Schorstein memorial lecture on lymphadenoma (Hodgkin's lymphogranuloma) : Delivered at the London Hospital on December 4th, 1925 / by Sir Humphry Rolleston, Bart., K.C.B., M.D.Camb., Regius professor of physic in the University of Cambridge; President of the Royal College of Physicians of London.

SCHORSTEIN MEMORIAL LECTURE

ON

LYMPHADENOMA

(HODGKIN'S LYMPHOGRANULOMA).

Delivered at the London Hospital on December 4th, 1925,

BY

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LYMPHADENOMA
(HODGKIN'S LYMPHOGRANULOMA).

THE honour of giving the Schorstein lecture is a welcome opportunity of paying a brief tribute to a contemporary of peculiar charm and broad culture whom I first met at a small class in the late 'eighties, held by the late E. E. Klein, on the then recently recognised subject of bacteriology.

HISTORY AND NOMENCLATURE.

Morgagni (1769) briefly noted the condition, and no doubt there are other early records of the morbid change, but Thomas Hodgkin (1798–1866), demonstrator of morbid anatomy at Guy's Hospital (1825–37), is usually regarded as its sponsor. In 1832 he described "Some Morbid Appearances of the absorbent Glands and Spleen," recording six cases of his own and one of Sir Robert Carswell's. How many of these can be accepted as definitely examples of the disease now called after him it is rather difficult to decide; Samuel Wilks excluded two of the six original cases, but later critics have been more drastic: for example, Dorothy Reed and Symmers accepted two only of the seven. Except for a reference in Bright's lectures on Abdominal Tumours, Hodgkin's paper did not attract any attention, and probably would have remained unnoticed but for the loyal action of his junior, Samuel Wilks, who, in the course of a paper "On Cases of Lardaceous Disease and Some Allied Conditions," in 1856 included an account of a "Peculiar Enlargement of the Lymphatic Glands," which, though not lardaceous, was described because it is either a variety of it or closely akin to it. This is interesting as amyloid disease occasionally complicates Hodgkin's lymphogranuloma, though not so commonly as does tuberculosis which several writers have regarded as its underlying cause. After this paper was completed, but before it was finally printed, Wilks found that Hodgkin had described some of the cases actually in his series, and being one of the editors of *Guy's Hospital Reports* added a paragraph to say that had he been aware of this some of the statements pointing to the originality of his observations would not have appeared. In 1865 he collected 15 cases and perpetuated Hodgkin's name by calling them after him; this was just before Hodgkin's death from dysentery at Jaffa in 1866 and long after he had ceased to be connected with the hospital.

In the meanwhile, Virchow (1864) had described the disease from a pathological point of view as lymphosarcoma, an unfortunate name, as it is often used for a special form of an undoubtedly malignant growth. Cohnheim, in 1865, used the term pseudo-leukæmia for cases in which the glands showed the histological picture of leukæmia without the corresponding blood change, or as it would now be called aleukæmic leukæmia or aleukæmic lymphadenosis. The names lymphosarcoma and pseudo-leukæmia have caused

much confusion, but at this long interval of time it is not difficult to be wise. In the same year (1865) Trousseau gave one of his famous clinical lectures on *adénie*, a name which in the following year was expanded into lymphadenoma by Wunderlich, the title of whose paper is worth quoting in full as an epitome of the foregoing sentences—"Pseudoleukämia, Hodgkin's Krankeit oder multiple Lymphadenome ohne Leukämia." Cornil and Ranvier (1869) adopted lymphadenoma, and apparently it thus came to the notice of Murchison, who introduced it at the Pathological Society in 1870. But recently Agasse-la-font has drawn a distinction between Trousseau's adénie and Hodgkin's disease or lymphogranulomatosis.

From its familiarity and recognised meaning in this country the term lymphadenoma is the most convenient, but etymologically it is a little ambiguous, as it is not clear whether it implies a tumour of lymphadenoid tissue (lymphaden-oma) or, on the analogy of other adenomas, an innocent growth (lymph-adenoma), and also because it quite definitely suggests that it is a neoplasm, just as the alternative names, recently in vogue, lymphogranulomatosis, lymphomatosis granulomatosa, and granulomatosis, which some prefer, as the lesion is not necessarily confined to lymphadenoid tissues, declare it to be an infectious granuloma. From an international point of view, however, "lymphadenoma" has the drawback of being used by some writers, especially the French and by Ewing (1923), and Fox and Farley in America, for conditions, such as lymphoma and hyperplastic lymphadenitis, different from Hodgkin's disease; lymphogranulomatosis benigna has been applied to Boeck's sarcoid of the skin and allied conditions (Schaumann), and malignant lymphadenoma and lymphogranulomatosis maligna or perniciosa has been used as a synonym for Hodgkin's disease.

The eponymous title, Hodgkin's disease, has the advantage of avoiding any hypothesis as to its nature, but it might be thought that as Sir Samuel Wilks was really instrumental in its recognition, it should in justice be called Hodgkin-Wilks disease. The name Hodgkin's lymphogranuloma, used for 17 years by Prof. H. M. Turnbull and also employed by Ewing, has much to recommend it as leaving no doubt as to what is meant. In what follows the names lymphadenoma, Hodgkin's disease, and Hodgkin's lymphogranuloma will be used as synonymous.

The *history of the histology of lymphadenoma* is of some interest. The credit of first describing the lymphadenoma cells and the other features in the glands has been variously ascribed in different countries to native workers on account of want of familiarity with the work of foreign observers. In 1864, the year before Sir Samuel Wilks made Hodgkin's name immortal by attaching his name to the disease, Virchow described the large multinuclear or "lymphadenoma cells" which subsequent observers, among them Langerhans (1872) and C. Sternberg (1898), also noted, so that the cells are sometimes called after these later pathologists.

In 1878, in the course of a debate on lymphadenoma and allied conditions, W. S. Greenfield described "a large number of multinuclear cells containing from 4 to 8 or 12 nuclei," with a drawing which, though quite forgotten, was recognised in 1902 by Butlin as quite characteristic; though he never published any further account, Greenfield had fully worked out the histological appearances and had been accustomed to give them in detail to his Edinburgh students (S. MacDonald). In 1892 Goldmann pointed out the local eosinophilia in lymphadenomatous glands. But the

characteristic microscopic appearances of lymphadenoma were not generally recognised until F. W. Andrewes gave a full account of the histological appearances independently of and practically synchronously with Dorothy Reed's similar description.

Nature of Hodgkin's Lymphogranuloma.

Four views as to the nature of Hodgkin's lymphogranuloma may be mentioned—namely, that it is (1) an atypical form of tuberculosis, (2) a specific infective granuloma of unknown nature, (3) a new growth, and (4) a transition between a granuloma and a new growth.

(1) *The relationship of lymphadenoma and tuberculosis* has long been discussed. Some of Hodgkin's original cases were almost certainly tuberculous, and even now to the naked eye the large-celled tuberculous hyperplasia of the lymphatic glands is often indistinguishable from lymphadenoma. In 1898 Carl Sternberg, of Vienna, considered that lymphadenoma was a special form of tuberculosis, just as lupus is of cutaneous tuberculosis, and hyperplastic tuberculosis of the cæcum and appendix a peculiar form of intestinal tuberculosis; he obtained evidence of tuberculosis in 10 out of 15 cases; but this was opposed on the ground, dimly foreshadowed by W. H. Dickinson in 1878, that the tuberculous invasion was a secondary process which the existing lymphadenomatous lesion favoured. Inoculation experiments were found to give varying results, sometimes positive, sometimes negative (Andrewes; Reed; Longcope), and it appears that the positive results were due to a mixed infection, and the negative to uncomplicated lymphogranuloma. This interpretation seems convincing, but it has not been accepted universally; Ewing, with the weight of special experience, considers the evidence in favour of tuberculosis somewhat formidable.

In 1910 Fraenkel and Much, using the antiformin method, described a granular form of the tubercle bacillus which they found in 11 out of 12 lymphadenomatous glands free from the structural changes characteristic of tuberculous adenitis, and considered that in addition to this organism some special constitutional anomaly was necessary to account for the lesions. Dr. Negri and Mieremet, in 1913, described a similar organism, and in 1923 Fraenkel and Much, employing a special technique, found their form of the tubercle bacillus in nearly all the cases they examined. Almost simultaneously Kuczynski and Hauck described a mycelial form in the multinuclear cells, an observation which appeared to fit in with the tuberculous origin, but this has not been confirmed by Sternberg. In 1924 Grumbach obtained a bacillus resembling Fraenkel and Much's by blood culture from a patient with the relapsing fever of Pel-Ebstein. Lukes and Jelinck, however, found Much's granules in three out of 11 persons without either tuberculosis or Hodgkin's lymphogranuloma.

It has been urged in favour of the tuberculous nature of Hodgkin's disease that the cases may terminate

in generalised tuberculosis; this had not been common in my experience, but its occurrence might be explained by the view that the presence of Hodgkin's lymphogranuloma favours tuberculous infection or activates it when latent.

(2) *A Specific Infection.*—Various organisms have been described as responsible for Hodgkin's lymphogranuloma, but none of them can be regarded as proved. The most attractive is a protozoal (Löwit) or spirochætal (White and Proescher) origin on account of the eosinophilia in the glands, the occasional hæmic eosinophilia, and the well-marked reaction, in the early stages at least, to arsenic. Dreschfeld, in 1892, and Delbet, in 1895, described a bacillus, as did Ford Robertson and Young, in a case reported by Byrom Bramwell. But the most persistent effort in this direction is that of Bunting and Yates, who found a Gram-positive pleomorphic diphtheroid bacillus which Bunting states can be found in every case and by experimental inoculation made to produce the early histological changes seen in man; but the last two statements have not been confirmed.

(3) The view that Hodgkin's lymphogranuloma is a new growth, allied to sarcoma or endothelioma, is probably derived from the impression that this follows from its extension beyond the limits of lymphoid tissues and its infiltration of tissues, such as muscle and bone, which do not contain any lymphadenoid tissue; but in this extension there is nothing incompatible with the behaviour of the infective granulomas, tuberculosis, syphilis, and actinomycosis. On the other hand, Gye and Barnard's discovery of an ultramicroscopic virus and a specific factor for new growths, and the existence of infective sarcomas make discussion of the pros and cons of the neoplastic nature of Hodgkin's lymphogranuloma rather an academic exercise than one of practical utility.

(4) The compromise that Hodgkin's disease is a transition between an inflammatory formation and a neoplasm and shares characters with both of these processes has been supported by Symmers,[84] who classes it with mycosis fungoides, Cohnheim's pseudoleukæmia, Sternberg's leukosarcoma, and Gaucher's disease. This view is expressed in Dietrich's title granuloma-like sarcoma of lymphatic glands, and by "granulation tissue tumour."

It has been stated by Symmers [83] that Hodgkin's lymphogranuloma is a systemic disease which simultaneously attacks the lymphadenoid tissues widely in the body. In the light of ordinary clinical experience this pathological conception can only pass muster if it be assumed that the simultaneous involvement remains latent in many parts while it advances in one focus.

As the cause of Hodgkin's lymphogranuloma has not been established it is premature to divide it into

different forms on the analogy of enteric fever which includes infections with *B. typhosus*, *paratyphoid* A, and *paratyphoid* B. But it is tempting to imagine that there are several allied forms of a disease characterised by much the same histological appearances but differing in their virulence, in their tendency to sarcomatous transformation, and so in their clinical manifestations. Symmers [84] definitely describes two forms of the disease, one confined to the lymphadenoid tissues, the other mechanically infiltrating other structures, skeletal muscles, blood-vessels, and so forth. The differences in the histological pictures as regards the presence of eosinophile cells and the puzzling variations in the blood picture are at least compatible with this view. But, on the other hand, the factor of the resistance of the individual's body must, of course, be taken into account in explaining the differences in the course and manifestations of this as of other diseases.

Nature of Malignancy in Hodgkin's Lymphogranuloma.

That Hodgkin's lymphogranuloma is malignant in the sense that it leads to death is undoubted, and it differs from tuberculosis, which in many respects it closely resembles, in being constantly fatal and not becoming obsolete.

It generalises like tuberculosis, and may appear in situations such as the liver and kidney, where the amount of lymphoid tissue is small, and in muscle (vide Figs. 1 and 2) in which there is none. But mere generalisation is in keeping with the characters of an infective granuloma. Even if it be held that true Hodgkin's disease is confined to lymphadenoid tissue, the occurrence of lymphogranulomatous masses in the liver and kidneys might be explained on the hypothesis that there is a compensatory hyperplasia of the lymphoid tissue around the vessels, and that subsequently this becomes infected with the virus of the granuloma (Longcope). But further evidence suggesting malignant characters, such as invasion of adjacent bone and the histological characters of sarcoma, described years ago by Yamasaki and by Karsner, are now established, and Ewing considers this transformation into sarcoma ("Hodgkin's sarcoma") as a tumour *sui generis* and as by no means rare. He describes the new cells as endothelial in origin, but losing this character and appearing as large round cells, so that the term endothelioma is hardly applicable. Such a transformation as the result of long-continued irritation is, of course, well recognised, and Ewing[20] has described it in lymphatic glands affected with chronic granulomatous infection. The occurrence of Hodgkin's sarcoma as a late result of Hodgkin's lymphogranuloma is rather remarkable, as it is very seldom recognised in the other infective granulomas.

The development of sarcoma in Hodgkin's lymphogranuloma might be explained in one of two ways: (1) that some of the constituent cells of the lymphogranuloma proliferate so vigorously as to become a sarcoma, or (2) that the tissues surrounding a mass of lymphogranuloma are excited by the chronic irritation to a proliferation which eventually becomes sarcoma; this process Ewing compared with the occurrence of cutaneous squamous-celled carcinoma in the site of lupus.

Prof. H. M. Turnbull, while fully recognising the existence of the condition which Ewing [21] terms Hodgkin's sarcoma, regards it as the "lymphosarcomatoid" form of Hodgkin's lymphogranuloma and as inflammatory rather than neoplastic. Lymphosarcoma—the form of growth concerned in the malignant transformation of Hodgkin's disease—he considers as closely allied to it, and like it an inflammatory and not a neoplasm.

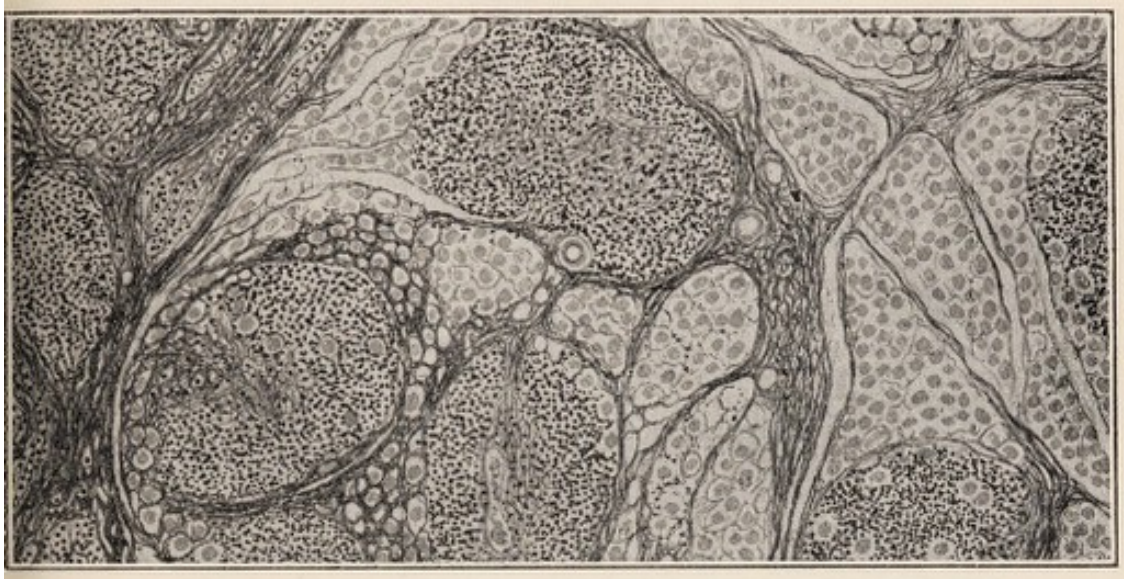
The Blood.

As the bone marrow, lymphatic glands, spleen, liver, and the reticulo-endothelial system regulate the formation and destruction of the blood-cells, it is obvious that, as these organs are the chief sites of Hodgkin's lymphogranuloma, the blood counts should be correspondingly affected.

If the lesion was one of the reticulo-endothelial system in particular and at times affected these phagocytic cells to the exclusion of the others, it might be expected that in the early stages of proliferation there would be increased hæmolysis, later followed, as the result of destruction and fibrosis, by a diminished hæmolysis with a rise in the red blood count and even a polycythæmia; but, unless the early increase in the platelets described by Bunting be regarded in the light of a hæmolytic process, and not as evidence of marrow stimulation, nothing of this kind occurs, even in the few instances of the splenic form of Hodgkin's lymphogranuloma. On the other hand, this last argument is not supported by the blood picture in fibrotic conditions of the spleen, such as chronic splenic anæmia in which polycythæmia is not seen; and there are only most exceptional instances of massive tuberculosis of the spleen in which it has been recorded (vide Weber [91]). Sooner or later there is a secondary anæmia which eventually may become so grave as to demand transfusion. How far in individual cases this is due to one or more of several causes it is difficult to say; toxæmia, infiltration of the erythroblastic bone-marrow, exhaustion after compensatory or arsenical stimulation of the bone-marrow, or the long-continued treatment by X ray exposures may each play a part.

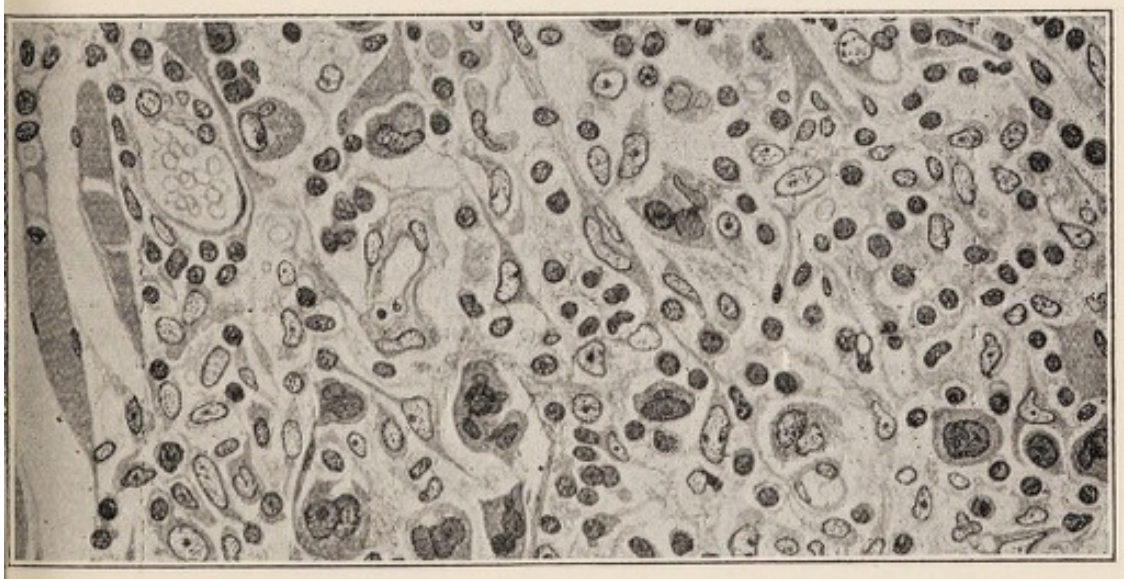
The white count does not show any constant or characteristic change. Usually leucocytosis is absent and there may be a leucopenia with a relative lymphocyte increase, especially, I believe, when the spleen is predominantly affected, a view shared by Weber.[95] Bunting described the blood picture in two stages: in cases under a year's duration, no leucocytosis, a relative lymphocytosis, diminished eosinophiles, and increase in the transitional

FIG. 1.



Iliacus muscle showing infiltration by Hodgkin's lymphogranuloma; small cellular and fibro-cellular nodules to the right of a larger more fibrotic nodule. Obj. 1 in., oc. Zeiss 4. (By the courtesy of Prof. H. M. Turnbull.)

FIG. 2.



Iliacus muscle showing Hodgkin's lymphogranuloma. High magnification of a cellular nodule. Obj. ⅛ in., oc. Zeiss K 6. (By the courtesy of Prof. Turnbull.)

cells. In more advanced cases when the disease is spreading widely there is a leucocytosis with a raised polymorphonuclear count (75–90), and later from exhaustion of the bone-marrow absence of blood platelets. Stewart lays most diagnostic reliance on a relative increase of large mononuclear cells—not lymphocytes—especially of the transitional type (19–33 per cent.); and also attaches importance to an absolute and relative neutrophile leucocytosis and to a relative and absolute eosinophilia. The rather exceptional occurrence of eosinophilia, which is specially seen in the rare acute cases, is interesting in connection with the characteristic though not absolutely constant presence of eosinophile cells in the glands. These cells are probably not produced locally, but are embolic immigrations from the bone-marrow (Goldmann; D. Reed; Symmers [84]; Turnbull). In a case of acute lymphadenoma Lincoln found 68 per cent. of eosinophiles and in his collection of previously recorded cases found that the highest count was 24·5 per cent. A percentage of 88 eosinophiles in a differential count of 83,000 leucocytes was recorded by Desjardins and Ford. Among 20 cases of the disease Pepper found it in 4 or 5 per cent. The relation of eosinophilia to pruritus has attracted much attention; the almost constant relation has been insisted on by Favre and Mariani, and the former drew an analogy between adénie éosinophilique prurigène and hydatid pruritus. No doubt eosinophilia and pruritus may be associated in lymphadenoma, but they may also occur independently. In a case without pruritus seen in 1910 there was 26 per cent. of eosinophiles, and in an advanced case under Dr. E. Bellingham Smith in St. George's Hospital the count was 69 per cent., but pruritus was then absent, though present at an earlier stage when the eosinophile percentage was 39. Megacaryocytes on their way from the bone-marrow to form the "lymphadenoma cells" in the lymphatic glands have been found in the blood-stream (Symmers [84]).

It would be interesting to correlate the blood picture with the contemporary changes in the structure of the lymphatic glands. But the complicated cellular changes in the lymphogranulomatous tissue and the variations in the blood picture make this a difficult problem. A lymphocytosis would correspond with a proliferation of the lymphoid cells; but that the leucopenia in the early stage would be more easily correlated with inhibition of the bone-marrow than with its destruction is rendered probable by the occurrence of a polymorphonuclear leucocytosis in the later generalisation of the disease.

The question whether lymphadenoma is primarily a proliferation of the lymphoid cells or of the reticulum has a bearing on the condition of the blood. If with Symmers [84] the primary change is regarded as a proliferation of the lymphoid cells, their escape into the blood and a lymphocytosis would be expected. Whereas if the first and essential change is proliferation of the endothelial cells and framework of lymphadenoid structures (Turnbull; Ewing; Webster), and proliferation of the lymphoid cells, when it occurs, a secondary process compensatory for destruction of lymphoid cells elsewhere

(Longcope), the absence of any characteristic blood picture is more satisfactorily explained. Acceptance of the view that the process is primarily a proliferation of the endothelial and reticular cells (the distinction between them being difficult) has been followed by the suggestion that it is, like Gaucher's disease and xanthoma (Krumbhaar), a disease of the reticulo-endothelial system—a reticulo-endotheliosis (Piney); but if it were, the Kupffer's cells in the spleen and liver should be constantly and predominantly affected, and this is not the case.

In the past, when blood counts were less minute, leukæmia was stated sometimes to supervene on Hodgkin's disease. This sequence is not supported by modern evidence. but the discovery of leukæmic blood changes would probably rule out a previous diagnosis of Hodgkin's disease. There may well be an analogy between the two questions of (1) the occurrence of Hodgkin's sarcoma or lymphosarcoma (in Turnbull's interpretation), and (2) leukæmic or proliferative changes in the blood picture. That stimulation of the bone-marrow may occur in cases of widespread generalisation of Hodgkin's disease is shown by the occurrence of a polymorphonuclear leucocytosis, and it is at least conceivable that riotous proliferation of the bone-marrow, analogous to sarcoma and leukæmia, might follow.

The Relapsing Fever of Lymphadenoma.

The *relapsing fever*, first recorded in 1870 by Murchison, but often called Pel-Ebstein after the descriptions by these two writers in 1885 and 1887, has attracted much attention, as shown by the papers of H. B. Shaw, F. Taylor, McNalty, Weber,[90] A. J. Hall and Douglas, and Galloway. Hall and Douglas estimate that less than 50 cases have been recorded; but it is probable that it is comparatively seldom reported rather than that it is as rare as is often stated, and Hall and Douglas appear to share this view, for they write, "in looking over old records of these cases it is surprising to find how many of them show a definite tendency to recurrent pyrexia." I am much indebted to Dr. A. S. MacNalty, who has given me the opportunity of seeing his notes of 11 cases additional to the 32 on which his paper in 1911 was based; among his new cases is one in a boy aged 3 years, the youngest on record. In a recent thesis for the M.B. degree at Cambridge, Mr. H. F. Brewer collected from St. Bartholomew's Hospital in four years, 1921–5, 62 (42 confirmed microscopically) cases of Hodgkin's lymphogranuloma, among which there were nine cases of relapsing fever.

This periodic fever is comparable with a protozoan infection such as malaria, relapsing fever, and rat-bite

fever, but has a longer span of 15 to 25 or even 36 days (Hall and Douglas). Although bacteria have sometimes been obtained by blood cultures, negative results are the rule, and there is not any convincing evidence of a secondary infection, probable as it would seem. But some change must occur, otherwise every case of Hodgkin's lymphogranuloma would show the relapsing type of fever. Symmers's view that the fever is due to absorption from areas of focal necrosis, especially in the spleen, which he finds are always present in enormous numbers in the chronic relapsing fever, has much to recommend it, and had been present to my mind before I read his paper in which he compares the sequence of events with the fever in cases of necrotic hypernephromas.

Dr. MacNalty has generously put at my disposal an analysis of 40 collected cases of this relapsing fever; 30 were males and 10 females, and half the cases occurred between the ages of 10 and 30 years, the oldest being a woman of 54 and the youngest a boy aged 3 years. He divides the cases into three clinical groups, the first, far the commonest, in which the external glands are moderately enlarged and may become soft, tender, painful, and, but not constantly, enlarge during the pyrexial periods. In the second, a rare form, the glands, small in the apyrexial intervals, with the onset of fever rapidly swell up, becoming extremely large, tender, hot, and painful, the skin over them becoming red or purple and sometimes œdematous. With the end of the febrile attack the glands and spleen shrink to an extreme degree. In the third form, of which he collected eight cases, the only glands affected are the internal, though the spleen may be palpable. As regards the duration of the relapsing type the extremes were five weeks and five years, the disease being more rapid when the enlargement was confined to the deep glands. When the internal glands alone are affected the differential diagnosis, of course, covers a large field, such as enteric fever, malignant endocarditis, and other conditions which need not be discussed. But reference should be made to the simulation of the Pel-Ebstein fever by tuberculosis. Among 500 cases of pulmonary tuberculosis at the Brompton Hospital MacNalty found six with a recurrent fever; in such cases splenic enlargement may be a clue. He also insists on the close clinical resemblance to Hodgkin's disease of widespread tuberculous adenitis.

The *primary site of Hodgkin's lymphogranuloma* is a subject of some practical importance, for enlargement of the superficial lymphatic glands, being usually the first indication of lymphadenoma, has accordingly been generally regarded as the starting-point of the disease. But it does not follow that the glands first palpably enlarged are necessarily those first attacked. Symmers,[84] from pathological experience, contends that this conception is erroneous, and that primary enlargement of the abdominal or of the abdominal and thoracic glands combined is ten times commoner than primary enlargement of the cervical glands. With this Ewing [21] agrees, and adds that the enlarged superficial glands which first attract attention are merely the outlying portions of an internal lesion. The idea that the glandular enlargement on the neck

may in any given case be secondary rather than primary, and, indeed, be analogous to the glandular metastases in malignant disease inside the chest and abdomen, should be more constantly in our minds, and, being based on post-mortem observations, demands clinical confirmation by systematic X ray examination of the chest in every early case; for if intrathoracic or abdominal involvement is present this should obviously be treated by deep radiation. The unsuspected existence of intrathoracic lymphogranuloma may help to explain some apparently hyperacute cases, such as Brunner's patient, a woman aged 27 years, who died with two weeks' symptoms suggesting acute cardiac failure, the necropsy revealing extensive Hodgkin's disease.

Enlargement of the superficial lymphatic glands may disappear under treatment, either entirely or partially, while insidious implication of the deep abdominal and thoracic glands progresses, and the patient becomes anæmic, emaciated, and eventually dies. Intercurrent infections, such as erysipelas, appendicitis, and lobar or influenzal pneumonia, may be followed by diminution in size or disappearance altogether of the glands which, however, subsequently reappear. The same temporary improvement, especially in the blood count, may occur in leukæmia, an event which is of interest in connexion with Symmers's [84] contention that Hodgkin's lymphogranuloma and myeloid leukæmia "are probably different quantitative responses to the same type of provocative agent." Further, this reaction is of interest in connexion with W. B. Coley's treatment of Hodgkin's lymphogranuloma by the mixed toxins of erysipelas and *Bacillus prodigiosus* and radium.

The variations in its distribution are on much the same plane as those in the infective granulomata, such as tuberculosis and syphilis, and it may be suggested that its localisation is determined by two factors: (1) the variations in the resistance of the different parts of the body, (2) the accident of a large dose of the virus at any one site. When generalisation occurs, the spleen is more often invaded than the liver, according to Longcope and McAlpine in the percentages of 57 and 48.

Intrathoracic Form.

The intrathoracic form is probably more frequent and primarily responsible for palpable glandular enlargement in the neck than is generally recognised. For a considerable time pressure symptoms may be absent, although a skiagram shows well-marked invasion of the mediastinum. The thymus may be predominantly affected and from this focus the disease may spread over the pericardium and even to the myocardium; fatal effusion into the pericardium may follow, and I have seen a chylous effusion. In 1924 Symmers collected five cases of predominant

thymus localisation; but probably it is much more frequent than these figures would suggest, and the question arises what proportion of mediastinal sarcomas should be regarded as Hodgkin's sarcoma, for there seems to be a special tendency to sarcomatous change in these mediastinal lymphogranulomas (Ewing [21]). The bronchial glands are often enlarged and from them the disease may creep along the bronchi into the lungs. The first clinical manifestation may be acute pleurisy, and palpable enlargement of glands may follow later. Pleural effusion, which requires repeated tappings, is a feature of some cases. In one case the effusion caused sudden death, and in another it was chylous. In the presence of a comparatively small effusion the dyspnœa may be out of proportion to the amount of fluid; in some cases this is obviously due to pressure exerted by enlarged glands on the bronchi, as shown by stridor and skiagraphy. Symmers [84] has recorded two cases with remarkable thickening of the pleura with Hodgkin's lymphogranuloma. Pressure symptoms resulting from compression of the trachea, bronchi, veins, and nerves make this the most distressing form of lymphadenoma, as the patient may eventually become strangled, deeply cyanotic, and terribly distressed. Before this stridor may be noticeable on exertion only; I have seen attacks of dyspnœa terminating in the expulsion of fibrinous cases. The fever of the Pel-Ebstein type may suggest pneumonia, and Weber considers that patients taking arsenic are prone to pneumonia, which, however, usually runs a favourable course.

In Dr. C. H. Miller's case, from which the sections showing Hodgkin's disease in muscle were taken, there was a large mediastinal growth, involving the root of the right lung and causing racemous lymphogranulomatous bronchitis, peribronchitis, and peribronchial pneumonia, with catarrhal, fibrinous, and fibroblastic pneumonia in the intervening pulmonary tissue of the upper and middle lobes of the right lung (H. M. Turnbull). Paracentesis of the right pleura, giving exit to three pints of clear yellow fluid (97 per cent. lymphocytes) was followed by pneumothorax. Death was due to the intrathoracic condition.

Pressure on the superior vena cava and innominate veins may induce cyanosis, distension of veins, œdema of the face and conjunctivæ, and an œdematous boggy condition in the supraclavicular fossæ. Clubbing of the fingers (Turnbull) and chronic pulmonary osteo-arthropathy (Weber and Ledingham) have been reported. Dysphagia may occur, but is seldom prominent. Pressure on the recurrent laryngeal nerves may lead to abductor paralysis. The oculo-cardiac reflex may be exaggerated (Jacob).

Abdominal Manifestations.

The abdominal manifestations of Hodgkin's lymphogranuloma may be divided into (1) the peritoneal,

(2) retroperitoneal, (3) gastro-intestinal, (4) splenic, (5) hepatic, and (6) renal forms. The last three are extremely rare in a predominant form.

(1) The *peritoneal form*, due to affection of the mesenteric glands, may imitate tuberculous peritonitis and give rise to ascites, which is usually serous, but in rare instances has been chylous or pseudo-chylous; among 46 cases Schreiner and Mattick had two with chylous ascites, and Schölberg and Wallis in their collections of 102 cases of chylous and 71 cases of pseudo-chylous found two in each group due to Hodgkin's disease. Ascites, which may be the first physical evidence of the disease, is occasionally associated with jaundice due to pressure on the bile-ducts by enlarged glands in the portal fissure. This jaundice may intermit; I have twice seen the jaundice appear and disappear with the periodic onset and resolution of the Pel-Ebstein fever. Enlargement of the glands in the neighbourhood of the liver and fever may imitate cholecystitis or hepatic abscess, as in a case I saw after laparotomy had revealed the true state of affairs.

(2) In the *retroperitoneal form* the glands may be involved alone or together with the mesenteric glands and the spleen, and from the greater enlargement of the retroperitoneal glands it may appear that the splenic enlargement is secondary. The special symptoms due to lymphadenomatous glands in the retroperitoneal space are those of pressure on adjacent structures, such as the inferior cava causing œdema of the feet and abdominal wall and albuminuria, on the bile-ducts causing jaundice, which in a case mentioned by MacDonald came on early in the course of the disease, on the spinal nerves causing pain, and on the sympathetic plexuses leading to dyspepsia, vomiting, and colic. Pressure exerted on the bowel has been associated with obstinate constipation; and periodic increase in the size of the glands, which may correspond with the bouts of fever, may account for attacks of pain in the back or the lower limbs. Pain associated with irregular fever and resistance in the upper abdomen suggested a leaking gastric ulcer, but at laparotomy the glands showed acute Hodgkin's disease (MacDonald).

The lymphogranulomatous change, when thus hidden at the back of the abdomen and impalpable, may be responsible for obscure fever, and when its character is that of the relapsing fever type the absence of enlarged glands does not justify the diagnostic exclusion of the disease (Horder[40]), but the diagnosis is very difficult, as shown in Whittington's case, in which an acute onset first suggested peritonitis, then appendicitis, enteric fever, splenic anæmia, tuberculous peritonitis, and obscure malignant disease.

Cutaneous pigmentation has been reported in association with a mass of lymphadenomatous glands

around the adrenals (Nieczkowski ; Fowler ; B. Bramwell ; Symmers), and may be due to irritation of the sympathetic or with less probability to interference with the adrenals. Lymphogranulomatous glands around the aorta may invade the dorsal vertebræ and pass through the intervertebral foramina into the spinal canal, and even lead to compression of the spinal cord and paraplegia. It is possible that some cases of herpes zoster are due to irritation of the ganglia on the posterior nerve-roots.

(3) *Gastro-intestinal lymphogranulomatosis* is a difficult subject ; more cases were recorded in the days before the histological characters were established in 1902. Among Desjardins and Ford's 135 cases there was no instance of gastric or intestinal implication, but Prof. Turnbull found one case with extensive implication of the intestine among his 47 necropsies, and Steindl has recently reported nodular lymphadenoma of the gastric mucosa, the glands in the mesentery being the only other site involved. In 1904 Salaman denied that the alimentary canal was ever affected, and, indeed, that Hodgkin's disease is a pathological entity. Although it would be natural to expect that Peyer's patches and the solitary follicles would be affected, especially in cases in which the abdomen bears the brunt of the disease, and is presumably the portal of entry, this is evidently very rare now.

The cases formerly described as lymphadenoma of the stomach and intestines, such as Pitt's collection of 25 cases divided into two groups of (1) seven cases in which the lesion began in the mucous and submucous coats of the stomach and intestine and projected into the lumen, and (2) the 18 cases in which it spread from the mesenteric glands to form diffuse sheaths in the subserous coat, would now be regarded as allied to, if not examples of, infective lymphosarcoma, or lymphoblastoma, a tumour of lymphocytes, of which Graves has collected 249 examples of the intestine.

In addition to dyspepsia due to irritation of the sympathetic and abdominal distension caused by ascites and glandular enlargement, the effect of treatment by arsenic and irradiations must not be left out of account in considering the causation of gastro-intestinal symptoms. I have seen melæna six weeks after the application of radium to the abdomen, as if from a duodenal ulcer ; McAlpine and von Glahn record perforation of the transverse colon in a woman aged 28 years, who had during six years been treated by X rays on 95 occasions ; and Sir Thomas Horder allows me to mention a patient in whom perforation of the ileum occurred after two courses of X ray treatment to the abdomen.

(4) *Splenic form.*—The spleen is nearly always affected in cases which run their full course ; Prof. Turnbull found the spleen invaded in all his 47 necropsies, and regards this as an important point

in the diagnosis. Massive infiltration of the spleen by Hodgkin's lymphogranuloma with insignificant enlargement only of the lymphatic glands is infrequent, and it is very rare to find the disease entirely confined to the spleen.

Symmers described two cases; in the first[82] no glandular enlargement was detected in life, and the spleen showed the microscopic appearances of Hodgkin's lymphogranuloma, but there was no necropsy. In his second case[84] there were some palpable glands. In Wade's case no enlarged glands were detected clinically or at operation, but here again there was no necropsy. In Mellon's case there was slight enlargement of the inguinal glands. Cornwall reported a case without any disease in any glands. Dr. Krumbhaar has kindly sent me the notes of a necropsy showing lymphogranuloma of the spleen and bone-marrow, but not of the lymphatic glands. L'Esperance reported an enormous spleen, simulating a ventral hernia, with slight infection of the retroperitoneal, but not of the superficial lymphatic glands; the liver also showed invasion. Although Donhauser regarded his case of splenomegaly with sclerosed bone-marrow as a compensatory hæmatopoietic process, some later writers (Ewing) have referred to it as the splenic form of Hodgkin's lymphogranuloma. Ewing also quotes a case recorded by Kummel. In several of these cases there has been a special tendency to relapsing fever.

In some other instances after enlargement of the superficial lymphatic glands has subsided or even disappeared the spleen and liver have enlarged, and at this late stage the condition has imitated chronic splenic anæmia or the further stage with secondary hepatic cirrhosis or Banti's disease. Poynton, Thursfield, and Paterson record a case of a boy at first with some enlargement of the cervical glands, which had disappeared at the necropsy when the spleen (25 oz.) and the liver (44 oz.) were both found to be invaded.

(5) *Hepatic form.*—The liver is affected in 50 or more per cent. of all cases of the disease, but usually this is a post-mortem, not a clinical, observation. Reference has been made to jaundice from pressure on the bile-ducts by the glands in the portal fissure, and to the possibility of mistaking an enlarged liver or apparent enlargement from glands in the neighbourhood when associated with relapsing fever for hepatic abscess. Limitation of Hodgkin's lymphogranuloma to the liver is unknown, but I have seen the organ greatly enlarged secondary to lymphadenomatous glands in the groin in one case, and at the elbow in another instance. Symmers[84] reported a case in which the liver was enormously and, except for the spleen and abdominal lymphatic glands, exclusively invaded.

(6) *The renal form.*—The kidneys occasionally show nodules of white lymphadenomatous growth, usually small in size, and in rare instances the perirenal lymphatic glands are much enlarged.

By the kindness of Prof. R. Muir and Dr. J. Carslaw, of Glasgow, I have been provided with the notes of a man,

aged 26, with extensive lymphadenoma (vide Fig. 3) of the right kidney (17 oz.), which was studded throughout with whitish nodules of soft cellular tissue resembling to the naked eye secondary sarcoma, the largest being ¾ inch in diameter. The left kidney (3 oz.), apparently small congenitally, contained one or two nodules of the same growth. Microscopically the liver (47 oz.) showed diffuse lymphadenomatous infiltration of the portal canals, thus contrasting with massive invasion of the right kidney. The spleen (15 oz.) contained nodules and the retroperitoneal glands were markedly involved. The bodies of the first four dorsal vertebræ and the dura mater were invaded, and the spinal cord softened; before death the patient had become paraplegic.

Apart from a trace of albumin clinical manifestations associated with renal invasion have not attracted attention, but J. Galloway recorded the case of a man with polyuria and a protein resembling in some respects, but differing in others from, Bence-Jones's protein. The kidneys contained cysts and microscopically showed small areas of lymphadenoma.

Cutaneous Manifestations.

The cutaneous manifestations of Hodgkin's lymphogranuloma are of various kinds, and raise some questions of interest. It has been estimated that 25 (Ziegler) to 39 (Cole) per cent. of the cases exhibit them in one form or another.

Pigmentation may be due to the local action of X rays, the administration of arsenic, the scratching induced by pruritus, or to nerve irritation by affected retroperitoneal glands, or possibly to adrenal disorder. Symmers's patient with acanthosis nigricans had lymphogranulomatous invasion of the cœliac plexus without any implication of the adrenals. The pigmentation may suggest Addison's disease.

The *hair* may become altered in colour; in Byrom Bramwell's patient it became lighter, finer, and more silky. Pruritus and itching may lead to perifollicular inflammation and loss of hair, but in Porter's account of a patient with almost universal alopecia no mention was made of pruritus.

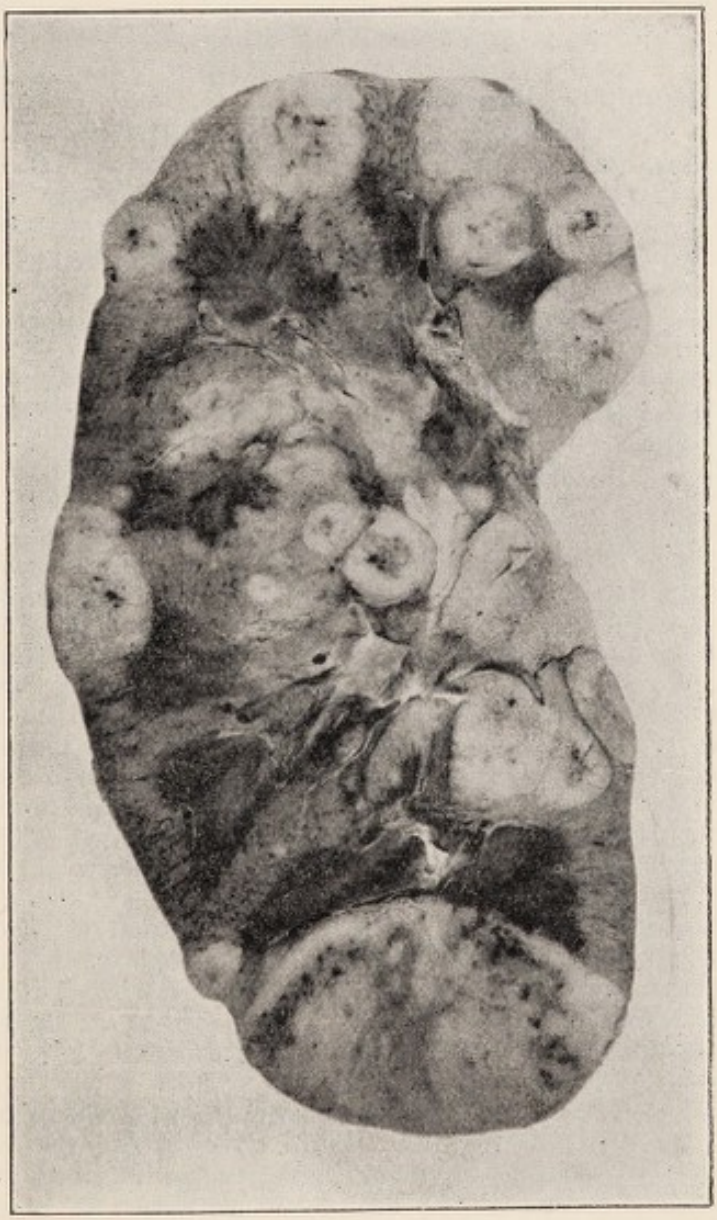
Perspiration may naturally accompany the swinging temperature in the Pel-Ebstein syndrome, but it may also be associated with pruritus. The parchment-like condition due to continued scratching has been noted to cause diminution in the sweat. (Nanta and Baubru.)

Œdema of the skin may be mechanical; areas of atrophy may depend on impaired nutrition, and in rare instances hæmorrhages have been recorded; it is tempting to associate recurrent purpura, as in Weber's[94] case, with the diminution in the platelet count known to occur in the later stages; but I do not know that thrombocytopenia has been found in purpura in Hodgkin's disease.

Ætiologically the cutaneous manifestations fall into two groups, (1) the toxic, and (2) those due to invasion of the skin by the lymphogranulomatous tissue characteristic of Hodgkin's disease.

The reported incidence of *pruritus* varies; Favre

FIG. 3.



Massive infiltration of the kidney by Hodgkin's lymphogranuloma. (By the courtesy of Dr. Carslaw and Prof. Muir.)

considers it constant, but apparently it is a diagnostic factor of his adénie éosinophilique prurigène; his pupil Colrat found it in 11 out of 13 cases, and no doubt inquiry from the patient would increase the

number of recorded instances. In Longcope's 86 histologically proved cases it was noted in 3 only; Desjardins and Ford found it in 9 per cent. of 135 similarly established cases. It is the commonest of the skin manifestations and is responsible for the next most frequent, namely, prurigo. When present it is usually an early symptom, often months before there is any glandular enlargement, and so may be regarded as scabies or analogous to the premycotic stage dermatosis of mycosis fungoides (Weber and Dove), and herein a clinical resemblance of these two conditions may be shown.

It may, however, occur after the diagnosis has become clear from the ordinary clinical picture, and then come and go, or in rare instances appear only in the terminal stage. It may be excited by stimulation of the skin by changes of temperature, X rays, or arsenic (Galloway). Its pathogeny leaves room for much speculation; on analogy it has been regarded as anaphylactic or to be toxic. Though irritation of the terminations of the sensory cerebro-spinal nerves would appear an obvious explanation, it has been regarded as due to spinal radiculitis (Milian and Blum) and analogous to tabetic pruritus, and even to irritation of the sympathetic (Golay). The easy explanation that pruritus may be toxic, does not perhaps carry great weight in the light of the inconstancy of its incidence and its occasional appearance long before there are any palpably enlarged glands. But it may be that deep-seated lymphadenomatous glands provide the pruritogenic poison long before the more outlying and superficial glands are affected. The occasional occurrence of amyloid disease in Hodgkin's lymphogranuloma, of which Fabian collected 22 examples, points to the action of a powerful toxin, but there is no reason to believe that the occurrence of amyloidosis and pruritus are associated. Abnormal sensitiveness of the nervous system might be thought to play a part in the occurrence of pruritus, and Galloway's observation that arsenic, which is a nerve tonic, sometimes excites pruritus, might be mentioned to support the view that an inherent or acquired susceptibility of the central nervous system plays a part.

Pruritus is far commoner in Hodgkin's lymphogranuloma than in leukæmia, in which it is generally stated to occur. I have never seen it, and of 12 recorded examples of leukæmic pruritus it is noteworthy that 6 are cases of universal leukæmia of the skin collected by Ketron and Gay. It would be interesting to correlate the incidence of pruritus with the structural changes in the two conditions, especially whether the presence of small areas of necrosis, which are common in Hodgkin's lymphogranuloma, account by a resulting anaphylactic mechanism for the pruritus. The pruriginous papules are small-celled collections, and would appear to be

purely inflammatory, and so to be distinct from lymphadenomatous invasion of the skin; but this differentiation may be far from easy in the early stage of the latter. Difficulty may also arise in distinguishing these pruriginous papules from the cutaneous infiltrations in aleukæmic leukæmia.

Among other cutaneous manifestations presumably of a toxic nature are eruptions of an erythematous, morbilliform (Webster), urticarial (MacNalty), bullous character, and universal exfoliative dermatitis. The occurrence of these different forms may perhaps be explained by differences in the resistance and susceptibility of the skin.

Infiltration of the skin by Hodgkin's lymphogranuloma, apart from extension from immediately underlying lymphadenomatous glands, is much rarer than the skin changes of prurigo. In 1924 I could collect 12 cases only. It thus contrasts with mycosis fungoides, which, indeed, has been thought by Ranvier (1869) and K. Ziegler (1911) to be the cutaneous form of Hodgkin's disease, a view difficult to harmonise with the histological appearances. The cutaneous tumours in Hodgkin's lymphogranuloma may be small or large and flat; they grow slowly and seldom, as in Langley and Cole's cases, ulcerate. As a rule, the presence of the tumours has not been associated with pruritus. As they are usually part of the generalisation of the disease they are a late phenomenon in its course.

Herpes Zoster.

Herpes zoster is probably more frequent in lymphadenoma than in any other disease, though it is not at all common. The questions arise, is it always due to arsenical treatment, does arsenic only render the patient more susceptible to the responsible virus, or may it in some instances be due to irritation of the posterior root ganglia by enlarged glands close to the spine? Weber's conclusion that patients taking arsenic are disposed to acute pneumonia, which is so often associated with febrile herpes labialis, is perhaps of interest in this connexion. Weber [93] has never seen herpes in Hodgkin's lymphogranuloma apart from arsenical treatment; but this has probably occurred in some recorded instances (O'Flynn; Pancoast and Pendergrass). It may appear early or late in the course of the disease, and may even recur; in a boy seen in consultation there had been three attacks. I have seen it generalise like varicella. The scars left by an attack of herpes may show up as leucodermic patches against the skin of the trunk rendered pigmented by arsenical treatment.

Synovitis.

Very little attention has been paid to arthritic manifestations in Hodgkin's lymphogranuloma, and no doubt they are rare. From the two cases I have

seen they would appear to be transient and not well marked.

In a man in St. George's Hospital with generalised lymphogranuloma there was œdema of the left thigh and leg from pressure and at one time evidence of considerable effusion into the corresponding knee-joint, but this had disappeared at the necropsy. A boy, aged 11 years, seen in consultation in 1923. had recurrent attacks of synovitis with considerable effusion in the left wrist and elbow, knee and ankle, and right temporomaxillary joint, followed by darkening of the skin suggesting hæmorrhage Some of the attacks were febrile, others afebrile ; they subsided spontaneously ; as salicylates were employed in one attack only and the heart was normal, there was no reason to regard them as rheumatic. It may be noted that he also had three attacks of zona on the right side of the chest, pruritus, and a rash. The question arises whether toxæmia due to liberation of a protein from X ray exposures, which had been freely employed, were responsible for the synovitis.

As Hodgkin's lymphogranuloma appears to invade the bone-marrow in about half the cases, it might, on the analogy of tuberculosis, have been expected that the joints would be prone to invasion. On the other hand, it may be pointed out that myeloid leukæmia, which, according to Symmers,[84] is fundamentally related to Hodgkin's disease, does not cause arthritic manifestations.

Skeletal Invasion.

Lymphadenoma in bone was described by Weber [88] some years before the histological features of lymphadenoma were established ; his case would appear to be one of multiple myeloma. Invasion of bone by lymphadenoma is now generally recognised.

Among 14 cases Symmers found it in seven, or 50 per cent., and describes two changes which may be present at the same time, (*a*) hyperplastic compensation in response to demand for more blood corpuscles, which he regards as identical with that in chronic myeloid leukæmia, and (*b*) invasion by lymphogranulomatous tissue. Among 39 necropsies at the London Hospital Prof. Turnbull found the bone-marrow invaded in 19, or 49 per cent., the femur and the lumbar vertebræ being the parts of the skeleton most often affected ; from comparison of the sites of the glandular groups most enlarged, and therefore presumably primarily affected, on the one hand, and the bones affected on the other hand, he obtained results which suggest that the femur is invaded through the blood-stream, and that the lumbar vertebræ are involved as a result of direct spread from the retroperitoneal glands.

On the question whether the changes in the bone-marrow are part of a widespread reaction to the stimulus of the unknown virus or whether they are secondary, in the same way as generalised tuberculosis is, to infection from a primary focus, there may be room for discussion. Prof. Turnbull concludes that they are secondary. It is noteworthy that spontaneous fracture of bones, which may occur in secondary carcinoma and in endosteal sarcoma, is not

known in invasion of bone by Hodgkin's lymphogranuloma. Bence-Jones's proteinuria, which is a feature of multiple myeloma, appears to have been recorded in one case only of Hodgkin's disease (Galloway).

Paraplegia.

In rare cases paraplegia occurs in the course of Hodgkin's disease; Weber[92] refers to 12 examples, in six of which a necropsy was performed. The paraplegia may apparently be due to: (1) Pressure on the spinal cord by lymphogranulomatous growth gaining entrance into the vertebral canal either through the intervertebral foramina or from the infiltrated vertebræ; this form of pressure paraplegia appears to have occurred in five of Weber's cases. These cases would probably be those with retroperitoneal localisation of the disease, in which sarcomatous change has supervened. (2) Pressure on the nerve roots; in a case of W. Hale-White[92] this was exerted inside the vertebral canal. (3) Myelitis and acute meningitis without any evidence that the spine or dura mater had been invaded by the lymphogranuloma (Allan and Blacklock); in view of the rarity of paraplegia in Hodgkin's disease the myelitis may well have been independent of that disease except in so far as it reduced the patient's power of resistance and so favoured the infective cause of the lesion in the central nervous system. (4) It would be natural to expect that arsenical neuritis might be responsible for paraplegia; I have seen one case, recorded by Carlill, which might bear this interpretation.

Diagnosis.

The distinction from other forms of glandular enlargement, tuberculous, leukæmic, chronic inflammatory, and sarcomatous, and from other pyrexial states would, if systematically considered, occupy much space, and a few points only will be touched on.

The Value and Fallacies of Biopsies.—From the difficulties of clinical diagnosis a dogmatic opinion is uncertain and often unwise until a gland has been removed and found to show the characteristic histological changes. Unfortunately a gland excised from a case of Hodgkin's lymphogranuloma does not always show the lesions; its enlargement may be due to simple non-specific inflammation or to compensatory hyperplasia. According to Prof. Turnbuil the histological changes are best seen in glands which are very hard and from contraction not necessarily enlarged, and not very infrequently the microscopical report cannot go further than "lymphogranuloma, possibly Hodgkin's, but histological characters are not definite." In contrasting the value of microscopic examination of excised glands Webster found that it gave much more correct diagnostic results in Hodgkin's lympho-

granuloma than in cases finally shown to be lympho-sarcoma.

Diagnosis from Sarcomatous Lymphomas.—The greatest difficulty is the clinical differentiation of Hodgkin's lymphogranuloma from lymphosarcoma and the closely allied malignant lymphocytoma composed of small lymphocytes, and from endothelial sarcoma. I have seen cases apparently running the clinical course of Hodgkin's lymphogranuloma show these histological appearances finally; the question arises whether, as probably most would consider, these conditions have existed from the start, or whether they have supervened as the result of Hodgkin's lymphogranuloma. Is there any evidence of this change, such as a biopsy early in the course of the disease showing the appearances of Hodgkin's disease, and later a necropsy proving the sarcomatous nature? It does not appear to me that the therapeutic test of X ray exposures helps in distinguishing them. I have personal knowledge of what appeared to be Hodgkin's disease, but turned out to be malignant lymphocytoma reacting in a wonderful manner, life being prolonged for three years after an early termination seemed inevitable, to Dr. W. B. Coley's personal treatment by the mixed toxins of erysipelas and *Bacillus prodigiosus* and massive doses of radium.

Undetermined forms of glandular enlargement, such as those spoken of as infectious mononucleosis and glandular fever, may, though of comparatively short duration, give rise to difficulty in diagnosis. Infectious mononucleosis according to Sprunt and Evans presents a slight leucocytosis with some increase in the large mononuclear-transitional cells and many pathological lymphoid forms.

Cases of aleukæmic leukæmia—namely, leukæmia in an aleukæmic phase, and cases which come under Bunting's heading of lymphoblastic aleukæmia, can hardly be differentiated from Hodgkin's disease except by histological examination of an affected gland.

Under the heading of *splenomegalia lymphatica hyperplastica* Brill, Baehr, and Rosenthal describe a generalised lymph follicle hyperplasia of the lymphatic glands and the spleen with a normal blood count and readily curable by X rays. The spleen is enormously enlarged and shows giant Malpighian bodies the size of a barley grain ¼ in. in diameter, and almost entirely composed of endothelioid or reticular cells. The follicles of the lymphatic glands are greatly enlarged due to cells of an endothelioid or reticular type, like those seen in the germinal centres of lymph follicles, especially in children. The appearance is said to be quite different from that of ordinary follicular hypertrophy and of lymphatism. Before the curative effect of X rays was found out, splenectomy was performed in two out of three cases recorded; in one it weighed 56 oz. (1800 g.). The cause of this condition was not determined, whether from toxic influence within or without the body; they quote Kusczinski as having produced generalised lymphoid hyperplasia in

mice by special diets. How often cases of this kind come to hospital, and after being diagnosed as Hodgkin's lymphogranuloma are treated with X rays and arsenic and are then lost sight of it is impossible to say ; a case of general hyperplasia of all the lymphoid tissues except the thymus with a leucocyte count of 23,235 (polymorphonuclears 82 per cent.) was reported by C. H. Miller.

I have twice seen a symptom-group which may imitate lymphadenoma—namely, a " hypernephroma " of the left kidney or adrenal body producing a tumour imitating splenomegaly and glandular metastases above the left clavicle ; from the fever described in necrotic hypernephromas (Symmers [84]) the resemblance might be increased.

Prognosis and Treatment.

The universal fatality of this disease, which in other respects has many resemblances to tuberculosis, may perhaps be correlated with the much less marked tendency of the lesions to undergo necrosis and fibrosis, as if the unknown cause were more persistent, though not necessarily more virulent, and the resisting powers of the body less able to bring the disease to an end. The absence of extensive necrosis and of caseation might suggest that the process is less acutely virulent.

The duration of symptoms varies ; acute cases lasting a few weeks are rare, and the suspicion may arise that from the presence of internal glandular disease they are not so acute as the duration of obvious signs, due to generalisation, would suggest. When the primary site is in the thorax or abdomen and extension later occurs to superficial glands, the course may, when calculated from their detection, be very short ; the primary enlargement, especially in the chest, may, owing to the adaptability of the viscera, remain latent for a long time and be detected by skiagraphy only.

Prognosis as to duration of life depends on treatment by arsenical preparations and irradiations, for there is not any evidence that, as in tuberculosis, a spontaneous cure occurs. The effect of arsenical preparations is at first most successful ; but relapses occur, and eventually the drug fails to control the disease, as if the unknown virus became arsenic-fast or the morbid process underwent some change. The same appears to be true with regard to the radiations of X rays and radium ; but in most exceptional instances this does not hold good ; Schniffner recorded the case of a woman who for 11 years was benefited by X rays. It has even been suggested that X rays may lead to generalisation of the disease (Weber [95]), just as it has sometimes appeared to do in carcinoma. Simmonds and Benet prefer radium to X ray treatment, and urge that it should be applied on all the lymphatic areas in the body and not only on those obviously affected.

Vaccines of the diphtheroid organism have not proved successful, but Bunting mentions trials with an immune serum (to this organism). Success has attended the treatment, by Dr. W. B. Coley, of New York, of Hodgkin's disease by repeated injections of the mixed toxins of erysipelas and *Bacillus prodigiosus* and of massive doses of radium; of this I have had much recent information from him.

Surgical opinion has long been adverse to removal of lymphadenomatous glands on account of the difficulty of complete extirpation and of the frequency of similar intrathoracic disease. Symmers [84] throws out a warning of the danger of secondary infection as a result of excision of the inguinal glands. Removal of infective foci, such as the tonsils, and free surgical extirpation of the disease in an early stage has been advocated by Bunting and Yates on the lines of the Halstead and Crile operations for the lymphatic glands in mammary carcinoma. But the cases are not necessarily analogous, for the primary growth in the mamma is removed, whereas in lymphadenomatous glands in the supraclavicular fossæ and neck the thorax or abdomen may be the primary focus.

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