INTRODUCTION TO A DISCUSSION ON LYMPHADENOMA AND ITS RELATION TO OTHER MORBID GROWTHS.¹

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LYMPHADENOMA is a suitable name for those affections the various forms of which have one feature in common—a growth of lymphadenoid tissue closely resembling in structure that of the lymphatic glands. An overgrowth of lymphadenoid tissue may happen not only in places where such tissue is well marked, but also in parts such as the liver, kidney, testicle, or skin, where traces only of such tissue are to be found in health. Lymphadenoid tissue originates at certain spots around blood vessels in close association with the blood. Indeed it is not differentiated widely from the original embryonic tissue, and in agreement with this slight differentiation its power of regeneration and of compensatory hypertrophy is great. For instance, the whole of the spleen has been removed from a dog except a bit remaining apparently in the very grasp of the ligature, yet within a few months a new spleen of normal shape has been found.² Beyond the fact as to its structure we know as yet very little about the real pathology of lymphadenoma. There is, however, a large and important mass of information respecting this disease which has been gathered together by clinical observation, and it is the main purpose of this meeting to discuss facts so gathered.

Much advantage will follow if in this discussion some methodical grouping of cases be adopted, so that the different forms under which an overgrowth of lymphadenoid tissue takes place may be more orderly arranged than hitherto. For of the names which have been given to the varieties of lymphadenoma many are not used in the same way, and any two of the cases included under the same name will on full examination be found to differ from one another in important points. There has been a tendency to classify by some one prominent feature and to lose sight of the rest, the result being, as in the Linnean system, to separate cases closely related. In the present state of our knowledge it is better to rest content with some general classification such as can be inferred from clinical facts, and to use as few names as possible.

It appears to me that this meeting may best direct its attention to a consideration of the causation of lymphadenoma, and, as experimental data are wanting, the subject of causation must necessarily be considered chiefly from a clinical standpoint. If we do this we may take for a guide at the start the analogy of tubercle, and distinguish a local disease, lymphadenoma, from a general affection, lymphadenomatosis, the latter being related to the former, perhaps, as general tuberculosis to a local mass of tubercle.

We may further mark out two local types of lymphadenoma. In simple lymphadenoma the cause is acting more or less continuously upon the lymphadenoid tissue from the surface of the skin or mucous membrane, whereas in the more malignant form there is a lack of evidence as to the external source of the irritation; but, on the other hand, a manifest proclivity on the part of the cells to proliferate from some cause which must lie within the tumour itself.

SIMPLE LYMPHADENOMA.

The term "lymphoma," since it includes no reference to lymphatic gland, requires qualification when used. Simple lymphadenoma forms a strictly local overgrowth of lymphadenoid tissue kept up by some cause acting from without, and stopping when the cause ceases to act. In many cases we have already some knowledge as to the nature of the cause. Trachoma and lymphadenomatous masses in the upper eyelids, hypertrophy of the nasal mucous membrane, adenoid vegetations, enlarged tonsils, projecting solitary and agminated follicles in the intestine are all due to an irritant acting upon lymphadenoid tissue from mucous surfaces. An absorption of the virus by lymphatics results in a similar affection of lymphatic glands. Chronic eczema of the skin, a

carious tooth, a discharging sinus may excite lymphadenomatous enlargement of glands. The tubercle bacillus itself, if it does not actually invade the gland, may simply cause an overgrowth of lymphadenoid tissue by irritation. Tumours certainly parasitic in origin, such as the infectious granulomata of animals, rhinoscleroma, actinomycosis, and mycosis fungoides have an appearance in microscopic section closely resembling lymphadenoma.

MALIGNANT LYMPHADENOMA.

The name "lymphosarcoma" is apt to confound the growth with sarcomas of lymph glands which have a very different character.

In malignant lymphadenoma we have a factor distinct from the local irritation to which we ascribe the simple form, for in it there is an essential tendency on the part of the cells to proliferate indefinitely. We fail to find, at any rate after the earlier stage, any sufficient source of irritation acting simply from without. The cause of the continued multiplication of cells must lie within the growing tumour. In these respects malignant lymphadenoma resembles sarcoma, in other points they are unlike. Malignant lymphadenoma does not infiltrate neighbouring structures, exercising its influence by compression. It can be shelled out, since it is only encapsuled and connected with surrounding structures by loose connective tissue. Organs such as the spleen or kidney retain their shape even when greatly enlarged. Large tubes, such as the œsophagus, intestine, or blood vessels, are surrounded by the growth without the lumen being narrowed. The cell elements show a remarkably long life, and ulceration and degeneration do not occur. The existence of a reticulum between the cells serves also to separate lymphadenoma from sarcoma growing in lymph glands. Another remarkable difference from true sarcoma is shown by the reaction to arsenic. Even when the disease has become widespread, the administration of arsenic may cause the tumours to speedily vanish. Many cases, at first diagnosed as widely disseminated cancer, have been cured by means of this drug. A woman came up to a hospital after having had both breasts removed by a surgeon in the country for tumours which had grown simultaneously and symmetrically. A mass of enlarged glands filled both axillæ and supraclavicular fossæ. The surgical staff of the hospital in consultation agreed with the country surgeon's opinion that the case was one of hopelessly extensive cancer. The woman however was treated with arsenic, and the whole of the disease disappeared. Another case was taken at first to be multiple sarcoma of the skin, but recovery followed the administration of arsenic.

The poison, therefore, which causes the malignant form of lymphadenoma can be neutralised by arsenic; not only do the cells cease proliferating, but they degenerate and undergo absorption. When arsenic fails to exert a favourable action, the disease may nevertheless be lymphadenoma. The arsenic may be administered in too small a dose, whether absolutely or relatively to the size of the tumour. A larger dose of arsenic may be tolerated in one form more than in another. Arsenic may act on a small mass, although insufficient to overcome a large one. A man was under my colleague Dr. de Havilland Hall for a typical lymphadenomatous tumour in the neck. Growth continued in spite of full doses of arsenic until pressure symptoms occurred. I then removed the greater portion, leaving only those pieces which had extended into the thorax, or which were in close contact with the large vessels in the root of the neck. Since the operation the patient has attended me for three years. So long as he takes arsenic the lymphadenoma remains stationary, whenever he leaves it off growth begins again. He cannot be quite cured, because he soon sickens of any arsenical preparation in full doses.

The recognised tendency of simple lymphadenoma to become more malignant lends support to the surgical treatment by excision whenever drugs fail. So easily do the masses shell out, that lymphadenoma has been removed from otherwise unfavourable positions—for example, from behind the peritoneum. The surgeon need not try to remove the whole; if he can remove the major part arsenic may complete the cure.

LYMPHADENOMATOSIS.

There is clearly some general affection of lymphadenoid

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tissue wherever placed. Great variations are met with in different cases both as regards the severity of the attack, the incidence upon the several parts, and also there are changes which happen in the course of any single case. Hence a number of names have been given to the disease, each taken from one prominent symptom. The spleen, thymus, the lymphatic glands, the bone marrow, the lymphadenoid tissue around the alimentary canal or in the skin—one or all of these structures may be found involved in a general disease, accompanied by symptoms of anæmia, hæmorrhages and swollen gums, cachexia, intermittent irregular fever, and increase of white blood cells. "Lymphatic cachexia," "anæmia splenica vel lymphatica," "splenic lymphatic or myelogenic leucocythæmia," "Hodgkin's disease," "multiple lymphosarcoma,"—these and other names have been used just as a number of names have been used in the past for tuberculosis.

But it tends to promote confusion if one of the symptoms of the general malady be thus elevated to the rank of a special disease. As illustrating this we may take the word "leucocythæmia" or "leucæmia." Some of the cases so recorded are without any statement as to the examination of the blood, and even where a microscopical examination has been carried out no note has been taken of the number of red cells, so that the question of anæmia was overlooked. An increase of leucocytes is probably a sign that the products of cell destruction are acting upon lymphadenoid tissue, healthy enough to react. Marked leucocytosis can be produced by injecting broken-down cells³ obtained from the spleen, thymus, or bone marrow, or isolated products of cells such as nuclealbumin, albumoses, or peptones.⁴ After a meal rich in proteids there is a marked increase of white cells in the blood, the cells in the centre of the Malpighian corpuscles in the spleen showing karyokinetic changes in their nuclei indicating rapid multiplication. The injection of chemical substances may also induce leucocytosis.⁵ Other diseases are attended by an increase of white cells, such as pneumonia, acute osteomyelitis, and cancer. Moreover, the simple counting of white cells is insufficient.⁶ We must follow Ehrlich, and distinguish the lymphocytes which come from lymphatic glands from the eosinophile cells and myelocytes which arise from the spleen and bone marrow, and both of these from the polynuclear and neutrophile cells, which appear especially during inflammation. If too much stress be laid on leucocythæmia, the result is that all the various cases, otherwise alike, have to be arbitrarily split up into two classes—leukæmic and aleukæmic. If there be no increase of white blood cells, this may be due either to the poison being insufficient to excite proliferation of the gland cells, or to the disease being so severe that the glands fail to react⁷ against the poison. Indeed, in a few instances, where marked anæmia was present, the leucocytes have been found actually fewer than normal.⁸ It is easy to see how leukæmia may appear or disappear in the course of a case without influencing the prognosis.

Again, we may note the difficulty which occurs in defining any one form of lymphadenomatosis. Some writers speak of Hodgkin's disease as an enlargement of the lymphatic glands without the spleen being involved; but it must be remembered that in only one of Hodgkin's cases, namely, Case vi, was the spleen apparently free, and the same general tendency to involvement of the spleen was noted in the further cases published by Dr. Wilks. Some call Hodgkin's disease "lymphatic pseudoleukæmia," but the greatest number of white cells, namely, 200,000 per 1 cubic mm. (normal 7,500), may be seen in general enlargement of the lymphatic glands. In fact, leucocythæmia is one symptom, among others, of a general disease.

It is better to try to divide the cases of lymphadenomatosis according to the several modes of origin and the various ways by which the virus may enter. In one group the cause of the disease appears to enter by the alimentary canal. Children suffer from anæmia, cachexia, hæmorrhages, irregular fevers, enlarged intestine lymph follicles, enlarged spleen or retroperitoneal glands with or without an increase of white cells. The cases are numerous; they may be acute in course, or last for years. One of the conditions just noted may be present, alone or in combination with others, or all may coexist. The connection with intestinal catarrh, inherited syphilis,

rickets, and tuberculosis, forms a matter of great practical importance.

Again, young men and boys—army recruits⁹ or young prisoners—are subject to sudden attacks in which mediastinal glands are affected, either those in connection with the thymus or those behind the lungs. This form is often attributed to cold, damp, or foul air. Does the poison in such cases enter by the lungs? Some of the cases are most acute. A boy died in four and a-half days after the first sign of illness, the immediate cause of death being cerebral hæmorrhage, but there was also general enlargement of lymphadenoid tissue.¹⁰ In some cases an infectious disease precedes the outbreak—for example, influenza. Although some cases suggest a virulent infection, there is no evidence as to its transfer to others. The only exception which has been brought forward is that of a clinical assistant who helped to plug the nostrils and examined the urine and fæces of an acute case. He was attacked in a similar manner, and died a month after. Injuries in the region of the spleen or to the bones reported to have preceded the disease may be treated as mere coincidences. It is very difficult in some cases to distinguish lymphadenomatosis from general enlargement of glands in tuberculosis and syphilis; indeed, some appear to be instances of a mixed affection. Cessation may occur in some glands along with lymphadenomatous enlargement of others, including the spleen, which is seldom attacked by tubercle, except in children. I have myself had to incise caseous glands in the neck of a boy who had been in prison, and who died a week after from characteristic lymphadenomatous masses filling the thorax. Similar combinations of tuberculous and lymphadenomatous glands have been met with in animals—for example, the horse.¹¹ In such cases histological appearances of tubercle may be absent from the lymphadenomatous glands, although they may cause tubercle on inoculation.^{11 12} We must allow, I think, that the tubercle bacillus, if it does not actually invade the gland, may irritate and cause lymphadenomatous enlargement. Syphilis may do the same, the glands subsiding when iodide of potassium is administered and the poison neutralised.

In the absence of exact knowledge it is impossible to discuss the relation between the infection and the resistance on the part of the individual, the relation between the seed and the soil; but we may feel sure that individual differences in resistance may give rise to many varieties from one and the same kind of infection. If we arrange the facts gleaned from the bedside in some general way according to the probable mode of entry of the poison, we shall be prepared to receive the new light which will doubtless be thrown upon lymphadenoma by biological and chemical research. The experimental work on this subject is as yet merely in a laboratory stage, and the results hitherto obtained, interesting and extremely suggestive as they are, indicate the need for further work, as well as the direction such work should take. Microorganisms have been found in the growths, leucocytosis and anæmia have been produced by the injection of substances into the blood of animals, and clinical observations on the administration of materials obtained from the thyroid, thymus, spleen, and bone marrow are going on. Some amount of mutual contradiction and of negative results inevitably take place in the earlier stages of any experimental inquiry, and for the present any opinion on this part of the subject can scarcely be formed.

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MR. JACKSON CLARKE read a paper based on 19 cases of lymphosarcoma on which he had made necropsies. They were

taken from 730 consecutive necropsies made at St. Mary's Hospital, and in all the pathological diagnosis was established by histological examination. In the same group of necropsies the other examples of malignant neoplasms were as follows:

		Cases.
Primary cancer of large intestine	...	6
" " stomach	...	6
" " œsophagus	...	7
" " uterus	...	1
" " breast	...	1
" " bile duct	...	2
" " kidney	...	1
" " ovary	...	2
Cases of sarcoma, other than lymphosarcoma	...	9
Glioma (brain and cord)	...	4

Thus in the series lymphosarcoma proved to be almost as common as all cases of cancer taken together, and more common than all other forms of sarcoma. *Distribution of Lesions.*—In 10 out of the 19 cases the bronchial glands appeared to have been the original seat of the disease. In one of these cases there was a pink nodule of growth in the corium beneath the left breast. Such cutaneous growths are useful for diagnosis in doubtful cases. After the bronchial glands the hepatic glands in the small omentum came next in point of frequency as the original seat of the disease. The lumbar glands were affected in six, the cervical and axillary glands in only two cases. *Associations, etc.*—In four cases gout with osteo-arthritis was present. In these cases it was difficult to distinguish between the lymphosarcomatous and the gouty lesions in the lower end of the femur. This was first pointed out to the author by Dr. Berkart. Two other cases were associated with chronic lead poisoning as well as gout. In one case, under Dr. Lees, the later stages of the disease exactly simulated tuberculous disease. Hæmoptysis and evidence of pulmonary cavities were present in life, but no tubercle bacilli were found in the sputum. An empyema formed on the left side and was drained. After death all the lesions were found to be due to lymphosarcoma. In another case tuberculosis of the lungs was present as well as lymphosarcoma of bronchial glands and lungs, and before death pyæmia supervened, streptococci being found in foci of suppuration in lymphosarcomatous nodules in one pectoralis major and one sternomastoid muscle. This occurrence of pyæmia probably explained the conclusion arrived at by some authors to the effect that lymphosarcoma is caused by staphylococci or streptococci. The author concluded that there was no essential difference between hard and soft lymphosarcoma, and that Virchow's term lymphosarcoma should replace that of lymphadenoma used in this country. Cases of soft lymphosarcoma were not easily separable from those cases of leucocythæmia in which enlargement of glands occurred. In one of the latter class of cases spontaneous rupture of the bladder had occurred at the seat of a vesical papilloma, the base of which was occupied by a lymphosarcomatous nodule.

Dr. MURRAY LESLIE argued strongly in favour of the view that the disease was organismal in nature. He thought that considerable light was thrown on the pathology of the disease by a careful study of aberrant forms and allied diseases. With regard to the splenic form, he emphasised the fact that instead of the typical suet-like nodules described by Dr. Wilks one might get nothing more than an indefinite mottling of the spleen, while in still other cases the enlarged organ appeared uniformly red and homogeneous, and microscopically showed simple adenoid hypertrophy of the splenic pulp, with none of the usual characteristic changes in the Malpighian bodies. These changes might or might not be associated with enlargement of lymphatic glands. Another variety of the disease was that in which the only observable pathological change was a lymphoid deposit in the adenoid tissue of the solitary glands and Peyer's patches of the intestine, first described by M. Béhier as "leukæmia intestinalis." Other varieties described were those where the lymphoid deposit occurred mainly in the tonsils, bone marrow, and other lymphatic structures. Some of the above varieties were curiously combined in a case published by Dr. Leslie in the *Edinburgh Hospital Reports* of 1894. A similar case had previously been published by Dr. Pye-Smith in the *Transactions of the Pathological Society of London* in 1875 under the title "Enlarged Spleen and Liver from Overgrowth of Adenoid Tissue without Leukæmia." The symptomatic features of

both cases were those of lymphadenoma. In both cases there was very little actual anæmia. In Dr. Pye-Smith's case the number of leucocytes was normal, while in the speaker's case they were much diminished in number (about one-fifth of the normal), which fact induced him to describe the case as one of "oligo-leucocythæmia." The spleen was enormously enlarged, and presented very much the characters of the spleens seen in leucocythæmia. The liver was also much enlarged, and was the seat of numerous minute circumscribed masses of lymphoid tissue situated between the lobules and resembling closely those multiple miliary tubercles met with in the livers of children dying of acute general tuberculosis. The solitary glands and Peyer's patches were much hypertrophied, forming little greyish non-caseating nodules scattered over the mucous surface of the bowel. In Dr. Pye-Smith's case there were similar non-caseating granulations scattered over the abdominal surface of the diaphragm, having presumably spread by extension from the liver and spleen. The bone marrow in the speaker's case was transformed into pinkish lymphoid marrow. In both cases there were none of the usual manifestations of tuberculosis. He had subsequently seen another case with similar immensely enlarged spleen associated with marked diminution in the leucocytes, but in addition well-marked anæmia, entitling the case to be considered one of "splenic anæmia." These unusual varieties exemplified the fact that one, more, or all of the lymphatic structures might become involved in different ways, and also drew attention to the close relationship existing between lymphadenoma and such diseases as leukæmia and splenic anæmia. All intermediate varieties seemed to exist. Leucocytosis might possibly be a comparatively unimportant diagnostic feature. The relative number of leucocytes or even hæmocytes might simply depend on the relative degree of involvement of the blood-forming and blood-destroying structures. As regards the essential pathology of lymphadenoma, the facts seemed to be much in favour of the organismal hypothesis, the organisms probably finding in the lymphoid tissue a suitable nidus for their development. The course of the disease presented many close and remarkable analogies to that of tuberculosis, though the comparative absence of caseation stood out in marked contradistinction. Varieties might depend on power of resistance of the individual. Dr. Murray Leslie adduced the following arguments in favour of the organismal hypothesis: (1) Certain cases seem to owe their origin to exposure to foul air. (2) Micrococci and other organisms have been found in the affected structures. (3) Close analogy with tuberculosis and syphilis. (4) Occasional pyrexia, night sweats, and other symptoms point to the presence of organismal toxins in the system. (5) Probable sites of infection and mode of extension: If by the mouth, then we will get enlargement of the cervical glands, with extension to the mediastinum. If by the lungs, then the mediastinal glands will be first involved. If by the alimentary canal, then the lymphatic structure of the portal system will be affected, notably the mesenteric glands, spleen, and liver. (6) The beneficial effect of arsenic in some cases is probably to be attributed to its germicidal action, and is comparable to that of mercury in syphilis. For these and other reasons he would class lymphadenoma in the great group of lymphadenomata of which tubercle, syphilis, and leprosy are our great examples. A little was known about the organisms of tubercle and leprosy. We might yet know something of those of syphilis and lymphadenoma.

Dr. G. NEWTON PITTS said: (1) Chronic irritation of a mucous membrane and more rarely of skin precedes the development of lymphadenomatous gland infection. Gonorrhœa, tonsillitis, carious teeth, etc., are common sources of chronic irritation; besides these, the group of cases commencing as lymphadenoma in the mucous membrane of alimentary canal must be included. These differ from the cases where bowel is involved secondarily, when the subserous tissue is infiltrated by a sheath of growth, and when a muscular coat is invaded it pouches. (2) True lymphadenoma is limited to lymphatic tissue and never invades other tissues; it never fungates and is a very stable tissue, rarely degenerating or undergoing fibroid change; the effects exerted on organs are purely mechanical—for example, bile ducts and vessels which can be traced through large masses in

the liver and organs do not alter in shape but only in size. (3) The process is often associated with tubercle, syphilis, etc., and two views may be held: either the process is an infective lymphadenoma similar to an infective granuloma in connective tissue, in which case it may own several causes; or it may be a specific new growth of lymphatic tissue, as sarcoma is of connective tissue or carcinoma of glandular and skin surface epithelium. At present we cannot decide which is the more accurate view. (4) Microscopically the tissue consists of small mononuclear round cells, with very fine fibrous stroma; the cells rarely vary; sometimes hyaline and sometimes lardaceous changes take place. If there is caseation, tubercles will probably be found also to be present. (5) For simplicity of classification the typical case should be one in which the spleen is not involved; when the spleen is infiltrated there will almost always be leucocytosis, and the condition should be classified as lymphadenoma complicated with leukaemia.

Dr. HERBERT SNOW strongly protested against the inclusion of malignant growths of the adenoid tissues under the title lymphadenoma. He recognised three chief forms of lymph gland or adenoid enlargement: (1) Simple lymphoma. (2) The true lymphadenoma or Hodgkin's disease, a general simultaneous enlargement of glands throughout the body, pyrexial. Microscopically there is a cirrhosis of the glands, the cells being crowded out of existence by redundant fibrous tissue. There is no invasion of any other tissue. (3) Lymphosarcoma, or lymphocarcinoma, a true cancer, always primarily local, commonly following injury, steadily progressing to death. There is exuberant cell proliferation; the cells have multiple huge nuclei; they erode all the tissues with which they come in contact, and tally in every respect with the features of malignant lesions elsewhere. The marrow is an important adenoid tissue, which gives rise to round-celled growths indistinguishable from the malignant lesions of lymph glands. Its implication by malignant tumours beginning elsewhere may account in part for the multiple hæmorrhages noticed in some cases of lymphosarcoma.

Dr. CLAUDE WILSON said: I have been much struck by the tendency of many speakers, particularly exemplified by Mr. Spencer's thoughtful paper, to group together the whole series of cases, including typical Hodgkin's disease, leucocythæmia, and the cases between them, rather than to make an attempt to differentiate them. Mr. Jackson Clarke too would seem to link the one end of this chain very closely with sarcoma. My own attention has been specially directed to the subgroup of cases which have been called "splenic anæmia," "splenic cachexia," "splenomegalia primitiva," etc., and which seem to occupy a position midway between typical leucocythæmia and typical lymphadenoma, being characterised by anæmia and enlarged spleen, but without leucocytosis or enlargement of lymph glands. A series of cases which I have described include six cases extending over three generations of the same family, and have shown these characters—in one or two instances for fully thirty years—without showing any tendency to relapse either in the one direction or the other; and my impression is that, however useful it may be in our present state of knowledge to group the whole class of diseases covered by the present discussion, it will be found necessary eventually to differentiate them into at least as many subgroups as has hitherto been customary.

Mr. S. G. SHATTOCK remarked upon Dr. Leslie's observations that, although there were analogies between lymphadenoma and tuberculosis, there were equally analogies between lymphadenoma and new growths. The tissue in question was lymphatic tissue, not granulation tissue, and so differed from that of tubercle. He did not agree with Mr. Jackson Clarke's view that lymphoma was a sarcoma as the word was generally understood. Sarcoma was a tumour of connective tissue origin, and exhibited the metaplasia known between different forms of connective tissue; but leucocytes, it was generally held now, did not produce connective tissue. Mr. Butlin had described the spontaneous diminution of a swelling of the testicle in a boy affected with bilateral disease of the testicles and multiple growths in the skin; this case was at the time regarded as one of round-celled sarcoma, but the speaker thought it more probably one of lymphomatosis. The tissue of lymphomatosis was a normal tissue; so was that of a columnar-celled carcinoma; he considered it safest,

therefore, to relate the disease lymphoma, whether in its local or generalised forms, with new growths in general.

Mr. SPENCER, in reply, said that the President, Dr. Wilks, in his paper in the *Guy's Hospital Reports*, had been the chief person in this country to enlarge our knowledge of this disease. He maintained that histologically there was a sharp distinction from sarcoma, although, as in other disease, a growth of primary lymphadenoma might take on secondarily malignant characters and infiltrate. He denied the necessity of assuming a micro-organism; it might be due to a chemical irritant. He could not agree that gout and osteo-arthritis had any connection with lymphadenoma, which occurred in children and young people. On the other hand, the connection between gout and osteo-arthritis and true sarcoma was frequent. He believed that all the forms of lymphadenoma might be included under one name, as had already been done for tubercle and syphilis.

NOTE ON EHRlich's DIAZO-REACTION.¹

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THE diazo-reaction, or Ehrlich's diagnostic test for typhoid (enteric) fever is now well known. In Ehrlich's original method² two solutions are made use of—(A) a saturated solution of sulphanilic acid in a 5 per cent. aqueous solution of hydrochloric acid, and (B) a 0.5 per cent. aqueous solution of sodium nitrite. For use 40 parts of (A) are mixed with 1 part of (B); this may be termed the test solution. Equal parts of this test solution and of the urine are mixed, and the mixture is rendered alkaline with ammonia. Normal urine gives a yellow or orange colour, while the urine of typhoid fever gives a deep reddish colour, very like that of port wine; on shaking the froth becomes pink, and on standing for twenty-four hours a greenish precipitate forms.

Various modifications of the test have been employed. Ehrlich mixes the urine with five times its volume of absolute alcohol, filters and tests the filtrate as in the original method. Simon³ adds the ammonia by means of a pipette, so that it forms a layer on the surface, and a coloured ring is produced at the junction of the liquids. Rutimeyer⁴ makes his test solution by adding to 200 parts of a saturated aqueous solution of sulphanilic, 10 parts of pure nitric acid, and 6 parts of a 0.5 per cent. aqueous solution of sodium nitrite. Lastly, Greene⁵ claims that the reaction is much more reliable if the test solution be prepared by mixing (A) and (B) in the proportion of 100 to 1 instead of 40 to 1, as originally recommended.

I do not propose to deal at any length with the clinical aspect of this reaction, as my experience of it is not sufficiently large. In the comparatively few cases in which I have tried it, I have been struck by its accuracy, and I gather from a survey of a considerable amount of literature that most authors consider it a very valuable test, and one of considerable diagnostic importance. While the reaction is almost invariably present in typhoid fever during the second and third weeks, it is also met with in some other diseases—frequently in advanced phthisis and other forms of tuberculous disease, and in extensive malignant disease, sometimes in measles, pneumonia, and typhus fever, and occasionally in other specific fevers, acute rheumatism and septicæmia. In typhoid fever the test is, perhaps, most valuable when negative, that is, if in a febrile condition during the second or third weeks the reaction is not obtained the disease is almost certainly not typhoid fever. Greene claims that by using less sodium nitrite (A : B :: 100 : 1 instead of 40 : 1. See above.) phthisis and pneumonia do not give the reaction, while it remains distinct in typhoid and advanced malignant disease.

In employing the test certain precautions must be observed. The solution of sodium nitrite should not be more than a day

¹ Read in the Section of Pathology at the Annual Meeting of the British Medical Association held in London, July-August, 1895.

² *Charité-Annalen*, viii, 1883.

³ *Johns Hopkins H.-sp. Bull.*, i, 1890, p. 93.

⁴ *Correspondenzblatt f. Schweiz. Aerzte*, No. x, p. 90.

⁵ *Journ. Amer. Med. Assoc.* (Chicago) xxii, 1894, p. 256.