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PATTISON PRIZE.
in
CLINICAL SURGERY.

JOHN THOMSON.

1925
The Permission of
Mr. John Fraser, M. C.
Regius Professor of Clinical Surgery,
Surgeon in charge of Case 1.
Has been given for the use of case 1.

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The Permission of
Mr. A. A. Scott Skirving,
Surgeon in charge of case 2.
Has been given for the use of case 2.
One subject only, namely, Hodgkin's Disease, has been taken up for this prize.

The subject has been investigated both from the Etiological and the Pathological standpoint, and treated with a view to its further investigation in the future, as opportunity permits.
Hodgkin's Disease.

Introduction:

The subject of Hodgkin's disease first presented itself to me 3 years ago when working in Prof. Meakins' clinic. Since then I have seen several cases and have been impressed by the fact that at present the condition is considered incurable, that the cause is unknown, and that there is even diversity of opinion concerning its proper place in pathology.

My interest in the condition being aroused, and my ordinary text-books being unable to help me, I had recourse to the many articles and monographs written on this subject, in an endeavour to learn something regarding the history of the disease, and the more recent views regarding its etiology and pathology.

Having given a brief resume' of these three aspects of Hodgkin's disease, I will then describe two cases which I have personally examined, and will give a short commentary on them.
Historical:

A historical survey of Hodgkin's disease falls naturally into 4 periods.

1. The discovery of the disease.

2. A period of uncertainty and doubt concerning the existence of Hodgkin's disease.

3. The establishment of Hodgkin's disease as a pathological entity.


Though it is now nearly an hundred years since Hodgkin gave the first description of the pathology of Hodgkin's disease, the honour of having given it's first clinical description has been awarded to Morgagni; (1769.) 1. & 2.

In 1856, and again in 1865, Dr. Samuel Wilks 3 & 4. Published a series of cases, and made Hodgkin's name immortal by calling the condition Hodgkin's disease.

He gave us more accurate and complete clinical descriptions of Hodgkin's disease from which there has been very little change up to the present day.

Following upon it's description by Wilks the condition was described by many writers, many of whom gave the condition a new name, largely depending upon
upon which feature of the condition was the more striking in the particular case described. Thus there are many synonyms for Hodgkin's disease, and, as was to be expected this has led to great confusion in the literature.

In 1858, Wunderlich described it as "a progressive multiple lymph-gland hypertrophy". It was called Lymphosarcoma by Virchow, (1864.) and Pseudo-leukaemia by Cohnheim (1865.) Trousseau called it Adénie while Billroth called it malignant lymphoma, (1869.)

In 1870, Murchison described a case which was peculiar in that it showed a particular type of intermittent pyrexia. Pel and Ebstein at a later date also described such cases and suggested that the appearance of fever was sufficient to put these cases in a class by themselves. Clinically this separation is observed today and the type is spoken of as the Pel-Ebstein type. As yet, however, there is no pathological evidence to warrant this subdivision.

About this time Hodgkin's disease entered upon the second period of its history, for some investigators brought forward the view that the condition was merely a special type of tuberculosis of lymph-glands. Sternberg was the most prominent exponent of this theory
and his researches were considered to be of great importance from the etiological standpoint. He found that out of 13 cases of Hodgkin's disease which he examined post-mortem, tuberculosis was present in 8. The enthusiasm for Sternberg's theory for a long time overshadowed the opposing view of Fisher even though his view was based on more scientific grounds. Gradually however, Sternberg's view was given up, and in 1901 Clarke gave as the opinion of his day, that there is no foundation for Sternberg's view whatsoever. This opinion of Clarke's has been confirmed experimentally by many investigators notably, Reed, Ruffin, Lemon & Doyle, and Harrison.

This period of controversy was ended by the classic work of Reed, who showed that Hodgkin's disease was a pathological entity, having no relationship to tuberculosis, and being probably a chronic inflammatory lesion. Reed's work and views were corroborated by Simmonds and Longcope, and until more recently this view has held full sway.

Of late however, cases described by Mueller, Webster, Gibbons, Krasner, Symmers, and Yamasaki have raised the question of whether Hodgkin's disease is
not a sarcoma. Thus there are now two schools which view the pathology and etiology of Hodgkin's disease from a different aspect: the one considers it a neoplastic growth, and the other that it is an inflammatory lesion of a toxic or organismal origin.
Etiology:

At the present time there are two schools each advocating an entirely different view of the etiology of Hodgkin's disease: viz. that of malignant growth and that of an organismal origin. In addition there is a small section in which W. E. Coley is a weighty speaker: Coley favours the idea of a malignant growth and considers Hodgkin's disease to be a sarcoma. In addition, however, he believes that sarcoma is organismal in origin, and so he agrees with neither theory and sides with both.

Many points in favour of one or other of these theories have been brought forward by the clinician and the laboratory investigator, but no one on either side appears to have been able to bring forward any evidence of a definite tangible nature which could not equally well be used by a member of the opposing school to support his view, or to detract from the attitude taken up by his opponent.

Gibbons and Mueller, the former a warm advocate of the neoplastic theory, bring forward the various points in favour of malignant disease very concisely.

1. There is tumour formation with very little
necrosis. This tumour, like any malignant growth may grow rapidly or slowly: also it may exist for a long time locally, and then suddenly grow more rapidly.

2. Hodgkin's disease, like malignant disease spreads from gland to gland, and in Hodgkin's disease as in malignant disease infiltration of the capsule does occur. Gibbons\(^{20}\) describes two cases of Lymphadenoma with extensive infiltration and destruction of the surrounding tissues.

3. The cells seen in a gland in a case of Hodgkin's disease are, like those of a malignant growth, developed in situ and not carried there by some agent. Also the irregular arrangement or rather want of arrangement, of the cells is suggestive of malignant growth, while the large giant cells bear a resemblance to those seen in some sarcomas.

4. Gibbons\(^{20}\) also points out, that it is not yet proved that the metastases seen in Hodgkin's disease are a proliferation of pre-existing lymphoid tissue and not true metastases analogous to secondary malignant growth.

5. The reports by Mueller\(^{18}\), Webster\(^{19}\), Gibbons\(^{20}\), Krasner\(^{21}\), Symmers\(^{22}\) and Yamasaki of border-line cases, which appear to be part Hodgkin's disease and part Lymphosarcoma is looked upon by advocates of the
neoplastic theory as strengthening their view.

Mueller describes two such cases very minutely showing that in one instance, a case of Hodgkin's disease appeared to pass into a condition resembling lymphosarcoma while in another case apparently of lymphosarcoma, the definite pathology of Hodgkin's disease was later made out.

6. The fact that many investigators have failed to isolate any organism from patients suffering from this condition, is also looked upon as strengthening the neoplastic theory. Fisher could only obtain negative results from blood culture, gland culture, and animal inoculation. Oliver, Lemon & Doyle, Harrison, and Ruffin all failed to obtain positive results from animal inoculation, no matter whether the specimen was taken during a pyrexial or an anypyrexial period. Shemman, Ruffin, and Whittington corroborate Fisher's negative findings in the blood cultures even if cultures were made during pyrexial bouts. Harrison also obtained negative gland cultures, while Abrahams obtained negative results from a culture of splenic blood taken during pyrexia in a typical Pel-Ebstein case.
7. In addition to these findings, Coley and Gibbons point out that the fever seen in Hodgkin's disease is of a very variable nature, and Coley declares that he has seen similar fever in malignant disease.

Through the whole of this argument it is evident that there is no point which one can take up and say with confidence "that is so". True the negative laboratory findings already mentioned might be brought forward as at least being something definite, but when we come to consider what is to be said for the organismal theory, we will find that a whole host of organisms have been discovered by other workers.

It might be said that the borderline cases already mentioned are something to work upon. Here again however, the opposing school will accommodate such cases by either suggesting that the two conditions Hodgkin's disease and lymphosarcoma may have co-existed in those cases which are reported, or that Hodgkin's disease is capable of undergoing a sarcomatous change.

Infiltration of the capsule of the gland, usually looked upon as a very definite indication of malignancy, is admitted by Bunting & Yates who are among the most authoritative of the supporters of the organismal theory, and who admit the possibility of a
sarcomatous metamorphosis.

Eve, who believes that the disease is caused by a parasitic infection, also agrees that the glands may become conglomerate, and the surrounding parts infiltrated.

Organismal Theory:

If we now take up the organismal theory, we will find that the school is divided within itself, for though Bunting and Yates,\(^2^9\) and Eve\(^3^0\) believe that there may be infiltration and periadenitis and a sarcomatous metamorphosis, there are many who say that this is not so. There is a great deal more to be said for the organismal theory than there is to be said for its rival, but there is equally much more to be said against it.

I have already alluded to Sternberg, who looked upon the condition as being a special type of tuberculosis. Admittedly there is a great similarity to tuberculosis in the clinical manifestations of the disease; so much so that in some cases it is impossible clinically to differentiate them. At autopsy too a large number of cases have been found to be tuberculous, while macroscopically the glands may appear very similar to those seen in tuberculosis. Microscopically however, however, there is a difference: see pathology.
In addition the number of cases in which the tubercle bacillus could not be demonstrated, seems sufficient justification for saying that Hodgkin's disease is not tuberculosis. Even Sternberg, in 5 out of the 13 cases he submits, failed to demonstrate the presence of the bacillus. It is now more and more realised that tuberculosis is a terminal infection in many debilitating conditions, and the lowered vitality and secondary anaemia seen in Hodgkin's disease is very favourable soil for the tubercle bacillus to flourish in. Of the 12 cases which compose Fisher's article 4 came to autopsy. 2 of these were found to be tuberculous, but it appeared to be a recent and apparently terminal infection. This view was supported by the fact that inoculation experiments made 14 weeks and 14 days previous to death yielded negative results.

Therefore in considering the organismal origin of Hodgkin's disease we may, with a fair amount of confidence leave out the tubercle bacillus as a possible cause.

Clarke,10 and Mueller18 have admirably summed up the clinical evidence in favour of this theory.

1. The fact that there are two types of the condition, acute and chronic is looked upon by Reed11 and Clarke10 as evidence in favour of this theory, while, despite the
assertions of Mueller\textsuperscript{12} and Gibbons\textsuperscript{20}, to the contrary

2. Clarke claims that the fact that the disease may remain local for years and then suddenly advance rapidly, is evidence in favour of an organismal origin and suggests that on this point at any rate there is a similarity to tuberculosis, - miliary type -.

3. A strong point, which is made much of by all supporters of this theory, is that the primary site of the disease is usually in one of the glands most easily affected through the skin or mucous membrane, while the finding of a septic focus in the region drained by the affected glands is by no means uncommon. For example, carious teeth or unhealthy tonsils are frequently associated with Hodgkin's disease of the cervical glands.

Cautley\textsuperscript{31} gives the following figures as the frequency with which the various glands are involved. Those most commonly involved are the Cervical glands, which are the primary site in 50\% of the cases. Next in order of frequency, come Axillary, Supraclavicular and Inguinal glands which together account for 30\%. 10\% begin in the spleen and the remaining 10\% are distributed between the mediastinal, retroperitoneal and other glands.

4. Clarke,\textsuperscript{10} Reed,\textsuperscript{11} and Moynihan\textsuperscript{31} point out that it is a disease of one tissue only, and that its gradual extension from gland to gland is not at all like the spread of a
sarcoma. Moynihan goes farther, and in his classification of diseases of the reticulo endothelial structure, classes Hodgkin's disease along with syphilis and tuberculosis, to which two conditions he believes it has some relation. He sums up his view on the nature of the disease in these words, "It may be a distinct disorder, or it may be a special form of a type of morbid process seen also in tuberculosis and in lymphosarcoma". Thus he corroborates the earlier view of Spencer.

5. These writers too are of the firm belief that the metastases seen are not real metastases but are merely a proliferation of a pre-existing lymphoid tissue. Adami considers that this proliferation is in the nature of a compensation for the disordered state of the normal lymphoid tissue as a result of disease.

Other points brought forward by Mueller in favour of this theory are these.

6. That there is little interstitial in early lesions, but an increasing fibrosis as the condition advances.

7. The fact that metastatic carcinoma and sarcoma of the spleen are a relatively rare occurrence, while the spleen frequently shows a typical lesion in Hodgkin's disease.

8. Clarke considers that the final stage with cachexia, diarrhoea, haemorrhages and pyrexia resembles the end of a septicaemia. This is however, considered by Gibbons.
to be equally true of malignant disease.

9. Fever, a symptom invariably present in Hodgkin's disease is looked upon by many as being indicative of the presence of organisms. The type of fever is very variable, but Taylor\textsuperscript{34} has given a possible classification. He makes 4 groups:

1. Continuous fever with slight diurnal variations.

2. Cases showing alternating periods of fever and normal temperature.

3. Daily variation of the normal temperature in excess of normal limits.

4. A mixed type, which includes any not already classified under the first three heads.

The significance of the pyrexia is not really understood. There is no doubt but that in some cases it is due to secondary infection, but nevertheless there are cases in which secondary infection cannot be demonstrated. In such cases Ruffin suggests that some auto-intoxication is the probable cause of the pyrexia, or that owing to the imperfect lymphatic drainage some toxic material is retained, and that that might account for the pyrexia.

It has also been suggested that the pyrexia is associated with a breaking down of the tissue in an affected gland, or with the involvement of fresh tissue in
the process of the disease. Moynihan\textsuperscript{32} puts his view of the pyrexia very cautiously. He regards the periodic pyrexia as a specific typical feature, but says he is uncertain whether it is the result of secondary infection. The Pel- Ebstein type of pyrexia is the type which has attracted most attention, and no doubt because it lends itself to the theory that it is a fever similar to the pyrexia seen in malaria. But, however well this symptom or indeed any other clinical manifestation, fits into a theory, one must always bear in mind that one is theorising and must not give undue prominence to a symptom which is only found in considerably less than 50\% of the cases.

The exact nature of the Pel- Ebstein wave is not agreed upon, though that described by McCrae\textsuperscript{35} is the one usually accepted. It differs from that described by Galloway mainly in that it shows a treppe effect at the beginning and end of the wave. Gulland and Goodall\textsuperscript{38} believe that the Pel- Ebstein temperature, chronicity of the disease and a polymorph leucocytosis with or without eosinophilia is distinctive of the condition.

In considering all the clinical phenomena brought forward in support of this theory one finds but little which is of real help, and it is somewhat surprising to find that not infrequently some clinical manifestation advanced by one school in favour of its view, is also
advanced with equal confidence by the opposing school in favour of its theory.

Turning to laboratory experiments in search of evidence in support of this theory, Mueller\textsuperscript{18} quotes the following experiments of Kopsch. Kopsch fed frogs on the larvae of nematode Rhabditis-pellio. These larvae migrated through the mucous membrane of the stomach and caused a localised reaction. Eosinophils and lymphocytes were attracted and finally fibroblasts ranged themselves concentrically round this area. After the worm had died or migrated away, from this nodule a casseous mass was formed and gradually absorbed. Should, however, the frog be heavily infected the fibrous capsule in many of the nodules will disappear and be replaced by epithelial cells derived from the fibroblasts. Infiltration follows and the surrounding tissue is destroyed. Metastases are frequent and thus the characters of a neoplasm have been assumed. The malignant change is due to metabolic products of the larvae, because the first change is seen in the part of the capsule which is in contact with the worm. It does not take place suddenly for the toxic agent must act in a certain concentration and for a certain length of time. Thus it is never seen till the 5th month after the commencement of infection.

The analogy to Hodgkin's disease is:
1. That cellular proliferation is in response to a toxin.

2. That there is a simple hyperplasia if the toxin is not allowed to accumulate or if the process is stopped.

3. That accumulation of or some inherent quality of the toxin may stimulate all or only some elements of the lymphnode to overgrowth giving rise to a neoplastic process.

Actual search for an organism causing the condition has led to many varied and conflicting results: and indeed the finding of bacilli, streptococci, staphylococci and pneumococci by early investigators as Verdelli in 1895, appear to point to a secondary infection.

In 1907, White and Proeschel demonstrated spirochaetes in a gland from a case of Hodgkin's disease. They used the Levađitti, Giemsa, and Iron Haemotoxylin methods. They report that the spirochaetes were seen in the vessels, in the cells and in the intercellular substance and that they were present in great numbers. They state that they found them in three cases: these findings have never been confirmed.

Ford Robertson and Young claim to have demonstrated a minute granular elongated body resembling a minute bacillus. It was found both intra and extracellularly, and stained more intensely at the ends than in
the middle. They state that they accomplished this by using an ammonio-silver process, whereas with ordinary stains, Shennan using the same material had failed to demonstrate such structures. These findings also await confirmation.

More authentic work, authentic in as much as the findings have been obtained by more than one investigator, dates from 1910.

In that year, Much demonstrated a definite granular gram positive nonacid fast bacillus almost constantly in the lymph-gland of Hodgkin's disease. He claimed that these were closely allied to the tubercle bacillus and that they were the sole etiological agent in Hodgkin's disease.

In 1913, Bunting and Yates and de Negri and Mieremet, working separately isolated in pure culture an organism which they called a diphtheroid and believed to be identical with that stained in the tissues by Much. Cultivation of the organism was most successful with Dorset egg medium and Glycerine Phosphate Agar. The organism was gram positive, and showed clubbed shaped involution forms and rods with branching filaments. Rhea and Falconer in 1915, were next successful in isolating and cultivating this organism, growing it on Hydrocele Agar.
Rosenow recovered the organism from the blood in 4 cases of Hodgkin's disease.

The idea that this bacillus was the sole etiological agent in Hodgkin's disease is now somewhat discounted for in subsequent investigation the bacillus was isolated from other conditions than Hodgkin's disease. Thus, Rosenow isolated it in cases of Arthritis Deformans and Goitre. Simon and Judd obtained it in Lymphatic Leukaemia. Bunting found it in Leukaemia, Lymphosarcoma, Chloroma and Banti's disease, while Bloomfield obtained it from apparently normal glands.

These latter findings have been in the nature of a setback to the idea that this so-called B. Hodgkinii is the cause of Hodgkin's disease. Bunting, however, thinks these are varied diphtheroids all with an affinity for lymphoid tissue including bone marrow and its products.

The suggestion of Billings and Rosenow that a staphylococcus frequently associated with the diphtheroid was a phase in its life has culminated in the recent researches of Mellon. Mellon has shown that this organism so far from being always the same morphologically and physiologically, has a life cycle which is dependant on the type of environment and the length of time spent in that environment. He worked with single cell cultures obtained from Bunting, and showed that beginning with a
diphtheroid the organism could pass into a large coccoid form, and then into dyad, tryad, or tetrad forms which had streptococcal characteristics. A similar result was obtained in a control experiment by Barber of the Rockefeller Institute.

One is, in the face of such knowledge tempted to ask whether there is not a relationship between the pyrexia and the lifecycle of this organism, and whether this lifecycle takes place in the body or not? Clearly much work must yet be done before the relationship of this bacillus to Hodgkin's disease is known.

More recently interest has been aroused by cases described by Koffoid, Boyers and Swezy in which they found amoeboid cysts in the stools, and cells in the gland sections which cells they think are amoebae. For their differentiation of the cells they rely chiefly upon the difference in the number of the chromosomes seen at mitosis. In the amoeba the number is probably 6 and not more than 8, as compared with the 24 or 48 of the human cell.

Lambright has also reported a case of Hodgkin's disease following Dysentery and with recovery following the use of antiparasitic measures. This is the most recent development in the search for an organism, but it remains to be seen whether these findings are not
mere coincidence, and confirmation is most necessary.

Animal Inoculation:

In an endeavour to prove that the diphtheroid which they had discovered was the cause of Hodgkin's disease Bunting and Yates injected a pure culture of the B. Hodgkinii into the subcutaneous tissues of the axilla of a monkey. (Macacus Rhesus). There was extensive necrosis and suppuration of the glands. If the animal survived long enough the lymph node picture of Hodgkin's disease was seen. A pure culture recovered from this animal and injected into a second monkey produced the disease. No one else however has obtained positive results, and confirmation of this experiment is still awaited. Rhea and Falconer only obtained negative results in similar experiments, as did Moore. \(^54\) Lanford and most recently Stewart and Dobson. \(^55\)

In the investigation of compliment fixation too, only negative results are recorded. Olitsky and Moore, working separately, both failed though they used apparently satisfactory antigens. Moore found no increase whatever in the agglutinative power of the patient's serum.

In his study of the blood in Hodgkin's disease Bunting came to the conclusion that there was a definite blood change in the course of the disease. The feature of the blood picture, which Bunting believes
to be diagnostic, is a relative and absolute increase in the mononuclear and transitional cells, also an increase in the size and number of the blood platelets. In late cases he finds a marked neutrophil leukocytosis. He claims to have reproduced this picture in monkeys by inoculation with the B. Hodgkini, and to have reproduced it in man: Dr. Yates being the victim; by a subcutaneous injection of killed cultures.

These findings though corroborated by Speese and Skillern\(^5\) are by no means unanimously accepted. Langley\(^6\) and Ness and Teacher\(^6\) report that they found a gradually increasing polymorph leukocytosis towards the end of the condition. Moore\(^5\) and Naegeli failed to confirm this finding, while the great mass of workers Gulland and Goodall\(^3\), Stiles\(^6\), Hall\(^6\), Stewart\(^6\), Rolleston\(^1\), Byrom Bramwell\(^2\), Ruffin\(^1\), Martin and Mathewson\(^6\), and Lemon and Doyle\(^1\) believe that the blood picture is only of value in a negative sense as it excludes the leukaemias.

Thus we see that the present position regarding the etiology of Hodgkin's disease is a very contradictory one, and there is much room for research work yet to be done before the actual cause of the disease will be found. The general trend of opinion is at present swinging in favour of the organismal theory and in this
respect it may be noted that Gulland, Stiles and Eve are converts to this theory. It still remains to be seen however, whether this is a move in the right direction.

Pathology:

Just as the accurate diagnosis of Hodgkin's disease must be made from the microscopic examination of an excised gland, so is the study of the pathology of the condition essentially a histological one. The reason for this is of course, that in some cases the macroscopic characters of the condition are not always definite and may be confused with other conditions, notably, tuberculosis. The generally accepted macroscopic characters of the condition are:

1. A painless enlargement of lymph-glands.
2. The glands nearly always remain discrete even after they have reached a large size.
3. The glands usually remain freely mobile in the subcutaneous tissues.
4. The consistency of the gland varies with the stage of the disease. If it is early the gland is soft owing to cellular proliferation, whereas if it is late the gland is
hard on account of fibrous tissue overgrowth.

- The words early and late used here do not refer to the general condition but to the stage of involvement of a particular gland.

5. Glandular tissue only is involved.

6. Metastases, which are either true or false - vide ante - are seen in all parts of the body.

7. There is blood disturbance in the form of a secondary anaemia, while the significance of the white blood corpuscle changes is still debated.

In addition the question of infiltration of the capsule and periadenitis is advanced by those who believe in a neoplastic origin of the condition, and is also supported by some members of the opposing school, notably Gibbons, Bunting and Yates, Eve, and even Reed. Adams that infiltration may be present to a slight extent.

The appearance seen on section of the gland largely depends on the stage of the disease in that particular gland. If the gland is still very cellular, it will be greyish on the cut surface, while later, when there has been much fibrous tissue overgrowth, the grey surface becomes broken up by opaque lines which represent the
fibrous tissue. In the end stage of the disease the gland is completely fibrosed. Such characteristics it is obvious, might apply equally well to the glands seen in the leukaemias, in lymphosarcoma and tuberculosis.

It is stated that the spleen is affected in about 75% of the cases either secondarily or primarily, but most usually secondarily. Ewing. The spleen becomes enlarged and presents all the characteristics in sequence, to greater or less degree, which are seen in the lymph-glands.

The changes always originate in the malphighian corpuscles. In the late stages of the condition this results in the spleen showing masses of fibrous tissue in its substance.

The microscopical structure seen in the spleen, lymph-glands and so called metastases is the same. On this subject the work of Reed is regarded as a classic, and it corroborates the earlier views of Greenfield, while the work of many investigators notably Symmonds, Longcope, and Bunting and Yates has but emphasised the value and accuracy of Reed's observations.

The process seen on microscopic examination may be rapidly summarised as follows:

1. There is proliferation of the endothelial cells forming the reticulum, and of those lining the lymph sinuses. These two different cells have been shown by Gulland to arise from the same
mesenchyme cell. There is also proliferation of the large cells at the centres of the lymphnodes, and these in the absence of evidence to the contrary are believed by Flemming to be derived from the same source. These cells show much mitosis. There is hyperaemia and dilatation of the blood vessels and lymph sinuses. This is a marked feature.

2. The lymph spaces and reticular sinuses are filled with masses of lymphoid cells and proliferating endothelial cells. The distinction between sinuses and lymph follicles is gradually lost, so that an occasional lymph follicle may be the only clue to the origin of the section with which you are dealing.

3. The endothelial cells give rise to large epithelioid cells which have a vesicular nucleus.

4. These in turn give rise to giant uni- and multinuclear cells. These have prominent nucleoli. The nuclei in these cells are large and similar to those seen in the proliferating endothelial cells; they are larger than those seen in the giant multinuclear cell of tuberculosis; while the whole cell is usually smaller than the cell seen in tuberculosis. The arrangement of the nuclei is different too. In Hodgkin's disease they tend to be clumped together at the center of the cell while in tuberculosis they are
arranged peripherally in the cell.

5. The lymph cell which gradually disappear towards the late stage of fibrosis, but which are numerous in the early stages are small and are derived from the endothelial cells.

6. Eosinophils are usually abundant but are not always present and it is not usual to get them at the germ-centres of the follicles.

7. Later: Connective tissue overgrowth occurs. It arises from the existing fibrous trabeculae, the connective tissue about the walls of the vessels and and the capsule of the gland.

8. The blood vessels become obliterated and there is much periarterial thickening.

9. Small foci of anaemic necrosis may appear in consequence and a few polymorph leukocytes may be found invading such an area.

Such is a brief summary of the histology as described by Reed. There are two points, however, which are debated. The first of these is with regard to the origin of the eosinophils seen in the glands. Reed and many others believe that they are attracted to the gland from the blood stream by some chemotactic agent, while Gulland believes that they are produced locally at the site of the disease and not in the bone marrow.
That the presence of eosinophils is a distinguishing feature from sarcoma or tuberculosis, in which conditions eosinophils are not present, is an idea which has been somewhat shaken by the fact that some people, (Reed) now believe that eosinophils may be entirely absent in a typical case of Hodgkin's disease without endangering the diagnosis.

Further, some people hold that there are two types of giant cells to be seen. All agree as to the nature and origin of the one described by Reed, but others McCallum and Ewing describe other giant cells with many nuclei arranged peripherally in a ring or horse-shoe and very closely resembling the cells seen in tuberculosis. They state that they are only rarely found and their significance and origin is not known.

While this histological structure is now generally accepted as being typical of Hodgkin's disease, it is not unusual to find cases which clinically are Hodgkin's disease but which show in the examination of a gland some indefinite form of lymphoid hyperplasia. It is such cases as these which are known as borderline cases and which give rise to so much controversy regarding the etiology of Hodgkin's disease. A very lucid explanation of such cases is given by Ewing. He points out that in both typical and atypical cases there is always endothelial
proliferation, and this is prominent from the first. This proliferation may appear in 3 ways:

1. The cells appear as large flat pavement-like cells.
2. As a collection of giant cells.
3. As a diffuse reticular overgrowth.

The typical Hodgkin's disease, that is the common type, appears to be represented by a mixture of classes 1 & 2. The third type of growth appearing alone gives rise to the so-called borderline cases, while its superposition upon the typical case gives the appearance seen in the cases said to be undergoing sarcomatous metamorphosis. That all these three types may be found in different glands from the same case has been demonstrated in the cases described by Mueller, Yamasaki and Krasner. Thus it would appear, pathologically speaking, that Hodgkin's disease is not a stable condition, but as Ewing very aptly sums it up, "It illustrates in the same patient and in its various gradations as a primary tumour, the transformation of an infectious granuloma into a true neoplasm. It demonstrates the relation of a tumour to the presence of a microorganism or its toxins. Its malignancy is apparently founded upon peculiar features, rather less upon cellular anaplasia than upon the association with a toxic agent which is readily disseminated, and seems to prepare the soil for its subsequent changes."
Properly speaking this so-called sarcomatous type of Hodgkin's disease might be classified as an endothelioma since the cells have an endothelial origin. Such cells however usually lose their endothelial characters and appear as large round cells with a vesicular nucleus and a prominent nucleolus. The number of lymphocytes seen in these atypical cases varies, but the more definitely neoplastic the process is the fewer lymphocytes there are. Reed believes that the lymphocytes which are seen are not true lymphocytes, and that they are developed from the reticular cells. Thus to such cases the term Hodgkin's Sarcoma has been given.

Ewing differentiates it from true lymphosarcoma because—1. perforation of the capsule is very slow; thus there is a difference in invasive power.

2. The field is not absolutely dominated by one type of cell as is the case in sarcoma.

Ewing also considers that the origin and type of the cells is quite different from a sarcoma.

These views of Ewing's are those most generally accepted at the present time. Until however, the question of the etiology of the disease is definitely decided, one must accept them with reserve, always bearing in mind the possibility of the absence of an organismal cause for the disease.
CASE 1.

Name.        George Fairhairn.
Age.         6 Years, 11 Months.
Occupation.  Schoolboy.
Birthplace.  Kelso.
Complaint.   Swellings in the sides of the neck and in the armpits.
Duration.    Since the middle of December 1923.

History.

Dec. 1923.    Mother noticed a swelling in the side of the neck.

Jan. 1924.    Swelling became painful.

10 : 3 : 24.  Consulted Doctor who states that the patient was then rather pale, anaemic and had a chain of enlarged cervical glands, in the line of the left St-Mast.

24 : 3 : 24.  Admitted to hospital, but discharged until a cold and herpes had cleared up.


Local Examination. Neck, left side. Two hard discrete glands, just posterior to the middle of the sternomastoid. They are movable. There is also a large mass consisting probably of enlarged
Wood's Glands and Omohyoid Glands. The posterior carotid group are also enlarged.

1:5:24. Urine, acetone present.

W. B. Cs. 8,5000

Differential Count.

- Polymorphs, 74%
- Lymphocytes, 22%
- Basiphils, 1%
- Eosinophils, 3%

1. Left oblique incision.
2. Enlarged Wood's Glands dissected away.
3. Lower posterior Carotid glands could not be excised and were curetted. The material obtained on curettage was gelatinous and suggestive of acute lymphadenoma.
4. Wound closed and a drain inserted in a stab puncture.

16:5:24. Healing occurred by first intention, and the patient was discharged.

10:11:24. Readmitted to hospital complaining of weakness and pain in the left abdomen. The swelling in the neck had also increased rapidly in size during the last 6 weeks.
Previous Illnesses: At 4 Years Measles. No history of Tuberculosis. No history of accident. Previous health good.

Home environment is good. Patient lives in the country some distance from Kelso. He probably does not get the attention he ought to, as his father is dead and the mother requires to work to support a family of four.

Family History. Father, Dead, Influenza.
   Mother, Alive and well.
   Brothers, 2. Alive and well.
   Sisters, 1. Alive and well.
   No brothers or sisters dead.
   No family history of tuberculosis or any lymph-gland disease.

State on Examination. For its age the child is of average intelligence. It is well developed and its muscularity is good. The general appearance and expression of the face denotes languor, but the child is quite cheerful when spoken to. No characteristic attitude is adopted by the child: as usual when resting in bed all the joints are slightly flexed. The child is obviously anaemic and the complexion is of a pasty nature. There is no evidence of dropsy or of any previous disease.
Haemopoetic System. There are no subjective phenomena.

The thyroid is of normal dimension. There is a general enlargement of lymph glands. Those most enlarged are the left cervical group, and the left Axillary group. No group of glands has entirely escaped, except the Occipital glands and the glands of the forearm and leg.

In Detail: 1. A very obvious swelling below and lateral to the angle of the jaw on the left side, also just below the centre of the scar of the old incision.

2. Upper Posterior Carotid- (Deep Cerv.)- are enlarged and discrete. They are soft.

3. A few small discrete enlarged glands near the lateral border of the criciod cartilage.

4. A large mass of glands immediately below the posterior carotid group. They are soft and discrete.

5. A large mass of glands in the left axilla, soft and discrete.

6. The glands of the right side of the neck and right axilla are also involved, but to a much less degree.

7. The glands in both groins are enlarged,
also the mesenteric glands in the ileocaecal region.

Each gland is quite separate from its neighbour, there being no matting together. On palpation they are somewhat elastic and rubbery. In shape they are either oval or round. In size the largest is about the size of a bantam's egg.

Integumentary System. There are no subjective phenomena. The skin is dry and scaly, and of a yellowish grey tint. There is no oedema. A few macules are seen here and there in the skin, but chiefly in the emi-gastric region and less so in the neck. -(see etiology)


Respiratory System. There are no subjective Phenomena. The thorax is normal and symmetrical in shape. There is no evidence of Rickets. Vocal Fremitus is normal. Percussion. No abnormal region of dullness is found except in the region of the clavicular glands. There is no area of hyperresonance. The breathing is of the Thoraco-Abdominal type.

Auscultation. The breathe sounds are typically muerile and no accompaniments are heard. Expiration is
prolonged. The vocal resonance is normal.

**Alimentary System.** There are no subjective phenomena.

The lips are paler than normal. The mucous membrane is slightly anaemic. The teeth are milk teeth and are decaying. The gums are pallid and unhealthy looking. They are inflamed at the point of junction with the tooth. The tongue is clean. The secretions are normal. The fauces and soft palate are pallid and of a bluish colour. The tonsils are not enlarged but are diseased looking. The whole interior of the mouth is very unhealthy. There is no vomiting and no interference with deglutition. There is a tendency to constipation, no doubt referable to the presence of enlarged mesenteric glands.

**Abdomen. Inspection:** The superficial veins are just beginning to be seen. No Medusa head is visible. The abdomen is large and has a tendency to be protuberant. There is no local swelling or prominence visible. The abdomen moves freely on respiration.

**Palpation.** Tenderness can be elicited only on very deep pressure. It is most marked in the ileocaecal region, and just above that area. There is no fluctuation. The abdomen feels doughy. There is no dullness in the flanks.

**Percussion.** The lower border of the liver is \( \frac{3}{4} \) inch
below the normal. The stomach is difficult to outline, but appears to be pushed well over to the left side. The spleen is not enlarged.

**Circulatory System:** There are no subjective phenomena.

**Pulse.** The vessel wall is healthy and shows no thickening. The rhythm and frequency of the pulse is regular: the wave has a regular rise and fall.

**General Circulation:** There is commenceing interference with the venous return. This is denoted by a commenceing distension of the superficial veins of the abdomen.

**Heart, Inspection:** The apex beat is seen in the 5th. intercostal space on the left side inside the nipple line. There are no pulsations visible in the epigastrium.

**Palpation.** The apex beat is very firm and forceful there is no thrill.

**Percussion.** The outline of a normal heart is obtained. The right border corresponds to the right border of the stermum. The heart is not enlarged.

**Auscultation:** The heart sounds are closed in all areas. The aortic sound is accentuated. The frequency is the same as that of the pulse. There are no murmurs.

**Reproductive System:** There are no subjective phenomena.
A varicocele is present on the left side, it may be due to the commencing interference with the venous return. There is no history of its being congenital. 

**Locomotor System:** There are no phenomena other than the wasting of muscles due to disuse. The muscles are flaccid. The joints can be hyperextended and flexed without pain. (That is the small joints of the hand only to which reference is made.)

**Nervous System:** In the whole of the nervous system there are no signs or symptoms to note. The reflexes superficial and deep are all present and normal. There is no Babinski sign, and no clonus. The reaction of the pupil to light and of the eye to accommodation is present and normal. There is no nystagmus.

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**Clinical Diagnosis:** Hodgkin's Disease.
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PATHOLOGIST'S REPORT.

7:5:24.

Specimen: Glands from the neck.

Report: The condition is Lymphadenoma, although the sections show a fairly early and cellular stage, proliferation of fibrous tissue is quite apparent. The typical Multinucleated cells are present in considerable numbers. Eosinphils are present but are not very numerous.

In one of the glands examined there are multiple areas of necrosis.
CASE 2.

Name. Wm. Logie.

Age. 21. Years.

Occupation. Miner.


Admitted. 6 : 2 : 23.

Complaint. Swellings in the neck.

Duration. Since August 1922.

History.

August, 1922. The patient noticed that the left side of his face was gradually swelling. It was most marked under the jaw, and was due to the presence of a lump, which gradually grew larger. The patient paid no attention to it till its persistence caused him to go to the Doctor. He was given an ointment which he applied for three months, but with no beneficial results.

Dec. Came to the R. I. E.

6 : 2 : 23. Admitted to hospital. At this time there was only one large lump in the left side of the neck and it was the size of a walnut. Up to this time it had given him no trouble, and he had been regularly at his work. There were no other enlarged glands.
A small gland was excised for diagnostic purposes. He was then treated for three weeks by intramuscular injections of Collosal Copper. No apparent benefit was derived from this treatment, and the patient was discharged in statu quo.

March, 1923. Returned for one injection of Collosal Copper.

May, 1923. Re-admitted to Hospital. X Ray treatment for three weeks. This treatment lessened the swellings markedly, even though they had been becoming progressively larger.

July, 1923. Discharged from Hospital. Returned once monthly for X Ray treatment, until,

Jan, 1924. Re-admitted to hospital complaining of pain in the swelling of the neck. X Ray treatment was stopped. At this time the patient noticed that lumps were now beginning to appear in the right side of the neck, and also in the groins. Treatment was medicinal until 6 : 3 : 24.

Liq. Arsenicalis, m. iii. T. I. D. No benefit resulted from this treatment. Three tubes of Radium were inserted. Site, Left side of the neck. The Radium was left in till,
13: 3: 24. The swelling had then lessened greatly in extent.


25: 4: 24. Re-admitted to hospital. Patient then stated that he was beginning to have difficulty with his breathing, and his speech was also affected, being thick and indistinct, like that of a child suffering from adenoids. He had no pain. Radium for insertion was not available, and a Radium applicator was used which the patient succeeded in holding in position for periods aggregating 45 hours in 4 days. The application was made to the interior of the mouth. After this period of exposure however, the mucous membrane was beginning to be affected by the Radium. It became red and inflamed looking and the patient had a good deal of pain in the throat. White patches also were beginning to appear on the mucous membrane. The great feature of this treatment was the striking diminution in the size of the swelling and the resulting improvement in the respiration, which had previously been stertorous.
13:6:24. Radium was implanted. 1 tube just above the Thyroid cartilage in the left side of the neck.

21:6:24. Radium was removed. As a result of this Radium treatment the enlarged group of glands in the neck became still smaller, and the left pupil which had been smaller than the right now became equal in size with it.


Previous Illnesses: Measels, Chickenpox, and Influenza. No history of tuberculosis.

Home Environment: is very good. Patient lives with his father and mother, 1 brother and 1 sister in a 4 roomed house. He has good food, and gets plenty of fresh air.

Alcohol, practically none.

Family History: Father and mother alive and well. Age approx. 50 Years.

Brother 1. alive and well, age 16 years.

Sister 1. " " " 19 "

No member of the family is dead. No family history of tuberculosis, or any lymph gland disease.
State on Examination:

Jan. 1925. Patient is of average intelligence. Height, 5' 11". Weight, 8st. 2lbs. Development good. Muscularity is now poor but obviously has been better at one time. Temperature tends to be subnormal. General appearance and expression of the face, gives one the impression of a contented cheery patient. He looks anaemic and is of a pasty complexion. There is no evidence of Cyanosis, Jaundice or Dropsy, or of any previous injury. He can lie on either side, but prefers the right side, as lying on the left side causes a certain amount of pain in the swelling of the neck. The left side of the neck and face is grossly deformed by the swelling. Though weak the patient is not entirely confined to bed, and is able to get outside a little.

Haemopoetic System: There is a general glandular enlargement. 1. Left side of the neck. The largest glands are seen here. It is quite impossible to say which glands are involved in this area. All that one can make out is a mass of swollen glands stretching from below the clavicle to the mastoid process above. The glands are discrete, not adherent to the skin or
to each other. They are of a rubbery consistency. The larger ones are about the size of a large walnut. Such is the size of the mass that the Thyreoid Cartilage is pushed to the right of the median plane, while inside the mouth the Uvula is almost touching the right anterior pillar of the Fauces.

2. Right side of the neck. Here the involvement is just as extensive, but the glands are not nearly so large. Those most affected are the Inferior Deep Carotids.

3. The Submental glands are involved, the largest being about the size of a small bean.

4. The glands of both Axillae are involved. They have the same characters as the enlarged glands elsewhere. The largest is about the size of a hazel nut.

5. Enlarged glands are palpable in both groins. They are the size of a large bean.

6. One cannot be sure whether the mesenteric glands are involved or not, but the periodic vomiting which is occurring, can only be explained by something such as enlarged glands causing obstruction and dilatation of the stomach from pressure. The characteristics of the glands are the same no matter what site they are found in. The spleen can just be felt on palpation, and is not much enlarged. The Thyreoid is of normal size.
To show swelling in the region of the Anterior Pillar of Fauces.

- Upper Lip.
- Palate.
- Swelling, note position of the Uvula.
- Tongue.
- Lower Lip.
Integumentary System. There are no subjective Phenomena. The skin is moist, but is of a very sallow pasty colour. No macules were observed on any part of the body.


Respiratory System. The patient complains greatly of dyspnoea, but there is no other symptom. The cause of the dyspnoea is seen immediately one looks into the mouth. There is a very large swelling at the site of the left anterior pillar of the Fauces; it is of such a size that the uvula is pushed against the right anterior pillar. This has the effect of narrowing the air passage down to about a third of its normal size. The thorax is normal and symmetrical in shape. It measures at full expiration 36", and on full inspiration 38½". The breathing is of the thoraco-abdominal type. 24, per min. Vocal Fremitus is normal. There is no evidence of Rickets.

Percussion. No abnormal region of dullness is found except in the neighbourhood of the enlarged clavicular glands. There is no area of hyperresonance.

Auscultation.
Auscultation. Normal Vesicular Breathing is heard. There are no accompaniments. Vocal Resonance is normal. Tidal percussion 1".

Alimentary System. There is periodic vomiting. It comes every few days. The vomitus is always sour and appears to contain the remains of undigested food. Nausea accompanies the vomiting. The vomiting appears to be obstructive in character. There are no other symptoms. The lips, teeth and gums are in good condition though anaemic in appearance. The mucous membrane is also very pale. The tongue is a little furred. In the region of the swelling at the left side of the nasopharynx the mucous membrane is much more red, and scattered over its surface are numerous small greyish yellow points. These points are firmly adherent to the mucous membrane, and are not at all easily separated. The Tonsils are not visible.

Abdomen. Inspection. The abdomen is symmetrical and somewhat large. It moves freely on respiration. No abnormal swelling is visible.

Palpation. There is tenderness on deep pressure in the umbilical region. The abdomen is soft and easily palpated. The Abdominal superficial veins are a little distended. There is no dullness in the flanks.

Percussion. The Liver is not enlarged. The stomach
appears to be distended, and to be lower than usual. It comes nearly an inch below the umbilicus.

**Circulatory System.** There are no subjective phenomena.

**Pulse.** The vessel wall is not thickened and is easily compressible. The wave is regular in its rise and fall, and the wave is well maintained. There is nothing to note in the general circulation.

**Heart, Inspection.** The apex beat is in the 5th intercostal space on the left side and is inside the nipple line. A pulsation is seen in the Epigastrium.

**Palpation.** The apex beat is full and strong. No thrill is palpable.

**Percussion.** Outline of the heart. Apex beat $3\frac{1}{2}$" to the left of the middle line. In the third left intercostal space the border of the heart is an inch from the sternal margin. The right border of the heart is $\frac{1}{2}$" from the right border of the sternum. The heart is not enlarged.

**Auscultation.** The heart sounds are pure and are closed in all areas. There are no murmurs nor is either second sound accentuated.

**Reproductive System.** No Symptoms and no abnormality to note.

**Locomotor System.** The muscles are somewhat wasted and
this is no doubt partly at least due to disuse. The muscles are flabby and flaccid. There are no other phenomena to note.

**Nervous System.** The left pupil is smaller than the right and is more sluggish in its reaction to light. There are no other symptoms or signs to note in the nervous system. The superficial and deep reflexes are present and normal. There is no nystagmus. No Babinski sign and no clonus.

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**Clinical Diagnosis.** Hodgkin's Disease.

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March, 1925. Patient is now at home. He is suffering almost continuous pain, and morphia is being freely used by his Doctor.

April, 29, 1925. Patient died this morning. No Autopsy.
Tempertature: 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96°

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TREATMENT.

The treatment of the condition is a very unsatisfactory one, both from a medical and a surgical aspect. Some advocate the use of arsenic and report an improvement with its use. It was used in case 2 for 6 weeks, giving m. iii. T. I. P., but there was no improvement.

Galloway advocates the use of Sodium Cacodylate in pyrexia cases, giving ¼ gr. doses to begin with, and gradually increasing the dose till as much as 1 to 1½ grs. is being given daily. It may of course cause, or increase an existing pruritus. He advises to stop the drug when a garlic odour can be appreciated in the breath.

The salvarsan compounds give no better results than treatment with ordinary arsenic, although Gulland and Goodall37 believe the contrary to be the case.

Colloidal copper advocated by Gulland is equally unsatisfactory.

Benzol has also been used, but with similar disappointing results.

On the hypothesis that the cause is an amoeba, emetine has been used with apparently beneficial results. Only one such case is reported however and confirmation of this result is still awaited.

Radium and X Rays, short of excision, appear to be the
only thing which has any appreciable effect in improving the condition. Of the two Radium is the more powerful. Not only do the glands diminish in size as a result of Radium treatment, but the percentage of polymorphs in the blood falls and the amount of eosinophilia is diminished. This occurred in both cases described.

Both patient's on their discharge from hospital were greatly improved. In case 1. The largest glands were then found in the right axilla. One large soft one was palpable and it was the size of a bantam's egg. In the left axilla the glands were of the size of peas, and were hard. In the right side of the neck, they were equally small and hard, but in the left side of the neck, 2 were felt, each the size of a small bean. They were also hard. The submental glands were not palpable. the right and left inguinal glands were the size of large peas.

This decrease in size was probably more due to the radium than to the X Rays, since it was always more marked after Radium treatment than after X Ray treatment.

The only other procedure adopted in this country is operative. Obviously this is not a cure for it is impossible to eradicate all the diseased glands, and hence the condition is bound to recurr. Case 1 is an example of this.
The other treatment adopted in America is in the nature of vaccine therapy, and depends upon the acceptance of the B. Hodgkini as being the cause of Hodgkin's disease. This serum used by Bunting and Yates was not available for the treatment of either of these cases.

Bunting and Yates describe the action of this serum as follows:

1. It is capable of reducing pyrexia in Hodgkin's disease.
2. After injection it causes an enlargement of the diseased glands which soon subsides, and leaves them smaller than they were before. This reaction is apparently analogous to the focal reaction of tuberculin.
3. Tissues which formerly yielded a culture, fail to yield one after serum treatment.
4. The blood from which the B. Hodgkini could previously be cultured, yields no culture after the patient is treated by serological means.

Bunting and Yates claim that 20% can be cured by means of this serum. Unfortunately however, all investigators are not agreed as to the efficacy of this serum.

The large number of drugs and the various measures which have been used in the treatment of the condition indicate that none of them are of much value.
COMMENTARY.

These two cases of Hodgkin's disease illustrate several of the characteristics usually found in that condition, and also something which is atypical. I shall first take the two cases together as far as possible and compare them with each other, and with the usual clinical features seen in Hodgkin's disease; then take up the features which are only peculiar to one or other of the cases.

The onset of the condition was extremely gradual and the probability is that it was present for sometime before it was observed. This is the usual history one gets in such cases. The site of the primary focus is usually the glands of the neck, and these two cases are no exception. It is claimed by Cautley that the right cervical glands are more frequently involved than the left; here in each instance it was the left cervical glands which were primarily involved, and it is perhaps questionable if any side is more liable than the other.

The glands exhibited the typical characteristics of softness with an elastic feel, discreteness with a great freedom of movement, such as is usually associated with Hodgkin's disease. In other words, the glands were hypertrophied, and in a highly cellular condition, with little fibrous tissue overgrowth and no sign of infiltration or periadenitis. In each case therefore, the diagnosis...
would appear to be relatively easy. From the history however, it appears that in the early stage, there was difficulty in differentiating both cases from tuberculosis.

In case 1. the original diagnosis was tuberculosis, while in case 2. the early treatment suggests that tuberculosis or an adenitis was first diagnosed. In case 1. however there is no history of tuberculosis in the patient or the patient's family and no tubercle bacilli were found in an excised gland. In case 2. similar negative results were obtained, and in addition there was a negative Von Pirquet reaction.

This points to the absolute exclusion of tuberculosis in both cases and the diagnosis in each patient was confirmed by the examination of a section from an excised gland. This finding is in accordance with most peoples views, that Hodgkin's disease though clinically it may resemble tuberculosis, is a distinct disease of itself.

Both cases then are of the soft type of Hodgkin's disease. Perhaps it would be better to say in the soft stage of Hodgkin's disease, for the glandular enlargement is now accepted as being of a chronic inflammatory nature ending in a sclerosis of the gland. It appears however, that this sclerosis may be slower in some cases than in others, and it is obvious that the less the sclerosis and
the greater the cellular overgrowth, the softer the gland will be. This then is really the difference between the soft and the hard types described, a difference in the stage of the disease, and not two types of the disease.

The two stages may exist in different glands in the same patient and according to which predominates, so is the stage of the disease named. In both these cases the majority of the glands were soft.

The glandular enlargement, it is agreed, is the first manifestation of the disease, and it is interesting to note that except for a small percentage, about 5%, which appear to be primary in the spleen, the glands primarily involved are glands which drain an area very liable to toxic absorption, or invasion by organisms. E. G. The cervical glands drain the tonsils, tongue and mucous membrane of the mouth; the inguinal glands drain the genital and anal regions; The bronchial glands may be directly infected through the mucous membrane of the bronchus. This feature then is common to Hodgkin's disease and tuberculosis. The enlargement of the glands in both cases was slowly progressive, and the glands primarily involved- cervical left - were liable to disease as a result of absorption from a focus in the mouth.

In case 1. there were undoubtedly decaying milk-teeth and pyorrhoea alveolaris.
In case 2, there was no focus of sepsis demonstrable in the mouth, but as the condition had been going on for about 18 months, it is not unlikely that a primary focus of infection may have been cleared up in that time. Whether there is any real significance in this association of a focus of sepsis in the mouth and the occurrence of Hodgkin's disease is not yet known. Certainly it is a point well worth keeping in mind, and it may help to explain the finding of the B. Hodgkini in other local inflammatory conditions of the buccal cavity.

As one expects in Hodgkin's disease, there is an entire absence of symptoms in either case. The signs and symptoms which are seen in case 1, namely pain and a varicocele are probably the result of mechanical pressure by enlarged glands. The same explanation shows the origin of the pain, sterterous breathing, altered voice, inequality in the size of the pupils and the periodic vomiting seen in case 2. To confirm this the case report shows that after radium treatment when the glands had decreased in size, all these symptoms improved and the two pupils became equal in size.

The examination of the blood was carried out in both cases and a secondary anaemia was demonstrated. This is in keeping with the ordinary descriptions of Hodgkin's disease. The actual red blood count was never low and it
**CASE 1.**

**BLOOD EXAMINATIONS.**

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<th>28:11:24</th>
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<td>5,400,000</td>
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<td>8,500</td>
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<td>74%</td>
<td>72%</td>
<td>82.5%</td>
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<tr>
<td>Lge. Lymphocyt.</td>
<td>(</td>
<td>(</td>
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<tr>
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<tr>
<td>Lge. Hyalines</td>
<td>---</td>
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<td>---</td>
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<tr>
<td>Haemoglobin</td>
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<td>Colour Index</td>
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<td>Lge Hyalines</td>
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## CASE 2.

### BLOOD EXAMINATION.

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<td>1%</td>
</tr>
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<td>Large Mononuclears.</td>
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<td>3%</td>
<td>---</td>
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<table>
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<th>26 : 3 : 24</th>
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<tr>
<td>Polymorph.</td>
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<td>74%</td>
<td>70%</td>
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<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>Sm.</td>
<td></td>
<td>7%</td>
<td>10%</td>
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<tr>
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<td>8%</td>
<td>5%</td>
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<tr>
<td>Basiphils.</td>
<td>1%</td>
<td>1%</td>
<td>---</td>
</tr>
<tr>
<td>Lge. Mononuclear.</td>
<td>---</td>
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</table>
CASE 2.

BLOOD EXAMINATIONS.

<table>
<thead>
<tr>
<th>Date</th>
<th>R. B. Cs.</th>
<th>W. B. Cs.</th>
<th>Polymorph</th>
<th>Lge. Lymphocyt.</th>
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<td>10:4:24</td>
<td>6.790.000</td>
<td>9.000</td>
<td>68%</td>
<td>12%</td>
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<td>28:4:24</td>
<td></td>
<td></td>
<td>68%</td>
<td>7%</td>
<td>14%</td>
<td>9%</td>
<td>2%</td>
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</tbody>
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varied between 4 and 5.5 millions per cmm. The percentage of haemoglobin however, was below normal resulting in a secondary anaemia though not of an extremely marked type. There was no deformity in the red blood corpuscles. Merely the want of haemoglobin, thus suggesting the action of some factor which prevents the formation of haemoglobin.

The white blood corpuscle count varied between 5,000 and 8,500 per cmm. in case 1, and between 6,400 and 10,400 per cmm. in case 2. Nothing however can be learned from the differential count the results being so apparently contradictory and irregular. This is not in keeping with the finding of Bunting and Yates⁴⁹,⁵⁷,⁵⁸, who believe that there is a definite distribution of the white blood corpuscles, (see etiology).

All that one can say definitely is, that there is an increase in the percentage of the polymorphs. This according to Bunting and Yates⁴⁹,⁵⁷,⁵⁸, is found towards the end stage of the condition. The irregularity in the differential count is so pronounced in many of the cases published, that many investigators now regard the white blood picture as a side issue of no direct diagnostic importance, other than that by it you can exclude the leukaemias.

There does however seem to be some relationship between the percentage of polymorphs and the effect of
radium treatment, for after each period of treatment the percentage always falls.

Thus in case 1 there is a drop of 5% after a 6,000 mgms. hours exposure. In case 2, after 2,500 mgms. hours of radium with 45 hours of the radium applicator, followed by a further 2,500 mgms. hours of radium, there is a drop of 14%. Whether this is beneficial or not is no doubt open to argument.

Here it is convenient to note the dangers which may arise from radium treatment, for in case 2, the radium applicator was rushed to such an extent that the mucous membrane of the throat appeared to be in the first stages of leukoplakia. This was denoted by a red and inflamed mucous membrane, the appearance of white patches on it and pain. These signs all subsided on removal of the applicator, thus leading one to the conclusion that they were due to the radium.

The only other point which the two cases have in common, is the great irregularity in the rhythm of the heart when the heart rate is looked at over a period of some weeks. In case 1 it varies between 78 and 134 per min. (normal about 100). In case 2 it varies between 74 and 124 per min. (normal about 72). This seems to me to be too great and too irregular a difference to be accounted for by the presence of a secondary anaemia.
In this connection it is well to remember that organisms have been cultured from the blood of patients suffering from Hodgkin's disease. That being so, one is tempted to ask whether the organisms or their toxins may not have some action on the heart or upon its nerve supply. It is well known that the heart is affected when there is a blood infection, and I think that this irregularity of the heart might be looked upon as a point in favour of an organismal infection. I have not been able to find any reference to this in the literature.

In addition to these features case 1 shows what appear to be the macules described by Sir Jas. Galloway. These macules he described as being cutaneous manifestations of Hodgkin's disease, and being similar to the lesion seen in Mycosis Fungoides. These macules in this case were observed chiefly in the epigastric region, and in the neck in the region of the enlarged glands. When first observed they were about the size of a large pin-head, and of a dark brownish colour. When the patient was discharged from hospital however, they had largely disappeared, being very faint yellowish brown in colour. This change was probably due to the X Ray and radium treatment. Galloway suggested that this was a special type of Hodgkin's disease, attacking the skin. This however does not seem to be likely, for Hodgkin's disease seems not to metastasis.
by cellular transplantation, but by causing a cellular proliferation in pre-existing lymphoid tissue apparently anywhere in the body. No macules were observed in case 2.

This appearance seen in Hodgkin's disease may have somewhat the same relationship to Hodgkin's disease, as the wellknown De Morgan's spots have to malignant disease. The majority of people say that De Morgan's spots are of no diagnostic importance in malignant disease, yet it seems that they are to be found in that condition just as frequently as macules are to be found in Hodgkin's disease. It is at least a noteworthy fact that they are both the result of an endothelial overgrowth, and it might well be that there is here a connecting link between malignant disease and Hodgkin's disease.

The temperature charts in the two cases are entirely different. In case 1, the temperature is subnormal the whole time practically, except for a slight rise after the operation. This rise of course is due to the operation. Now while fever is a very variable symptom in Hodgkin's disease, some type of fever is invariably present, so that in this respect case 1 is atypical. This is all the more marked when we find that in the soft type, especially where there is rapid growth, fever is practically always present.

In case 2, we have a different chart. There are
Type of Pyramidal Waves Seen in Case 11.
distinct pyrexial waves but they do not recur at regular intervals. In character they are of the remittent type, the variation in 24 hours being as much as 4 deg. Fahr., though 3 deg. is about the average. These pyrexial attacks last for a period varying between 4 and 8 days. The temperature shoots up suddenly in 12 hours to 101 or even 102, and at the end of the wave drops just as suddenly to below normal. The period between the waves varies between 14 and 21 days. 6 months after his discharge from hospital, these waves of fever are still present and looked for every 2 to 3 weeks by the patient's mother. The interval between the bouts of pyrexia is the only point which is common to this case and a typical Pel-Ebstein case. The wave itself is entirely different because of the daily variations which compose it. There is a tendency for the rise on each succeeding day to be not quite so high as the rise on the preceding day, and for the fall to be a little greater. --see chart, cf. Pel-Ebstein charts. Pel-Ebstein charts on the other hand show very little in the way of daily remissions of temperature. This case would be included under class 2 in Taylor's classification, since it shows alternating periods of pyrexia and normal temperature.

Radium treatment appears to have some effect on these pyrexial bouts, because after its use the patient
enjoyed a period of subnormal temperature for 11 weeks, though the pyrexial waves returned later. This observation has also been noted by other investigators, but how the diminution of the fever is actually brought about is not known.

There are two theories which endeavour to explain these pyrexial bouts.

1. That they are due to localised necrosis of lymphadenomatous tissue and toxic absorption.

2. That it is due to the cause of the disease being an organism which passes its life cycle within the body as in the case of the malarial parasite. This is suggested by the periodicity of the pyrexia and the fact that organisms have been cultured from the blood during these pyrexial attacks but not during the apyrexial period.

An unusual protein, after the nature of the Bence-Jones protein, is described by Galloway as appearing in the urine in cases of Hodgkin's disease. I was unable to detect it in either case here. He describes it as being not coagulable under 75 deg. cent. only coagulable in the presence of much acid and salt, NaCl and \((\text{NH}_3)_2\text{SO}_4\). It is insoluble if kept at 80 deg. cent. for some minutes and not precipitated by HCl. It is doubtful if it be a product of disordered metabolism but is more likely to find its origin in the diseased lymph glands.
Pathology of the excised gland in Case 1.

Naked Eye Appearance:

The gland is yellowish grey in colour. It is exceedingly soft to the touch and feels as though it would burst on the slightest pressure. When it was excised it was not found to be adherant to any of the surrounding structures. There was however, much softening of the tissues in the immediate proximity of the gland. The gland was the size of a bean and oval in shape.

Cut Surface:

is greyish yellow with lighter coloured patches in it, grouped chiefly at one end. The surface is also streaked lightly with this same rale coloured tissue.

Microscopic Appearance:

The capsule is thickened but not uniformly so. Some parts of it are of a thickness in keeping with the size of the gland, but elsewhere the thickness is out of proportion to the size of the gland. That the thickening of the capsule is recent is shown by the fact that the fibrous tissue is still cellular, while there are large numbers of blood vessels to be seen in it. This overgrowth of the capsule is continued in a great many cases into the trabeculae of the gland, while in at least two parts of a section the growth has become diffuse, and spread generally into the gland substance, breaking up the
lymphoid tissue into islets as it does so. Apart how-
ever from the general overgrowth of the gland, there is
infiltration of the capsule seen. Thus in addition to
the spindle-shaped fibrous tissue cells there are infiltrat-
ing cells present. There are two types of infiltrating
cells seen. One is a small round cell like a lymphocyte.
It has an exceedingly deeply staining nucleus and relative-
ly little protoplasm. The other is a larger cell with
much more protoplasm, a larger well defined nucleus with
a well marked nucleolus. The nucleus does not stain
deeply, but shows a fine reticulum. These cells have the
appearance of endothelial cells.
The pulp of the gland is entirely transformed. There is
no differentiation between cortex and medulla and very
few germ centres are left. Also those which are seen are
very small. The reticulum of the gland is much over-
grown: this is particularly noticable if a section
stained by Mallory's Method is examined; while in a few
places the pulp is entirely replaced by fibrous tissue.
The cells occupying the reticular spaces are mainly of
two kinds: 1. Lymphocyte like cells, similar to those
seen invading the capsule.

2. Endothelial like cells, also like those
seen invading the capsule.

These are found scattered in a somewhat diffuse
manner throughout the whole section. They are found in the reticular spaces and lymph sinuses. Nearer the germ centres the lymphocytes are in the majority, but elsewhere the majority are of the endothelial type.

The typical giant cells of Hodgkin's disease are conspicuous by their absence. Very rarely an endothelial cell is seen which is larger than the usual size but which is not so large as the typical cell of Hodgkin's disease. More than one nucleus cannot be satisfactorily demonstrated in these cells. Eosinophils are also entirely absent from the sections.

The lymphsinuses are very distended and are packed with cells chiefly of the endothelial type, though lymphocytes are also found. The cells forming the wall of the sinuse are seen to be active and proliferating giving rise to more endothelial cells. Indeed one of the features of the section is the presence of many mitotic figures.

The blood vessels show various changes. Where they are in a fibrous part of the gland they are thick walled and even a few are occluded. The endothelial lining cells in the great majority of the vessels are much swollen and appear to be proliferating giving rise to endothelial cells which appear to be able to migrate away from the vessel. Many of the younger thin walled vessels are distended and engorged with blood. Red blood
corpuscles are also seen in many parts of the section lying loosely in the reticulum of the gland.

Commentary:

Obviously here we are dealing with some atypical phase of Hodgkin's Disease. The section is not at all typical and it resembles very closely the appearance seen in an endothelioma. This however, is not at all unnatural as Ewing point's out since Hodgkin's disease is a disease of the endothelial reticulum. The chief difference from a case of typical Hodgkin's disease is the want of the giant cells multi and uni-nuclear. The diffuse growth of the endothelial cells suggests that here we are dealing with a case which would come into the third group in Ewing's classification, and would therefore constitute one of the so-called border line cases.

This view is very greatly strengthened when we know that previously when a gland was excised for examination the typical picture of Hodgkin's disease was seen.

Obviously there are two ways in which this unusual picture may be explained.

1. An Endothelioma may have arisen per se, since the commencement of the Hodgkin's disease, and thus the patient would be suffering from two conditions
at the same time, neither condition having anything to do with the other.

2. That this is a phase of Hodgkin's disease in its process of undergoing a sarcomatous change, because the case has already shown the typical picture of Hodgkin's disease.

Which explanation is the true one is one of the most warmly debated subjects in relation to Hodgkin's disease at the present day, though general opinion is at present tending to support the view of a sarcomatous metamorphosis. Beyond however, the cases described by Mueller, Webster, Yamasaki, Krasner and others, there is no definite proof of this theory. This case now being described is comparable to those described by the above mentioned writers, and appears to be but one more case going to support the view held by Ewing that in Hodgkin's disease endothelial proliferation may take place in more than one manner, and that this leads to the difference in the types which are seen.
CONCLUSIONS.

1. The cause of Hodgkin's Disease is probably organismal.

2. Hodgkin's Disease is a Pathological Entity, distinct from Tuberculosis, though the latter may be related to it.

3. It is a disease of the reticular structure of the lymph-gland and ends in a fibrosis.

4. Hodgkin's Disease In some cases is not a stable pathological condition. Case 1. demonstrates this fact.

5. There is no typical blood picture in Hodgkin's disease.

6. Treatment of Hodgkin's Disease is at present largely palliative.

Case 1.  

a. An atypical type of Hodgkin's Disease coming into group 3 of Ewing's Classification.

b. It is of the soft variety.

c. Suggests that Hodgkin's Disease may not be a stable pathological condition.

d. Radium and X Rays are of most value in the treatment.
Case 2.
a. A soft type of Hodgkin's Disease, with an accompanying pyrexia.
b. The type of pyrexia places it in group 2. of Taylor's Classification.
c. Radium and X Rays are of most benefit in the treatment.
ILLUSTRATIONS.

1. Infiltration of Capsule of Gland.

   - Infiltrating Cells.
   - Capsule of Gland.
   - Gland Tissue.
   - Trabecula.

2. Infiltration of Capsule of Gland.

   Note the vascularity of the Capsule.

Part of the Capsule, X. 200.

Note 2 Types of cells.

1. Small, very dark staining like a lymphocyte.

2. Larger not darkly staining somewhat granular cell.

4. To Show Diffuse Growth of the Reticulum.

Note, This section shows a diffuse endothelial overgrowth, and very few lymphocytes are seen.
5. To Show Fibrous Tissue Invading the Gland Substance. X. 75.

Cellular Tissue of gland.

Note, much of the fibrous tissue growth is beginning from around the Blood Vessels.

6. To Show Lymph-sinus distended and full of cells, largely of the Endothelial type. X. 200.

Note, The Lining cells of the lymph-sinus are taking part in the proliferation.

Note, an Endothelial Cell with apparently 2 nuclei. Probably it has just undergone mitotic division.

8. To Show the Fibrosis of Vessels, leading probably to areas of anaemic necrosis. Section Stained, Mallory.

Note, relatively few lymphocytes in the section.
9. To Show the Preponderance Of Lymphocytes near one of the few remaining Germ Centres.

Note, the great variations in shape of the cell.

I am indebted to Mr. R. Muir, of the University Pathology Department for photographs nos. 2, 3, 5, and 6. Actual specimen is in the care of Mr. R. Muir.
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