

SECTION OF PATHOLOGY.

HÆMATOLOGICAL OBSERVATIONS. A CASE OF CHRONIC LYMPHÆMIA.

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I HAVE been fortunate in observing during the last couple of years a series of cases representing most of the recognised morbid conditions of the blood. These cases occurred for the most part in the wards of the Mater Misericordiæ Hospital, to which I am pathologist.

In view of the great interest attaching to them, and of the rapid development of our knowledge as to their mutual relations, classification, and pathogenesis which we owe to the methods associated with the name of Ehrlich, I have thought it well to lay my observations before the Royal Academy of Medicine in Ireland. When giving notice of this paper I intended to include all the cases in the one comparative study, but on looking over the mass of notes and specimens which I have accumulated I saw that I could not adequately deal with them in the time at my disposal, and I have accordingly decided to confine myself on this occasion to the description of two cases of lymphatic leukæmia, one of chronic and one of acute character.

J. N., aged fifty-five, farmer, was admitted Sept. 2nd, 1904, to Mr. Blayney's Ward, complaining of abdominal tumour. Patient

was a tall, spare man, with pallid face and stooping shoulders. He had no serious illness previous to the present attack. In January last he fell from a hay-rick, when his left side struck the handle of a hay-fork, since which time he felt uncomfortable in that region. About Easter he began to notice his neck swollen, and first detected a distinct tumour in the left side of the abdomen on May 20th. He complained of dragging sensations, dyspnoea on exertion, loss of appetite and general weakness.

On examination the left side of the abdomen was found occupied by a large solid tumour, evidently the spleen, extending down two inches below the umbilicus. The liver was also distinctly enlarged. On both sides of the neck was a chain of enlarged lymphatics extending from the suboccipital region to the clavicle. The glands were harder and smaller on the right side. Both axillæ also contained glands, which were small and superficial on the right side, whilst on the left they formed a mass as big as a hen's egg, more deeply situated. In the right groin was a mass of glands, each of which was nearly as big as a walnut. Those in the left groin were quite small and shot-like. He did not complain of hæmorrhage from the mucous membranes, but there was a spot of suffusion under one of the conjunctivæ. The blood-count, which I made on the day after admission, gave reds, 3,908,000; whites, 163,200; whereupon the case was diagnosticated as leukæmia, and removed to a medical ward under the care of Dr. Martin Dempsey. The blood was noticed to be pale, watery, and coagulated slowly. The differential leucocyte count made two days later yielded no less than 96 per cent. of mononuclears, of which 81 per cent. were lymphocytes and 15 per cent. large mononuclears, whilst only 4 per cent. were polymorphs, the relation of mono- to poly-nuclears being as 24 to 1. The following table gives the details of the several blood-counts that were made. In the first differential count, which was made on a Jenner-stained preparation, it seemed possible to differentiate between lymphocytes and large mononuclears; the former were smaller, averaging about 8 μ ., but reaching in some cases 10.8 μ ., with deeply-staining nucleus and scanty hyaline protoplasm; the latter were larger, 11 to 15 μ ., with larger, less deeply-staining nucleus, which was often coarsely lobulated. Their protoplasm was more abundant, and in triacid and Jenner preparations it often presented a minute basophilic

granulation. In hæmatoxylin-eosin preparations the distinction between large and small lymphocytes could not, however, be maintained. Intermediate forms occurred in every field, and I was obliged to abandon the attempt to discriminate between these two varieties of leucocytes. Granule cells were extremely few; at no time did the finely granular polymorphs ever reach 10 per cent. of the total leucocytes. Myelocytes were extremely scarce, and such as were found seemed very fragile. I missed them altogether from the preparations made towards the end of the case, though they occurred in the lung-blood taken *post mortem*. Eosinophiles were even scarcer. Out of several hundred leucocytes examined on a hæmatoxylin-eosin preparation only one was seen, and it was remarkable in several respects. It was $13.2\ \mu$. in diameter, with a small deeply-staining nucleus, $6.2\ \mu$. in diameter, nearly central in position. The aspect of the cell was totally unlike that of any eosinophile I can remember to have seen. The nucleus exactly resembled that of the neighbouring lymphocytes. No undoubted mast-cell was seen. The red corpuscles showed but little alteration. On the one occasion (September 7th) when the hæmoglobin was tested with Sahli's modification of Gower's instrument, it worked out at about 65 per cent., with a red count of somewhere about 3,000,000. The specific gravity (Roy-Hammerschlag) on that occasion was 1.047. Nucleated forms were, considering the anæmia, surprisingly scarce. Megaloblasts were absent altogether, and normoblasts were very uncommon. A few, with much fragmented nucleus, were, however, detected. Granular degeneration and polychromatophilia were not observed. Glycogen was not present to a very marked extent at any time. It was seen only in the polynuclears, and never in the lymphocytes. The urine showed no marked abnormality save the presence of amorphous urates in large amount. Crystals of uric acid were not seen. There was no albumen. The total nitrogen, estimated on one occasion by my pupil, Dr. Farnan (Student in Pathology of the Royal University), was found to be 1.428 per cent. by Kjeldahl.

Progress of the Case.—On September 25th the patient, who had been allowed to walk in the garden, developed lobar pneumonia of markedly asthenic type, his temperature rose to 103° . On the 27th the respirations were gasping and hurried, pulse 128, with a tendency to intermit, face and lips pale. The breathing was

much embarrassed by the abundant muco-purulent exudate, which he was unable to expectorate. He died on the following day.

His blood was examined about 36 hours *ante mortem*, when, as will be seen from the table, there was not only no diminution of the total leucocytes, such as usually occurs when pneumonia or other infective process supervenes on leukæmia, but they were actually increased in number. Of the polynuclear leucocytosis so characteristic of pneumonia, there was no trace in the peripheral blood. This, of course, means absence of reaction against the infective agency, and accounts for the rapid collapse of the patient, who may be said to have sunk without a struggle, being deprived of his normal defensive mechanism—the polynuclear leucocytes. The vast majority of the few he did possess were found at the autopsy, as might be expected, in the blood and exudate of the lung. Another point noted in the differential blood-count made on that day was the obviously degenerate condition of the nucleus of many of the lymphocytes and large mononuclears. It was often incurved, reniform or bilobed, or else it presented a highly stained or unstained belt dividing it in two, as though it had just undergone direct division. It was often vacuolated, and a darkly stained granule, resembling a nucleolus, sometimes appeared in the centre of a large vacuole. The nodal points of the nuclear reticulum seemed also unduly prominent. The protoplasm of many of the smaller lymphocytes was reduced to a hardly visible ring. Many of the polynuclears were unusually large, with completely fragmented nucleus and protoplasmic granulations tending to be basophilic in their colour reaction to the Jenner stain.

AUTOPSY.

This was done within 12 hours after death, and was complete, with the exception of the nervous system. Only the points of importance are here given. All the lymphatic gland groups were enlarged: those in the neck, axillæ and groins moderately so (pea to cherry size); those in the mediastina, retro-peritoneal tissue, portal and coeliac regions were larger (up to a hen's egg). The bronchial glands were three times as big as normal, slate-grey in the middle, pinkish and pulpy towards the periphery of the cut surface; they were highly vascular. The capsule of all

TABLE OF BLOOD-COUNTS IN A CASE OF CHRONIC LYMPHÆMIA.

Date	Dilution used in making count	Reds, in thousands	Whites, in thousands	Relation of whites to reds	No. of Leucocytes examined in making differential count	Polymorphs, per cent.	Large mono-nuclears, per cent.	Lymphocytes, per cent.	Total mono-nuclears, per cent.	Relation of mono- to poly-nuclears	OBSERVATIONS
3	1:100	3,908	163	1:24	—	—	—	—	—	—	Blood, pale, watery—coagulated slowly.
5	1:10	—	154	—	200	4	15	81	96	24:1	—
10	1:100	2,848	206	1:14	307	7.8	2.3	89.5	91.8	12½:1	Differential count made on a Jenner prep.
15	—	—	—	—	303	5.3	—	—	94.7	18:1	Toluydene-blue prep. Mononuclears not sub-divided.
20	1:10	—	167.2	—	—	—	—	—	—	—	—
27	1:100	3,048	332	1:9	477	6.2	—	—	92.4	15:1	Hæmatox-eosin prep.—a few (1.6 per cent.) very large mononuclears seen; but, generally speaking, it was impossible to distinguish large from small mononuclears.
29	—	—	—	—	175	20.5	—	—	75.5	3.7:1	Film of lungblood taken <i>post mortem</i> and stained with Jenner. It contained 0.5 per cent. of eosinophils and 3.5 per cent. of myelocytes.

the glands seemed intact, and the glands, though swollen and soft, could not be said to be confluent; their intense vascularity was a marked feature. The largest masses were as usual found along the course of the aorta in the posterior mediastinum, and from the coeliac axis to the bifurcation.

The *lungs* showed red hepatisation of the whole left lower lobe, and of the lower fourth of the right upper, and upper two-thirds of the right middle lobe. They were elsewhere cedematous, and presented obsolete tubercle in both apices. The left pleura was nearly full of fluid; none in the right.

Heart.—Beyond some irregular raised white plaques on the surface of the right auricle, this showed no abnormality. There was slight mottling of the myocardium, but no pronounced condition of fatty degeneration.

Spleen.—This weighed 51 ozs. It was adherent to the diaphragm and omentum. Without and within it presented an appearance that might perhaps be most fittingly described as “marbled”—studded over with small irregular grey and red areas, with here and there a larger bright-yellow cheesy area of necrosis, surrounded by a vivid red zone of hæmorrhage. Its consistency was decidedly firmer than normal. Neither follicles nor trabeculæ were visible on the cut surface. In the hilum were several enlarged glands as big as a horse-bean.

The *liver* weighed no less than 83 ozs. It was soft and pale, with slight “nutmeg” discoloration. Though extensively altered, as will be seen lower down, it presented no marked change to the naked eye.

The *kidneys* were about normal in size, and studded over with small yellowish-white patches, which proved to be leukæmic infiltrations. These were mostly superficial, not penetrating more than about 2 mm. beneath the capsule.

The *mesenteric glands* were all moderately enlarged. The lymphoid structures in the small and large intestine were enlarged, and projected about 1 mm. above the surface of the mucous membrane. They were greyish-pink in hue, and not ulcerated.

Marrow.—That of the left femur and left humerus was examined, 6-inch lengths of each bone being removed. It was found to be yellow, fatty, non-vascular, and quite normal, both macro- and micro-scopically.

The *manubrium sterni* was bisected, squeezed in a vice, and

films made from the pinkish marrow-like fluid that exuded. They will be described lower down.

HISTOLOGICAL EXAMINATION.

This was done by means of films and sections. The former were all air-dried and fixed in alcohol and ether, equal parts. The tissues were fixed in triplicate :—(a) In 10 per cent. formalin ; (b) in saturated sublimate ; (c) in Flemming's solution.

1. *Bone-marrow*.—(a) Of the Long Bones.—After removal of the fat by immersion in alcohol and ether only a few red discs and lymphoid cells were left. Neither eosinophiles, nor myelocytes, nor nucleated red cells were discoverable. The normal fatty character of the marrow had evidently persisted. (b) Of the Sternum.—This was seen to be of lymphoid character, most of the cells being small, non-granular, mono-nuclear elements, with a narrow rim of protoplasm, mostly more basophilic than the nucleus. There were also much larger cells with a single faintly stained nucleus which often nearly filled the cell. Their protoplasm was either (1) hyaline or (2) studded with extremely fine basophilic or neutrophilic granules (myelocytes). A few eosinophiles, both poly- and mono-nuclear, were also seen. Polynuclear neutrophiles of the ordinary kind were almost absent. There were many nucleated red cells, all of normoblastic character, and possessing either a single or a fragmented nucleus.

2. *Pleural Exudate*.—By means of the centrifuge an abundant deposit of leucocytes was readily obtained. These were mostly lymphocytes, the polymorphs being relatively few and degenerate, their granules being scanty and often basophilic in affinity. There were also many large mononuclear cells with non-granular protoplasm so basophilic as to be hardly distinguishable from the nucleus. These cells were often much vacuolated. They were probably desquamated endothelium. Pneumococci were present in small number outside of the cells.

3. *Lymph-glands*.—The films showed only lymphoid cells of moderate size, with a large nucleus and a narrow fringe of basophilic protoplasm. Mitoses were not seen, nor was there any difference between films taken from different glands. In material fixed whilst still warm with Flemming, paraffined, and cut in ribbons, not exceeding 5 mikra in thickness, mitoses were readily found, especially in safranin preparations. In some sections they were

quite numerous, several in each high-power field. The lymph-channels were filled with structureless coagula, containing many lymphoid cells, some of which lay near the outer wall, and seemed as though wandering into or out of the sinus. The distinction between endothelioid germ-centres and ordinary small-cell lymphoid tissue was obliterated. The lymphoid tissue in some of the glands was divided up into follicles by trabeculae coming in from the capsule, and many of these follicles contained large thin-walled vessels. Giant and eosinophile cells were not seen in the glands.

4. *Spleen*.—Films made at the autopsy presented mainly two sorts of cells—viz., ordinary red corpuscles and lymphocytes—mostly small, many being reduced to a nucleus with a barely discernible ring of protoplasm. Occasionally there occurred much larger, more faintly-staining elements, with a large faint nucleus, nearly filling the cell; the protoplasm was charged with exceedingly fine acidophil granules. These cells would therefore appear to be of myelocytic nature. Their significance in the spleen is doubtful in a case of lymphatic leukæmia. They were often vacuolated. A single large mononuclear with eosinophil granules was also found. The presence of these two last-mentioned varieties of cell suggests the question: Could there have been a myeloid transformation going on in the spleen? One would hardly expect it to occur in lymphatic leukæmia unless, indeed, the bone-marrow had undergone such an amount of lymphoid transformation as to react by an overgrowth of its granule-cell-forming tissue, and that this had then become generalised. None of the sections made from portions (four) cut from various parts of the spleen showed any myeloid cells. In this connection it is also to be noted that there were extremely few polynuclears in the spleen. Sections showed (a) reduction of the trabecular system, the cords being few and small. (b) Reduction of the follicles, very few being present, and these of small size. The general appearance of the sections was one of nearly equal distribution of the lymphoid cells, between which a fine reticulum of nucleated fibres, often reinforced by unstriped muscle, could readily be made out. Long lines and columns of large mononucleated cells, perhaps identical with Mall's lymph-cords, could be seen all over the sections, but a lobular division, as described by that writer, could certainly not be detected. (c) Presence of patches of

necrosis corresponding to the opaque patches seen on the whole specimen. The centre of these stained a diffuse violet with hæmatoxylin, and showed complete karyorrhexis. The periphery showed evident signs of re-organisation in the shape of many layers of fibroblasts and new thin-walled vessels filled with lymphocytes. Here and there was an extra-vascular polynuclear leucocyte, though the majority, even in these re-organising parts, were mononuclear. Outside of the fibroblastic area were effused red corpuscles, which became more and more numerous and distinct as one passes outwards, until finally they formed a bright purple-red ring, visible to the unassisted eye, round the necrosed patch. (*d*) Presence of brown amorphous pigment in granules, lumps and scales, especially at the periphery of necrotic parts and near the hæmorrhages. This pigment gave a typical iron-reaction with ammonium sulphide, and a less distinct one with ferrocyanide of potash and HCl. (*e*) Amongst the red corpuscles, so numerously present in the spleen-sections, nucleated forms were not seen. (*f*) On the reticulum a large few mononucleated endothelial plates could be made out, but no giant cells. The general impression left by a study of the spleen sections was that of an enormous and uniform increase of lymphocytes, forcing apart the trabeculæ, obliterating the follicles, and producing a uniform microscopic picture, varied only by patches of hæmorrhage, necrosis, pigmentation, and fibroid transformation. Giant-cell formation, so often encountered in cases of Hodgkin's disease, was not found. In concluding this description of the spleen I wish to lay special stress on the rarity of mitotic figures, even in thin paraffin sections of Flemming-fixed material stained with safranin, whereas they were readily demonstrated in sections of the lymphatics, similarly treated. Apart from the hæmorrhages there was very little necrosis.

5. *Liver*.—Despite the macroscopically unaltered appearance of this organ, the sections showed the most exquisite lymphocytic infiltration of the portal canals. The walls of the veins, and occasionally of the arteries, were infiltrated, and, indeed, replaced by the small-cell growth, in which the bile-ducts were immersed; the cells composing it were typical lymphocytes, with scanty protoplasm and darkly-stained nucleus, and they lay upon a distinct reticulum. They did not penetrate between the liver cells, which, save for the presence of golden-brown pigment,

seemed quite normal. The pigment was amorphous, and did not give the iron reaction. It lay chiefly near the centre of the lobules. In many of the liver cells there were also isolated granules of iron-containing pigment. Amongst the lymphoid cells, which so abundantly infiltrated the liver, it was very difficult to find any in a state of mitotic activity, yet we must suppose them to be actively proliferating.

6. *Kidneys*.—These were thickly studded with small patches of lymphoid infiltration, which for some reason were strictly confined to the sub-capsular region of the cortex, into which they penetrated in a wedge-like manner, like minute infarctions, for the distance of a millimetre or two. The lymphoid cells seemed to be insinuating themselves between the tubules and forcing them apart. Degenerating tubules and glomeruli, quite immersed in lymphoid cells, could be seen here and there. Typical mitoses were again very difficult, almost impossible, to find amongst these closely-crowded lymphoid cells, even on Flemming preparations stained with safranin and iron-hæmatoxylin.

7. *Suprarenals*.—These were normal, save for the presence of lymphoid infiltrations amongst the large cells of the medulla.

8. *Pancreas*.—A minute patch of lymphoid cells was found amongst the acini, and doubtless others would have been seen if sought for. The islands of Langerhans seemed unduly prominent and large.

9. *Lungs*.—In view of the rarity of polymorphs in the general circulation, the histological examination of the pneumonic lungs promised to be of great interest. The alveoli were found distended with coagulated fibrin, in which were entangled many red corpuscles and great numbers of polymorphs, apparently nearly all the patient had to dispose of. Many of them seemed degenerate, with completely fragmented nuclei. In every field there were small numbers of pneumococci. They were mostly extra-cellular. The contrast between the snake-like vessels crowded with lymphocytes and the alveoli packed with polynuclears, between which they coursed, was very curious.

This case must be looked upon as a typical one of chronic lymphæmia. In the course of events the only departure from normal was the absence of any polynuclear leucocytosis or diminution of the lymphocytosis

as the result of pneumococcal infection. From the anatomical standpoint the chief departure from the conditions usually found in such cases was the state of the marrow of the long bones, which, instead of undergoing a lymphoid transformation, retained its normal fatty character. Possibly the lesion was unevenly distributed focal, and might have been detected had a more complete examination been made. Another point of interest is that whereas fresh blood-preparations always contained leucocytes crammed with large refractive granules, which might readily have been taken for eosinophiles, stained films showed practically no trace of this variety of cell.

I have to express my thanks to Dr. Martin Dempsey for permission to bring this case forward.