FROM THE

# LIVERPOOL MEDICO-CHIRURGICAL JOURNAL

JULY 1908

# THREE CASES ILLUSTRATING THE RELATIONSHIP OF CERTAIN BLOOD DISEASES AND SARCOMA.

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## Case I—A Second Case of (so-called) Leukanæmia (Von Leube). Atypical Lymphocytic Leukæmia with Aleukæmic or Pseudo-Leukæmic Blood Condition (Drysdale).

W. D. W., 20 years, male, labourer, unmarried. Admitted 5th July 1907, under the care of Dr E. Hobhouse, F.R.C.P., for anæmia. Some alcoholic excess (beer). Previous health good; no phthisis.

*Present History.*—Illness began ten weeks before admission, with weary, sleepy feeling, being unfit for work; been in bed five weeks; no other symptoms. Attributes illness to extra work of eleven hours daily. Temperature = 98·4°; pulse = 112; respiration = 28.

Breathing short; speech causes dyspnœa. No œdema of limbs or trunk; no enlargement of glands. The cardiac first sound is followed by a soft systolic murmur heard over precordia. There is a loud pulmonary second sound; capillary pulsation present; there is marked pulsation in all vessels. Mouth and teeth clean. Liver extended from fourth rib to supra-iliac spine; surface smooth, tender, edge sharp. Spleen large, two inches below costal margin. Nil in abdomen. Opsonic index to streptococcus per mouth was 1·3. Blood (see chart).

Treatment by drugs was by arsenic and atoxyl.

CASE I.

| | 6/7/07. | 18/8/07. | 8/9/07. | 18/9/07. |
|---|---|---|---|---|
| Erythrocytes . . | 2,922,800 | 1,888,000 | 3,360,000 | 1,360,000 |
| Leucocytes . . | 7,200 | 3,200 | 4,000 | 6,900 |
| Hæmoglobin . . | 56–58% | 46% | 40% | 26% |
| Index . . . | 0·973 | 1·15 | 1·7 | 1·0 |
| Polynuclears . . | 21 | 46 | 35·8 | 30·3 |
| Eosinophils . . | ... | 1·7 | ... | ... |
| Lymphocytes { large / small } | 78 | 46·7 | { 3·7 / 60 } 63·7 | { 12 / 51·2 } 63·2 |
| Transitionals . . | ... | 2 | 0·4 | 3·5 |
| Myelocytes . . | ... | 2 | ... | 2 |
| Mast . . . . | ... | 0·9 | ... | ... |

6/7/07.—Many of the lymphocytes are atypical, being large, with much cytoplasm.

18/8/07.—There were 9 megaloblasts, 13 normoblasts, and 4 microblasts in the slides examined.

8/9/07.—2 megaloblasts, 15 normoblasts, 5 microblasts in the slides examined.

*Autopsy.*

(By Mr A. W. Anderson, House Physician, 11th October 1907.)

Body very pale, well nourished, soft. Rigor mortis barely present; post-mortem lividity absent.

*Lungs.*—Pleuræ not abnormal; no fluid present. Right lung: two patches of consolidation the size of a large marble in upper lobe; lung was œdematous. Left lung: very œdematous.

*Heart.*—Pericardium contained about six or eight ounces of clear serous fluid. There was no thickening or inflammation of pericardium. Heart very large. Right ventricle dilated. Much ante-mortem clot in both auricles. Numerous minute hæmorrhages beneath pericardium and endocardium, especially about auriculo-ventricular valves. Heart muscle flabby, and shows "tabby-cat" striations of fatty degeneration on endocardial surface, especially on papillary muscles. Valves show no abnormality. Aorta healthy.

*Liver.*—Generally and enormously enlarged; 4750 grammes weight. The substance showed some fatty and fibrous changes. A feeble Prussian blue reaction was obtained in a reticular formation on cut surface.

*Spleen.*—Weight 1775 grammes, surface dark red, substance firm.

*Kidneys.*—Left, 475 grammes weight. Right, 250 grammes. Both were very pale, cortex and pyramids being indistinguishable; surface without striation. Capsules stripped easily.

*Pancreas.*—No abnormality.

*Mesenteric glands* all somewhat enlarged, red and soft.

*Bone Marrow.*—Right femur dark red and firm.

*Stomach.*—No naked-eye change.

*Other organs* not examined.

### *Bacteriological Examination.*

Cultures were made from the marrow and spleen, and were sterile.

### *Microscopical Examination.*

*Liver* showed no reaction for iron. The capillaries were stuffed with large mononuclear cells. There were a few megaloblasts.

*Marrow* showed large mononuclear cells in large numbers, with myelocytes, eosinophil myelocytes, normoblasts, and megaloblasts (a differential count was not made). Mitoses were frequent, fat diminished.

*Spleen.*—Malpighian bodies were inconspicuous, and the pulp appeared uniform and resembled marrow. Large mononuclear cells were very numerous. These had very large pale nuclei; others had deeply staining irregular nuclei and some mitoses. There were also eosinophils, lymphocytes, and erythrocytes.

*Kidneys* showed deposits of large mononuclear cells and some lymphocytes among the urinary tubules.

*Stomach* showed its small vessels choked with large mononuclear cells. There were mast cells in their neighbourhood, and in the inter-tubular spaces of mucosa.

*Lymph Glands.*—Germ centres were composed mainly of lymphocytes, with some large mononuclears. The germ centres were inconspicuous in many fields. The medulla contained many large mononuclear cells with pale rounded or deeply staining irregular nuclei. Some cells were of great size. Numerous mitoses were present, especially in lymph sinuses, as if the endothelium were proliferating. The lymph sinuses and the capillaries were choked with large mononuclear cells, which have in places penetrated the capsule and passed into the periadenoid fat.

*Remarks.*—In 1906 I recorded a case of leukanæmia or myeloid splenic anæmia at this Society. Briefly, the patient was a male, aged 25, under the care of Dr D. Hall, who had been jaundiced for years. There was great enlargement of the liver (59 ounces) and spleen (42 ounces). The blood was of the type of classical pernicious anæmia; the leucocytes were about normal in number, and contained myelocytes and transitional cells in small numbers. The hepatic capillaries were found to be stuffed with mononuclear cells, myelocytes, and nucleated red cells, and similar cells were seen in the spleen. The case now described differs only in lymphocytes being present in the blood and viscera, and in larger numbers relatively in the former. In both cases evidence of hæmolysis was absent.

Von Leube first described a case under the term leukanæmia, and Dr Drysdale describes one and quotes eleven others in the *Quarterly Journal of Medicine*, vol. i. No. 1, 1907.

As to classification, Von Leube was led to give the disease a distinctive name on account of the combination of changes in the red and white blood-cells, and the deposits in the viscera which characterise types of these diseases. Dr Drysdale, on the other hand, considered that the blood-picture of pernicious anæmia, which he believed to be always sympto-

matic or secondary, may be found in simple anæmia (post-hæmorrhagic), and in infections, as *Bothriocephalus latus.* Dr Drysdale, therefore, regarded the anæmia in this disease as a severe secondary anæmia differing only in degree from the anæmia seen in ordinary leukæmia. Thus Dr Drysdale would regard my cases as atypical leukæmia, myeloid and lymphocytic respectively, with aleukæmic or pseudo-leukæmic blood-state. For my own part, I attach much significance to the large number of nucleated red cells present in these cases; *e.g.*, besides megalocytes, there were 370 normoblasts and 2200 megaloblasts per c.mm. on one occasion in Drysdale's case, and 1400 megaloblasts in Hunter's. It is known also that in myelocythæmia, when the patient is rosy in appearance and even vigorous, and when there is no, or slight, anæmia, large numbers of nucleated red cells have been observed. There is, then, no absolutely necessary connection between the anæmia and these nucleated red cells. Therefore the terms leukæmia or lymphocythæmia or myelocythæmia are, strictly speaking, not sufficiently comprehensive: they do not denote the concurrent changes in the red cells of the blood. Moreover, the anæmia in these cases of "leukanæmia" is markedly of the pernicious type, while the leukæmia *per se* is minimal.

It is clear that the unknown influence which disturbs the balance of output of the white cells affects irregularly the red cells also.

## Case II.—Lymphatic Leukæmia with Malignant Lymphomata.

A. V., æt. 23, unmarried, domestic servant. Admitted under the care of Dr E. Maynard, 11th September 1907, for pleural effusion. There was a past history of anæmia and measles, but not of tubercle. Family history good.

*Present History.*—One month previous to admission patient began to feel weak, to lose appetite, and to have feeling of tightness after food. On rising from bed patient noticed the

face was swollen, especially below the eyes. There was no shivering, vomiting, or diarrhœa. A fortnight previous to admission patient saw a doctor for her weakness, but not for pain; she gradually became short of breath and her cough became worse. On admission patient was pale but well nourished, and was short of breath. The tongue was foul, covered with a thick white fur; the teeth were fair, and the breath offensive.

The heart's apex beat was 2½ inches outside the nipple line in the fifth space, and the left border was 2½ inches outside the nipple line. The right border could not be defined owing to the dulness of the right chest; the right side of chest was dull to the clavicle in front, and to the spine of the scapula behind, above which it was hyper-resonant. Vocal fremitus was absent, vocal resonance diminished. Breath sounds were very weak, and were scarcely audible below. The left lung was resonant all over abdomen. Liver lower border was at costal margin, and the spleen was not felt. The lymph glands were not enlarged. The temperature ranged from 97° to 103°, and usually reached 100° or 101° daily.

*Blood Examination* (see Chart).

12*th September*.—42 ozs. fluid, clear yellow, withdrawn from right chest.

21*st September*.—72 ozs. of fluid removed from right chest. X-rays applied to the spleen for five minutes daily.

27*th September*.—76 ozs. of fluid drawn off from right chest.

9*th October*.—32 ozs. of fluid drawn off from right chest. Culture sterile. Excess of lymphocytes in fluid. No T.B. in fluid or in sputum.

19*th October*.—The lower edge of the spleen was at the level of the anterior supra-iliac spine. The liver extended to 1½ inches below costal margin.

31*st October*.—X-rays continued, spleen smaller. The lymph glands were generally enlarged, but not tender.

## Case II.

| | 18/10/07. | | 24/10/07. | 5/11/07. | 14/11/07. |
|---|---|---|---|---|---|
| Erythrocytes . . | 4,056,000 | | 3,328,000 | 3,350,000 | 2,138,000 |
| Leucocytes . . | 222,200 | | 124,000 | ... | 66,138 |
| Hæmoglobin . . | 80% | | 70% | 64% | 50% |
| Index . . . | 1·0 | | 1·0 | 0·86 | 1·1 |
| *Leucocytes*— | Per cent. | Per c.mm. | Per cent. | | Per cent. |
| Polynuclears . | 8·4 | 18,664 | 10·6 | ... | 8·4 |
| Eosinophil . . | 0·5 | 1,111 | 0·7 | ... | ... |
| Small lymphocytes | 65·1 | 144,430 | 50·6 | ... | 85·0 |
| Large lymphocytes | 17·4 | 38,662 | 26·7 | ... | 3·6 |
| Transitionals . | 1·4 | 3,110 | 1·0 | ... | ... |
| Myelocytes . . | 7·0 | 15,554 | 9·4 | ... | 3·6 |
| Eosinophil myelocytes | 0·6 | 1,332 | | | |
| Mast cells . . | ... | ... | 0·3 | ... | ... |

18/10/07.—3 normoblasts ; megalo-, micro-, and poikilocytes present.

### *Post-mortem Examination.*

(10th December, by Mr Wootton, House Physician.)

Autopsy made outside the hospital, and a brief report only could be obtained.

The body was pale, but there was no loss of fat. The liver was enlarged and fatty, but there was no growth seen. Weight, 3 lbs. 4 ozs.

The kidneys showed no abnormality. Weight, 4½ ozs. each.

The spleen was very large and firm. No new growth was seen. Weight, 2 lbs.

The lungs showed no new growth, either about bronchi or in parenchyma. There was some bloody pleural effusion. The lymph glands were generally enlarged, both superficial and deep; those above the right clavicle were especially increased in size, and also those in the right axilla and about the pancreas and spleen, where they were dark in colour. The mediastinal glands had fused into a mass the size of a mature cocoanut, and appeared to have malignant characters.

The ovaries and uterus appeared normal.

The alimentary tube showed no thickening, ulceration, or increase in size of the follicles.

There were no hæmorrhages present, other than those into the lymph glands.

*Microscopical Examination.*

*Liver.*—The perilobular zones, the hepatic capillaries, and the capsule of Glisson showed lymphocytes in numbers.

Marrow of ribs and sternum showed marked excess of lymphocytes, with many nucleated red cells (a differential count has not been made).

*Lymph Glands.*—Cervical showed lymphocytes aggregated in the sinuses and lymphatics of capsule. There were numerous germ centres of large round cells. There were large areas of necrosis. The capsule was thickened and invaded by lymphocytes. Within the apparent capsule of the gland, which was probably not the original capsule of the gland, were collections of round cells, which appeared to be forming new lymphoid tissue. The endothelial cells were in excess; some were of giant size. There was excess of lymphoid tissue.

*Mediastinal glands* showed the same characters as cervical, with higher development of the stroma in large areas. The lymph sinuses were choked with lymphocytes, and lymphocytes invaded the capsule and adjacent muscular tissue.

*Peri-pancreatic gland* as cervical. There were many giant cells with single nuclei, and there were hæmorrhages into the gland.

*Ovaries* showed numerous round cells in the stroma and within the vessels, and around the corpora albicantea and lutea.

*The kidneys* contained foci of round cells.

*Supra-renal glands.* — The capillaries were stuffed with lymphocytes, and there were masses in the adjacent areolar tissue.

*The spleen* was congested. Its vessels, its framework, and its capsule were hyaline in places. There were many lymphocytes in the sinuses.

*Remarks.*—It was clear that there was, in addition to the leukæmic condition, a disease of the lymph-glandular system which might be called properly malignant. What relation did it bear, if any, to the blood-condition?

In leukæmia the glandular enlargement is within the limits of their capsules as a rule, and contiguous glands do not fuse. Histologically, the glands present a more or less normal appearance, with an increase in quantity of germ-centre material, which may equal or exceed in quantity that of the normal medullary substance. The reticular structures remain normal.

Lymphosarcoma, according to Kundrat, quoted by Salaman (*Trans. Patholog. Soc. London*, 1904, "Sarcoma of Stomach"), is an entity with the following characters:—It is composed of lymphoid cells in a fibrillary meshwork, and either cells or meshwork may be in excess, giving rise to medullary or fibroid forms. It infiltrates "without restraint," whereas in leukæmia this property is not so destructive. It does not show degenerative changes as in leukæmia.

Recently Gibbons has described nine cases of Hodgkin's disease (lymphadenoma), with five autopsies, in which the blood-picture was normal and there were no relative changes in the leucocytes. In addition to the microscopic characters of lymphadenoma, the glands showed invasion and destruction of the adjacent muscle and other tissues. Metastases on the liver, spleen, kidney, and cardium and pancreas were observed. The metastases resembled gland tissue with sharply defined limits but no capsule. The cases showed *malignant invasive* characters.

Thus the blood and gland enlargement in our case presented characters described in leukæmia and lymphosarcoma, and in lymphadenoma by Gibbons.

Similarly, Salaman has observed a case of lymphatic leukæmia in which the glands had formed a solid malignant mediastinal mass as of lymphosarcoma; and again one of lymphadenoma of the neck which had given rise to a large malignant mediastinal tumour.

## Case III.—Large Round-cell Sarcoma of Cervical Glands, with Transitional Cells in Blood.

J. W., æt. 30 years. Admitted under the care of Mr Verrall on 21st November 1907 for swelling of the neck.

*Summary of Clinical Condition.*—There was a swelling of the lymph glands on the left side of neck, which started as a small lump nine weeks previous to admission. It gave rise to no inconvenience until 7th November, when it became painful at night. There was pain in the left shoulder, arm, and side of head An abscess, supposed to be septic, was opened in this region in 1905 at Guy's Hospital.

There was a large, diffuse, brawny swelling on the left side of neck. No signs of metastases of hæmorrhages. Microscopical examination of a small piece removed for diagnosis showed a large round-cell sarcoma among lymphoid tissue. It was undergoing necrosis.

Trypsin and amylopsin were given without obvious effect on the growth.

*Blood Chart, 14th December* 1907.

| | |
|---|---|
| Erythrocytes . . . | 5,500,000 per c.mm. |
| Leucocytes . . . | 13,400 per c.mm. |
| Hæmoglobin . . . | 108 per cent. |

*Differential Count of Leucocytes.*

| | |
|---|---|
| Polynuclears . . . . . | 69·0 |
| Eosinophiles . . . . . | 3·0 |
| Small lymphocytes . . . . | 18·7 |
| Large lymphocytes . . . . | 2·1 |
| Transitional cells . . . . | 6·4 |
| Mast cells . . . . . | 0·4 |

The blood showed 6·4 per cent. of transitionals, which were three or four times the size of red blood cells. The nucleus was rounded, but indented and without granulations, or deeply indented and with slight fine granulations.

Transitional cells are rare in normal blood and difficult to identify. Probably they are derived from the large mononuclear cell, which is believed by many to be of the lymphocyte series. Large mononuclears and transitionals have been seen by Buckmaster in lymph glands, and possibly their source is multiple bone marrow (Ehrlich), lymph glands (Gulland), and spleen (Turk), each supplying small numbers to blood.

This case showed evidence of over-production of various elements of the blood as well as sarcoma of the lymph glands. The patient died in February 1908, but an autopsy was not obtained.

## Summary.

(1) These cases afford evidence that the glandular enlargement and visceral deposits of leukæmia are closely allied to lymphosarcoma, and that pseudoleukæmia (and lymphadenoma) possess the characters of malignant new growths.

(2) In leukæmia the lymphocytes may be regarded as elements of malignant character.

(3) In sarcoma of the lymph glands (and in sarcomatosis) the blood may show distinct changes in the leucocytes.

(4) No absolute distinction can be drawn between leukæmia and sarcoma.