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A STUDY OF THE LYMPHOGRANULOMATA.

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IT is proposed to introduce this paper with an account of the case history of an individual who is the victim of the disease which has been variously described as Hodgkin's disease, lymphadenoma, and lymphogranuloma.

Mrs H. is a woman of 45 years. She enjoyed good health until 1926. At that time she was resident in the Argentine, and in the later months of the year (1926) she suffered from an acute intestinal disorder, diagnosed as a ptomaine poisoning, and characterised by general illness, persistent pyrexia, body oedema, and diarrhoea. The symptoms continued over a period of six weeks, and even after they subsided there was a measure of body weakness and general ill-health.

In 1928 the debility became more noticeable, and in November of that year an enlargement of the *right* supraclavicular glands was detected (Fig. 1). In January 1929 glandular swelling appeared in the supraclavicular glands of the *left* side, and these features persisted with an increasing degree of general debility during 1929 and the first six months of 1930.

The patient came under personal observation on 4th June 1930. Examination at that time revealed enlargement of the lymphatic glands in both supraclavicular regions, in the right scalene area, and in the right axilla. The glands were discrete, firm, and freely movable; they presented the clinical characteristics that are associated with a lymphadenomatous condition. X-ray examination of the chest revealed the presence of a pathological deposit in the apex of the left lung; the mediastinum appeared to be clear. Further investigation and treatment were refused at this time, but a year later (in June 1931) the patient's condition had so far deteriorated that she agreed to enter hospital. Examination at this time showed a further extension of the glandular enlargement; both supraclavicular areas were the site of glandular swellings the size of a closed fist, the glands in the axillæ

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were considerably enlarged, the deposit in the upper portion of the right lung had extended, no change could be demonstrated in the abdominal area, there was anaemia with an eosinophilic count of 5 per cent. One of the enlarged glands was removed, and a microscopical examination revealed the characteristic pathology of lymphadenoma (Fig. 2, Plate I.). The treatment recommended consisted in a series of deep X-ray exposures. The result was most gratifying, the glandular swelling subsiding, and the general health improving.

In February 1932 the patient reported. Her general health was distinctly better; a single gland about the size of a cherry could be detected in each suprACLAVICULAR region, the blood-picture was normal.

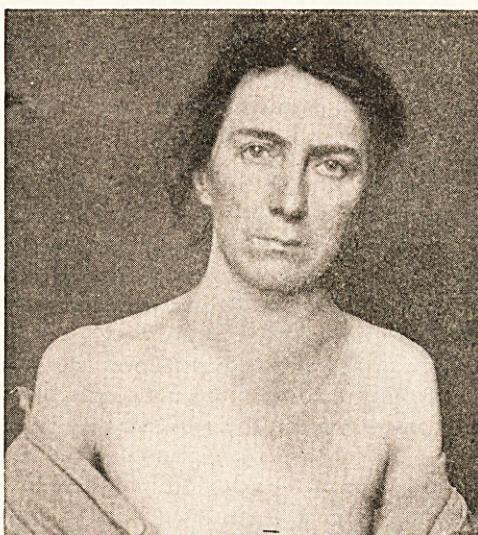


FIG. 1.—Mrs H. Clinical photograph.

In June 1932 there was a renewed failure in general health, shortness of breath becoming a most distressing symptom, and investigation revealed that the left lung was almost completely solid, with an overlying pleural effusion. There was a persistent cough with haemoptysis, and it seemed that the left lung was the site of a diffuse tumour formation, which had led to obliteration of the air-containing alveolar spaces (Fig. 3). A small amount of clear fluid was removed from the left pleural space by aspiration, no cytological elements were demonstrable on microscopical examination, and a bacteriological investigation was negative.

Although the position appeared desperate, a further course of deep X-ray therapy was recommended, and the most dramatic results

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followed—the lung areas cleared, aeration was resumed, the fluid disappeared, and when the last review was carried out on 10th September 1932 remarkable benefit was evident. Her general health had improved, there was no accumulation of pleural fluid, and X-ray examination revealed a satisfactory aeration of the great bulk of lung tissue. Such is the present position; we shall see what the future may reveal, but the story is in many respects a characteristic one, for it is the record of a woman whose life is imperilled by a disease the essential pathology of which is the development of a granulomatous



FIG. 3.—Mrs H. X-ray showing lung involvement.

change in those areas in which lympho-reticulo-endothelial tissue exists. The first demonstrable change in her economy was a granulomatous formation in certain of the lymphatic fields; at a later date there was a similar change in the reticulo-endothelial tissue of the left lung—a development which almost proved fatal. Both changes have responded to the influence of radiotherapy, but we await with apprehension the developments of the future.

We have had an opportunity in the past five years of following the case histories of seventeen individuals affected by this grave disease, and it therefore seemed appropriate to review our present knowledge of the subject.

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Historical.—We do not propose to elaborate this aspect of the question, though it forms an interesting record of the discovery and the gradual piecing together of knowledge in respect of a most puzzling clinical entity, but it is well to record that we owe the recognition of the disease to the man whose name is still associated with the nomenclature.

Hodgkin¹ first described the disease in a paper which he read before the Medico-Chirurgical Society of London in 1832, and, though we recognise that the original contribution was not without inaccuracies (for it is evident that the cases which formed the subject of Hodgkin's paper included conditions which we to-day would classify as examples of lymphatic leukaemia) this does not detract from the importance and significance of the original contribution. Twenty-four years later (in 1856) Wilks² of Guy's Hospital stimulated fresh interest in the subject, and it was he who suggested that it would be a courteous act to designate the disease by the name of the man who gave the first description of the lesion. In 1864 the problem attracted Virchow's³ attention, and he so sifted the matter that leukaemia, hitherto confused with Hodgkin's disease, received separate recognition. We need not pursue the historical record further; the names and dates that have been mentioned are milestones in the journey of our knowledge, and, though many new points of information have been and continue to be recorded, the foundation, so well and so truly laid, remains secure. Since Virchow's time the literature, immense as it is, has been concerned with an elaboration of the pathology, the enumeration and exploration of various theories regarding the etiology, and a discussion of the ever-present problems of treatment.

Some Aspects of the Pathology.—On first consideration it might seem as though the pathology of lymphogranuloma necessitated the consideration of a variety of lesions differing widely in constitution and in distribution. Such an impression might be gained from the study of the cases which have come under our personal observation. Certain of these presented a pronounced affection of the lymphatic glands, some showed nodular deposits in the spleen and liver, and in two instances the lungs were the site of a tumour-like infiltration. In one case multiple ulcerating tumours existed in the small intestine, in another the stomach was the site of an ulcerating granuloma; two of the cases demonstrated skin involvement, and in one

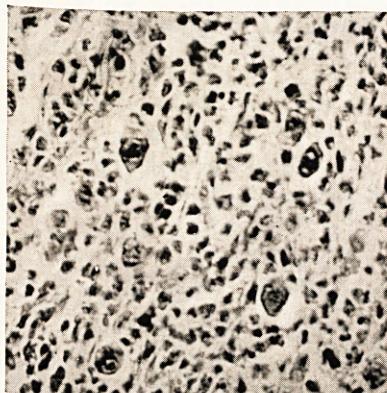


FIG. 2.—Mrs H. Photomicrograph of section of glandular swelling.



FIG. 4.—Structure of lymph gland showing the gland corridor.



FIG. 5.—Germinal centre of lymph nodes showing reticular cells in active proliferation.

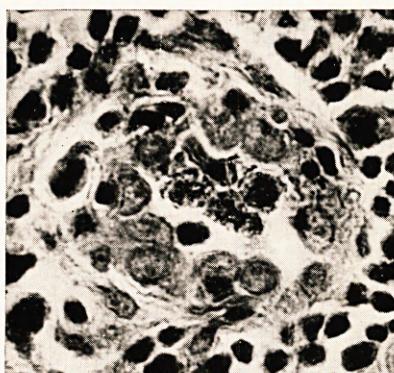


FIG. 6.—Endothelium of lymph node capillaries.

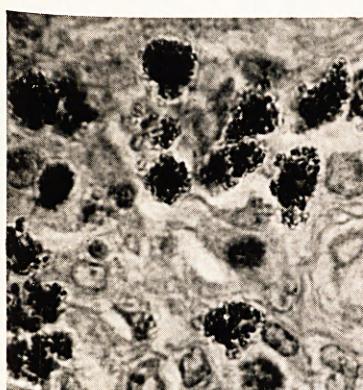


FIG. 8.—Hodgkin's disease: the eosinophilic reaction.

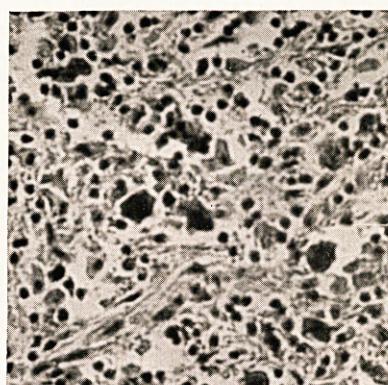


FIG. 9.—Hodgkin's disease, early phase, showing the presence of giant cells.

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instance there was a widespread granulomatous infiltration of the bone marrow. Many of these lesions were individual and independent, and it certainly would seem to an onlooker as though we were dealing with a disease capable of assuming a variety of forms in a diversity of organs and tissues; yet, when we come to investigate and analyse the position we find that there is one common factor—the lesion essentially affects what may be collectively described as lympho-reticulo-endothelial tissue, and, while it may extend into varying situations, its genesis is in areas in which this tissue normally exists. The varying forms which the deposits assume depend upon the situation in which the disease arises, and so it is that we find the circumscribed tumour with affection of lymphatic glands, the ulcerating deposits of hollow viscera, the diffuse infiltration of marrow, and the multiple nodules of such solid organs as the liver and the spleen. If we accept this generalisation, it is evident that the problem is simplified.

Let us now consider the more intimate pathology as it is revealed in one highly characteristic situation, a lymphatic gland, and let us trace the changes as they reveal themselves in different stages of the disease.

We may begin by recalling the normal tissue arrangements of a lymph gland as they are revealed in section. Beneath the capsule and between it and the lymphoid tissues of the interior there is a layer of loose tissue. It constitutes a pathway for the circulation of lymph, and it has been given the appropriate and descriptive title of the "gland corridor" (Fig. 4, Plate I.). It is bridged across by strands of fibrous tissue, which pass from the deep surface of the capsule to the underlying medulla, and it contains large numbers of reticular and endothelial cells. The centre of the gland is occupied by true lymphatic tissue; there are accumulations of lymphocytes supported by a loose connective tissue framework, and scattered throughout the field there are the germ centres—concentric collections of endothelial cells usually grouped around a blood vessel (Figs. 5 and 6, Plate I.). We may say that three special types of cell enter into the constitution of a healthy lymphatic gland—the reticular and endothelial cells of the corridor, the endothelial cells of the germ centre, and the mature small lymphocytes occupying the bulk of the gland centre.

Such being the distribution, we ask ourselves—What is the function and rationale of the arrangement? The answer is that

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it concerns influences upon the lymph which at one and the same time are selective, filtrative, and reinforcing (Fig. 7). The lymph fluid derived from peri-vascular sources in the tissues passes by afferent lymphatics into the gland corridor, it is there submitted to a certain measure of filtration action, while the reticular and endothelial cells exert a phagocytic influence upon any foreign particles or organisms that may have been conveyed in the lymph stream. It may also be the case that products of metabolism acquired from tissue reactions are neutralised by the biochemical influence of the reticulo-endothelium. The lymph thus purified and altered percolates through the lymphocyte field and around the germ centres, and at this stage the fluid receives a large number of young and it may be immature lymphocytes; thereafter purified and enriched, it

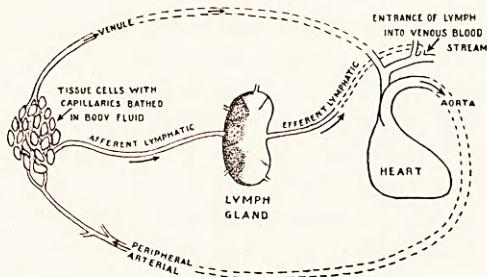


FIG. 7.—Diagram demonstrating the circulation of the lymph.

makes its way by efferent lymphatics into the larger lymph channels, and thence into the blood stream, where the older and mature lymphocytes are destroyed.

With this appreciation of normal structure and function, let us consider the changes which are evident when the gland becomes the site of a lymphogranulomatous disturbance. To the naked eye the gland is enlarged, and on section the cut surface shows a grey oedematous appearance with here and there the darker points of a haemorrhagic, or it may be a necrotic, change; lines of fibrous tissue arising from the deep surface of the capsule radiate in the gland substance.

What are the cytological changes which underlie the morbid anatomy? The answer given might be that they are so varied and even confusing that a concise description is very difficult, but let us attempt to trace them as they are revealed in a series of stages, and, if we have an opportunity of examining

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a number of glands removed by dissection from such a region as the neck, we shall find the varying stages manifested in different individual glands.

The earliest disturbance may be described as an overgrowth of the various specific cells of the gland tissue; the change is therefore shared by the reticulo-endothelial cells of the corridor, the endothelial clusters of the germ centres, and the lymphocytes of the central areas. One is left with the impression that in some way a stimulus has been conveyed to the gland, the effect of which has been to lead to a proportional overgrowth of the various cell elements. Presently the picture changes, and the next impression is one which might be described as a metamorphosis in which the gland area harbours a number of cells of an immature type. While normal and fully developed tissues are represented, the great bulk of the microscopical field is occupied by cells which are clearly abnormal in outline and in staining reaction. There are multiplications of shape and size, there are reticular and endothelial cells so deformed that their recognition is difficult, there are lymphoblasts, and many large and intermediate types of lymphocytes. Many of the cells show intracellular accumulations of a basophilic fluid, and in a certain proportion an extrusion of the nucleus can be demonstrated. It is significant, however, that in the midst of so much metamorphic activity there is very little evidence of nuclear mitosis, and it must be confessed that this is a puzzling feature.

At this stage an impressive and new development makes its appearance in the form of large numbers of eosinophilic leucocytes (Fig. 8, Plate I.). They are scattered throughout the field, and it is evident that they do not persist for any great length of time. One naturally surmises what part this cellular development plays in the tissue economy, and by analogy it is suggested that they appear in response to the presence of a toxic factor. The significance of the change will be alluded to later.

Once more the picture alters, and on this occasion the distinction arises by the appearance of two peculiar cells, the large mononuclear and the multinuclear Dorothy Reed or Sternberg cell. There is evidence that both of these originate from the endothelial cells of the germ centres and the gland sinuses (Fig. 9, Plate I.).

The final stage is characterised by the appearance within the gland of an increasing amount of fibrous tissue. It is apparent that the reticular cells are the source from which the fibrosis

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mainly proceeds, but there is evidence that the lymphoblast and the large mononuclear are also sources from which fibrils arise. At any rate, the process is progressive until the gland tissue is virtually replaced by a fibrous stroma (Fig. 10, Plate II.).

Such is a summary of the various changes which may be detected in a review of the microscopical pathology as revealed in a series of glands representative of different stages of the disease, and it is possibly helpful to recapitulate the phases in the following manner:—

Phase I.—A proliferation of the reticulo-endothelial and lymphocyte tissue.

Phase II.—A disturbance of the natural evolution and development of the lympho-reticulo-endothelial group so that numbers of immature types appear.

Phase III.—A development of the protective cell elements—the eosinophils, the multinuclear cells, and large mononuclears.

Phase IV.—A conversion or (as it may be termed) a degeneration of the cell elements into fibrous tissue.

The Similarity of the Pathology in Various Situations.—We have already indicated that the manifestation of lymphogranuloma may be evident in a variety of tissues and situations, and that, while lymphatic glands are at one time or another almost invariably involved, lesions may be demonstrated in the lungs, the skin, the stomach, the small intestine, the bone marrow, and such solid viscera as the liver and the spleen. The frequency of glandular affection is probably a matter of great significance, and this point will be discussed later; but for the present we are anxious to know if there is any uniformity in the pathological picture of what would seem to be a wide diversity of lesion types and situations. We believe that the answer may be given that there is a similarity in the cytological picture, whatever the situation, and the morbid anatomy of the lesion. In each instance there is a representative of one or other of the morbid phases which have been described in relation to the glandular pathology, and, if it has been impossible to demonstrate the sequel of phases as one can do in the glandular lesion, the explanation is that the situation of the lesion makes such a demonstration difficult and often

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impossible. To recapitulate the position, we believe that in every instance the lesion affects deposits of lympho-reticulo-endothelial tissue, and therefore it is conceivable that the pathology may arise in whatever situation such tissue may exist. Let us add further illustration of this conception. Here is a scheme which tabulates certain of the clinical facts as revealed in a series of 14 cases (see Table on page 454).

It is evident from a study of such a table that glandular enlargement in some situations has been a constant factor in every case, but in five instances there was involvement of areas outside the glandular groups. Case No. 5 illustrated a deposit in the left lung. The physical signs were compatible with a tumour formation, the morbid anatomy suggested infiltration of the lung tissue by an infiltrating neoplasm extending into the centre of the lung from the region of the hilum, the microscopical examination yielded an appearance comparable in almost every respect to that described in lymph gland tissue, but altered, as one would anticipate, in virtue of the peculiarities of the organ concerned. In more detail, the alveoli were occupied by syncytial masses which had apparently arisen through proliferation of the lining epithelium, while the peri-acinar space contained collections of characteristic cells—lymphoblasts, monocytes, reticular cells, and the distinctive multinuclear Dorothy Reed cell. Case No. 9 had been under treatment in another hospital on account of an enlargement of the left axillary glands, which on microscopical examination had shown the characteristic features of a lymphogranulomatous lesion. A few months later intestinal symptoms developed, and a laparotomy revealed the existence of two tumours in the jejunum, the higher of which was eighteen inches from the duodeno-jejunal flexure, the second eight inches lower. Each tumour was about the size of a small hen's egg, they had originated in the gut wall at the point of the mesenteric attachment, and each showed some degree of ulceration at the middle of the mucous membrane-covered surface. In the mesenteric field relative to each tumour there was a number of enlarged lymphatic glands, those in closest proximity to the tumour area being most markedly enlarged. The microscopical examination of the primary gland tumour showed a typical picture, but in the intestinal lesions, while definite evidence of Hodgkin's disease was present, the major portion of the tumour resembled

TABLE I.

No.	Age.	Sex.	Complaint.	Lymph Glands First Involved.	Additional Pathology.	Red Cell Count.	White Cell Count.	Eosinophils.	Mediastinal Glands.	Duration of Life after Onset.
1	67	M.	Enlarged cervical glands .	Cervical	?	15 months.
2	38	M.	Enlarged glands . .	Supraclavicular	2 years 9 months.	
3	43	F.	General weakness and enlarged cervical glands .	"	4,000,000	7,000	5%	...	3½ years.
4	27	M.	Enlarged cervical glands .	Left jugular	4,200,000	7,500	3%	...	15 months.
5	18	F.	Dyspnoea . . .	Supraclavicular . .	Involvement of left lung.	4,300,000	7,200	nil	...	3 "
6	31	M.	Enlarged cervical glands .	Jugular and supra-clavicular.	Papular eruption of skin.	...	6,400	5%	...	unknown.
7	38	F.	Enlarged cervical glands . Skin itch.	Supraclavicular	2,680,000	4,300	2%	also retro-peritoneal.	1 year.
8	59	M.	Axillary and groin glands enlarged also increasing weakness	Axillary	3,800,000	15,000	5%	...	3 years.
9	58	M.	Enlarged axillary glands .	Right axillary . .	Tumour of small intestine, enlarged spleen and liver.	7 months.
10	24	M.	Weakness and abdominal pain.	Abdominal . . .	Tumour of stomach.	1,670,000	5,500	3 "
11	52	M.	Left axillary glands .	Axillary . . .	Involvement of skull diploc. and bone marrow.	4,800,000	72,000	4%	...	6 "
12	30	F.	General weakness and gland enlargement.	Left cervical (supra-clavicular.	...	3,700,000	5,400	15 "
13	19	M.	Cervical gland enlargement.	"	4,300,000	7,200	6 "
14	28	F.	Cervical gland enlargement.	Supraclavicular	3,400,000	5,400	3%	...	2 years.

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a fibro-sarcoma (Figs. 12, 13 (Plate II), 14). It is well to add that the extent and the distribution of the associated glandular enlargement suggested a conveyance of diseased material by



FIG. 12.—Case No. 9. Lesion in the small intestine.

way of the lymphatics from the primary tumour to the related glandular groups.

Case No. 10 represented an atypical lymphogranulomatous

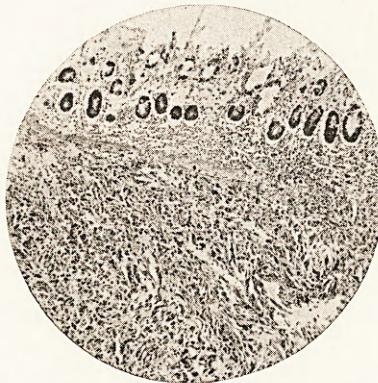


FIG. 14.—Case No. 9. Photomicrograph of intestinal lesion showing the malignant nature of the cells.

lesion in relation to the lesser curvature of the stomach. The general structure suggested a large round cell sarcoma, but in places eosinophils and Dorothy Reed cells could be observed (Figs. 15; 16, 17A and 17B, Plate II.).

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Case No. 11 was introduced by an enlargement of the left axillary and cervical glands, these areas showing charac-

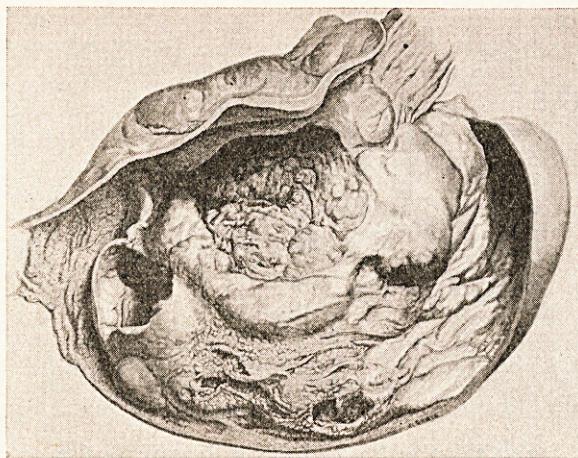


FIG. 15.—Case No. 10. Hodgkin's disease affecting stomach. Diagram of stomach.

teristic pathological changes, but a distinctive feature was the degree of lymphogranulomatous involvement of the bone

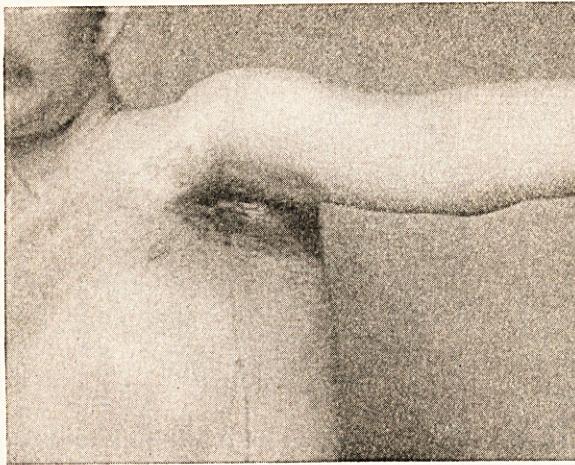


FIG. 18.—Case No. 11. Clinical photograph showing axillary swelling with invasion of the skin.

marrow (Fig. 18). The change was particularly evident in the diploic marrow of the skull (Fig. 19), and it is probably a significant fact that the original and most pronounced

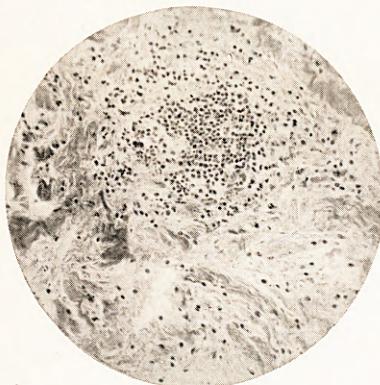


FIG. 10.—Hodgkin's disease, later phase showing fibrosis.

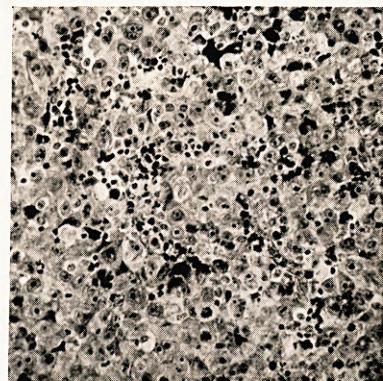


FIG. 11.—Case No. 9. Photomicrograph of section of gland swelling demonstrating malignant phase of Hodgkin's disease.

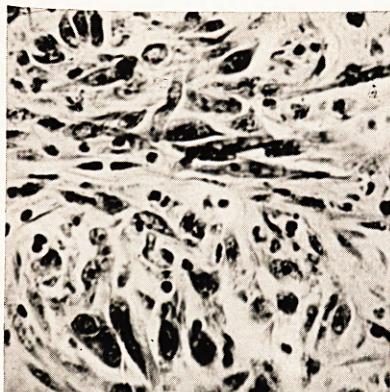


FIG. 13.—Microphotograph of intestine tumour of Case No. 9 demonstrating the various cell types.



FIG. 16.—Case No. 10. Sections of Hodgkin's disease affecting stomach.

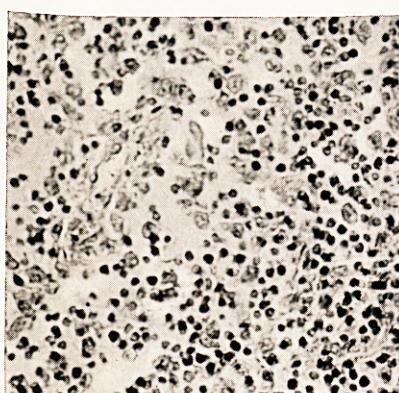


FIG. 17A.—Clinical Case No. 10. Microphotograph of lymphogranuloma lesion developing in stomach wall.

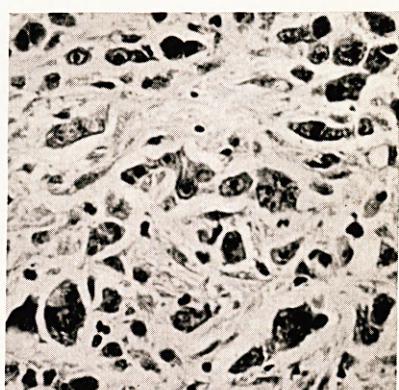


FIG. 17B.—Clinical Case No. 10. Microphotograph of lymphogranuloma of stomach showing characteristic cells of the Hodgkin's type.

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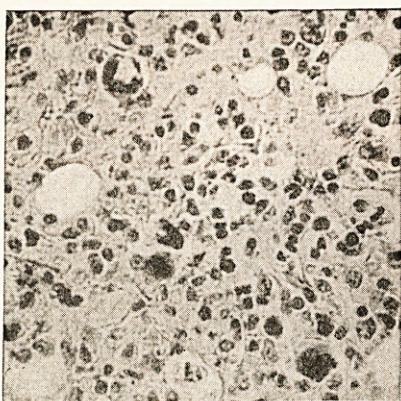


FIG. 19.—Case No. 11. Section of bone marrow.



FIG. 20.—Case No. 11. X-ray of skull.

deposit occurred in the perivascular areas around the larger vessels (Figs. 20 and 21). The microscopical picture showed a hyperplasia with a pronounced increase of what evidently were

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immature types of cell lymphoblasts, reticular cells, and megakaryocytes. In the nodules of the liver, the spleen, and the skin a very similar picture was obtained, and in every instance it was the presentation of deposits of immature cells derived from the group source of lympho-reticulo-endothelial

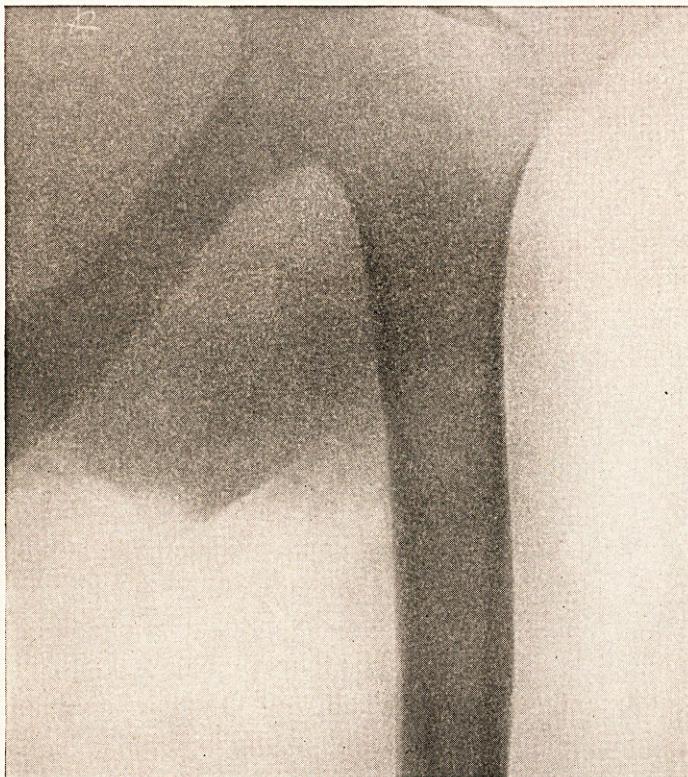


FIG. 21.—Case No. 11. X-ray of humerus showing area of rarefaction in the head of the bone.

tissue. The fact appears to be established, therefore, that, however varied might be the morbid anatomy encountered in different situations, there was a similarity of the cytology and a constant reproduction of immature cell types of lympho-reticulo-endothelial tissues.

Problem of the Morphogenesis.—If the supposition is correct that immaturity of lympho-reticulo-endothelial tissue is the basal feature in the pathology of lymphogranuloma

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lesions, it is logical to inquire regarding the morphogenesis of the cells which are included in this group.

It is probable that the mature cells are represented by three types—the *lymphocyte*, the *reticular cell*, and the *endothelial cell*. Let us briefly consider the facts which are known regarding the origin and the life-history of these three varieties.

A. *The lymphocytes*.—There are probably three types of adult lymphocyte: the large lymphocyte, provided with a big

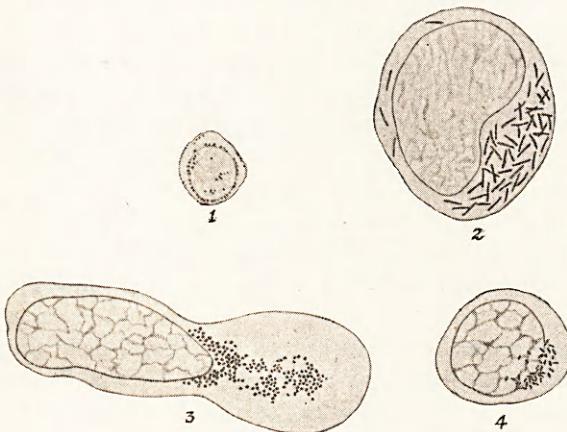


FIG. 22.—Maturation of *lymphocyte*, monocyte and leucocyte (Miss Sabin).

- (1) Lymphoblast from a mesenteric gland of the rabbit. Mitochondria clustered around the nucleus. No neutral red granules.
- (2) Large lymphocyte. Human. Rod-like mitochondria.
- (3) Intermediate lymphocyte from blood of rabbit. Nucleus is advanced in the direction in which the cell is travelling.
- (4) Small lymphocyte from the blood of a rabbit. Mitochondria clumped in the neighbourhood of the nucleus.

nucleus and possessing a relatively clear protoplasm, a medium type with mobile properties, and the small lymphocyte, the distinctive feature of which is the relatively large size of the nucleus. It is distinctive of all adult types that mitochondria exist in the cytoplasm, and that the granules tend to collect in localised areas. We ask ourselves—What is the source from which these various mature types take origin? According to Professor Sabin,³² a mesenchyme cell of a reticular type is the progenitor (Fig. 22). This cell is somewhat pear-shaped in outline, with a curious stalk-like prolongation of the cytoplasm. When vitally stained with janus green and neutral

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red, the cytoplasm is shown to contain dark bodies, which Miss Sabin believes may be the precursors of the mitochondria. From this source there arises a circular primitive white cell, the cytoplasm of which shows a number of unequally distributed rod-shaped mitochondria. The next phase is the formation of a lymphoblast, possibly by the process of extrusion of the primitive cell's nucleus; at any rate, there arises a small cell possessing a relatively large nucleus, while the mitochondria adopt a perinuclear distribution. It is from the lymphoblast that the three types of lymphocyte originally adumbrated (large, intermediate, and small) take origin. The life-history sequence is therefore as follows: a mesenchyme reticular cell, the lymphoblast, the large lymphocyte, the intermediate lymphocyte, the small lymphocyte (Figs. 23 and 24). It should be noted that the small lymphocyte is, as far as we know, the final and adult stage in the sequence.

B. *Reticulo-Endothelial Cells*.—It is well to consider the reticular and the endothelial cell together, because they have much in common, both in respect of morphology and of function.

Aschoff was probably the first to appreciate their significance, and he called attention to the important part which they play in the physiology of the tissues and in the development of disease. Included in the group are two types of cell, the reticular and the endothelial. Both are mesenchymal in origin, and it is likely that they originate from a common stock, but a subsequent differentiation of structure and of function has justified the recognition of two separate and independent types of cell.

The *reticular* cell originates from the mesenchyme. In its fully developed state it assumes the form of a branched cell of the connective tissue type, in which form it acts partly as a macrophage and partly by fulfilling certain obscure biochemical functions. It has, however, other possibilities and potentialities. Some workers claim that it is the source from which the primitive white cell arises, in which event it is the progenitor of such a variety of leucocyte types as the myelocyte, the monocyte, and the lymphocyte. The disposition of reticular cells has been described as "fixed" and as "wandering," the former group being distributed in the spleen and the liver, in lymphatic tissue, bone marrow, and adrenals, while the second group is represented by the tissue histocytes, the splenocytes, and the blood histocytes (Woolard).

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The *endothelial* cells, like the reticular group, are also fixed and wandering in so far as a certain number line the lymph and blood channels, while others are distributed throughout the body fluid and the tissues. They are mesenchymal in origin, and it is understood that they are responsible for the formation

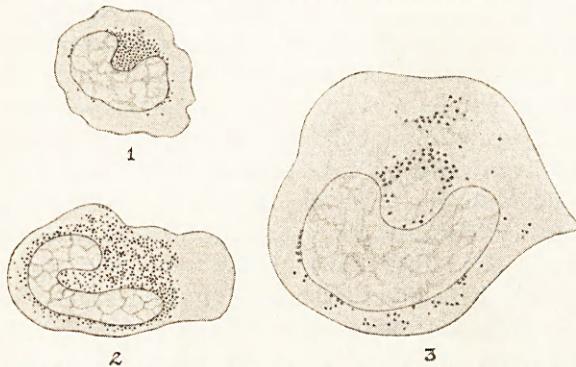


FIG. 23.—The maturation of lymphocyte, monocyte and *leucocyte* (Miss Sabin).

- (1) Monoblast from the spleen of the rabbit. Mitochondria small and clustered in the bay of the nucleus.
- (2) Monocyte from the bone marrow of the rabbit.
- (3) Monocyte from the peritoneal exudate of the rabbit. The mitochondria are blue and the neutral red granules red.

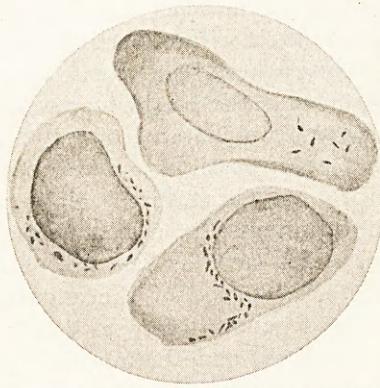


FIG. 24. Mitochondria as seen in scrapings obtained from a lymph gland.

of two types of cell, the fixed endothelial cells, progenitors of the red blood cells, while the wandering types are the source from which the phagocytic clasmacytocytes arise.

The Function of Lympho-Reticulo-Endothelium.—With this appreciation of the morphogenesis we may ask ourselves—What are the functions which the tissue group fulfils in the

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body economy? As far as the lymphocyte section is concerned there is evidence that the cells in this group are essentially protective in function—protective not by the phagocytic inclusion method observed in the polymorphonuclear leucocytes, but by a method which is chemiotactic and biochemical in its influence. The tissue invasion of the malignant cell with its associated lymphocytic reaction affords a striking demonstration of the process. The function of the reticulo-endothelial section is not yet fully understood. That it plays an important part in biochemical activities is evident when we consider its rôle in relation to liver structure and activities. It is abundantly clear that as macrophages the cells of this group are among the body's most important phagocytes, while it is evident that under conditions of certain stimuli they undergo a metamorphosis which results in the formation of such a variety of cells as the fibroblast, the epithelioid cell, and the giant cell.

It may seem as though the discussion had been carried into questions outside the sphere of pathology, but there has been a definite purpose in the diversion, and the time is now appropriate to link up the various side issues to which allusion has been made. An observer cannot fail to be impressed by the fact that the cytological pathology indicates a disturbance of the lympho-reticulo-endothelial tissues manifested by the appearance in these selective areas of numbers of immature cell types, and when we analyse these cell types, we find that they represent various stages in the life-history of the individual cell elements. For example, in the area of a lymph gland affected by lymphogranuloma it is possible to demonstrate the primitive cell types which precede the mature lymphocyte and also the cell types which represent the metamorphosis of which the lymphocyte is capable, such as the fibroblast. A similar demonstration can be afforded of the ancestral types and of the metamorphic or degenerative types which exist in relation to the reticular cell and the endothelial cell.

The point that we desire to make is that in analysing the pathology of a lymphogranulomatous lesion we are visualising the many-sided phases in the life-history of a lympho-reticulo-endothelial group of tissues from the primitive stages of the cell progenitors up to the terminal fibroblastic and alternately fibrous types of tissue reaction. The matter will be alluded to and presented in a more complete form when the historical aspects of the etiology have been discussed.

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A Discussion of the Etiology.—When one considers the immensity of the literature dealing with the problem of the etiology it seems a forbidding task to attempt any reasoned analysis of the position, but we anticipate that it will be sufficient for our purpose to present the various views in a series of questions.

Is the Condition a Form of Tuberculosis? — Sternberg⁴ appears to have been the first to promulgate this view, although it had previously been recognised that the association of lymphogranuloma and tuberculosis was not infrequent. His observations and experiments attracted much attention, and the claim received a measure of support from Ewing,⁴⁴ who pointed out that when an animal is inoculated with lymphogranulomatous material an interval of nine or even twelve months may elapse before the disease becomes manifest. Positive results following the inoculation of guinea-pigs with material from cases of lymphogranuloma were reported by a number of observers, among whom may be mentioned Sticker and Lowenstein,⁵ Baumgarten,⁶ Cignozzi,¹¹ and Schaeffer.¹² Negative results were recorded by Cieler and Rabinowitsch,⁷ Kraus,⁸ Labarsch,⁹ and Cunningham.¹⁰

More recently L'Esperance¹³ has aroused fresh interest in the question, for she has advanced the view that lymphogranuloma is due to the action of the avian bacillus. After demonstrating that the guinea-pig is naturally resistant to avian tuberculosis, six to eighteen months elapsing before the disease is evidenced, that the disease when it occurs is glandular in type, and that susceptibility can be increased by previous inoculation of the animal with killed human or bovine tubercle bacilli, she infected five chickens with an intravenous injection of an emulsion of lymph nodes from a case of Hodgkin's disease, and all the birds developed typical or atypical tuberculosis. A guinea-pig inoculated from one of the chickens developed tuberculosis, and from this animal an organism resembling the avian tubercle bacillus was isolated and cultured. L'Esperance added further evidence of a serological nature in support of her view that the disease is the result of an avian tuberculosis infection of an atypical kind. Van Rooyen⁴⁵ disputes these findings.

A further interesting suggestion in this connection has been put forward by F. W. Stewart.¹⁴ Recalling the recent work of Anderson demonstrating that the phosphatid fraction from the

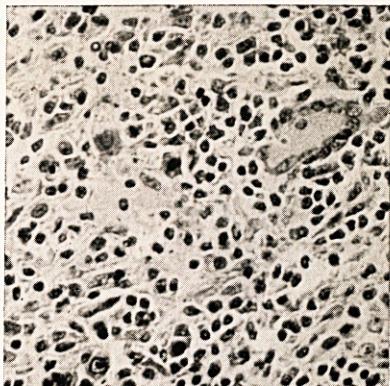
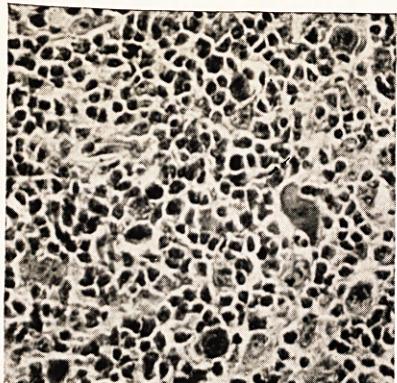
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lipoid of the tubercle bacillus when injected into normal tissue produces a reaction of epithelial cells and Langhan's cells closely resembling the tuberculous follicles, he asked: "Is it not possible that the phosphatid content of avian tuberculosis is the factor which originates the disease?"

While much careful work has been done on the question of the disease having a tuberculous origin, it is evident that two possibilities are apt to vitiate certain of the results which have been recorded, these being that the animal inoculated may have previously been infected with tuberculosis, and that the glandular material chosen as the injected medium may have been coincidentally the site of a tuberculous change. It is obvious how difficult it is to eliminate with certainty either or both of these possibilities, and yet they must be most rigidly excluded if results are to be above suspicion (Figs. 25 and 26, Plate III.). One is left with the impression that, if lymphogranuloma owed its origin to some modified type of tuberculous infection, it might be anticipated (1) that the organism would be recognised in the lesion in a certain proportion of cases, (2) that the cytology would show changes in some measure characteristic of tuberculosis, (3) that the experimental reproduction of the disease would be capable of fulfilment, and (4) that a certain proportion of cases would recover from the disease.

Is a Diphtheroid Infection the Exciting Cause?—It will be recalled that in 1910 Fränkel and Much¹⁶ isolated an organism from the glandular swelling of a case of lymphogranuloma which they found to be pleomorphic—non-acid fast but anti-formin fast. These observations were confirmed by Bunting and Yates¹⁷ and by De Negri and Mieremet.¹⁸ Bunting and Yates's work on the problem is often referred to, and perhaps the most significant of their experiments was that in which a group of five monkeys (*Macacus rhesus*) inoculated subcutaneously with a diphtheroid bacillus recovered from lymphogranuloma lesions showed glandular enlargement with cell changes resembling that disease.

These results appeared to carry conviction, but doubts were raised when Favere and Cobet²⁹ reported the finding of identical organisms in lymph glands from a variety of sources, both normal and pathological. Later Jukes and Jelinck³⁰ recorded the finding of an organism similar to that described by Much in three out of six cases of lymphogranuloma, and also in three instances out of eleven control cases. Then followed a period



Figs. 25 and 26.—Section of gland, the site of both Hodgkin's and tuberculous disease.
The photomicrographs are taken from the same section.

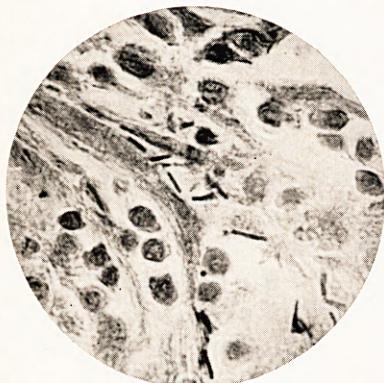
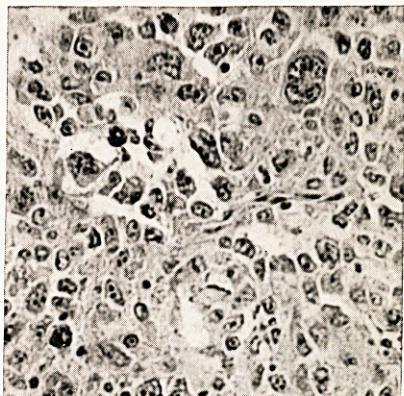
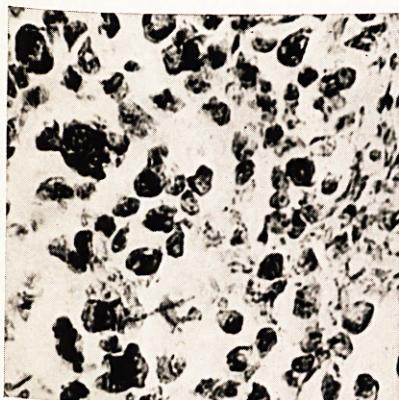


FIG. 27.—Hodgkin's disease showing organisms in the gland.



(By the courtesy of Col. Harvey, R.C.P. Laboratory.)
FIG. 33.—Malignant change in Hodgkin's disease.



(By the courtesy of Col. Harvey, R.C.P. Laboratory.)
FIG. 34.—Malignant change in Hodgkin's disease.

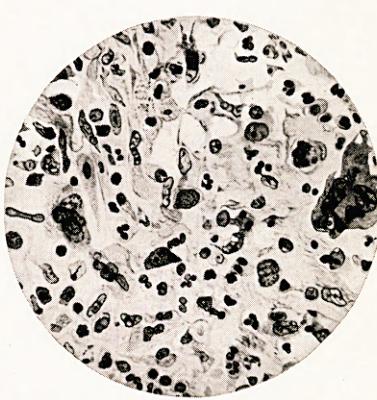


FIG. 35.—Diagram showing cell series present in Hodgkin's disease.

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of animal experiment, most of it directed towards the question of attempting to reproduce the disease on the assumption that, if it were due to a diphtheroid infection, its transmission to animals ought to be possible. This aspect of the problem was investigated by Torrey,¹⁹ Bloomfield,²⁰ Harris and Wade,²¹ Olitsky,²² Cunningham and M'Alpin,¹⁰ and Longcope.²⁴ The last named inoculated monkeys with diseased glandular material; two months later glandular enlargement was noted, but examination showed that the swelling had none of the characteristics of lymphogranuloma, and eventually it subsided spontaneously. In general it may be said that the animal experiments have yielded negative results. One of the last contributions on this matter has been by Stewart and Dobson,²⁵ who, in their own words, felt it appropriate to put this matter of the results of animal inoculation to further test, and accordingly carried out a group of experiments on three Macacus monkeys and on one Bonnet monkey. Their results were negative, but they drew attention to a feature which may explain previously recorded and supposedly positive results. In one instance a Macacus monkey, the glands of which had been inoculated with material from a lymphogranuloma case, developed a glandular swelling at the point of inoculation. Microscopical examination of the tumour revealed the existence of giant cells, but a closer investigation showed that they were of the foreign body type, and that the swelling was reactionary to the disturbance. We should add that a vaccine therapy was originated on the basis of a diphtheroid infection, and that satisfactory results were recorded by Billings and Rosenow²⁶ and by Hutchen and Lennox.²⁷

One further point of interest in this matter. The Pretsz-Nocard organism, one of the diphtheroid group, is apparently responsible in animals for a generalised glandular enlargement, but the glandular change has none of the histological characters of what we regard as lymphogranuloma.

In reviewing the evidence on the question of a diphtheroid origin we must recognise that, while it appears to be established that when portions of lymphogranuloma glands are implanted upon Loeffler's medium or upon Dorset's egg medium, and the tubes so inoculated, sealed and incubated for about ten days, a scanty growth is obtained, such a demonstration is no proof that an organism of the diphtheroid class is responsible for the development of the disease. The only inference we are at

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liberty to draw is that, when glands are affected by a lymphogranulomatous lesion, they are apt to harbour organisms of various types (Fig. 27, Plate III.), probably on account of the tissue reaction and disturbance which the gland manifests, that, in other words, the gland has largely lost its protective function, so that, instead of being both receptive to and destructive of organisms, it is now merely receptive. We have been able to afford microscopical proof of the frequency with which micro-organisms can be displayed in a gland affected by the process of a lymphogranulomatous disturbance.

Some Further Infective Possibilities.—There are some who believe that the origin of the disease will be found in one of the fungoid group. This view has been expressed by Dias,³³ who holds that the lesion arises from a mycosis infection. Gordon²⁸ in a recent suggestive article put forward some interesting questions on the same lines. He recalled the granulomatous tumour that arises from the action of such widely different sources as the tubercle bacillus, certain types of spirothrix, and *Torula histolytica*, and the white mould *Coccidiodes immitis*. He reminded us that, when the disease is investigated with a view to a fungoid etiology, certain special considerations must be kept in view, as, for example, that cultural results may be very sparse, that incubation at room temperature is probably demanded, and that growth may be considerably delayed.

Gordon²⁸ put forward the further interesting possibility that the disease may be due to the action of a virus, conceivably one akin to that which produces the Rous sarcoma, or even such types as the vaccinia virus or the herpes. These are interesting and suggestive possibilities, but, while it is conceivable that one or other may hold the key to the solution, such views are either hypothetical or they are based upon observations which remain to be confirmed.

It is not surprising that the ubiquitous streptococcus has been held in suspicion as the infecting element, and we find that Poynton and Moncrieff⁴⁶ record certain cases in which a streptococcal infection resulted in lesions comparable to those described in lymphogranuloma. The view is expressed that when a certain type of streptococcal infection is encountered the results will vary according to the resistance of the individual. Certain conditions of virulence and resistance result in septicæmia, in other cases lesions similar to those of lymphogranuloma arise.

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The existence of inclusion bodies in certain cells characteristic of the disease has recently been described. Kuczyinski and Hanck³¹ claim to have demonstrated such bodies in the Dorothy Reed cells (Sternberg's Reizensellen), and they regard them as characteristic of the disease. From a pathological standpoint they consider that these cells are *Virus Zellen* or disease carriers, and that the inclusion bodies demonstrable in their interior are a type of Pilzinfekteon, a higher type of bacteria in a class between tubercle bacilli and the organisms of actinomycosis. Their papers are illustrated by representations of these bodies, and no doubt further work will be done in investigation of their claim.

A filamentous pleomorphic bacillus has been isolated from lymphogranuloma glands by Boot.³⁴ The organisms have been described as an anaerobe growing on glucose agar and ox serum. It stains well with aniline dyes, it is non-acid fast, and is inconstant in its reaction to Green's stain. No inoculation experiments have been carried out, and, in view of the readiness with which organisms of various types are encountered in lymphogranuloma glands, it is more than likely that this organism is an accidental and non-pathogenic occurrence.

Are there Parallels in Comparative Pathology?—It might be anticipated that if the disease has an infective basis, it would have comparable manifestations in animals, and particularly those who live in association with man. As a matter of fact Hodgkin's disease (lymphogranuloma) has been described in the pig (Hodgson³⁵), in an Aberdeen terrier (Simons³⁶), and in horses (Reid³⁷ and Holiday³⁸). None of the cases, however, has been authenticated, because the diagnosis was either based on physical examination without microscopical confirmation, or the microscopical examination when carried out did not confirm the diagnosis. Wooldridge³⁹ has described a diffuse lymphadenitis in dogs, but the condition is in no way comparable to human lymphogranuloma, and, so far as veterinary science is concerned, no proven cases of lymphogranuloma in animals has ever been recorded.

Is the Disease a Type of Tumour Formation?—It is interesting to recall that it was the view of the older pathologists that the disease under discussion was of the nature of a tumour formation, and it was Ebstein who first questioned this theory, and instead advanced the claim that the origin was infective. To-day the pendulum tends to swing back to the original point, partly

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because the various claims of an infective origin have remained unsubstantiated, and in the recent literature the tumour theory is receiving increasing support. It is unnecessary to review the literature in detail, but attention may be drawn to important contributions by Warthin,⁴⁰ Levin,⁴¹ M'Junkin,⁴² and Medlar.⁴³

Warthin believes that lymphogranuloma is a neoplastic condition in the same class as the aleukæmic and leukæmic lymphoblastomata and mycosis fungoides. He holds that these are transition types depending upon the degree of differentiation of the tumour cells and the organ or tissue involved, the tumour originating from the perivascular reticulo-endothelium, the originators of the original lymphoblasts. In the case of the lymphogranuloma the neoplasm originates in the perivascular reticulo-endothelium, while the leukæmic and the pseudo-leukæmia arise from the more fully differentiated maternal lymphoblasts.

Levin advances very similar views. In the course of his paper he says, "Both lymphosarcoma and malignant lymphoma (Hodgkin's disease) begin as a purely local condition in one lymph node. In the lymph node either the lymphocyte or the reticular cell or both acquire the characters of a cancer cell."

M'Junkin draws an interesting comparison between the histopathology of the Rous chicken sarcoma No. 1, and the Hodgkin granuloma. After stating that the principal reacting cell of Hodgkin's granuloma appears to be identical with the monocyte of the blood, and that the blood monocyte is itself a derivation of the reticular cells of lymphoid tissue, he concludes, "Since the type cell of Hodgkin's granuloma corresponds very closely to monocyte derivations, the chicken sarcoma resembles the Hodgkin's granuloma and is unlike the usual fibro-sarcoma."

Medlar, while a supporter of the neoplastic theory, holds that the primary lesion of Hodgkin's disease is in the bone marrow, and that the condition is really a malignancy of the marrow, the condition arising in a parent cell which is probably multipotential and the originator of various types of marrow cells. This multipotential cell takes on an erratic growth and subsequently wanders into other parts of the body.

Our own experience leaves us in no doubt that the tumour view has much to support it, and we are convinced that only such a conception enables us to understand rationally the profound disturbances of the life-history and economy of the lympho-reticulo-endothelial cells. In how far does such a view

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explain the many problems, clinical and pathological, associated with this condition?

When we consider the pathological picture in the first stage of the disease we recognise that the essential feature is one of multiplication of the cell elements without loss of differentiation or gross disturbance of cell proportions. We have further been interested by the fact that, except in relation to the reticulum cell, mitosis is infrequent. We believe that this phase is essentially one of neoplastic growth, but that as yet the process is a benign one, showing accordingly full differentiation and little evidence of marked proliferation. The actual cell which has undergone this tumour change is the reticular cell, and, since

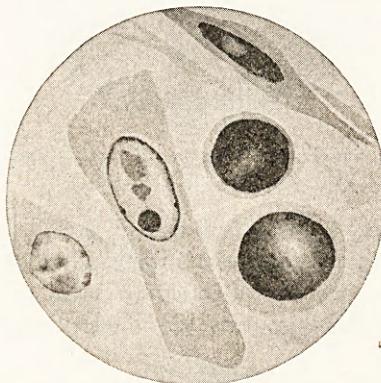


FIG. 28.—Reticular cell. Diagram showing characteristic features of the different cells.

it is the progenitor of both the lymphocyte and the endothelial cell (Maximow⁴⁷), proliferation with differentiation does not lead to any gross disturbance of the relative numbers of cell units of the different types. This polymorphism is a feature which in no way invalidates the assumption that the condition is a neoplasm, for analogous instances may be cited. The teratoid tumour of the testis is an outstanding example, and the explanation generally accepted of the gross diversity of tissue found is that the process is one of proliferation with differentiation of a totipotential cell. We have further evidence of the benign nature of the lesion at this stage in the absence of infiltration by the proliferating cells of the gland capsule (Fig. 28).

With the onset of the second stage the picture changes. The fully differentiated cells become associated with others of

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a less perfect development, and representing the various stages in the life-history of the mature forms. This stage in the disease is characterised also by evidence of greater mitotic activity and we regard it as a transitional phase of the process

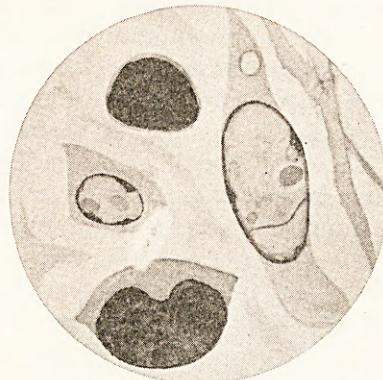


FIG. 29.—Cell series present in Hodgkin's disease. (Note the lymphoblast and reticular cells.)

towards malignancy. Miss Pullinger²³ has drawn attention to the development in this stage of fibrils which she believes may be regarded as the product of reticular cells.

In addition to the immature forms of cells, other cells appear

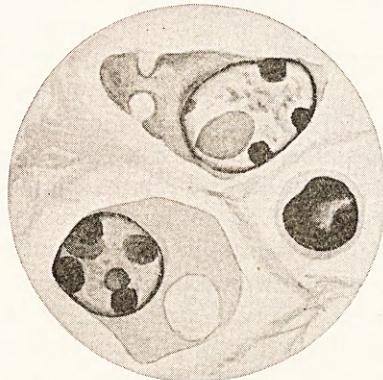


FIG. 30.—Cell series present in Hodgkin's disease. (Note the monocytes.)

as the condition progresses, and the significance of these is not as yet fully known. These are the Dorothy Reed cell and the large mononuclear cell (Fig. 29). These both arise from the reticulum of the sinuses, and in many instances transition stages

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have been observed (Figs. 31, 32). The frequency with which they appear varies within wide limits, and, while they are absent in the earliest phases of the process, their presence is characteristic of the disease. Indeed, it is apparent from a

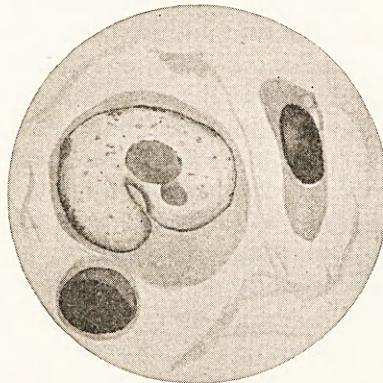


FIG. 31.—Cell series present in Hodgkin's disease. (Note the monocyte, lymphocyte and endothelial cell.)

histological study of the condition that the production of these cells is not incidental, but is an inherent and characteristic expression of the disease process.

The significance of these giant cells has been the subject

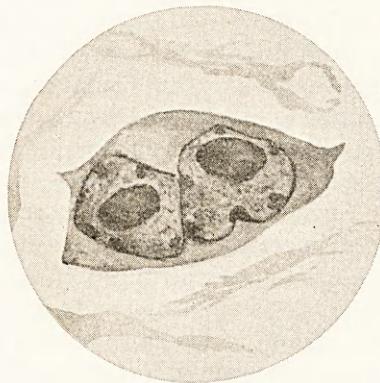


FIG. 32.—Cell series present in Hodgkin's disease. "Dorothy Reed" cell.

of divergent theories, for they have been compared, on the one hand, to the giant cells found about foreign bodies and in tuberculosis, while, on the other hand, they have been held to represent the end result of atypical intracellular nuclear division,

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such as is seen in true neoplasms. We have been unable to satisfy ourselves fully as to their precise economy, for, while we cannot subscribe to the view that they represent specific reaction to a causal infective agent, we must recognise that their appearance coincides with a phase during which there is a definite toxic influence, and that their advent is simultaneous with the appearance of an eosinophilic reaction.

The similarity between the Dorothy Reed cell and the normal megakaryocyte, however, is striking—a feature to which Medlar has drawn special attention. The view that the Dorothy Reed cell is of this nature is strengthened by the fact that the megakaryocyte is itself derived from the reticular cell (Schafer).⁴⁸ The evidence at our disposal therefore indicates that the Dorothy Reed cell is most probably the result of the atypical proliferative activity of the reticular cell, and that its appearance in the later phase represents the increasing deficiency of normal control of the mitosis of the progenitors of the lympho-reticulo-endothelial series. This behaviour of the process, then, in so far as we have observed it, is strictly in accordance with the general principles of oncology.

The picture may, however, proceed still further, and in the cases which come under review in our series we have two examples of a final degree of increasing alteration, and the further change is one of an unmistakably malignant tumour growth.

The relationship of Hodgkin's disease to true neoplasms has long been the subject of study, and many instances have been recorded of undoubtedly examples of lesions in which the characteristic pictures of lymphogranuloma and "sarcoma" co-exist (Figs. 33 and 34, Plate III.). To these cases must be added the less certain cases in which the picture is more uniform, in which there is the most intimate blending of histological features, and in which there appears to be superimposed on the characteristic changes of Hodgkin's disease a secondary neoplastic growth. Ewing⁴⁴ appears to be of opinion that the sarcomatous structure seen in such cases is the terminal stage of Hodgkin's disease, and this view is expressed by many other writers.

Case No. 9 in our series would fall into this group, for, in addition to sections revealing a more or less typical picture of Hodgkin's disease, there were sections obtained in which the tissue was composed of relatively large round cells with scanty granular cytoplasm and large, somewhat irregular nuclei. In

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such areas the giant cells and lymphocytes were largely, but not wholly absent, and the picture was essentially one of a large round-cell sarcoma. According to Ewing, such "sarcoma" cells are derived from the endothelial cells, and with this view our own studies are in accord.

Another type of malignant degeneration was exemplified in Case No. 10. The main points of significance from the pathological aspect were that disease commenced as an enlargement of the axillary glands which histologically were proved to be typical lymphogranuloma. The disease, however, progressed, and the patient developed evidences of intestinal tumour formation. As in Case 9 the histological picture presented by these later tumours was a complex one. In some parts the histological appearances were unequivocally those of Hodgkin's disease, but in other parts the tissue was almost wholly composed of immature fibroblasts, with here and there a distorted though plainly recognisable Dorothy Reed cell. The recognition of such malignant forms of Hodgkin's disease is so frequent as to rule out the possibility of mere coincidence, and the nature of the relationship of the frankly malignant process with that of the typical lymphadenoma requires consideration.

We have already dealt at some length with the genesis of the various cell types found normally present in lymphoid tissue, and have expressed the belief that in the characteristic picture of Hodgkin's disease the multiplicity of cell types is to be regarded as differentiation associated with neoplastic proliferation of a relatively benign nature (Figs. 35, Plate III., and 36). Alteration from a benign to a malignant process may result in dedifferentiation, but it is also recognised that where the neoplastic change is affecting not one cell type but several the malignant change may be predominatingly manifest in one or other cell type. In this respect we believe the analogy between Hodgkin's disease and teratoid tumours of the testis is further borne out, and it is our belief that the varied malignant types of Hodgkin's disease as described above and as reported in literature may best be comprehended as a unilateral malignant process superimposed on a simple multicellular tumour.

The Fibroblast.—More commonly found than malignant degeneration in Hodgkin's disease is the transition to a terminal phase of fibrosis. The significance of this phenomenon is the subject of divergence of opinion, as indeed is the origin of the cells which predominate. Throughout our study of the

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subject we have been impressed by the fact that in every phase the disturbance is one of cells derived from a common parent by a process of proliferation and differentiation.

While it is true that the fibroblasts may be derived from the connective tissue about the lympho-reticulo-endothelial elements, it is no less true, and indeed is usually demonstrable, that there is a direct transition of reticular cells into fibrous tissue. The importance of this feature cannot be overlooked, for it implies that the terminal fibrosis is not solely secondary reaction of surrounding tissues to an irritative factor, but is an integral part of the essential primary process. We have to conclude, therefore, that whatever the nature of the disturbance

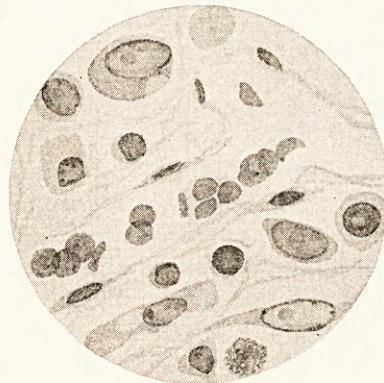


FIG. 36.—Relation of the endothelium of capillaries to the cellular elements of Hodgkin's disease.

within the reticular cells may be, the production of fibrous tissue is the direct result of its influence.

The presence of fibrils, however, is not confined to the late stages of the disease, although it is the predominant feature at that period (Pullinger). It is our view that the fibrous tissue formation represents one aspect of the process of differentiation. The fibroblast is the terminal "fixed" product of reticular cell proliferation, and its predominance is due in the later stage of the disease to, not a sudden metaplasia of reticular cells, but to the gradual accumulation of "stable" cells and the disappearance of the unstable elements.

Disturbances of Lymphatic Function.—The protagonists of the granuloma theory of the nature of Hodgkin's disease have always demanded that due attention must be paid to the clinical manifestations as well as the histological changes. The

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eosinophilia, the recurrent pyrexia, and leucocytosis, are features suggestive more of toxæmia than tumour growth, and any theory of the nature of the disease must satisfactorily explain these phenomena. The function of lymphatic glands has already been indicated, and we would again stress their economy. The afferent vessels collect the body fluid from the tissue spaces, and, charged with end products of metabolism and other toxic materials of possibly bacterial origin, convey it to the lymph gland. Within the gland a filtration of the lymph takes place, the toxic products being to some extent detoxicated and neutralised. In addition, the efferent lymph is reinforced by additional lymphocytes.

Are these functions normally maintained when the profound disturbances of Hodgkin's disease are present? Before commenting on this problem, let us inquire into the actual cause of death, for the study demonstrates some features of significance.

We may dismiss as obvious those cases which succumb to the secondary mechanical disability due to actual enlargement of glands or involvement of a vital organ with suppression of its function, and those cases which, passing on to a malignant phase of the disease, exhibit all the clinical manifestations of a rapidly spreading neoplasm. Such cases, however, only form a small part of the total, and there remain a majority in whom the cause of death is different. The clinical features have been enlargement of successive groups of glands, and these have been improved by treatment, and yet, in spite of all therapeutic measures taken, there develops a progressive æsthenia, occasional attacks of pyrexia (Pel-Ebstein waves), increasing secondary anaemia, and loss of weight. The blood-picture varies and may show either a leucocytosis or a leucopenia, and increase of the eosinophil count may be observed.

We believe that the explanation of this problem of toxæmia (for such it must surely be) lies in the loss of the filtrative action of the lymphoid tissue. The Pel-Ebstein waves represent exacerbations of absorption into the general circulation of the toxic products of metabolism as the lymphoid tissue of the body becomes increasingly involved in the disease. This view is not irrational, when we consider how profound and widespread within a lymph node is the replacement of normal elements by abnormal and presumably aphysiological cells.

The histology of the diseased tissue is also suggestive. It

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will be remembered that the appearance of the eosinophil cell is not an early feature of the disease; its appearance occurs only after the normal cells have been replaced by immature forms. By some authorities it has been suggested that these cells are themselves derived from the proliferating reticular cells, but it would be a strange phenomenon were this production of the highly specialised eosinophil cell to be simultaneous with the gross immaturity and abnormality of the other progeny of the reticular cell, and in this connection the Biblical question might well be asked—"Can the same tree bring forth both good fruit and bad?" We have been forced to the conclusion that the presence of the eosinophil cells is a secondary infiltration in response to a specific form of toxin, and if so what is the nature of the toxin? It is recognised that eosinophilia is of significance in parasitic diseases, and in certain virus diseases, but we suggest that the reaction seen in lymphadenoma is rather allied to the eosinophilic reactions to protein toxins as seen in anaphylactic states.

One other factor which may well play a part in this phase of the disease is the secondary invasion of the gland by organisms. The loss of the phagocytic and antibacterial function of the gland elements must surely predispose the organ to the invasion of bacteria, and the presence of purely inflammatory cells which are occasionally found may be explained on this basis.

The Extension of the Disease.—It is a well recognised fact that Hodgkin's disease is initially localised to one group of lymphatic glands, and Levin⁴¹ asserts that the disease begins as a purely local condition in one lymph node. This fact was well demonstrated in a recent case. The patient was a young man admitted to the surgical wards after investigation in the medical wards with a history of progressive intestinal obstruction. At operation an ulcerative tumour of the ileum was found a few inches proximal to the ileo-caecal valve. It was associated with enlargement of the mesenteric glands, but the special feature to which attention was drawn was that, although the whole abdominal lymphatic system was reviewed and examined the distribution of demonstrable lesions was strictly localised. The spread, however, from the primary focus is rapid, a feature which is borne out by the failure of local excision as a therapeutic measure in even the earliest cases. It may be argued that this is an evidence of malignancy, but on the other hand it must be remembered that the cells affected

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are not "fixed" cells. To quote Levin, "Since these cells are very mobile, they are immediately transported into other regions throughout the organism." The metastases, however, are limited in the earlier phases of the disease to those parts where lympho-reticulo-endothelial cells are normally found ; even in the late phases of the disease it is characteristic that the secondary organs affected are those which contain endothelial cells, and in this respect the phenomena of Hodgkin's disease are comparable to the multiplicity of the lesions in multiple myelomatosis.

Which Cell is Primarily Affected? — In the foregoing paragraph we have attempted to express our views on the nature of Hodgkin's disease, and explain the clinical and pathological phenomena which are exhibited. In conclusion it is necessary to consider briefly the cell which is primarily affected.

We interpret the complexity of the histological picture as due to a process involving differentiation, and it is therefore our thesis that it is multipotential cells which must be regarded as the site of the obscure change associated with the origin of tumour growth.

The researches of Miss Sabin have been already alluded to. She has shown how the lymphocyte and the endothelial cell may be traced to the reticular cell. This view is supported by Maximow and others, and it has been emphasised that the reticular cell, in contradistinction to the endothelial cell, is endowed with multipotential properties. Our investigation has indicated that it is this cell which is most probably the primary site of Hodgkin's disease.

The view that Hodgkin's disease is a true neoplastic process, local in origin, and spreading thence throughout the organism has been ably advanced by Warthin.⁴⁰ He regards the condition as being in the same class as a leukæmia and leukæmic lymphoblastomata and mycosis fungoides. In his opinion the tumour originates from vascular reticulo-endothelium, although in this connection it should be pointed out that Maximow sharply differentiates between the reticulum of the sinuses of lymph nodes and the endothelium lining vascular and lymphatic channels. Medlar,⁴³ on the other hand, asserts that in all cases the primary error is in the bone marrow, and he attributes the specific histology of Hodgkin's disease to the peculiar features and potentialities of the megakaryocytes.

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The close relationship of Hodgkin's disease to lymphosarcoma, while stressed by many writers, has as yet not been fully shown, and until further evidence of a more definite nature is forthcoming, the precise nature of the disease must remain unproved.

Other Evidences of a Neoplastic Nature.—So long as the exact nature of what constitutes neoplasia and the influences which initiate the change are unknown, so long must the criticism of those who adhere to the neoplastic origin of lymphadenoma be guarded in regard to the experimental study of that disease. The experimental researches which have been carried out have been chiefly along two lines, those calculated to demonstrate the presence or absence of a causal organism and those attempting to reproduce the disease by transplantation of tissue.

The enormous volume of literature has already been briefly analysed, and it may be stated that the results of bacteriological investigation are essentially negative. The multitude of organisms described, the inconstancy of their presence, and the inability of observers to exclude the possibility of such bacteria as may be found being purely coincidental are features which may be stressed. M. H. Gordon,²⁸ in his summary of the bacteriological investigation of Hodgkin's disease states:—"The possibility mentioned that a search for micro-organisms might prove unsuccessful in solving the problem of its etiology has been realised."

The attempt to transmit the disease to animals by transplantation of diseased tissue has proved no more successful. The suggestion that the implantation of lymphadenomatous tissue is followed by the occurrence of tuberculosis after a prolonged interval is open to the most serious criticism, for in no instance has the possibility of subsequent or coincident transmission of the tuberculous infection been adequately excluded. In no authenticated case, however, has the implantation of tissue been followed by the development of the typical lesions of Hodgkin's disease. The position has been reviewed by C. C. Twort,⁴⁹ and his conclusion is that "so invariably did the different procedures we adopted lead to nothing that one might have been dealing with a true new growth instead of what is generally accepted to be a granuloma."

The Treatment of Hodgkin's Disease.—The methods of treatment of this disease are as varied as the theories of its etiology. The number of therapeutic agents suggested the

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diversity of their nature, and their transient popularity are evidences of their inability to arrest the course of the process.

It is convenient to group the various measures according to the general underlying conceptions of the disease.

1. *Those advanced on the Assumption that the Disease is a Granuloma.*—The administration of *salvarsan* has been advocated on the analogy of the effect of this drug in prolonged and spirochætal diseases. Such benefit as may accrue, however, may also be obtained by the use of simple arsenical preparations and the therapeutic value appears to be less due to any specific action than to the general tonic effect.

Kofoid, Byers and Swezy⁵⁰ described the occurrence of the entomœba dysenterica in association with Hodgkin's disease, and they advocated the administration of *emetine*. We have employed the drug in two cases, but without appreciable effect.

The value of *vaccines* has been tried by various writers. Wallhouse and Whitehead⁵¹ have recently employed an auto-gogenous bacteria-free extract, and report a short series of cases with apparent improvement.

2. *Methods advanced Empirically.*—The administration of *colloidal preparations of metals* has been suggested from time to time. Our experience is limited to the use of colloidal copper in two cases, and the results being unsatisfactory we have not felt justified in using this method further.

3. *Methods advanced to deal with a Neoplastic Lesion.*—On the assumption that the disease is essentially neoplastic and initially localised, *excision of the affected glands* has long been practised. Whatever may be the value of this method as a local palliative measure, the ultimate fatal issue of the disease is not averted, recurrence either locally or in another site being inevitable. Indeed, it has been our experience that, far from being a beneficial procedure, except in so far as it is urgently required for local mechanical disturbance, the course of the disease is accelerated by the interference.

The results of *irradiation* are more successful. Desjardins⁵² has pointed out that the lymphoid cells of the spleen and of the lymph nodes and the circulating lymphocytes are, next to the genital glands, the most highly radio-sensitive structures in the body, particularly if the cells are in a state of hyperplasia. The influence of X-ray therapy or of radium applications is striking. Early and considerable shrinkage of the lymphatic

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tumours is often dramatic, and it is our experience that this method or therapy not only ameliorates the local condition but also improves the general one. On the other hand, while suffering is alleviated and life prolonged, we are not yet satisfied that we have obtained complete arrest of the disease. Of five patients treated by this means only one has survived after a period of nearly three years.

X-ray therapy is indubitably superior to radium applications, because, while both give satisfactory local improvement, X-ray therapy is more generally applicable, and enables more widespread irradiation of the body region to be carried out.

In one instance a type of *autogenous tumour extract* was used as a means of treatment. A group of glands removed at operation was emulsified under aseptic conditions, and the filtrate injected intramuscularly in amounts beginning with 1 c.c. and increasing to 10 c.c. It was our impression that improvement followed this therapeutic measure, although we realise that our judgment in this matter may have been rather prejudiced. The reports and observations were certainly encouraging up to the time when death occurred suddenly from what appeared to be angina pectoris, and unfortunately no post-mortem examination was possible. We think there is room for further investigation of the therapeutic possibilities on these lines.

In the three most recent cases which have come under our observation we have employed a combination of deep X-ray therapy with injections of Coley's fluid.⁵³ This method of treatment has not yet been employed in a sufficiently large series of cases, nor has the progress of the patient been observed over a sufficiently long period of time to enable us to come to any definite opinion as to the value of this method of treatment. It is our impression, however, that the local response to the radiation has been more rapid in these latter cases than where radiation was used as the sole therapeutic agent.

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