Some aspects of lymphadenoma (Hodgkin's Disease) / by H.D. Rolleston.

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SOME ASPECTS OF LYMPHADENOMA (HODGKIN'S DISEASE).

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History.—Although the condition was briefly described by Morgagni (1769), and in this country by Bright and Carswell, the credit of first drawing attention to it is usually given to Hodgkin—demonstrator of morbid anatomy at Guy's Hospital—who, in 1832, contributed a paper "On some morbid appearances of the absorbent glands and spleen."[1] It is probable that only a few of the seven cases given in his paper would now be regarded as lymphadenoma, and his account did not attract any attention and probably never would have done so had it not been for the loyal efforts of Sir Samuel Wilks[2] who, in 1856, gave an account of "A peculiar enlargement of the lymphatic glands" in a paper "On cases of lardaceous disease and some allied affections." He says that this affection is not lardaceous but is brought forward in connexion with that disease because it is either a variety of it or closely related to it. At the end of the paper there is an addendum saying that it was only after he had completed the article that he came on Hodgkin's paper, and that had he been aware of its contents the statements about the originality of some of his own observations would not have appeared. Wilks[3] finally, in 1865, made Hodgkin's name immortal by calling the disease after him. About this time (1864) Virchow described the large multinuclear or "lymphadenoma cells" which subsequent observers also noted, among them Langhans (1872), and Greenfield[4] in the course of a debate on the subject at the Pathological Society of London in 1878. General attention, however, was not paid to this until Andrewes[5] described fully the histological characters of the disease in another discussion at the same Society on "Lymphadenoma in its

[1] Hodgkin, T.: *Med.-Chir. Trans.*, Lond., 1832, XVII., 68.
[2] Wilks: *Guy's Hosp. Rep.*, Lond., 1856, 3. ser., II., 131.
[3] Wilks: *Ibid.*, 1865, 3. ser., XI., 56.
[4] Greenfield: *Trans. Path. Soc.*, Lond., 1878, XXIX., 292; Pl. XIII., Fig. 2.
[5] Andrewes, F. W.: *Ibid.*, 1902, LIII, 305.

relation to tuberculosis" on December 13, 1901. In the introduction to this discussion Butlin[6] recalled Greenfield's forgotten observation, just as at an earlier date Wilks unearthed Hodgkin's buried paper. It appears that, although he did not publish any further description, Professor Greenfield had fully worked out the histological structure of lymphadenoma years before Andrewes, Reed, and Longcope gave their well-known accounts. For, according to Stuart McDonald,[7] "modern research has only confirmed the views which Professor Greenfield, of Edinburgh, has held and taught for many years. My own notes taken in his course of pathology in 1893 include all the essential characters of the lesions."

Nomenclature.—Various names have been given to this disease. In this country it is often called Hodgkin's disease, and it has been suggested that this name should be confined to the cases showing the special histological structure described by Andrewes, Reed, Simmons, Longcope, and others; but the title in the official "Nomenclature of Diseases" drawn up by the Royal College of Physicians of London (1906) is "lymphadenoma," a name invented by Wunderlich, "Hodgkin's disease" being given as a synonym. Trousseau called the disease adénie; in Germany pseudo-leukæmia has been erroneously used as a synonym, but it should, as originally intended by Cohnheim,[8] who introduced it, be restricted to the cases in which the lymphatic glands show the histological changes of lymphocytic leukæmia but in which the lymphocytes do not pass into the blood—in fact an aleukæmic stage of lymphocytic leukæmia. Virchow called it lymphosarcoma, which was unfortunate as it led to confusion with the definite form of sarcoma now known by this name. It was also called malignant lymphoma (Billroth). Quite recently the title lymphomatosis granulomatosa has been employed by Fraenkel and Much.[9]

Etiology.—Lymphadenoma usually begins in glands much exposed to infection—namely, those in the neck. I have seen

[6] Butlin: *Ibid.*, 1902, LII., 302.

[7] McDonald, S.: *North of England Clin. Journ.*, Newcastle-upon-Tyne, 1911, I., 38.

[8] Cohnheim: *Virchow's Arch.*, 1865, XXXIII., 451.

[9] Fraenkel und Much: *Ztschr. f. Hyg. u. Infectionskrankh.*, Leipz., 1910, LXVII., 159.

it in the armpit after an infected wound of the finger. In an acute case with considerable implication of the liver and spleen recorded by Parkes Weber[10] there was a duodenal ulcer. It is three times commoner in males than in females; most of the cases begin in early adult life.

The cause is unknown. Bacteriological investigation has not shown any constant infection. The results in some cases have been positive and several organisms—for example, pyogenic micrococci and *B. proteus* (Longcope)—have been described, but were probably due to intercurrent or terminal infection. Dreschfeld,[11] in 1892, described a small bacillus; Delbet,[12] in 1895, cultivated a bacillus, and by giving large injections of the culture to a dog he produced glandular enlargements from which he isolated the bacillus in pure culture. These results have not been confirmed. In 1909 Byrom Bramwell[13] mentioned that in two of his cases protozoan organisms resembling minute bacilli had been found by Ford Robertson and Young. Quite recently Fraenkel and Much have described a bacillus morphologically identical with the granular form of the tubercle bacillus, but not acid-fast. They have not been able to cultivate it. White and Proescher,[14] using the Levaditi method, described a spirochæte in lymphadenoma and regarded the disease as a spirillosis. Their observation, which has not been confirmed, though McDonald, Turnbull, and others have attempted to do so, is attractive for the following reasons:—(*a*) The frequency with which an increase in the number of eosinophil cells occurs in the lymphadenomatous glands; this was first noticed by Goldmann[15] in 1892 and is now fully recognised. As is well known, eosinophilia is characteristic of infection by animal parasites. (*b*) The occasional occurrence of eosinophilia in the blood; though, as a rule, there is no eosinophilia, it may be very remarkable, as in Lincoln's case of acute lymphadenoma in which there was 68 per cent. of eosinophils.[16]

[10] Weber, Parkes: *St. Barth. Hosp. Rep.*, Lond., 1907, XLIII., 81.
[11] Dreschfeld: *Brit. Med. Journ.*, 1892, I., 892.
[12] Delbet: *Semaine méd.*, Par., 1895, XV., 271.
[13] Bramwell: "Clinical Studies," Edin., 1909, VIII., 131.
[14] White and Proescher: *New York Med. Journ.*, 1908, LXXXVII., 9.
[15] Goldmann: *Centralbl. f. allg. Path. u. path. Anat.*, Jena, 1892, III., 668.
[16] Lincoln: Medical Papers dedicated to R. H. Fitz, 1908, p. 273; *Boston Med. and Surg. Journ.*, 1908, CLVIII.

This writer has collected the previously recorded cases of eosinophilia, the highest of which is 24·5 per cent. (Nowack). Among 20 cases of lymphadenoma Pepper[17] found eosinophilia in 4, or 20 per cent. Last year I saw a case of lymphadenoma, also acute, in which the percentage of eosinophils was 26·5. (*c*) The influence of arsenic on the disease. The extraordinary effect of the organic compounds of arsenic, especially "606," on the *Treponema pallidum* and the spirilloses suggests that the cause of lymphadenoma may also be of this nature. Inoculation of lymphadenomatous glands into animals and even into monkeys (Longcope,[18] S. McDonald[7]), which can be infected with *Treponema pallidum*, has failed to reproduce the disease.

The Relation of Lymphadenoma to Tuberculosis.—In 1899 it was stated by Sternberg[19] that lymphadenoma is a special form of tuberculosis of lymphatic glands, just as lupus is a special form of cutaneous tuberculosis. The main basis for this view is that inoculation of lymphadenomatous glands into guinea-pigs has given rise to tuberculosis. For some time this view was favourably received, but it has now been abandoned, for it has been shown (Andrewes,[5] Reed,[20] Longcope[21]) that the results of such inoculations vary. Some inoculations are positive, others negative. The explanation of this appears to be that the cases in which a positive result was obtained were not pure cases of lymphadenoma but of mixed infection in which tuberculosis had been implanted upon lymphadenoma; whilst the cases in which inoculation gave negative results were examples of uncomplicated lymphadenoma. It also appears that the damage done to lymphatic glands by the presence of lymphadenoma favours the occurrence of local tuberculous invasion. Death from generalised tuberculosis may occur in lymphadenoma. Parkes Weber[10] suggests that secondary tuberculosis in a lymphadenomatous gland sometimes causes retrogression of the primary lymphadenoma.

Morbid Histology.—Although the "lymphadenoma cells"

[17] Pepper, O. H. P.: *Bull. Ayer Clin. Lab. Penn. Hosp.*, Phila., 1907, No. 4, p. 22.

[18] Longcope: *Ibid.*, 1907, No. 4, p. 18.

[19] Sternberg: *Ztschr. f. Heilk.*, 1898, XIX., 21.

[20] Reed, D.: *Johns Hopkins Hosp. Rep.*, 1902, X., 133.

[21] Longcope: *Bull. Ayer Path. Lab. Penn. Hosp.*, Phila., 1903, I., 4.

were described by Virchow in 1864 and the preponderance of eosinophil cells in the affected glands by Goldmann in 1892, the morbid histology of lymphadenoma was not fully established until Andrewes in 1901 and Reed in 1902 published their independent investigations. Andrewes' work came out in 1901, being briefly reported in the medical journals (*Brit. Med. Journ.*, 1901, II., 1662), and fully in the *Transactions of the Pathological Society for* 1902, but has not received full recognition except in this country. The following is a brief summary of the histological characters on which the diagnosis of lymphadenoma depends :—the whole gland is altered and homogeneous ; lymphocytes are diminished and no longer conceal the framework of the gland, which undergoes hyperplasia. There is an increase in number of the endothelial cells and of the cells of the reticulum, some of which attain a large size and contain four or more nuclei ; these are the "lymphadenoma cells" which differ from the giant cells of tuberculosis. Eosinophil cells are always present, sometimes but not always in greatly increased numbers. The local eosinophilia is most marked in acute cases, and has been explained as due either to (*a*) immigration from the bone marrow, or (*b*) to a local production on the ground that their nuclei differ from those of the hæmic eosinophil cells (Turnbull [22]).

Like other inflammatory and granulomatous formations, lymphadenoma does not show the same structure at all stages of its life history. In the early stages the lymphadenoma cells are absent or rare, and the later stages show a great preponderance of fibrous tissue. At these two extremes there may hardly be sufficient histological evidence to diagnose the condition as lymphadenoma. It appears that the difference between the soft and hard forms is merely one of duration.

The *blood* in lymphadenoma does not show any characteristic change. The occasional occurrence of eosinophilia has already been mentioned (p. 3), and though a relative increase of lymphocytes may occur, and has even been thought by Pincus to be characteristic, it is far from constant and therefore cannot be regarded in this light. There is, as in most chronic diseases, a secondary anæmia. It is important

[22] Turnbull : *Arch. Path. Inst. Lond. Hosp.*, 1908, II., 130.

to realise these two essential characters of lymphadenoma, namely, its histological structure and the accompanying blood picture, so as to distinguish it from the conditions with which it is so likely to be confused, namely tuberculosis, the glandular hyperplasias included under the title pseudo-leukæmia, lymphocytic leukæmia, and malignant disease, especially lympho-sarcoma.

The Spread of the Disease.—Although the spread of the disease might be regarded as analogous to that of sarcoma, it is generally agreed that the disease always arises in lymphoid tissue, however slight the amount of that normal lymphatic tissue may be; and that it is a widespread reaction of the lymphatic tissue to the unknown irritant and not a metastasis. As the larger lymphatic glands become affected, the minute lymphatic masses enlarge and subsequently also become affected; this explains the impossibility of curing lymphadenoma by excision. Adami,[23] who compares the process of lymphadenoma to cheloid growth, considers that the secondary changes in the liver and other parts are in the first instance a compensatory hyperplasia of the lymphoid tissue normally present in small quantities around the vessels. Moreover, as this lymphoid tissue is not contained within a capsule comparable to that of the lymphatic glands, its early proliferation in the liver and kidney may simulate a malignant infiltration or even suggest that a process which began as lymphadenoma has become sarcomatous (Yamasaki [24]). Subsequently, however, these hyperplastic lymphoid collections show the same characteristic changes as those seen in the lymphatic glands first attacked.

The Clinical Manifestations.—Lymphadenoma may be divided into three main groups; (1) when the superficial glands are mainly enlarged, (2) when the symptoms are mainly due to the presence of intrathoracic lymphadenoma, (3) when the symptoms are mainly abdominal. The thoracic or abdominal symptoms not uncommonly supervene in cases which begin in the ordinary way. The disease is usually local for a varying time and then becomes widespread; the usual course is therefore chronic, but acute cases occur. It is usually stated

[23] Adami: *Principles of Pathology*, 1910, I., 740.
[24] Yamasaki: *Ztschr. f. Heilk.*, 1904, XXV., 269.

that the whole course of the disease occupies two or three years, but the interval between its local appearance and its generalisation varies. A man, aged 36, who died under my care with widespread lymphadenoma, had had for more than 15 years a mass of glands in the right axilla: this is a most exceptional interval. Another patient had had a pedunculated mass of lymphadenomatous glands in the left groin for 8 years before death occurred, mainly from lymphadenoma in the liver.

Acute Lymphadenoma.—Although some doubt must exist as to the nature of the cases described by Dreschfeld [11] in 1892, for the blood-counts given do not exclude acute lymphocytic leukæmia, a number of authenticated cases exist which Parkes Weber [10] has recently reviewed. In many cases which may at first appear to be acute, the disease, though undetected, is really of some standing and the symptoms have only been noticed when the disease became widespread. In a recent case published by Michell Clarke [25] a boy had enlarged glands 6 months before death; these rapidly subsided under treatment, but 3 months before his death the glands in various parts of the body became enlarged.

Before describing some aspects of the thoracic and abdominal forms attention will be drawn to some interesting features which may occur in any form of lymphadenoma.

Behaviour of the Enlarged Glands.—The growth of the glands varies much in different cases; it may be extremely rapid or very slow. The size of the glands may vary from time to time; alternate enlargement or diminution may correspond with febrile and non-febrile periods. Apart from the effects of treatment, the glands may greatly diminish in size, probably from fibrosis; but this change in the superficial glands may be accompanied by increased activity in those more deeply seated and in the viscera, and is therefore not a good prognostic. The size attained by the glands may be remarkable. The patient may not notice the enlargement for a considerable time, or may find it out quite accidentally.

Temperature.—In the early stage of chronic lymphadenoma fever is usually absent, but most cases show it at some period or another, usually in the later stages, and there is much

[25] Clarke, Michell: *Journ. Path. and Bacteriol.*, Cambridge, 1908, XIII., 92

variation in different cases. Three distinct types of fever were originally described by Sir William Gowers[26]; these types are:—(i) a persistent mild fever—usually 101° to 102° F. with a daily variation of a degree and a half only; this may continue for months. (ii) Fever characterised by a high irregular temperature with morning remissions to 100° F.; this form is usually seen in the later stages and may be accompanied by sweating and chills. The temperature imitates that of suppuration and in cases with hepatic enlargement may strongly suggest abscess. (iii) A relapsing form of temperature characterised by alternating periods of fever and of a normal temperature; the duration of the febrile period is usually from 5 to 15 days and of the non-febrile period about the same; but there are considerable variations, perhaps due to the combination of this form of fever with one of the two previous forms. This type is so remarkable that it has been the subject of numerous papers (Pel,[27] Ebstein,[28] Fischer,[29] Musser,[30] F. Taylor,[31] H. B. Shaw,[32] J. Phillips[33]). Ebstein regarded it as a new infectious disease and called it "chronic relapsing fever," and Pinkus spoke of it as "Ebstein's disease"; but it is now recognised as being a complication of lymphadenoma, as indeed Murchison[34] described it in 1870. During the febrile attacks the glands and spleen commonly enlarge and become tender, whilst they recede in the non-febrile periods. In a case under my care jaundice corresponded to the febrile periods and was probably due to enlargement of the glands in the portal fissure. The skin over the glands may get red, and transient dilatation of the heart has been noted during the paroxysms. In the intervals an unusual appetite has been recorded. The febrile periods are accompanied by much constitutional disturbance. This relapsing fever has been known to go on for a year (Taylor, Westphal), or even 14 months (Fischer);

[26] Gowers: *System of Medicine* (Russell Reynolds), 1879, V.
[27] Pel: *Berlin. klin. Wchnschr.*, 1885, XXII., 3; 1887, XXIV., 644.
[28] Ebstein: *Ibid.*, 1887, XXIV., 565, 837.
[29] Fischer: *Deutsche Ztschr. f. Chir.*, Leipz., 1893, XXXIV., 233.
[30] Musser: *Trans. Assoc. Amer. Phys.*, 1901, XVI., 638.
[31] Taylor, F.: *Guy's Hosp. Rep.*, Lond., 1906, LX., 1.
[32] Shaw, H. B.: *Edin. Med. Journ.*, 1901, N.S., X., 501. (References.)
[33] Phillips J.: *Cleveland Med. Journ.*, 1910, IX., 604.
[34] Murchison: *Trans. Path. Soc.*, Lond., 1870, XXI., 372.

when it has once appeared it persists till death. From analysis of the recorded cases Batty Shaw finds that the average duration of the relapsing fever is about 7½ months.

This relapsing fever recalls the intermittent hepatic fever associated with a gallstone "floating" in the common bile duct. In this condition periodic attacks of fever, pain, and jaundice occur with non-febrile intervals. It has been thought that these periods correspond with periods of susceptibility and of immunity to organisms present in the bile duct. From his analysis of bacteriological examinations Batty Shaw concludes that this relapsing fever of lymphadenoma is due to infection, but that the infection is not the same in all cases. It appears that there is not any leucocytosis during the febrile periods (Phillips).

Cutaneous Manifestations.—Bronzing of the skin, resembling that of Addison's disease, may of course be due to the administration of arsenic; but it may be seen in patients who have not had any treatment. The skin may also become brown as the result of the application of X-rays. Byrom Bramwell [13] describes two exceptional cases in which pigmentation of the skin combined with leucodermia preceded obvious glandular enlargement by one and two years respectively. In these cases there was also pruritus, and it is possible that scratching may have played some part in producing the pigmentation, but it would not account for the leucodermia. Pigmentation of the skin, apart from the influence of arsenic and scratching, occurs in cases in which the suprarenals, though intrinsically healthy, are surrounded by masses of lymphadenomatous glands. This can be explained either (i) as a result of irritation of the sympathetic nerve-fibres by enlarged retroperitoneal glands, the resulting pigmentation of the skin being like that seen in other abdominal conditions, such as some cases of tuberculosis and malignant disease of the peritoneum, and also in pregnancy; or (ii) by the internal secretion of the suprarenals being prevented from passing into the circulation—in other words, by suprarenal inadequacy as in Addison's disease.

Purpura.—As acute lymphocytic leukæmia and multiple sarcoma may imitate acute lymphadenoma, they must as far as possible be eliminated before a case with purpura is accepted

as one of lymphadenoma. Purpura must be rare in lymphadenoma, for Longcope[35] did not find it mentioned in any of his 86 collected cases, but apparently it occurs; very possibly it is due to a secondary infection. In a case reported by Herringham[36] in 1902 the glands showed the structure of lymphadenoma and the presence of tuberculous infection.

Itching of the skin may occur (i) in the absence of any visible alteration in the skin, (ii) in association with lymphadenomatous growths in the skin, or (iii) in association with eruptions such as exfoliative dermatitis.

(i) Itching without any obvious cause in the skin is rare, but it may be extremely severe and make the patient's existence unbearable and lead to such uncontrollable scratching that pieces of the skin may be torn out, with the result that the body becomes covered with sores, infection of which may be very troublesome. In 86 cases of lymphadenoma collected by Longcope,[35] mainly since 1903, it was mentioned in three. In 21, cases at St. George's Hospital, analysed by Mr. F. H. Watson, it was present in 3; and I have seen it in 2 cases in private.

It may be the first symptom of lymphadenoma before any glandular enlargement is obvious, so that the patient first consults a dermatologist. In some of these cases the disease has run a rapid course, and I am inclined to think that the prognosis of such cases is more grave on this account. It may, however, occur late in the course of the disease; thus, in a man aged 40, under the care of my colleague Dr. James Collier at St. George's Hospital, it came on 48 hours before death; the patient, who was delirious, complained that the nurses had put fleas in his bed. Pruritus may pass off permanently, or it may recur; in one case under my observation its recurrence appeared to correspond with enlargement of the superficial glands. The scratching may set up eczema of the skin. Sir Cooper Perry told me of a case of a man admitted with pruritus and a lichenoid condition of the skin due to scratching; as the inguinal glands were enlarged the diagnosis of Hebra's prurigo seemed probable, but the necropsy showed that the case was one of

[35] Longcope: *System of Medicine* (Osler and McCrae), 1909, VI., 492.
[36] Herringham: *St. Barth. Hosp. Rep.*, Lond., 1902, XXXVIII., 123.

lymphadenoma.

The question of the cause of this pruritus is unsettled. It is not due to arsenic or to the action of X-rays, for it may occur before these forms of treatment are begun. It does not appear to be specially related to lymphadenomatous invasion of the viscera, for it is often absent when this is well marked. I have seen two cases of lymphadenoma with jaundice in which there was no itching. Thus the incidence of itching in lymphadenoma is as capricious as it is in jaundice, and it is interesting to remember that itching may also precede the occurrence of jaundice. It is natural to refer the pruritus to toxæmia due to the evolution of the disease; but to explain why it occurs in only a small proportion of the cases, it might perhaps be argued that its occurrence depends on the patient's idiosyncrasy or on some intercurrent condition, possibly an infection.

(ii) Itching may be associated with the presence of growths in the skin, but there is not any very intimate relation between them; for lymphadenomatous tumours of the skin are rarer than pruritus, and are absent in most of the cases of lymphadenoma with pruritus. There seems to be a want of satisfactory evidence that the skin conditions assumed to be lymphadenomatous constantly show the characteristic structure of that disease. Their histological appearances have often been those of leukæmic infiltration, and a considerable amount of confusion has thus arisen. It is generally stated that itching occurs in the rare cases of leukæmic infiltration of the skin. My own belief is that this is based on the histological characters of the growths in the skin in lymphadenoma and not on the blood examination. My experience of such a rare condition as leukæmic infiltration of the skin is not sufficient to justify an expression of opinion, but I have never seen pruritus in leukæmia nor in the few examples of leukæmic invasion of the skin that have come before me.

(iii) Itching of the skin in lymphadenoma may be associated with general exfoliative dermatitis (Nicolau [37]), prurigo, or urticaria.

Other Eruptions—erythematous and bullous—may occur in lymphadenoma; and herpes may be induced by the arsenic

[37] Nicolau: *Ann. de dermat. et syph.*, Par., 1904, 4. s., V., 752.

given for the disease.

Lymphadenoma in rare instances attacks the skin, and, as just stated, this may be, but is not necessarily, associated with itching. It has been observed that, like lymphadenomatous glands, the skin growths may undergo involution and in some instances they have disappeared. Cutaneous lymphadenoma must be diagnosed from several rare conditions. (*a*) In mycosis fungoides the lymphatic glands are almost always and the spleen sometimes enlarged, and, as in lymphadenoma, pruritus may precede the appearance of cutaneous tumours. Mycosis fungoides give rise to much larger cutaneous tumours than those seen in lymphadenoma, and there may be ulceration, an event which practically never occurs in lymphadenoma. Further assistance in the diagnosis may be obtained by a biopsy or removal of an affected piece of skin and subsequent histological examination. (*b*) From lymphodermia perniciosa, which was described by Kaposi as a cutaneous form of leukæmia, but is regarded by the French school as mycosis fungoides. (*c*) From sarcoma of the skin. (*d*) From the leukæmic infiltration of the skin lymphadenoma is distinguished by an examination of the blood.

Hair.—The hair has been noticed in a few instances to show changes. In 1878 Porter [38] described loss of hair nearly all over the body in a man. Scratching might obviously play some part in this change, but in this case there is no mention of itching. Byrom Bramwell [13] describes falling off of the hair, and also a change in its character to a lighter colour and finer and more silky feel, in the two patients referred to above, who had pigmentation and itching of the skin. The female patient became almost bald.

A man under my care with generalised lymphadenoma had œdema of the left leg from pressure exerted by glands in the groin; at one time there was definite evidence of considerable *effusion* into the knee joint on that side, but at the necropsy there was not any excess of fluid in the joint.

The *thoracic form* of lymphadenoma is the most distressing, as the enlarged glands are prone to exert pressure on the contents of the chest. Thus pressure on the trachea or bronchi

[38] Porter: *Trans. Path. Soc.*, Lond., 1878, XXIX., 338.

may produce suffocative dyspnœa resembling that in ordinary mediastinal tumour. Pressure on the recurrent laryngeal nerves may give rise to abductor paralysis, though this may be, and probably more often is, induced by the pressure of glands in the neck in the groove between the œsophagus and trachea. In a case under my care in which lymphadenomatous glands had been removed from the neck and in which extensive recurrence subsequently occurred inside the chest, with paralysis of one vocal cord, there was remarkable distension of the superficial veins over the neck, face, and arms. There were also attacks of dyspnœa terminating in the expulsion of casts from the bronchi resembling those seen in plastic bronchitis. Clubbing of the fingers has been observed in mediastinal lymphadenoma (Turnbull [39]). Dysphagia has sometimes been present.

The presence of intrathoracic lymphadenoma not uncommonly induces pleural effusion, which may require repeated tappings. I remember one case in which sudden death was due to the presence of a pleural effusion. The effusion may be chylous. In a case of this kind osteoarthropathy was a prominent feature (Weber [40]). Pressure may also lead to an effusion into the pericardium, which is also a cause of sudden death (Weber). In a case of this kind, though not fatal from the effects of pericardial effusion, I have seen the effusion chylous. Pressure on the veins may produce cyanosis and venous engorgement. There may be some exophthalmos, and the conjunctivæ may be œdematous.

As a rule thoracic lymphadenoma is a comparatively late event in cases in which enlarged glands have been recognised and perhaps removed a considerable time before. Thus a youth aged 17 had had glands removed from the neck $3\frac{1}{2}$ and $1\frac{1}{2}$ years before his death from the effects of a large mediastinal growth of lymphadenoma. But in rare instances the intrathoracic growth constitutes the earliest and the main growth of lymphadenoma in the body. In Weber's case the intrathoracic growth weighed 66 ounces, the only other evidence of lymphadenoma in the body being moderate enlargement of the glands at the root of the neck. The histological examination made by Ledingham showed that the condition was undoubtedly lymphadenoma.

[39] Turnbull: *Arch. Path. Inst. London Hosp.*, 1908, II., 141.
[40] Weber and Ledingham: *Proc. Roy. Soc. Med.*, 1909, II. (Clin. Sect.), 66.

In cases of thoracic lymphadenoma in which the other evidences of the disease are slight, difficulties in diagnosis may occur. It may be thought to be an aneurysm; or, if glands above the clavicle are detected, to be a primary mediastinal tumour with secondary growth in the palpable lymphatic glands. The presence of high fever in a patient with intrathoracic lymphadenoma has suggested the diagnosis of pneumonia.

The Abdominal Form of Lymphadenoma.—Usually this follows primary disease of the cervical glands and consists in enlargement of the retroperitoneal and mesenteric glands and of the spleen and liver. But in some instances the retroperitoneal glands are primarily and even solely attacked. In such cases the diagnosis may be very difficult. Dreschfeld states that acute tuberculous peritonitis may be simulated. In one case which I saw the onset was marked by sudden acute dilatation of the colon. McDonald refers to a case in which the pain and indefinite resistance in the upper part of the abdomen and the irregular fever led to an operation for a leaking gastric ulcer; a large mass of glands was found. Abdominal pain may be due to pressure of retroperitoneal glands on the branches of the lumbar and sacral nerves, and give rise to a clinical picture difficult to explain. Enlarged mesenteric glands may imitate appendicitis. Pressure exerted by enlarged glands in the portal fissure may produce a serous ascites. In rare instances pressure on the lymphatic vessels may give rise to a chylous ascites; out of 102 collected cases of chylous ascites Schölberg and Wallis[41] found that two were due to lymphadenoma. The ascitic effusion in abdominal lymphadenoma may be milky, but not due to the presence of chyle; this pseudo-chylous ascites is also rare in abdominal lymphadenoma, for in 71 collected cases of pseudo-chylous ascites two only were associated with this disease (Schölberg and Wallis). The pressure of retroperitoneal glands on the inferior vena cava may cause œdema of the legs and albuminuria; and pressure on the ureters may interfere with the excretion of urine.

Pressure on the bile ducts by enlarged lymphadenomatous glands may produce jaundice. Usually this is a comparatively late event in the course of the disease in cases in which the superficial glands were first affected. But it may occur when

[41] Schölberg and Wallis: *Quart. Journ. Med.*, Oxford, 1911, IV., 170.

the disease is confined to the retroperitoneal glands, as in a case mentioned by McDonald in which biliary cirrhosis was described as resulting therefrom. The jaundice may vary from time to time, presumably because lymphatic glands in the portal fissure or along the course of the common bile duct become larger or smaller in the same way as the more easily palpable glands are known to do. In a girl aged 7 years under my care with enlarged glands in the neck and axillæ and enlargement of the liver and spleen there were febrile attacks at irregular intervals of a week to a fortnight, with increase in the size of the external lymphatic glands and very definite jaundice. As there was no enlargement of the gall-bladder the conclusion seemed justified that the pressure was exerted on the bile ducts above the opening of the cystic duct, and probably in the portal fissure.[42] In a case of advanced lymphadenoma the jaundice almost disappeared a few days after the injection of Ehrlich-Hata "606," or dioxydiamido-arseno-benzol.

In abdominal lymphadenoma there is usually enlargement of the spleen, and, less frequently, of the liver in addition. As the splenic enlargement may be the most obvious or even the sole physical sign, a few words may be devoted to this subject. When chronic splenic anæmia of adults was first described it was regarded as a splenic form of lymphadenoma or lienale pseudo-leukæmia. It is now known that this interpretation is incorrect, for the morbid changes in the spleen in chronic splenic anæmia are not those of lymphadenoma. Symmers,[43] however, has recorded what appears to be a unique case of primary lymphadenoma of the spleen in a girl aged 18 years, who, three years before her death from splenectomy, passed clots of blood by the bowel and noticed a lump in the abdomen. The clinical resemblance to chronic splenic anæmia must have been exact. The rare cases in which the retroperitoneal lymphatic glands and the spleen are the sole or main sites of the lymphadenomatous change may simulate chronic splenic anæmia and Banti's disease very closely. Parkes Weber [44] described a remarkable case of

[42] Rolleston: *Proc. Roy. Soc. Med.*, Lond., 1909, II. (Clin. Sect.), 155.

[43] Symmers, D: *Arch. Int. Med.*, Chicago, IV., 1909, 218.

[44] Weber: *Proc. Roy. Soc. Med.*, Lond., 1911, IV. (Clin. Sect.), 70, and personal communication.

lymphadenoma. The patient when first seen had the ordinary enlargement of the superficial lymphatic glands; subsequently he came under observation with an enlarged spleen, ascites, great anæmia and leucopenia, and no palpable lymphatic enlargement. The case then appeared to be one of Banti's disease—that is, the further stage of splenic anæmia in which a terminal cirrhosis of the liver supervenes. The necropsy showed considerable enlargement of the thoracic and abdominal lymphatic glands, especially in the hilum of the liver. Microscopical examination by Dr. Ledingham proved that the condition was one of lymphadenoma. Enlargement of the retroperitoneal glands and spleen when accompanied by fever may suggest malaria (Symmers), or enteric fever (Pel, Dreschfeld).

When there is considerable enlargement of the liver the question of diagnosis from malignant disease may arise; I have seen such a case in which exploration had been performed. Extensive implication of the liver is usually accompanied by fever, and in the absence of enlargement of the superficial glands the clinical picture may closely resemble hepatic abscess; in one such case which I saw laparotomy had been performed and revealed considerable enlargement of the abdominal lymphatic glands. Hepatic enlargement and fever may also simulate syphilis; a Wassermann reaction would exclude syphilis, but when lymphadenoma occurs in a syphilitic subject this reaction would be misleading. In a child with congenital syphilis lymphadenoma of the liver has been mistaken for syphilitic disease with the form of fever sometimes seen in association with it.

Reference should be made to the cases formerly described as lymphadenoma of the stomach and intestines. Newton Pitt [45] made a collection of these cases and divided them into two groups:—(*a*) those in which the growths begin in the submucous and mucous coats and project into the lumen of the bowel, and (*b*) those in which the growth begins in the mesenteric glands and spreads to the intestine, where it forms a diffuse sheath in the subserous coat and invades the muscular coat, with the result that it becomes paralysed and dilated.

[45] Pitt: *Trans. Path. Soc.*, Lond., 1889, XL., 80.

These cases were described before the histological structure of lymphadenoma was recognised, and Pitt's account of the microscopical appearances is compatible with the diagnosis of lymphosarcoma. Salaman[46] denies that true lymphadenoma ever occurs in the alimentary canal. Although there does not seem to be any clear reason why lymphadenoma should not occur in the Peyer's patches and solitary glands, I have not seen such a case; and I must admit that a remarkable case[47] of polypoid growths in the stomach of a child aged 18 months reported as lymphadenoma in 1898 cannot be so regarded in the light of the current histology of the disease. It obviously belongs to the group of cases of gastro-intestinal pseudo-leukæmia—that is, the anatomical changes in the glands without the blood changes of leukæmia—of which Symmers has collected 11 examples. The form of growth which spreads diffusely over the outer surface of the intestine appears to be a special form of sarcoma. I saw such a case with Dr. Libman in New York; the clinical features were those of high fever and suggested septicæmia; the blood was sterile and there were no physical signs. From the occurrence of such cases in small epidemics Dr. Libman was inclined to regard them as infective in origin.

Diagnosis.—The enlarged glands of lymphadenoma must be distinguished from those due to other causes, of which the commonest are ordinary inflammation, tuberculosis, syphilis, lymphocytic leukæmia, and malignant disease.

The periadenitis and the history of ordinary glandular inflammation usually make the distinction clear. In syphilis the enlargement is seldom sufficient to give rise to doubt, but a Wassermann reaction or specific treatment should settle the question. Whilst some cases of tuberculous glands are clear enough, others, especially the form with large-celled hyperplasia and little or no caseation, can only be recognised by a microscopical examination. As tuberculosis may complicate lymphadenoma, a positive tuberculin reaction must not have undue weight against lymphadenoma. A blood examination will at once exclude ordinary lymphocytic leukæmia; but in the presence of an aleukæmic phase

[46] Salaman: *Ibid.*, 1904, LV., 296.

[47] Rolleston and Latham: *Lancet*, Lond., 1898, I., 1333.

of the disease and in pseudo-leukæmia removal of a gland will be the only means of excluding lymphadenoma. As lymphadenoma seldom or never attacks the intestines and pseudo-leukæmia does, diarrhœa is in favour of the latter. The diagnosis from lymphosarcoma may be extremely difficult, especially when the disease is mainly abdominal or thoracic, or when it is not possible to remove a gland for microscopical examination.

Widespread malignant disease when it affects glands may closely simulate lymphadenoma. This is particularly the case when there is a large tumour in the left suprarenal, which imitates an enlarged spleen, and growths in the lymphatic glands in the neck.

Some time ago a woman was in St. George's Hospital under the care of my colleague Dr. Spriggs, by whose courtesy I saw her on several occasions, with enlarged glands on the left side of the neck, a tumour in the left hypochondrium which, though rather irregular, was regarded as an enlarged spleen, and a lump of a year's duration at the upper end of the left tibia. The case resembled one of lymphadenoma, but the necropsy showed that it was really one of a malignant hypernephroma on the left side, with secondary growths in the lymphatic glands above the left clavicle and in the head of the tibia. A somewhat similar case under the care of my colleague Dr. James Collier had enlarged glands in the neck and a tumour in the left hypochondrium. Here again the disease was malignant, there being growth in the left suprarenal and in the cervical lymphatic glands. The primary site was doubtful, and as the growth—which was of an endotheliomatous nature—was extremely degenerated in the cervical lymphatic glands and less so in the left suprarenal it is possible that it was an example of the so-called potato tumours, described by Sir Jonathan Hutchinson,[48] Mayo Robson,[49] and Hastings Gilford and Hart Davis,[50] which are primary growths in the intercarotid gland, and that the suprarenal tumour was secondary.

Prognosis.—Sooner or later lymphadenoma proves fatal. The duration of the disease varies greatly; in the rare acute cases it may be a matter of months; usually the fatal result occurs within three years of the onset of symptoms, but occasionally the interval is considerably prolonged. Death may be due to a secondary infection, especially tuberculosis, or be directly caused by the disease, either (i) mechanically as the result of pressure on vital organs—the trachea, bronchi,

[48] Hutchinson, Sir J.: *Illustr. Med. News*, Lond., 1888, I., 50.

[49] Robson, Mayo: *Ibid.*, 1889, III., 194.

[50] Gilford, H., and Hart Davis: THE PRACTITIONER, London, 1904, LXXIII., 729.

or great vessels; this is the usual event; or (ii), more rarely, from toxæmia, anæmia, and asthenia. When death is due to the mechanical effects the glands may have reached remarkable dimensions. On the other hand, the patient may die from toxæmia and anæmia with comparatively little lymphadenomatous growth in the body. I have seen this in two patients treated for considerable periods with X-rays.

Treatment may produce very considerable temporary effects, but does not cure the disease. Arsenic and the various organic preparations of it, such as soamin and orsudan, have a marked influence in diminishing the size of the glands, but the effects are not permanent. The new preparation "606" is being tried on lymphadenoma; it is, of course, far too early to judge of the results, but in one very advanced case in which I saw it used it produced a most beneficial effect as regards the glandular enlargement, which rapidly diminished; death, however, occurred within two weeks of its administration.

Operative removal of the glands is disappointing; it is difficult or impossible to remove all the affected glands, and recurrence follows. Possibly the use of X-rays very shortly after the operation might delay recurrence.

X-rays produce a rapid diminution in the size of the glands, and it is said that life is thus prolonged. X-rays destroy the lymphoid tissue, but leave the fibrous tissue unaffected. It must be borne in mind that by free application of X-rays the lymphocytes and the healthy lymphoid tissues may be too extensively destroyed and that harm may thus be done. It has been noted that in some instances although rapid diminution in size follows X-ray treatment the glandular enlargement returns very rapidly when the treatment is stopped (Reid,[51] Morton[52]). It appears that treatment by radium would be difficult from the large amount of radium which would be required to deal with the extensive lesions (Finzi[53]).

[51] Reid: *Proc. Roy. Soc. Med.*, London, 1910, III. (Electro-Therap. Sect.), 133.
[52] Morton: *Ibid.*, 134.
[53] Finzi: *Ibid.*, 132.