more

than very slight variation in size, shape, and staining. There is a marked quantitative with little qualitative change. Nucleated red cells are not common in the majority of the cases. This is in agreement with the blood condition in very rapid cases of pernicious anaemia. In these the nucleated red cells are usually few. Yet in some cases of acute leukaemia the nucleated red cells are numerous. Thus, Herrick,⁷ in one acute case with a red count below one million, found 1,800 nucleated red cells per c.mm., of which a few were megaloblasts. He also refers to another case which he had seen, in which nucleated red cells were common. In the case reported by Miller and Hess,⁸ there is no note of the exact number of nucleated reds. They are said to be numerous, and chiefly megaloblasts. In Case III of this series there were 3,720 nucleated red cells per c.mm., or one to every 330 red cells. Of these 45 per cent. were normoblasts, 48 per cent. intermediate forms, and 7 per cent. megaloblasts. This was a rapid case with severe haemorrhages.

A curious case, with somewhat similar findings, is reported by von Leube.⁹ This was a child, aged 10 years, who came under observation with a blood count of haemoglobin 10 per cent., red cells 256,000, and leucocytes 10,500 per c.mm. There were 225 nucleated red cells per c.mm., of which 75 were normoblasts and 150 megaloblasts. Of the leucocytes, 14 per cent. were myelocytes, 40 per cent. polymorphonuclears, and 40 per cent. lymphocytes. Death occurred in four days after she was first seen. There was no glandular enlargement, the spleen was enlarged, and the liver showed amyloid change. Such a case is difficult to classify.

The drop in the red count may be very rapid. Thus in Case IV there was a drop of 10 per cent. of haemoglobin and 1,150,000 red cells in twelve days. In Churchill's¹⁰ case, in four weeks the haemoglobin fell from 60 to 15 per cent., and the red cells from 3,500,000 to 1,280,000 per c.mm. In Arneith's¹¹ case, after an illness of three weeks, the haemoglobin was only 10 per cent., and the red cells 256,000 per c.cm. Such figures emphasize the rapid blood destruction. It is a point of interest that so many of the patients come under observation with a very low count.

It may be suggested that the frequent severe haemorrhages are largely responsible for the low red counts. But this is not a probable explanation. In certain of the acute cases, especially in the younger patients, haemorrhage does not occur, and, besides, the type of anaemia is not that which we find after bleeding, although doubtless it contributes to the result.

It seems reasonable to consider that in acute leukaemia we have to recognize, in addition to what may be called the specific leukaemic features, also very severe changes in the red cells. As to the exact factors at work in causing these changes we can only conjecture. It is tempting to consider that if all the blood cells be derived from a common source, we must look for the essential cause of this disease as something affecting the primary lymphoid type of cell. If we regard the atypical lymphocytes found in the circulating blood as immature cells swept out from the bone marrow, it might be reasonable to expect that large numbers of immature reds should also be found. This is not the case as a rule, but as already noted, neither is it the case in rapid cases of pernicious anaemia. In connexion with the similarity of the anaemia in these cases to that of pernicious anaemia, we ought also to keep in mind the increased number of lymphocytes so frequently found in the latter disease. This is both a relative and an absolute increase.

The disease in all its features suggests a severe toxic process, and it may be quite a different process from the chronic forms of leukaemia. The work of Flexner and his pupils on lymphotoxic and myelotoxic intoxications seems most important along the possible lines of explanation.

Leube has suggested the term "leukanaemia" to describe cases with features both of severe anaemia and leukaemia. It would seem that many of the cases of acute leukaemia might be described as coming under such a heading. This name has, however, no pathological basis, and can only be used as a convenient clinical term to designate a certain group. There are probably cases which it is difficult to classify under any fixed rules. That such a complicated structure as the bone marrow when diseased should give many different conditions does not seem strange. It is possible that we may be able to separate certain of these cases as they are better understood.

DIAGNOSIS.

This can rarely be made without a blood examination.

The increasing number of cases reported is due undoubtedly to the greater frequency of routine blood work. The cases usually suggest an acute infection. If the throat symptoms be severe at onset there seems enough to explain the condition, and there may be no suspicion of the grave malady. In the cases with swelling and bleeding of the gums scurvy may be suggested. If there be many haemorrhages, either externally or into the skin, purpura naturally seems a proper diagnosis. As Kelly suggests, many of the cases have probably been mistaken for typhoid fever.

There are some cases which suggest features of the group suggested by Leube. Future work is necessary to determine their exact classification. Some may give difficulty in diagnosis between pernicious anaemia and leukaemia.

ETIOLOGY.

Discussion on this must be more or less theoretical. Neither hereditary conditions nor the previous health of the patient can be said to have any definite influence. The association of severe throat and mouth lesions may be causal or secondary. In some instances an etiological influence is strongly suggested. The frequent finding of streptococci and staphylococci may be regarded as perhaps of significance, but it seems more reasonable to regard these as terminal infections. The whole clinical picture suggests a severe infection, and also the possibility that acute leukaemia may be quite a distinct process from the chronic type. The observations of Löwit are as yet unconfirmed.

In conclusion, the following points may be emphasized:

1. That in the majority of the cases of acute leukaemia there is a rapid destruction of the red cells with the blood features of a severe primary anaemia.
2. That the essential changes in acute leukaemia are in the bone marrow.
3. That certain cases seem to justify the term of "leukaemia" suggested by Leube.
4. That in the study of future cases more attention should be paid to the changes in the red cells and the probable similarity to pernicious anaemia definitely decided.
5. That the clinical features of acute leukaemia suggest its being an acute infection, and perhaps a distinct disease from chronic leukaemia.

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A CASE OF ACUTE LYMPHATIC LEUKAEMIA.

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THE subject of this note was a boy, aged 12 years, as fine a sample of coming manhood as one could wish to see. He had always enjoyed good health, and I would only note in passing that he was an old man's child, his father being now nearly 90 years of age, although in vigorous health.

The boy was at a public school in England, and when he returned home for the Easter holidays last year his mother noticed a spotty rash on his chest, which he attributed to forcing his way through a hedge during a paper chase. It had also been observed that he was a little more languid than usual, and became rather short of breath after any exercise. As he was to return to school next day, I was called to see him on April 28th, 1903.

He expressed himself as quite well. There was distinct anaemia, showing especially in the mucous membrane of the lips and palate. The tongue was coated. A petechial rash was present on the chest and trunk, and particularly well marked on the legs. The heart appeared normal. The spleen could just be felt under the costal margin at the end of a deep inspiration.

For a fortnight he remained in bed with a slight rise of temperature, not exceeding 100°. He had some pain and

swelling in one knee, and the petechiae came out in crops, each set fading in a few days. The tongue remained coated, and constipation was present.

As the anaemia appeared to be deepening and the parents were dissatisfied with the slow progress of the patient, I recommended a blood count, and on May 12th Dr. Houston kindly came down. The result of the count was as follows:

Red cells ...	...	1,600,000 per c.mm.
White cells ...	...	40,000 "
Haemoglobin ...	...	30 per cent.
Differential count of white cells:		
Polymorphonuclears ...	...	0.8 per cent.
Small lymphocytes ...	...	7.4 "
Large lymphocytes ...	...	91.5 "
Transitionals ...	...	0.3 "

That is, 99 per cent. of the leucocytes were lymphocytes. This at once revealed the true nature of the malady, and only too clearly resolved our doubts. I am much indebted to Dr. Houston for his promptitude in completing the examination. He only got home after 8 p.m., and telephoned the result by 10.30 the same evening. I immediately put the boy on Fowler's solution (m.v.).

On May 14th he was seen in consultation with Sir William Whitla. The spleen was distinctly larger and could be felt easily well under the costal arch. There was no lymphatic enlargement. A fresh crop of petechiae had come out. Arsenic increased to m.vijss.

The after-history of the case was as follows:

May 15th.—Temperature 101°, pulse 128. The rise of pulse and temperature evidently portend fresh developments, and this was borne out by the occurrence of a sharp attack of epistaxis in the afternoon, recurring again in the evening.

May 16th.—Morning temperature 100.4°, pulse 136. Bleeding from nostril continues; right nostril packed with lint saturated in solution of adrenalin (1 in 1,000). Apparently as the result of the haemorrhage the spleen is much reduced in size, and can just be felt under the costal region. Has had intense pain in left ear, for which one-eighth of a grain of morphine given hypodermically. Put on 15 gr. of calcium chloride, and 10 minims of adrenalin every three hours. Evening temperature 103.4°, pulse 152. Slept several hours after morphine.

May 17th.—Morning temperature 101.6°, pulse 156. Bleeding again when plug removed. Evening temperature 103.4°, pulse 164. Fairly well all day; no return of bleeding, and has taken food well.

May 18th.—Morning temperature 101.5°, pulse 160. Fresh bleeding from nose. Seen again with Sir William Whitla. Ol. terebinth., m.v in capsule, ordered. Evening temperature 103°, pulse 168. Some mental confusion. Breathing slightly stertorous. Respirations 24.

May 19th.—Morning temperature 98.8°, pulse 176. Delirious. Pil. morph. 1 gr. In afternoon wildly delirious for a time, but quieted by another 1 gr. of morphine. Bleeding again when plug removed. Nostril packed with puff ball.

May 20th.—Temperature subnormal, pulse 180, and very feeble. Respirations 40. Had a fairly quiet night. Evacuations involuntary. Died at 8.15 p.m.

REMARKS.

The points of interest in this case are:

1. The age of the patient—namely, 12 years.
2. The complete absence of any palpable lymphatic enlargement, coupled with a moderate amount of splenic hyperplasia. The considerable increase in the size of the spleen only lasted a few days, and was reduced again rapidly by the nasal haemorrhage. The non-involvement of the glands appears to be rather the rule in the very acute cases, and is explained by the fact that the bone marrow is first invaded by lymphoid tissue, and the patient dies before the glands have time to react. The absence of this sign adds greatly to the difficulties of diagnosis.

3. Its exceedingly rapid course, so that one cannot help comparing it to a specific fever or septicæmic process. If we date its onset from three weeks before he was seen, the fatal malady ran its course in six weeks, and the symptoms were only acute from the first epistaxis—that is, six days before death. As his mother remarked, she absolutely refused to believe the contents of my note, informing her of the result of the blood count and of the fatal nature of the disease, when she looked at him sitting up in bed chattering to his brothers and sisters, and yet he was dead eight days later.

4. The absolute necessity for a blood count in every case where anaemia is a feature and the symptoms obscure. As Ehrlich says, "the microscopic examination of the blood alone, on dry preparations, without the assistance of any other clinical method, can decide whether a patient suffers from leukaemia, and whether it belongs to the lymphatic or myelogenic variety."

5. The profound anaemia, even before the onset of the epistaxis.

6. Although the case became critical from the time the nasal haemorrhage set in, still the patient did not appear to