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BY

F. PARKES WEBER, M.D.

WITH A REPORT ON THE HISTOLOGY OF THE CASE

By J. C. G. LEDINGHAM, M.B.

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The case was shown at the Clinical Section of the Royal Society of Medicine on ~~March~~ April 10, 1908,[1] and up to that date the main points observed may be summed up as follows:—

The patient, K. L., an unmarried woman aged 21, was admitted into the German Hospital on March 23, 1908, with great œdematous swelling and cyanosis of the hands and feet. The œdema was symmetrical; in the lower extremities it extended upwards as far as the knees, and in the upper extremities to about the middle of the forearms, but the upper limit was not sharply defined in either extremities. The swelling had commenced to appear gradually in the feet about five or six weeks, and in the hands about three weeks, before admission. There was no œdema of the face or loins, or elsewhere in the body. The patient said that she had previously enjoyed good health, and was not aware of having anything else the matter with her. Examination of the thorax, however, showed dullness, with diminished breath sounds and voice sounds, over the lower part of the left anterior and axillary regions, up to the second rib in front, and up to the sixth rib in the middle axillary

[1] *Proc. Roy. Soc. Med.*, Clinical Section, 1908, i, p. 192.

line. The upper part of the dull area was separated by about ½ in. from the left border of the sternum. There was some impairment of resonance over the left infrascapular region. Vocal vibrations could be felt over the right front, but not over the left front. There were no pulmonary adventitious sounds anywhere; the upper part of the left lung and the whole of the right lung appeared normal. The apex beat of the heart was in the normal situation, but the cardiac dullness extended rather too far to the right; there was no evidence of valvular disease. Röntgen-ray examination showed an extensive shadow on the left side of the thorax, which corresponded to the abnormal area of dullness, and was separated by a fairly sharply defined dome-shaped border from an upper normally clear area. The heart shadow, which was not separated from the abnormal shadow, extended rather too far to the right of the sternum. The superficial veins over the upper part of the left front of the chest were slightly enlarged. Nothing of pathological significance was found by examination of the abdominal viscera and urine; menstruation was regular; there was slight anæmia. The blood-count gave 4,150,000 red cells and 8,470 white cells to the cubic millimetre of blood; hæmoglobin (by Haldane's method), 80 per cent.; coagulation time (by Sir A. E. Wright's coagulometer), eight minutes. The superficial lymphatic glands were not enlarged; the thyroid gland was apparently of natural size; there was no paralysis of either vocal cord; the pupils were equal and reacted naturally to light and accommodation. Knee-jerks, very active, of the "trepidation" or "vibratory" type; no ankle clonus; plantar reflexes not obtained. The radial pulse, usually about 100 to the minute, was regular and equal on the two sides, and of low pressure. Systolic blood-pressure (Riva-Rocci method), 95 mm. Hg. in each arm. Ophthalmoscopic examination showed nothing abnormal; Calmette's ophthalmo-reaction (1 per cent. tuberculin) gave a positive result, as also did von Pirquet's cuti-reaction. The temperature varied between 99° F. and 101° F. (mostly about 100° F.). There was no cough or expectoration, or history of hæmoptysis; respiration, 30 to the minute. There had been no pain anywhere except a little when the feet were greatly swollen and the skin very much stretched. The swelling, and especially the cyanosis, of the extremities had great diminished on rest in bed.

Subsequent Course.—At the end of April the resonance over the upper part of the left lung disappeared, so that the whole of the left side of the thorax was dull to percussion, and 1,800 c.c. of a milky fluid was withdrawn by paracentesis. After this the left pleura had to be

tapped at fairly frequent intervals until the patient's death in October. At first the effusion was always milky, but at the end of July (after the first five tappings) it became clear. The œdema of the extremities gradually gave place to a chronic puffy-looking enlargement of the hands (*see* fig. 1) and feet (*see* fig. 2), apparently due to a condition of Marie's so-called "pulmonary hypertrophic osteoarthropathy." The existence of this was afterwards demonstrated by Röntgen-ray examination, and, in fact, at the end, when the patient was emaciated, the periosteal bony deposit could be seen and felt projecting in the forearm. Under treatment by hypodermic injections of atoxyl (commenced May 28), and a certain amount of exposure of the thorax to X-rays, there seemed at first to be some improvement in the general condition, but afterwards the patient began decidedly to lose ground. One or two lymphatic glands in the neck were felt moderately enlarged in August, and in the latter part of September one or two small glands could be felt in the left axilla on careful examination. Several glands could be felt in both inguinal regions, but they were not larger than they are in many healthy persons. About the middle of August one of the enlarged cervical glands (the first one noticed) was removed for "biopsy" purposes, and was found to show the changes characteristic of lymphadenoma; it contained numerous epithelioid cells and small giant-cells (megakaryocytes and small-sized polykaryocytes), and was permeated by an extraordinarily large proportion of eosinophil cells (Dr. Ledingham). The physical signs in the thorax after paracentesis and Röntgen-ray examination made it clear that there was a large and increasing tumour in the mediastinum. There was generally moderate pyrexia, but none after October 5. Emaciation and weakness progressed. The final cause of death, which occurred with asphyxia-like symptoms on October 28, was doubtless a serous effusion into the pericardium (see later). There was considerable general œdema at the end.

The Hypertrophic Osteo-arthropathy.—The swollen appearance of the hands, wrists, feet and ankles (*see* figs. 1 and 2) with the clubbing of the fingers was very striking. There was no, or very little, accompanying pain, even when the periosteal bony deposit could be seen and felt projecting in the forearm. Dr. N. S. Finzi kindly made skiagrams to show the bony changes (*see* figs. 3 to 5), and all the bones of the extremities were found to be affected in the way so well described and illustrated by Dr. H. E. Symes-Thompson in his paper before the Royal Medical and Chirurgical Society in 1904 [18]. In the hands and feet the terminal phalanges and the carpal and tarsal bones appeared least

affected. The shadow of the shaft of every long bone was enclosed by a somewhat fainter irregular shadow, evidently due to the formation of new bone under the periosteum. In fact, the diaphysis (in whole or part) of every long bone was encased by a cylindrical growth of new bone, which in the case of some of the bones of the feet and hands almost doubled the diameter of the shaft. The distal ends of the femora (*see* fig. 5) and humeri were more affected than the proximal, just as has been noted in other cases. Besides all the long bones of the

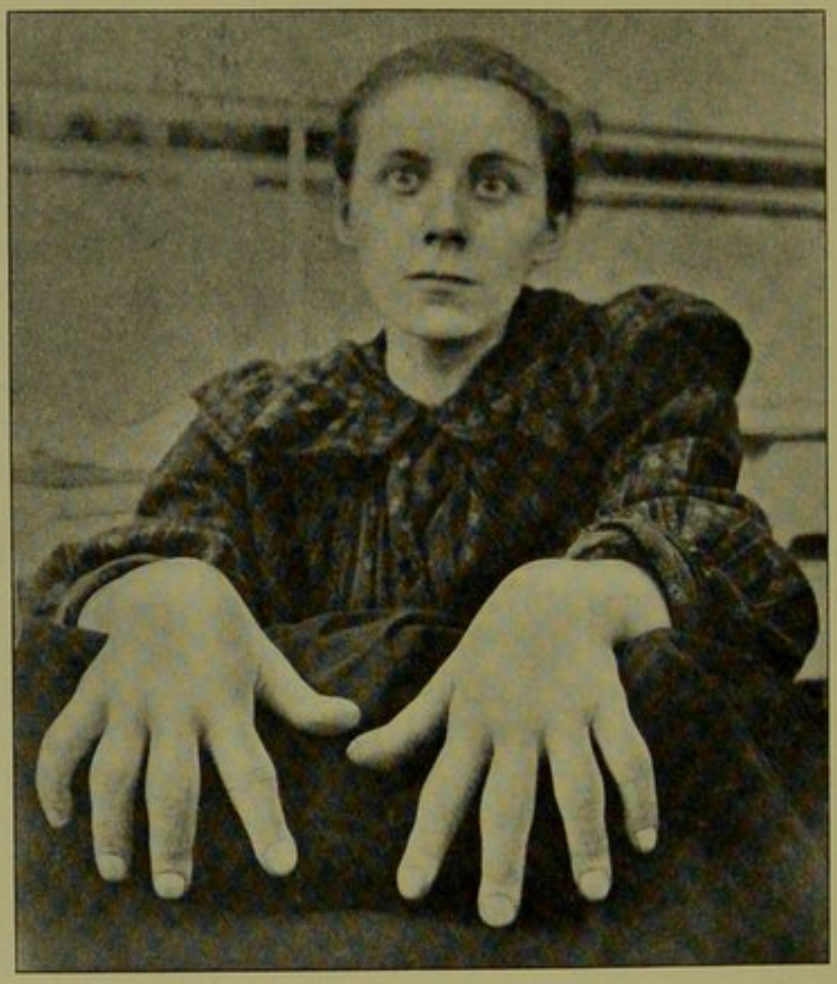

Fig. 1.

Showing appearance of the hands due to the secondary hypertrophic osteo-arthropathy.

extremities the clavicles were shown by Röntgen rays to be also affected in the same way, but the bones of the pelvis, the ribs, and apparently the vertebræ were not affected; the condition of scapulæ and cranial bones was not examined. It is highly probable that in the present case

the articular changes in the wrists and ankles, if there were any genuine ones at all, were entirely secondary to the bony changes in the carpal and tarsal bones—that is to say, changes probably affecting the outer surfaces of those bones (which were not specially examined by Röntgen rays).

The Pleural Effusion.—The "milky" fluid at first obtained from the pleura was of specific gravity 1,015 to 1,018, and appeared like cow's milk diluted (one in ten parts) with rather dirty water. Coagula formed quickly unless prevented by the addition of a little citrate of potassium. The fluid contained 3·5 per cent. to 4·5 per cent. albumin and 0·4 per

FIG. 2.

Showing appearance of the feet due to the osteo-arthropathy.

cent. to 0·6 per cent. of fat (Soxhlet's method); no sugar was found after freeing the fluid from albumin. Ordinary filtering did not get rid of the milkiness. Microscopic examination of the fluid showed a very finely-dotted or stippled appearance; there were a few red and white cells present, but no fat globules like those of milk and chylous fluids were visible even under high magnification. On treating 3 c.cm. of the

fluid with caustic soda and shaking with ether (method of Lenhartz) the milkiness disappeared, proving that it was due to the presence of fat, doubtless in the form of the exceedingly minute granules which gave rise to the stippled appearance under the microscope. Later on, at the end of July, when the pleural effusion became clear, the fat estimated by

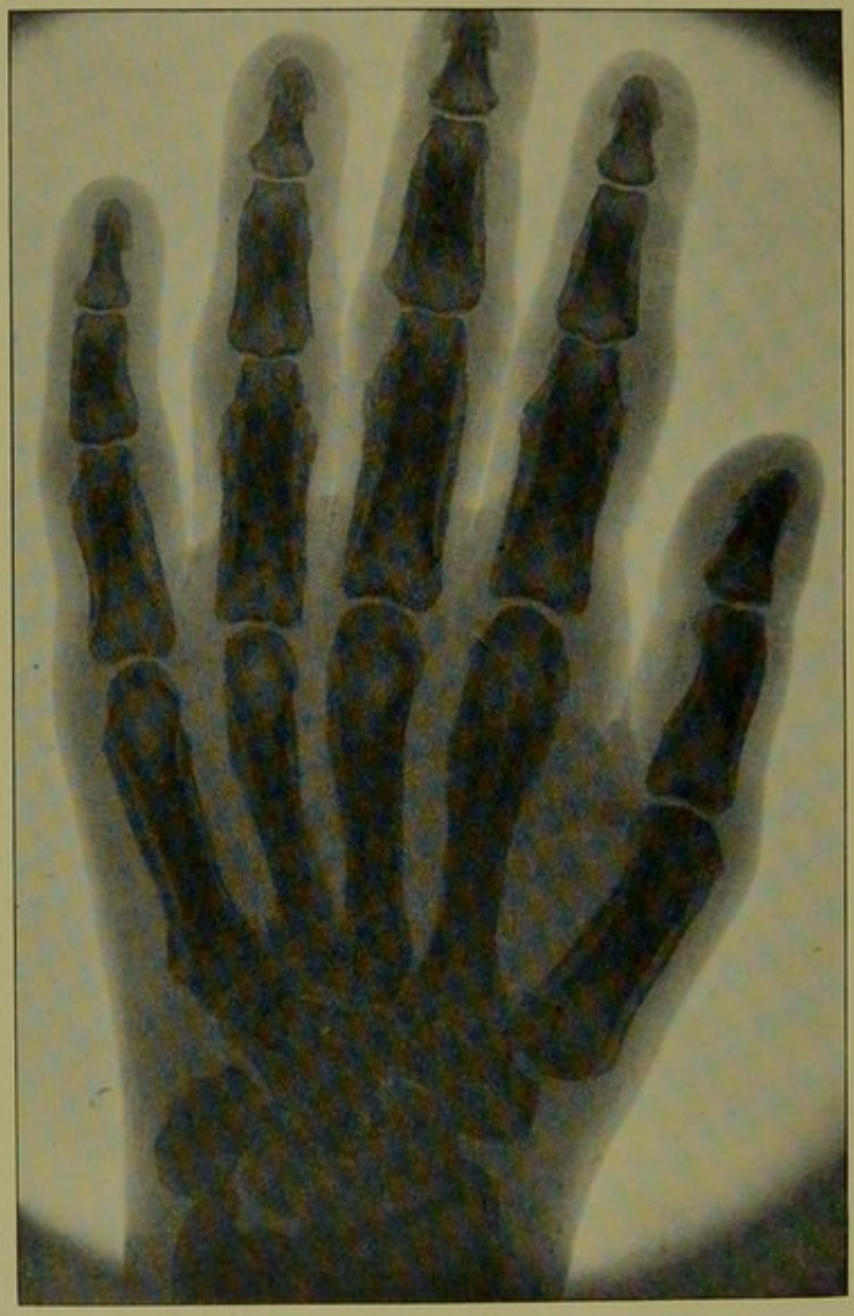

Fig. 3.

Skiagram of the hand showing the increased thickness of the metacarpal and phalangeal bones due to periosteal formation of new bone on the diaphyses.

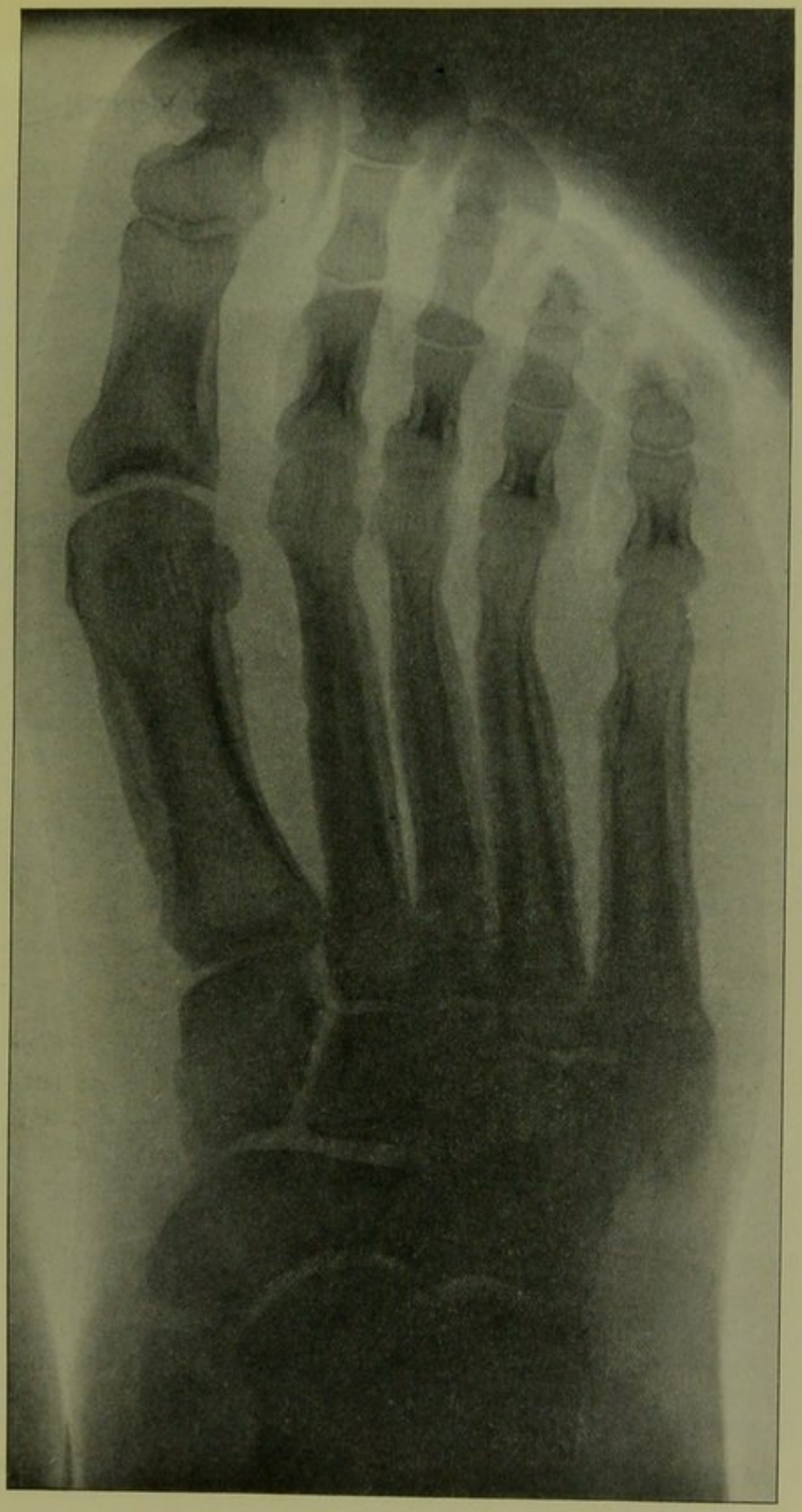

FIG. 4.

Skiagram of the foot showing the diaphysial formation of new bone in the periosteum, causing great increase in the thickness of the metatarsal and phalangeal bones.

Soxhlet's method was found to be only 0·02 per cent. to 0·05 per cent. The amount of albumin likewise was less (2·0 per cent. to 3·5 per cent.), and the specific gravity was lower (1,012 to 1,015) than when the effusion was "milky."

The *urine*, according to the last note entered (October 20), was of specific gravity 1,020, acid, giving uratic deposit, and free from albumin and sugar.

Blood Examination.—The last blood-count (October 8) gave: Hæmoglobin, 70 per cent. of the normal; red cells, 4,350,000 per c.mm.; white cells, 11,500 per c.mm. Differential count of white cells (October 8, kindly made by Dr. Ledingham): Small lymphocytes, 0·0 per cent.; large lymphocytes, 13·4 per cent.; large mononuclears and transitionals, 1·9 per cent.; polymorphonuclears, 82·5 per cent.; eosinophils, 3·6 per cent.; mast-cells, 0·0 per cent.; nucleated red cells, 0·0 per cent. Dr. Ledingham likewise made a differential count of white cells from blood-films taken on July 18: Small lymphocytes, 0·5 per cent.; large lymphocytes, 27·9 per cent.; large mononuclears and transitionals, 0·0 per cent.; polymorphonuclears, 60·9 per cent.; eosinophils, 10·6 per cent.; mast-cells, 0·0 per cent.; nucleated red cells, 0·0 per cent. He pointed out that in the interval between July 18 and October 8 the eosinophilia relatively decreased, whilst the polynuclears relatively increased at the expense of the large lymphocytes.

Necropsy.

On opening the thorax a large firm whitish mass of tumour was seen occupying the central region and a great portion of the left half of the thoracic cavity. The tumour weighed 66 oz.; it had a nodular surface, and appeared to be pressing on, but not infiltrating, the surrounding structures; it was quite distinct from the heart and lungs, though the left lung was collapsed, flattened out and adherent to it. It had the consistence of rather hard lymphadenoma, and its position, as well as its nodular surface, suggested that it was derived from mediastinal lymphatic tissue.[1] The heart and pericardium projected into the right half of the thoracic cavity, and the pericardium was tensely distended by a serous effusion tinged with blood. The heart was small, weighing only 8 oz., but otherwise normal. The right lung seemed not to be diseased. The abdomen showed nothing remarkable

[1] It might have developed in the lymph glands or in a remnant of the thymus.

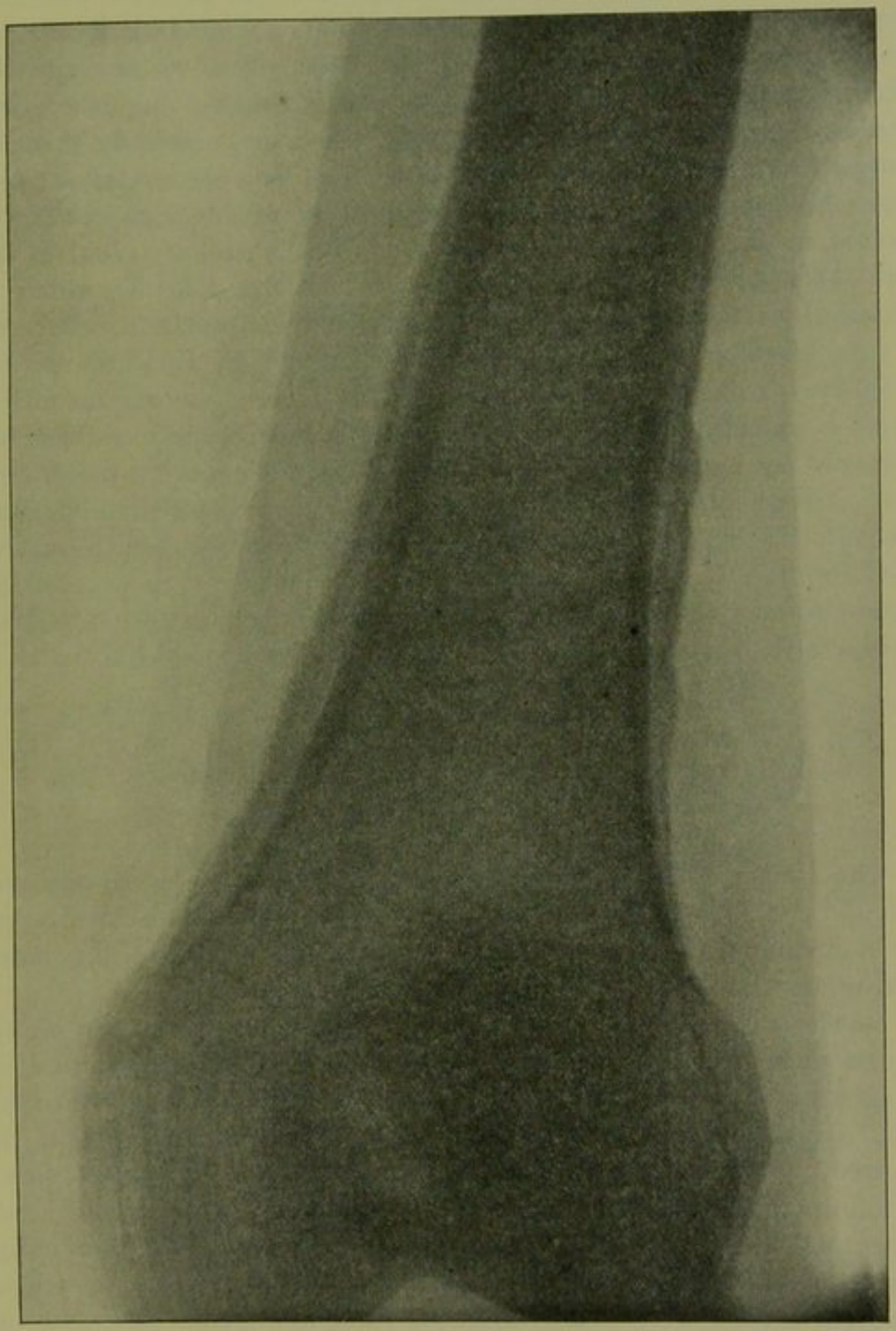

Fig. 5.

Skiagram showing the periosteal new bone formation on the lower portion of the shaft of the femur.

except that the diaphragm, owing to intrathoracic pressure, projected downwards in the gastric region. The liver (50 oz.) presented the naked-eye appearance of passive congestion. The spleen (6 oz.) and the kidneys (together 12 oz.) appeared normal. Besides the mediastinal tumour, no other growth was found in the body, excepting that the lymphatic glands about the clavicles at the base of the neck were moderately enlarged. No macroscopic evidence of tuberculosis was discovered in the lungs or anywhere else. The medullary canal of the shaft of the left humerus was opened, and the marrow which it contained was seen to have undergone a red transformation. Portions of this marrow, of the mediastinal tumour, of an enlarged cervical lymphatic gland, of the spleen and of the liver were removed for microscopic examination. The joints and cranium could not be examined, but a piece of the upper part of the left humerus was removed for maceration and microscopic examination. The macerated bone showed an irregular sub-periosteal deposit of new bone on the shaft. This new bone formation was seen by microscopic examination of a decalcified piece to consist of a more or less thick layer of spongy bone developed between the outer surface of the periosteum and the original compact bone of the shaft.

Report on the Microscopic Examination by Dr. J. C. G. Ledingham.

The tissues were fixed in Orth's fluid, embedded in paraffin and stained by various methods. The most useful stain for demonstrating the eosinophilia in the glands and the finer structure of the bone-marrow was Laurent's eosin-methylene-blue mixture.

Cervical Gland (stain Laurent) (*see* fig. 6).—Examination of the section under low magnification revealed a loose reticular structure, in the meshes of which were enclosed enormous numbers of eosinophil cells, giant-cells and lymphocytes. No lymphoid nodes could be detected. With high magnification (Leitz, oc. 4, obj. $\frac{1}{12}$ oil imm.) the most striking feature was the accumulation of eosinophil cells presenting either single or polymorphous nuclei. Their distribution was not confined to any particular portion of the gland area, though in some parts they were more numerous than in others. As many as a hundred or more could be counted in one field of the oil immersion. The giant-cells were of all sizes, and their nuclei did not conform to any one type. The most usual nuclear form was that which has been

described so frequently in lymphadenomatous lesions, being of the highly convoluted or mulberry type and strikingly deficient in chromatin. Mononuclear epithelioid cells corresponding to those associated with the giant-cells in lymphadenomatous glands were also found in great numbers; and all transitions could be traced out between the mononuclear forms and the large giant-cells with the most bizarre polymorphous nuclei. Some light was thrown on the histogenesis of these forms by a

FIG. 6.

Section of cervical lymphatic gland (× 460) to show the extreme abundance of eosinophil cells (Laurent's stain). The other cells are nearly all lymphocytes. Only one megakaryocyte happens to be present in the portion of the field illustrated.

careful examination of the reticular tissue of the gland. The endothelioid cells belonging to the reticulum proper showed marked proliferation. Mitotic forms were present, and in some cases the vesicular nuclei of these cells attained enormous dimensions with a tendency to convolution. Free forms, provided with long protoplasmic processes, were also seen in the neighbourhood of those still attached to the reticulum. Between

these giant reticular cells and the giant-cells all transitions could be recognised. A notable point also in connexion with the histogenesis of these giant-cells was the fact that they invariably lay in circumscribed open spaces among the reticular tissue.

Besides the giant-cells and eosinophil cells, lymphocytic cells formed the predominating elements, though small collections of plasma-cells

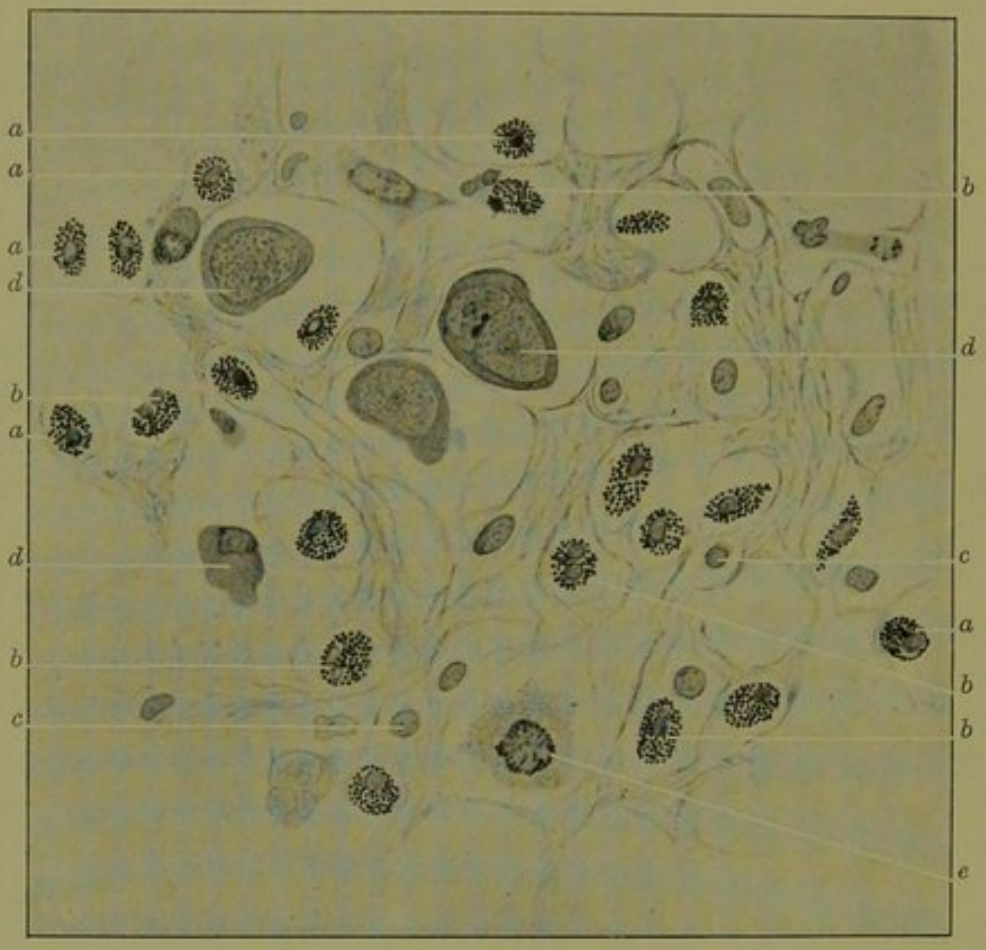

Fig. 7.

Section of the mediastinal tumour (× 1000) showing eosinophil cells and megakaryocytes (Laurent's stain): *a* eosinophil cells with single nucleus; *b* eosinophil cells with double nucleus; *c* lymphocytes; *d* megakaryocytes of various sizes; *e* mitotic figure in a small megakaryocyte.

were also recognizable lying alongside the more thickened portions of the reticulum.

Neither spirochætæ nor tubercle bacilli were present.

Mediastinal Tumour (stain Laurent) (*see* fig. 7).—The sections of the mediastinal mass presented features essentially similar to those of

the cervical gland, but here the thickening of the reticular tissue had advanced very much further. The degree of thickening varied greatly in different parts of the section. No lymphocytic nodes were present, but alongside the thickened trabeculæ were lymphocytic accumulations.

Giant-cells were less numerous than in the gland, but they, with the eosinophil cells, again constituted the most prominent feature of the

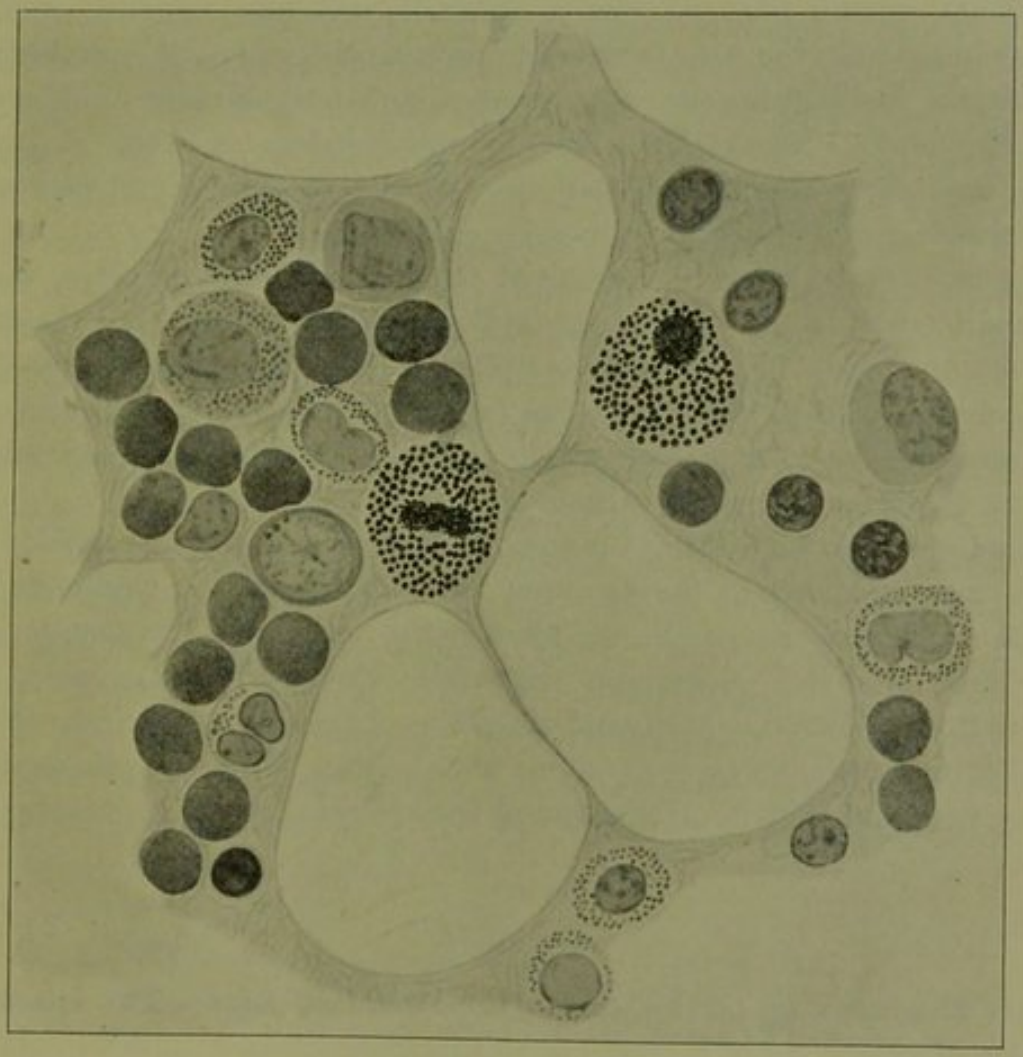

FIG. 8.

Section of bone-marrow from the shaft of the humerus (× 1000) stained with Laurent's stain. The cells represented with the coarse black granules are eosinophil myelocytes; one of them (that with the elongated nucleus) is undergoing karyokinesis.

histological picture. Many of the giant-cells showed karyolysis, while others had markedly pyknotic nuclei. A very common type was one which showed large twin nuclei lying side by side. Sometimes the giant-cells contained an eosinophil cell included in the cytoplasm.

Mitoses in the giant-cells were frequently noted, and the cytoplasm of dividing cells invariably presented a metachromatic reaction. The eosinophil cells were either myelocytic (with deeply stained round nuclei) or polymorphonuclear.

Neither spirochætæ nor tubercle bacilli were found.

Bone-marrow (stain Laurent) (*see* fig. 8).—The bone-marrow showed exactly the features which one would expect from the condition of the blood during life. It was a markedly myeloid marrow, and an eosinophilic reaction was specially pronounced. Large numbers of myelocytic eosinophil cells were present, and karyokinetic figures were very frequent. Neutrophil and basophil myelocytes were also very numerous. Very few normoblastic foci were detected. Giant-cells were rather more numerous than in normal marrow.

Liver.—There was no increase of the interlobular connective tissue, and the form of the liver acini was well preserved, the nuclei of the liver-cells staining well. Large numbers of liver-cells contained hæmosiderin-like granules in their interior. The lumen of the interacinous capillaries was almost devoid of cellular elements. No evidence of lymphadenomatous change was found in the liver.

Spleen.—The supporting tissue of the spleen was not increased. The nodes were reduced in number and irregular in form. One node presented a central karyorrhectic focus with numerous phagocytic cells containing included chromatic material. Eosinophil cells were very scarce throughout the pulp, and megakaryocytes were also few. Small blood extravasations were present in some parts. There was no evidence of any lymphadenomatous changes in the spleen.

Remarks.

(1) *Diagnosis of the Thoracic Disease during Life.*—The latency in respect of subjective symptoms of the thoracic disease must be regarded as remarkable when it is remembered that the patient came to the hospital on account of the swelling of her extremities, not knowing that there was anything wrong with her thorax. The position of the abnormal dullness to percussion over the front of the chest (especially after the left pleura had to be tapped), involving as it did the region above the heart and extending also to the right of the sternum, combined with the absence of signs of cardiac disease or aneurysm, showed that there was a tumour-like mass of some kind in the mediastinum. This was confirmed by examination with Röntgen rays, and likewise by

the presence of clubbing of the fingers and characteristic secondary osteo-arthropathy in the extremities.

What was the nature of the mediastinal mass? Localized tertiary syphilitic disease and thoracic aneurysm were both exceedingly improbable. The patient gave a characteristic positive response to Calmette's ophthalmo-reaction for tuberculosis, but I had already seen and read of cases which threw great doubt on the absolute reliability of that clinical test for tuberculosis [21]. The appearance of moderately enlarged glands in the neck and the "biopsy" examination of one of them made the diagnosis of mediastinal tumour absolutely certain. Although the microscopic structure of the gland removed was characteristic of lymphadenoma, according to the descriptions of Andrewes, Reed, Longcope and others, I hesitated to decide against the possibility of lymphosarcoma. The post-mortem examination made it certain, however, that the growth in the chest was really what is now generally regarded as lymphadenoma (Hodgkin's disease).

(2) *Histological Features of the Tumour.*—The microscopic appearance of the mediastinal tumour and of the enlarged lymphatic glands in the neck was characteristic of lymphadenoma (Hodgkin's disease), according to the description of F. W. Andrewes [1], Dorothy M. Reed [14], C. C. Simmons [15], W. T. Longcope [8], F. Warnecke [20], Robert Muir [11], F. S. Kidd and H. M. Turnbull [7], &c.—that is to say, in regard to the features on which these authors are agreed. In the present case the main histological features of the growth were (A) the presence of abundant epithelioid and giant-cells (megakaryocytes and polykaryocytes) scattered throughout the growth; (B) its extraordinary richness in eosinophil cells, which in properly stained sections at first sight constitute the most striking feature of all; (C) the secondary fibrosis. The fibrosis is characteristically more advanced in the older growth in the mediastinum than in the newer growth in the lymphatic glands at the root of the neck. In the present case the spleen, liver, and most of the lymphatic glands were as yet uninvolved.

(3) *Localization of the Primary Tumour and Remarks on Lymphadenoma.*—H. A. Hare, in his well-known monograph [6] on affections of the mediastinum (1889), gives a table of twenty-one cases of lymphoma and lymphadenoma of the mediastinum, some of which were probably examples of true lymphadenoma, though forming a definite mediastinal tumour, as in the present case. But subsequent authors have questioned the possibility of lymphadenoma (Hodgkin's disease) ever constituting a primary mediastinal "tumour." J. L. Stevens [16] (1892), for instance,

wrote: "There has of recent years been too great a tendency to search for some relationship between mediastinal tumours and Hodgkin's disease, when in reality there was no need to do so, and when the effort to demonstrate a connection simply led to the formation of erroneous views." Further on Stevens refers to Gowers's article on "Hodgkin's Disease" [5] (1879), and says [17]: "All this goes, I think, to prove that anything in the nature of a mediastinal tumour which can be regarded as essentially a local manifestation, whether liable to metastasis or not, can have no relationship to Hodgkin's disease." Even as recently as the present year (1908) H. A. Christian [3], although he is apparently acquainted with the modern description of the histology of lymphadenoma, or Hodgkin's disease, writes: "Cases, however, in which there is a tumour of the mediastinum having the histological characteristics as described by Reed, Longcope, and others, for Hodgkin's disease, but no general lymph-node involvement, may be included in the lymphosarcoma group for the present" (*see* supplementary note, p. 86).

The question is: What are we to regard as the criterion of a case being one of lymphadenoma or not? In regard to other growths, benign and malignant, the recognized classification of the various kinds of tumour is based on their microscopic features, and I am therefore certainly in favour of accepting the histological characteristics which have been demonstrated (not merely described) by Andrewes, Reed, Longcope, &c., as the criterion of lymphadenoma.

If this criterion be generally admitted, I believe it will be found that the old idea of lymphadenoma (Hodgkin's disease) being from the commencement, or almost from the commencement, a generalized disease of the lymphatic glands and lymphatic tissue of the body is erroneous—that is, the old view of lymphadenoma as a "pseudoleukæmia." In a recent article on Hodgkin's disease [22] I wrote: "For the diagnosis of Hodgkin's disease there ought to be *great* enlargement of some one or more regional groups of lymphatic glands. It is doubtful whether any of the so-called "pseudoleukæmia" cases showing a universal but *only slight* enlargement of lymphatic glands can be included as examples of Hodgkin's disease." I believe that in lymphadenoma (Hodgkin's disease), whether running an acute or chronic course, some one or more regional groups of lymphatic glands are generally specially affected, so as to constitute a regular tumour formation, before the lymphatic glands throughout the body become definitely involved. The first part of the body affected, constituting, in fact, a primary tumour, may be the glands on one side of the neck, or the glands in one axilla, or, as R. Muir [11]

points out, the retroperitoneal glands, or, as in the present case, some of the lymphatic tissue in the mediastinum. In a chronic case of Hodgkin's disease under my care in 1902 complicated by tuberculosis [23], as cases of Hodgkin's disease often are, there was a mass of chronic hard lymphadenoma at the back of the upper part of the abdomen, displacing the stomach and liver forwards.

The existence of acute febrile cases of Hodgkin's disease (lymphadenoma) and of a form characterized by "chronic relapsing pyrexia" [19]; the association of areas of necrosis (or occasionally of widespread hyaline or amyloid changes) in the liver and other viscera; the fibrosis in later stages (which I think is probably analogous to the conservative fibrosis or cicatrization [2] in chronic tuberculous and tertiary syphilitic lesions); the apparent dissemination or generalization of the disease from a primary group of enlarged glands to other glands and to the spleen and liver; and the occurrence of miliary "metastases," possibly analogous to miliary tubercles, in various organs (including the bone-marrow), all suggest that Hodgkin's disease (or a portion of the cases now classed together under that heading)[1] is due to some unknown microbe. In 1895 P. Delbet [4] obtained a bacillus from the blood and spleen of a woman supposed to be suffering from generalized lymphadenoma; and by repeatedly injecting large quantities of a pure culture of this bacillus he produced decided general enlargement of lymphatic glands in a dog. We do not, however, know that the disease in Delbet's case was really lymphadenoma (Hodgkin's disease) in the modern use of the term. In 1907 Pröscher and White [13] reported that, by the Levaditi and Giemsa methods of staining, they had discovered spirochætes in human lymphadenomatous glands, but Dr. Ledingham failed to detect any in the mediastinal growth or cervical lymphatic glands of the present case. In 1907 W. T. Longcope [9] tried to infect monkeys by inoculation with an emulsion of lymphadenomatous glands removed from patients by surgical operation, and though he did indeed set up a certain amount of general glandular enlargement, the histological picture was not that of Hodgkin's disease.

In acute cases[2] (or acute termination of cases) of lymphadenoma,

[1] There may still be more than one disease grouped together under the heading lymphadenoma or Hodgkin's disease.

[2] Acute cases of Hodgkin's disease have been described by F. W. Andrewes, *loc. cit.*, p. 310; W. B. Warrington, at the Liverpool Medical Institution, October 24, 1907, *Lancet*, 1907, ii, p. 1245; F. P. Weber, *St. Bart.'s Hosp. Reports*, 1907, xliii, p. 81; Hirschfeld and Isaac, *Med. Klinik*, Berl., 1907, iii, p. 1581; and J. Mitchell Clarke, *Journ. of Path. and Bact.*, Cambridge, 1908, xiii, p. 92.

several examples of which have lately been described, what takes place is, I believe, the acute dissemination or generalization of the disease throughout the body. This should probably be regarded as a "septicæmia of Hodgkin's disease"; using the word septicæmia in the broadest sense of the term, as it is used in "gonorrhœal septicæmia," "pneumococcal septicæmia," "influenzal septicæmia," and as it might justly be used in reference to the occurrence of the acutest forms of meningeal and general miliary tuberculosis, such as may result in predisposed individuals from mechanical injuries to old tuberculous foci. According to this view the lymphadenomatous nodules in the viscera are, of course, not metastatic growths in the ordinary sense of the term (that is to say, in the sense in which secondary carcinomatous nodules are metastatic), but are due to metastasis or generalization of the exciting cause of the disease, that is to say, of the hypothetical microbe.

One question (Dr. Ledingham) arising from the histological examination of the mediastinal tumour and glands in the present case is whether some cases classed as lymphadenoma, especially definite single tumours, would not really be better placed under the heading "lymphatic endothelioma."

(4) *Course of the Disease and Treatment.*—In the present case the relatively early occurrence of death was not due to acuteness of the morbid process, as it undoubtedly is in some cases, but to the position of the lymphadenomatous mass (in the mediastinum). The treatment by atoxyl (and to some extent by Röntgen-rays) seemed at one time to be doing good, but had not really a fair chance. In another patient (a man with very chronic Hodgkin's disease affecting the inguinal glands, &c.), now under treatment, I believe that atoxyl and X-rays have had some beneficial effect. The immediate cause of death in the case under consideration was undoubtedly the pericardial effusion, which is naturally very likely to escape clinical recognition when it occurs in association with a large mediastinal tumour.

(5) *The Condition of the Blood and the Bone-marrow Reaction.*—The blood in the present case, at all events at the end, showed a decided polymorphonuclear leucocytosis; and there was a variable degree of eosinophilia. Increase in the number of neutrophil polymorphonuclears is frequently observed in Hodgkin's disease, and by those who maintain that there are no blood-changes characteristic of Hodgkin's disease it is attributed to some counter-infection or other complication. In genuine cases of Hodgkin's disease, however, I believe that the neutrophil polymorphonuclears are at least more frequently found increased than the

lymphocytes; though a relative increase of the latter was by Pincus supposed to constitute a characteristic of "pseudoleukæmia."

The degree of eosinophilia, and doubtless the distribution of the eosinophil cells, varies considerably in different cases of Hodgkin's disease, and in the same case at different periods. The increase of eosinophil cells in the blood of the present case was very moderate when compared to the extraordinary number of eosinophil cells present in the mediastinal growth, the affected glands, and the bone-marrow. Up to a certain extent the findings in the present case would confirm the results arrived at by W. T. Longcope [10] in his investigations into the distribution of the eosinophils in Hodgkin's disease, though in the present case the eosinophils were not specially situated at the periphery of the lymph-adenomatous glands, as he found them to be. According to his observations it seemed probable that the eosinophil cells were not produced in the lymphadenomatous glands themselves; the distribution of these cells in the affected glands suggested rather that they were carried thither by the blood-stream—in fact, that they were derived from the eosinophil myelocytes, which were present in excessive numbers in the bone-marrow, and that they were carried from the bone-marrow to the affected glands in the circulating blood. It is therefore quite intelligible that at times the blood may show only slight eosinophilia, though the lymphadeno-matous glands may be crammed with eosinophil cells.

(6) *The "Milky" Pleural Effusion.*—The milkiness of the effusion was evidently due to fat, though in exceedingly fine division, since it was removed by shaking with caustic soda and ether, as already stated. In this respect the case may be compared to one at St. Bartholomew's Hospital described by Dr. J. A. Ormerod [12]. His patient was a boy, aged 13, with enlarged lymphatic glands (doubtless lymphadenomatous) on the right side of the neck, and a right-sided pleural effusion of fluid resembling thin milk in appearance. The fluid was of specific gravity 1,017, and alkaline in reaction; when shaken with ether the milkiness disappeared, leaving a clear opalescent fluid, of the usual type in pleural effusions. The fluid differed somewhat, however, from that in my case, since on microscopic examination it was found to contain actual fat globules besides multitudinous small refractile bodies. Moreover, in my case the milky character of the effusion disappeared spontaneously after the patient had been tapped five times, and from the sixth tapping to the patient's death it had the ordinary appearance; that is to say, resembled the fluid in ordinary cases of pleural effusion.

(7) *The Secondary Hypertrophic Osteo-arthropathy.*—In this connexion I have little further to add, excepting again to point out that the case was a typical one of what Dr. H. E. Symes-Thompson [18] terms the "diaphysial" (or "osteopathy") type of hypertrophic osteoarthropathy. The joints appeared very little affected. Probably they were hardly affected at all, but we had not the opportunity of examining them after death. An interesting point is that it was the œdema of the extremities (doubtless more or less connected with the osteo-arthropathy) which first called the patient's attention to the fact that anything was wrong with her, and thus led to the discovery of the intrathoracic disease. She had had no dyspnœa, cough, hæmoptysis, or expectoration.

In conclusion, I have to express my great indebtedness to Dr. Ledingham for his report on the histology and the blood-films, and to Dr. Finzi for his Röntgen-ray examination and skiagrams of the case. I have also to thank Dr. Chapuis, one of the house physicians at the German Hospital, for kind assistance in the various examinations, and Mr. Hillen, the dispenser, for analysis of the milky fluid from the pleura.

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[22] *Idem.* "Acute Cases of Hodgkin's Disease," *St. Bart.'s Hosp. Reports*, 1907, xliii, pp. 81-92.

[23] *Idem.* "Remarks on the Relations of Pulmonary Tuberculosis to other Diseases," *Lancet*, 1904, i, p. 924. [In the present case no macroscopic or microscopic evidence of tuberculosis was found after death.]

Supplementary Note.—In the case of a boy, aged 4, described by Dr. Cecil Wall in his paper on "Mediastinal Growths,"[1] a large mass of growth in the mediastinum constituted the earliest and most important clinical feature of a disease having the histological features now generally recognized in England and America as characteristic of lymphadenoma (Hodgkin's disease).

[1] Medical Society of London, January 11, 1909.