divided nuclei were always quite distinguishable by the characters given above from the ordinary polynuclear leucocyte; a coarse finger-like or amoeboid-looking lobulation was the commonest condition. Many of these large cells seemed very labile, and had been traumatized in the act of making the film. This was evidenced by the loss of the protoplasm of some, and by the spreading out of others into a delicate reticulated or vacuolated layer of basophilic matter very irregular in shape. A considerable number of these possessed protoplasm with a greater amount of basophilia than the nucleus, which was then discernible with difficulty as a clear, almost hyaline, mass embedded in or seemingly apposed to the darkly-stained protoplasm. No evidence of mitotic activity was observed in any of the leucocytes in this blood.

3. The second variety of mononuclear cell comprising 32 per cent. was smaller, and its nucleus took the basic stain much more deeply. It was sometimes round, sometimes reniform. In triacid preparations the so-called "perinuclear granules of Neisser," now regarded as artefacts, showed a peculiar predilection for these lymphocytic nuclei. The protoplasm was usually quite scanty, occasionally more abundant, and decidedly basophilic, so that when the bulk of the cell was larger than normal, and its nucleus a little less basophilic, a difficulty arose in the distinction of this from the larger variety of mononuclear cell.

4. Most cells were not specially stained for, and no undoubted specimen was seen in the Jenner preparation.

5. Glycogen in finely granular form was readily detected in many of the leucocytes.

This case agrees with the clinical pictures of acute leukaemia in its sudden onset, rapid course, moderate enlargement of lymph glands, enlargement of spleen, haemorrhages in skin and mucous membranes, and oral fetor. It agrees with the haemocytic picture of acute leukaemia in the following points: (1) Enormous preponderance of hyaline mononuclear cells, the larger variety preponderating as it is said by Ewing¹ and others to do in acute cases and in children; (2) rarity of polynuclear neutrophils, and, indeed, of all forms of granule cells; (3) presence of myelocytes in very small numbers; (4) rarity of both varieties of nucleated red corpuscles, as was first pointed out by A. Fraenkel.² We have no hesitation in diagnosing the case as acute leukaemia. A discussion of the significance of the blood changes in this interesting case, and of their relation to changes in the blood-forming organs, would, we consider, be lacking in objectivity unless accompanied by the results of autopsy, which we unfortunately have not at our disposal. We therefore abstain from entering on so difficult a task, merely referring to the recent papers of Glinski,⁴ Lustgarten,⁵ Januschiewicz,⁶ and Parkes Weber,⁷ as well as to Pappenheim's complete survey⁸ of the current theories as to the origin of the blood corpuscles.

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A CASE OF ACUTE LYMPHAEMIA.*

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(From the Pathological Laboratory of the Mater Misericordiae Hospital, Dublin.)

A BOY, B. F., aged 9, was admitted to the Mater Hospital on October 1st, 1904, under the care of Dr. John Murphy. He had swellings on both sides of the neck, breathlessness, and bleeding from the nose.

Family History.—His father, a tailor, hurt his leg when 4 years old, and subsequently developed hip disease, for which amputation through the hip joint had to be performed. The mother, who was described as having been always very pale, died in February, 1903, about a fortnight after the birth of a child, from what cause I was unable to ascertain. Patient's elder sister, aged 10, was ill with pneumonia when patient was admitted to hospital, and her life was despaired of, but she recovered. His younger sister, aged 5, was described as suffering from swellings in the neck. I had her brought to the hospital and found her to be a ruddy, healthy child, with perfectly normal blood. In the upper cervical and suboccipital regions there were a few enlarged glands, which were obviously associated with irritation of the scalp, due to pediculi.

Personal History.—Six weeks before admission lumps were first noticed in the neck, armpits, and groins. For a week prior to admission he

had been suffering from epistaxis and bleeding from the gums. The swellings under the left arm were painful.

Condition on Admission.—A good-looking, well-nourished, fair-haired boy, the lower part of whose face presented a peculiar square outline owing to the large glandular swellings beneath the jaw on each side. The face and mucous membranes were very pale. The tonsils were enlarged, and post-nasal adenoids evidently present and large. Tongue dry, and coated at the side; lips cracked on the inside. The skin of the abdomen and legs is mottled with dozens of small petechiae, which are said to have appeared before the glands began to swell. Masses of enlarged glands are seen and felt at the sides and back of the neck, in the submaxillary region, in both axillae and groins. The glands are moderately hard, discrete, and freely movable. One gland in the left axilla is both painful and tender, and the glands in the right are somewhat tender. Pressure over the other glands causes no pain; no glands palpable in the antecubital or popliteal fossa. The spleen is decidedly enlarged, its edge being felt about midway between the lower border of the ribs and the umbilicus. Temperature on admission 99° (100° the same evening), pulse 120, respirations 26. The patient was very dull and apathetic. The urine deposited an abundant sediment of uric acid crystals, and contained a distinct trace of albumen.

BLOOD EXAMINATION.

At the first glance the case might have been taken for Hodgkin's disease, but the fresh blood preparation at once settled the diagnosis. On the day after admission the blood count was R. 1,898,000, W. 212,000, the proportion being as 8.9 to 1. The stained preparation showed hardly any other form of leucocyte save lymphocytes—large, faintly staining, and evidently degenerating forms being very numerous. The diagnosis was therefore lymphatic leukaemia, and in view of the rapid development of the symptoms, temperature, haemorrhages, and general condition, the case had to be classed as an acute form of the disease. The haemoglobin was about 40 per cent., specific gravity 1.0435 (Roy-Hammerschlag). The fresh blood showed much fine molecular matter floating in the plasma, and displaying remarkably active motility, probably Brownian.

The first differential leucocyte count was made on a triacid preparation three days after admission, and showed that no less than 98 per cent. of all leucocytes were mononuclear. Polymorphs were only 0.5, transitionals 1.1 per cent., whilst out of several hundred cells examined, only a couple of doubtful myelocytes were detected.

Characters of the Mononuclears.—Somewhat less than half of them (42 per cent.) were of medium size, about as big as a red corpuscle or a shade larger. Their nucleus was strongly basophile, often delicately incurved or reniform, and sometimes double, with the apposed sides of the nuclei flattened as though direct division had recently occurred. The protoplasm of these lymphocytes was scanty and hyaline. It was often more basophile than the nucleus, and in Jenner and triacid preparations there was little distinction. A certain number (about 0.6 per cent.) had the same sort of nucleus, but a much larger amount of protoplasm. These might be described as large mononuclears. The other kind of lymphocyte was present in larger numbers (56 per cent.). It was larger, more faintly stained, and so easily broken down that most of them looked like mere irregular bluish expansions, about twice as big as a red disc, and scarcely showing any difference between nucleus and protoplasm. Their margins were often fringed with irregular protuberances. Subsequent observation showed that there was no fundamental difference between these two classes of mononuclear leucocyte, their relative proportions seeming to vary with the amount of pressure used in making the film. The large faint variety I consider to consist of the more labile, degenerating, or necrotic individuals.

A very few large mononuclears appeared to contain very fine granulations of acidophile character—possibly myelocytes. In others there were basophilic granules of various sizes. Polymorphs were remarkably few and hard to find, whilst eosinophiles and typical mast-cells were absent altogether. The red corpuscles were also labile, readily deformed, apt to run together in clumps, and did not stain well, being evidently poor in haemoglobin. With few exceptions, they did not display any basophilic tendency. Nucleated forms were, considering the profound anaemia, surprisingly uncommon, and all that I came across were of normoblastic character.

Progress of the Case.—On October 6th a bluish patch of ecchymosis, 2½ in. by 3½ in. in diameter, appeared in front of the left elbow round the vein from which blood had been taken for bacteriological examination. Another large ecchymosis appeared spontaneously over Poupart's ligament, on the same side. The temperature fluctuated between 99° and 101°, the pulse was between 130 and 140, respirations about 24.

* Being portion of a paper read at the Pathological Section of the Royal Academy of Medicine in Ireland.

The sensorium was generally dull, with occasional revivals of interest in his surroundings—on one or two days he even played with his toys. Towards the middle of the month he became steadily weaker, and moaned continually with pain, which he referred to the ears, teeth, neck, and right arm and hand. The glands increased in size, and there was almost continual weeping of blood in small quantity from the nose and mouth. On the 18th he vomited twice. On the 19th I examined his blood for the last time. He was then quite conscious, but the respirations were hurried and gasping. Death took place shortly afterwards.

Development of the Blood Condition.

On October 7th the reds were 1,648,000 and the whites 310,000, the relation being 5.3:1. On October 11th the count was reds 1,444,000, whites 245,000, or nearly 6 to 1. The last count was done on the 19th, when the little patient was moribund. It yielded the remarkable figures, reds 820,000, whites 783,000, or nearly 1:1. The blood looked decidedly milky, and in the fresh preparation most of the field was occupied by the leucocytes, patches of pale, degenerate-looking, coherent, red discs being visible here and there. Stained preparations showed practically nothing but large lymphocytes of the two varieties described above. Polymorphs were very few—perhaps 1 for every 200 or 300 lymphocytes. An occasional myelocyte was seen, the fine acidophile granules being few and faint. Both Jenner and triacid preparations showed a few small cells with haemoglobin-containing protoplasm of basophilic tendency, a nucleus of normoblastic type and coarse basophilic granules. Normoblasts were fairly abundant, but megaloblasts were absent. Despite the enormous numbers of lymphocytes which must have been the products of active proliferation, I could find very few mitotic figures, and these were not well preserved. The nuclei rather gave the idea of multiplying by direct division. The films were dry ones, however, fixed by heat or alcohol and ether, not with Flemming's solution.

Bacteriological Examination of the Blood.

On October 6th, rather more than 5 c.cm. of blood was obtained aseptically from a vein in front of the elbow, and at once introduced into 500 c.cm. of sterile bouillon which was then placed in the incubator at 37° C. No growth whatever occurred, and at the end of a few days the corpuscles, both red and white, appeared quite unaltered in the sediment. Stained films of this showed nothing resembling protozoa.

Effect of Stains on the Fresh Blood.

On October 6th the patient's finger was punctured through a drop of Unna's polychrome methylene blue, and the mixture of blood and staining fluid examined at once. The nuclei of the lymphocytes were then seen to have become deep violet, whilst those of the polymorphs remained colourless. After the lapse of a few minutes, the protoplasm of the polymorphs began to present a fine violet granulation—evidently due to staining of the neutrophile granules by the red constituent of the polychrome blue. Control preparations with healthy blood showed no staining of any leucocyte nuclei, though a similar tinging of the neutrophilic granules appeared after a time. The rapid penetration of the stain into the lymphocyte-nuclei of this patient I am inclined to ascribe to their being in a necrotic, devitalized condition.

Necropsy.

This was done a few hours after death. The body was still warm and the blood only partially coagulated. Its volume seemed much increased, and that contained in the heart looked exactly like anchovy sauce. On standing in a jar it deposited a layer of red corpuscles about an inch thick, whilst the supernatant fluid was cream coloured.* The coagula in the heart resembled lumps of fat. Charcot-Leyden crystals never formed.

Heart much distended with discoloured blood, its surface thickly sprinkled with petechiae. Endocardium normal. No valvular lesion. Muscles seemed unaltered. The pericardium contained about 2 oz. of turbid serum. On its apex was an enormously enlarged thymus, consisting of two well-defined triangular lobes and a connecting central part. Its colour was pale pink without, white within, its consistency quite soft, almost brain-like. Behind it a mass of enlarged glands adhered to the innominate veins and seemed almost to penetrate them.

Lungs.—These showed no sign of tubercle. They were sprinkled over with large subpleural petechiae, and contained many small haemorrhagic nodules like small infarctions. Bronchial glands enlarged to the size of good-sized beans, pinkish-grey on section. Glands in the posterior mediastinum moderately enlarged. Tonsils much enlarged.

* The coloured illustrations which accompany this paper will appear in the next volume of the *Transactions of the Royal Academy of Medicine in Ireland*.

The **peritoneum** was studded over with petechiae. It contained no fluid. The great omentum contained many glands as large as peas and bright red in hue.

Spleen moderately enlarged (12 oz.), pale-red without and within, consistency normal. The trabeculae and follicles were quite visible on the cut surface, which did not differ markedly from the normal. One small white infarct 6 by 2 mm. was seen.

Liver enlarged and hyperaemic, colour pale, with yellow dots as though fatty. Lobular marking obliterated. Gall bladder small; contained dark-green bile. A chain of enlarged lymphatics occupied the portal fissure and accompanied the vessels to the duodenum.

Suprarenals small, pale, flat.

Kidneys rather large; capsule stripped easily, leaving smooth, pale surface; cortex rather wide, pinkish, with large irregular, ill-defined pale patches; boundary layer distinct, bright red, a millimetre wide. Pyramids pink with white streaks. Weight of both organs 10 oz.

Stomach small, very pale externally; lesser curvature and posterior surface thickly studded with enlarged lymphatic glands. Mucous membrane cream-colour, mottled with petechiae.

Intestines.—Peyer's patches and solitary glands raised about a millimetre above the surface, swollen, grey, and pulpy; no ulcers.

Mesenteric glands as big as hazel-nuts, very red. The largest (size of a pigeon's egg) were at the ileo-caecal valve.

Cœliac and lumbar glands moderately enlarged, soft, bright red on section, hyperaemic.

Marrow of the long bones was dark-red in hue, and resembled spleen pulp.

C. N. S. and external lymph glands, in deference to request of the friends, were not examined.

MINUTE ANATOMY.

The tissues selected at the autopsy (which was done whilst the body was still warm) were fixed, some in Flemming's strong mixture, others in saturated sublimate, and the remainder in 10 per cent. formalin. Smear preparations of the organs were also made.

Marrow (of Femur).

(a) **Smears.**—These showed practically only one sort of leucocyte, namely, large mononuclear cells which at first sight appeared to consist entirely of a large, faintly-stained nucleus. On closer examination, a zone of protoplasm could be made out, of approximately the same affinity for basic dyes as the nucleus, and, therefore, inconspicuous. It was non-granular. The margins of these cells (or nuclei) were often peculiarly fringed or crenate. They took the stain in a patchy manner, and altogether gave one the idea of being labile, degenerate structures. Here and there one of their nuclei, more darkly stained than its neighbours, looked twisted or contorted as though undergoing mitotic change. But in none of the films (alcohol and ether fixation, staining with Ehrlich's haematoxylin) did I observe a genuine mitosis. On the other hand, many of these cells rather gave one the idea of multiplying by fission or budding, and this impression was still further increased by the frequent occurrence of masses of these nuclei lying close-packed together in an ill-defined protoplasmic mass, the whole structure closely resembling an immature giant-cell. The films also showed many red corpuscles, a large proportion being nucleated, and of normoblastic type. Their nuclei were, as usual, opaque black with haematoxylin, and many were rosette-shaped or otherwise fragmented, but no genuine mitoses were found on the films. Megaloblasts were not seen. Here and there was a very large cell (macrophage) with single or lobed, vesicular, faintly-staining nucleus, and an abundance of strongly acidophile protoplasm, in which were embedded irregular masses of deeply-stained chromatin, evidently nuclear debris undergoing intracellular digestion.

(b) Sections of sublimate-fixed marrow presented an aspect which at first sight differed widely from that of the films. This was because the cells looked so much smaller in sections than in the spread films. Closer examination, however, showed that the prevailing type of cell was the same—large lymphocytes with round or lobulated nuclei and scanty protoplasm. The fringed and crenate appearance of the cell borders met with in the films was not seen on the sections. The cells were supported on a very delicate stroma, through which coursed many wide vessels, the walls of which were composed of a single layer of endothelial plates. The cells within these vessels were the same as those without—namely, mononuclear leucocytes similar to those in the peripheral blood. Some of the larger vessels in the marrow were literally packed with them. Scattered through the mass of lymphocytes of which the marrow was composed were very large masses of protoplasm with single or lobulated vesicular nucleus and acidophile protoplasm (megacaryocytes).

The most remarkable feature about the marrow was that it contained no granule cells of any sort. The absence of neutro-

phile myelocytes was proved by the treatment not only with Ehrlich's triacid, but also with Dominici's eosin-orange-toluidin blue. It also contained very little fat.

With regard to evidences of mitotic division, the only preparations that yielded satisfactory results were those stained with Heidenhain's iron haematoxylin, after Flemming or sublimate fixation. In these, plenty of mitoses were seen, both within and without the vessels. It must, however, be remarked that the chromatin loops were mostly more or less "lumped," and that good diasters seemed unusually hard to find as compared with, for example, a rapidly-growing epithelioma.

Lymph Glands.—These were packed with large mononuclear cells with vesicular nucleus, containing several nucleoli. The protoplasm was often reduced to a narrow rim. These cells were evidently the same large lymphocytes which swarmed in the blood and marrow to the almost complete exclusion of almost every other sort of cell. Not only was the capsule of the lymph glands infiltrated with these cells, but also the fat-cells which occurred in the vicinity. The glands also contained large endothelial plates belonging to the reticulum, and large mononuclear elements with acidophile protoplasm often containing deeply-stained fragments of chromatin or vacuoles (macrophages). No distinction between germ centres and ordinary lymphoid tissue could be made out, nor could the lymph sinuses be distinguished. The only channels seen were large or small thin-walled blood vessels crammed with red discs and lymphocytes. A remarkable character of these blood vessels was that they contained many macrophages.

Mitoses were very numerous in preparations stained with iron haematoxylin, as many as twenty being seen in a single oil-immersion field, whilst as many as 17 were counted in the cross section of a blood vessel 0.06 mm. in diameter. In many cases the daughter nuclei seemed to be again dividing without going through a resting stage. The fat outside the capsule of some of the lymphatic glands was also infiltrated with proliferating lymphocytes.

The **thymus** presented, so far as examined, appearances identical with the lymph glands. Some concentrically whorled structures (Hassall's corpuscles) could be made out among the swarming lymphocytes. Mitotic figures were readily demonstrable.

The **spleen** presented the same minute structure as the lymph glands plus patches of extravasated red discs. Mitoses were, however, not so readily found in it. The distinction between pulp and follicles had disappeared.

Heart.—There were large perivascular accumulations of lymphocytes, which seemed to be forcing their way in between the muscle fibres and to be compressing or eroding them. Similar accumulations were seen beneath the epicardium and pericardium. Many of these extravascular lymphocytes were dividing.

The **nodules in the lungs** proved to be due to the occupation of superficially-placed groups of air cells by (1) oedema, (2) haemorrhage, and (3) lymphocytic accumulations. The vessels in the vicinity were stuffed with lymphocytes, which were dividing both within and without the vessels.

The **liver sections** presented an appearance all the more remarkable because the naked-eye characters were not strikingly altered. There was most extensive infiltration of the lobules with large lymphocytes which distended the capillaries and in places so compressed the liver cells as to cause them to atrophy and melt away. Whole groups of lobules were thus converted into lymphoid tissue, through which coursed strands of atrophic hepatic cells forming a scarcely visible network. The infiltration was not confined to any one region, both the centre and the periphery of the lobules as well as the portal canals seeming to suffer equally from the lymphoid intrusion. In places the capillaries were plugged in a very remarkable manner with large ovoid, oblong, or linear nuclei, hyperchromatic and degenerate, and seemingly devoid of protoplasm. These peculiar nuclei were often twisted together like cords, and seemed as though dividing by transverse direct division. Mitotic figures could not be seen in them even in iron haematoxylin preparations. There were transitions between these and accumulations of ordinary round lymphocytes more closely packed than usual, and of course, between these and less closely-packed individuals.

The capsule was intensely infiltrated, and cord-like masses of lymphocytes penetrated from it into the body of the organ. Mitoses were readily discoverable in all these accumulations by appropriate staining.

In the less deeply infiltrated parts the liver cells seemed healthy, and in iron preparations showed the intercellular

and intracellular bile capillaries with great distinctness. Giant cells were not seen in the liver, nor did the capillary endothelium seem to share in the proliferative process.

The **kidneys** showed, *mutatis mutandis*, precisely the same minute appearances as the liver. Proliferating lymphocytes seemed to have actually found their way, here and there, into the tubules. Mitoses were readily found.

Sections of the swollen intestinal lymphoid apparatus showed appearances similar to those already described in the lymphatic glands.

SUMMARY.

This case was typical of the acute form of the disease in the following characters:

1. The youth of the patient (9 years).
2. The duration (nine weeks).
3. The moderate enlargement of spleen and glands.
4. The clinical course, characterized by fever, haemorrhages, and increased uric acid excretion.
5. The predominance in the blood of the large mononuclear cell with hyaline basophile protoplasm. At no time were these less than 95 per cent. of all leucocytes.
6. The complete destruction or suppression of the myeloid element in the marrow, and the consequent total absence of granule-cells from the blood.

The following characters seem to me, from a study of such already recorded cases as are accessible to me, exceptional:

1. The severe and rapidly progressive anaemia, the reds falling from 2,000,000 to 820,000 within three weeks. The total absence of megaloblasts is highly interesting, as showing that the production of these elements is no part of the normal regenerative process, but takes place under the influence of some special stimulus which was absent in this case. (There were plenty of normoblasts in the marrow.)
2. The large proportion of leucocytes to erythrocytes. Osler states that it is never as great in the lymphatic as in the myelogenous form of leukaemia, and regards 1 white to 10 reds as quite excessive. In this case the first count yielded 1 white to 8.9 reds, and the ratio at the end was practically 1 to 1.
3. The absolute number of lymphocytes—over 700,000 at the end—was also higher than is usually met with in acute cases. Dominici says in his article in the second volume of the new edition (1902) of Cornil and Ranvier's *Pathological Histology*, p. 674, "le nombre des mononucléaires mis en circulation, ne dépasse guère quarante ou cinquante mille." It is only fair, however, to add that higher numbers than those mentioned by Dominici are given in some recent observations of the acute form of the disease—one by Januskiewicz¹ with 165,000 whites, of which 87 per cent. were large mononuclear, and the others by Kelly² with 119,000, 567,000, and 378,000 leucocytes respectively, nearly all being lymphocytes.
4. The great enlargement of the thymus.

CONCLUDING REMARKS.

1. The essential feature of the morbid state in this case is the abnormal activity of the lymphoid tissues throughout the body and the flooding of the blood and tissues with their products, the lymphocytes.

2. This activity in the recognized seats of lymphoid tissue is accompanied by a rejuvenescence of that tissue in places where only traces of it persist during adult life—for example, the marrow of the long bones, the liver and kidneys. In the bone marrow, this revival takes place with such revolutionary energy as to invade and completely suppress the other variety of haematopoietic tissue—the myelogenous; hence the profound oligocythaemia, and absence of granule-cells from the blood.

3. The behaviour of the lymphoid tissue in this case strongly resembles that of malignant new-growths, and the resemblance is still further accentuated by the fact that the stimulus, whatever it may be, does not appear to be of bacterial nature (cf. the negative result of the culture experiment). Like the cells of a malignant tumour, the proliferating lymphoid cells show a tendency to spread in all directions round their focus of origin, whether that focus be a lymphatic gland or a blood-vessel (cf. the appearances described in the heart).

4. The proliferating cells in this acute case are of distinctly *embryonic* type, resembling the *mother-cells* from which both varieties of blood-forming tissue spring, rather than *differentiated* lymphocytes. This feature still further accentuates the resemblance to malignant tumours in which the malignancy is the more pronounced the more *anaplastic* (to use Hansemann's expression) or undifferentiated are its cellular constituents. On these lines, one might compare a case of chronic

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-