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PREFACE.

This thesis represents a record of investigations carried out by the candidate in the University Department of Bacteriology during his tenure of appointment as University Assistant.

It consists mainly of his own experimental findings and no attempt has been made to summarise or abstract the views of other writers. Current literature contains many excellent summaries of previous work published on this subject and reference is being made to these. Although such reports furnish complete accounts of the historical, clinical and pathological aspects of lymphadenoma yet very little indeed is known about Thomas Hodgkin himself.

Few realise that he was a distinguished graduate of Edinburgh University, a member of the Royal Medical Society, an able classical scholar and a philologist. Furthermore, that he was responsible for having founded the Pathological Museum in Guy's Hospital Medical School and described a variety of different morbid conditions other than that which perpetuates his name. Lack of interest in his work is evidenced by the fact that during a survey of the original literature, the writer encountered an article by Samuel Wilks on the life of Thomas/
Thomas Hodgkin that had been published in 1877 and the pages of which had been unopened for the last 57 years during which it had lain in the University library.

The candidate has therefore decided to precede his account of experimental work on the etiology and diagnosis of Hodgkin's disease with a few remarks on the life of Thomas Hodgkin the morbid anatomist, and some early accounts of Hodgkin's disease.

The thesis has been illustrated by the author's own photographs.

ACKNOWLEDGEMENTS.

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NOTES ON THE WORK OF THOMAS HODGKIN THE MORBID ANATOMIST.

Thomas Hodgkin was born at Tottenham, England in 1798 and completed his course of medical study at Edinburgh, by obtaining his M.D. degree in 1823 with a thesis titled "de Absorbendie Functione". The work is written throughout in Latin and reveals the observations of a keen student of medicine expressed with the art of a classical scholar. The thesis was commended by the University authorities and is dedicated to George Baird, Principal of the University, Alexander Humboldt and Thomas Hodgkin (Snr.) S.P.D., and also to Andrew Duncan (Jnr.), to whom Hodgkin owed a debt of gratitude for having attended him during his attack of scarlatina contracted while a student, and whose resident house-physician he subsequently became.

The text contains frequent references to many eminent medical men at that period - such as Astley Cooper, Abernethy, John Hunter, Boerhaave, Dupuytren and others, including the unhappy Dr. Knox whose views the author regarded with great esteem. The conclusions reached by Hodgkin indicate that he regarded many diseases/
diseases to be the direct outcome of disorders affecting the lymphatic and absorptive system of the body.

Hodgkin was a member of the Royal Medical Society of Edinburgh and an ardent supporter of the Society of Friends whose characteristic dress he often wore. Accounts indicate that much of his time was spent abroad, where he studied principally in France, under Laennec at Hôpital Necker, Rostan at the Salpetrière and Professor Anstral then a student, at Hôpital de la Charité. He also received instruction in Italy and many of his accounts relating to the dawn of medical science in that country prove to be of considerable interest. Many and varied were his foreign qualifications, he was a Member of the Lycean Academy of Rome, the Geoenian Society of Catania, the Iatrophysical Society of Palermo, and the Medical Society of Ghent.

VALUE OF MORBID ANATOMY.

Hodgkin realised the importance of the study of pathology from an early date and repeatedly stressed the value of cadaveric inspection as an aid to the study of disease. Some indications of the lack of interest shown by medical students in London at that time with regard to post-mortem examinations is revealed by Hodgkin in his remark quoted by Wilks (1878).

- "The present meeting on this account appears to offer a favourable opportunity for me to express my regret that/"
that so small a number of the gentlemen who are seeking their education in this city are deriving the advantage which they might obtain from the practical acquaintance with Morbid Anatomy to be gleaned from the inspection of the patients who die in the hospitals".

Dealing further with Morbid Anatomy during the time of the ancient Egyptians he states that "those who, whether as priests or physicians, had to perform the office of embalming the dead must have had innumerable opportunities for having acquaintance with Morbid Anatomy. From the Egyptians it is highly probably that Hippocrates derived many ideas, not only respecting our internal structure but also respecting the alterations produced by disease; for although he has not given us the details of inspections it is evident from many of the terms which he employed that he was not wholly unacquainted with the morbid affections of internal parts".

Although the study of pathology was little encouraged at the time and those engaged in it very poorly paid for their services, we cannot help but admire the sentiments of a man whose love for his work led him to choose this comparatively unremunerative branch of the profession in preference to the more lucrative occupation of the practice of medicine.

The following paragraph quoted from his book on "The Morbid Anatomy of Mucous and Serous Membranes" expressed/
expressed his views in no uncertain manner.

"To those who may place the *summum bonum* of medical practice in converting the largest quantity of physic into gold, morbid anatomy must, I am aware, be an object of disgust rather than of attraction; but those who are aspiring to become worthy members of the profession which has for its object the restoration of health to our suffering fellow creatures, and of which it has been said, in the words of Cicero: "*Hominem ad deos nullus re proprius accendunt quam salutem homnibus dando*" must see that morbid anatomy, or the investigation of those physical derangements which as the consequences of disease or accident it is their business to avert or remove, constitutes a study the most essential to their art".

He concludes with the following words: "I cannot but admire the remark of Hogarth, when he says that "those students who confine their studies to the works of the dead need never hope to live themselves". Among his less known works were an essay on Medical Education in 1823, a paper read to the Hunterian Society in 1827 dealing with the state of the pulse in aortic insufficiency that antedated Corrigan's classical description by no less than 5 years and which will be referred to later.
TRANSLATION OF A FRENCH WORK.

We owe to him the English translation of the French volume by Dr. W.F. Edwards, M.D., dealing with "The Action of Physical Agents on Life", in which are also incorporated "Some Observations on Electricity" by Dr. Edwards, M. Pouilliet and Luke Howard, F.R.S., "The Microscopical Characters of Animal Tissues and Fluids" by J.J. Lister, F.R.S., and Dr. Hodgkin, also an article by Hodgkin himself on absorption and uses of the spleen. The writer can offer no greater testimony to the value of his work than to quote the words used by the Editor of the Edinburgh Medical and Surgical Journal who reviewed the book in 1833 and stated that - "The well known character of Dr. Hodgkin as a zealous anatomist and pathologist, and a physician who studies to keep pace with the progress of science in all departments, is a sufficient testimony of his competency for the duty of expounding the doctrines of Dr. Edwards to the English readers." The reviewer continues to praise the work further with the remark that "on the present occasion we adduce the example of Dr. Hodgkin as one which reflects equal credit on the original author and his interpreter - - - ."

AN EARLY TREATISE ON PATHOLOGY.

In 1836-40 he published in two volumes his work on
"The Morbid Anatomy of Serous and Mucous Membranes"; the book which was printed in London, is regarded by the historian McGarrison as being the earliest English treatise on Pathology, and was adjudged by Samuel Wilks of London to be the first book which treated the subject of pathology from the philosophical point of view.

In a lengthy preface to the volume the author explains that he has chosen the morbid anatomy of the serous membranes since they are the first to present themselves in the embryo. Furthermore, "Nature seems to delight in the production of reflected membranes, a form which many of the serous membranes present."

He also makes a passing comment on the existence of professional jealousy at the time by an appeal for more liberal feelings towards one another among men engaged in research and states that "The investigators of truth if at all successful in their labour must arrive at the same conclusions although their researches may not have had any connection with one another. Nor ought we to regard with dissatisfaction the labours of our foreign brethren as if nothing remained for us to do — The temple of science is founded upon a neutral territory to which no age and no nation can lay a particular claim."

**VIEWS OF CURRENT PHYSIOLOGICAL PROBLEMS.**

Although the science of physiology was still in its infancy/
infancy and problems such as the factors which led to a change in the colour of the blood, were matters of topical interest and an unsettled problem, yet the views held and voiced by Hodgkin were later found to be correct.

Thus he attributed the red colouration of the blood to the presence of iron and a peculiar animal principle called Haemostroin, and continues to say that "the translation from arterial to venous blood is, I conceive, with great probability ascribed to the addition of carbonic acid to the arterial blood" and also that the black colour of blood was due to retardation, for he says "I see no reason to recede from that opinion since the cases in which it is met with seem without exception to favour it".

His speculations concerning the black colouration of bronchial glands were equally correct for he thought that "they were not due to the blood as the glands received a very little"; he does not venture to suggest, however, what the colouration was due to, but adds that the condition was extremely common and was "scarcely an abnormal finding". Full of information, Hodgkin draws attention to the nervous factor concerned in discolouration of the skin by citing a case quoted by Professor Rostan from a tale of the French revolution concerning a terror-stricken woman, who was sentenced to the guillotine, but was later reprieved and who ever afterwards showed/
showed a dark discolouration of her skin which persisted up to the time of her death.

Regarding changes in the colour of the skin in other conditions such as Chlorosis, Icterus and Melanosis, he reveals his wisdom in attempting to solve the problems of human pathology by reference to comparative medicine by stating that Melanosis has been known to occur in the horse, dog, rabbit and bird and the terms ardea and leucardia applied.

PREVAILING VIEWS ON THE AETIOLOGY OF CANCER.

Accounts indicate that the aetiology of Cancer was as much a subject for debate in 1833 as it is to-day, with the exception that apparently the exponent of each theory expressed his views with such certainty as though he had arrived at a solution of the problem.

Thus Leenec and Beclard supported by John Hunter stated malignant tumours to be entirely new growths, while on the contrary Dupuytren and Cruveillier believed them with equal certainty to be the outcome of tissue degenerations. Professor Carswell of London maintained that they were due to an alteration in the nutrient fluids of the body, a theory which evoked the pertinent remark from Hodgkin who asked "how is it that the peccant humour confines its mischief to one spot and performs the function of good and healthy food elsewhere throughout the body?"

Even at this very early date there was no lack of adherents/
adherents to the theory favouring the infective origin of malignant disease, for Dr. John Hunter of the West Indies supported by Drs. Adams and Baron said that it was due to a vesicular worm of Hydatid origin, which they named the *Hydatis carcinomatosa*. This hydatid he describes as composed of a cyst with its contained fluid and the cancerous fungi the appendices of the animal. The causation of pulmonary tubercles was also included in the same category.

**HODGKIN ON THE CAUSE OF CANCER.**

None of the above theories appealed to Hodgkin, neither did the celebrated Brousseusiu view that stressed the rôle of chronic inflammation in the production of malignant disease, meet with his satisfaction. To Hodgkin the problem presented a great many difficulties several of which he was unable to solve; he attempts however to formulate an opinion on the subject by reference to comparative pathology and simple physical phenomena. Thus he raised the question as to whether Cancer ever occurred in cold blooded animals, a fact which we do know to be the case to-day, (see Haddow and Blake, 1933). He also observes that "the size and arrangement of adventitious growth suggests some general cause operating in their production", and that their spread may be compared to the diffusion of mucous in spirit or the flow of two separate coloured fluids/
fluids differing in their degree of viscosity such as may be observed "in the flow of custard through a fruit tart".

No definite conclusions have been reached by Hodgkin but he puts forward a tentative suggestion with the statement "I have no facts to warrant an opinion, whether the deviation from the healthy state exists previously in the nutrient fluid, or in the vessels which contain it. The functions of both, in their inseparable relations, appear to be disturbed".

It seems incredible to think that such views as these uttered over a century ago should even to-day grace the pages of an up-to-date text book dealing with the origin of malignant growth!

AN ASSOCIATE OF LISTER'S FATHER.

Together with J.J. Lister, Hodgkin wrote a paper (vide supra) on the uses of the spleen. "The very superior compound achromatic microscope" of the former enabled the latter to observe that "the whitish corpuscles are intimately connected with the lymphatic system; I have found them particularly conspicuous in a case where the lymphatic glands throughout the body were remarkably large", (Lymphadenoma). With the same microscope he demonstrated the difference between striped and unstriped muscle.
ATTITUDE TOWARDS ANIMAL EXPERIMENTS.

Although not averse to the performance of vivisection, his gentle nature desisted him from carrying out any experiments which were liable to cause pain to animals.

TRICHINA SPIRALIS.

This parasite was first noticed by Hodgkin when occurring in a portion of Sterno mastoid muscle, and the specimen in Guy's museum was thus reputed to be the first in the country.

At a later date J. Hilton a friend of the latter made a similar observation, which he communicated verbally to the Royal Medico Chirurgical Society but which never saw the light of print, as the council did not deem the work worthy of publication. The name Trichina spiralis was given to this parasite by Owen the Naturalist in 1832.

RETROVERSION OF THE AORTIC VALVE.

Commenting on Hodgkin's paper dealing with this subject, Wilks (1878) clearly states that he regarded himself as the first person to observe this important cardiac lesion, for although John Hunter first placed a specimen on view, Hodgkin described the thrill in the pulse and the accompaniment of the heart's action with a bruit de scie, which was double in character being present/
present both in systole and diastole.

It should be noted that it was not until 1832, five years later that Corrigan published his article in the Edinburgh Medical and Surgical Journal under the title of "Inadequacy of the aortic valve".

"It does not seem" states Wilks, "that from a perusal of this essay that Corrigan had any better views of the causes of the bruit than Hodgkin, and therefore it must not be presumed that this historical association with the disease rests upon his description of the pulse".

Reference to the original literature cited unquestionably reveals these facts.

THE LARYNGOSCOPE.

The laryngoscope was invented by Dr. Babington who proposed for it the cumbersome name of "glostiscope" but which was renamed by Hodgkin as the speculum laryngis or laryngoscope, which was subsequently unanimously adopted.

ANATOMY OF THE LUNGS AND PNEUMONIA.

It is of interest to relate that in an effort to imitate changes occurring in the lung during pneumonic consolidation, Hodgkin injected lungs with the white of egg and then boiled them until albumen underwent coagulation.
HODGKIN’S ATTITUDE TOWARDS DARWINISM AND COMPARATIVE ANATOMY.

Hodgkin was not slow to accept the doctrines expounded by another student of his own university in Edinburgh. Although Hodgkin was a "Friend" and had his own religious beliefs yet his purely scientific mind was not reluctant to accept truth as Wilks put it "in whatsoever guise it came". In January 1828 on the occasion of the opening of a new Morbid Anatomy theatre, he made frequent reference to congenital abnormalities as found in the human subject and drew attention to the existence of similar states in the lower animals. He concludes by stating that "Instead of limiting ourselves to the vertebrate animals we may even descend to those which exhibit the lowest form of life". Reference made by him to comparative pathology are quoted elsewhere in this paper.

THE DEVELOPMENT OF BONE.

Views on this subject as gathered from one of his essays reveals that he was at all times a strong adherent of the opinions put forward by his former teacher in Edinburgh, Dr. Knox the celebrated anatomist. They are summarised in the following original quotation: "that no new bone was ever formed except in connection with, or as a prolongation of pre-existing living bone, and that the periosteum and surrounding parts have no share in its production. - The periosteum is however a/
a very important agent in the process; it in great
measure furnishes the secretion, from which the separa-
tion of phosphate of lime takes place, and it exerts
its restraining influence in giving form to the deposit,“.

ON MENTAL DISEASE.

In an essay written on the occasion of the trial
of Oxford who was charged with an attempt on the life
of Queen Victoria in 1840, Hodgkin clearly defines from
the medical standpoint the differences which existed
between moral insanity or homicidal impulse and in-
tellectual insanity.

The last named being apparently the only form of
mental derangement which the law recognised at the time,
in support of his arguments he cites several cases
illustrating “A form of insanity under which individuals
are led to the commission of acts of great atrocity
without any of the ordinary inducements which influence
the acts of human beings". This was probably the type
of insanity from which the would-be-assassin Oxford
suffered, and the following case he quotes as being
another of a similar nature. “A gentleman of dis-
tinguished talent residing in Paris felt himself so
strongly tormented by the desire to kill that he
voluntarily placed himself in an asylum. He often
prayed to be delivered from this temptation and desired
to have his hands tied when he found the impulse be-
coming/"
coming too strong for his control, yet he ultimately made a homicidal attack upon one of his keepers.

WORK AT GUY'S.

Fresh with the knowledge derived from his Medical training in Edinburgh and post-graduate study on the Continent, Hodgkin took up duties as demonstrator of Morbid Anatomy and Curator of the Museum.

There was little doubt that he was instrumental in founding the scientific school of Medicine at Guy's Hospital for at the conclusion of his opening address he says: "I shall conclude by assuring you that it will be my constant aim — whether I may be fortunate enough to reach the mark or not — to co-operate with those who are strenuously endeavouring to render the school of Guy's Hospital the first medical school in the kingdom".

He occupied the lecture chair for ten years and then left it following an unsuccessful attempt to obtain a post as Assistant-physician. This tragic episode is alluded to by Samuel Wilks (1873), his lifelong friend and admirer, who remarks: "It was ever a day to be lamented when he turned his back on Guy's and his philosophical studies came to so premature an end — in him Guy's Hospital lost one of its greatest ornaments and the profession in England one who was destined to shed lustre on its ranks".

Leaving/
Leaving Guy's he went for a short time to St. Thomas's, where he practiced medicine, wrote articles on general subjects, interested himself in provident dispensaries, medico-legal affairs, and public health matters. His keen interest in philology assisted him in being able to found the Ethnological Society of which he remained an active member up to the time of his death.

HIS DEATH.

Following upon his unsuccessful application for the post of Assistant physician at Guy's Hospital, Hodgkin devoted the declining years of his life to philanthropic pursuits. He travelled extensively in the Near East in company with his friend Sir Moses Montefiore, Bart., and rendered considerable aid to poverty stricken members of the Jewish community resident in these parts. During his last visit to them, he contracted dysentery and died at Jaffa on 4th April 1866, where he was buried amid the scene of his labours.

Thomas Hodgkin was 68 years of age and was survived by his widow and brother.
Original observations made by him were numerous and he placed in Guy's Hospital Museum many rare pathological specimens the true nature of which escaped recognition for some considerable time afterwards.

On January 10th and 24th 1832 he presented a paper to the Royal Medico Chirurgical Society of London, titled "Some morbid appearances of the Absorbent Glands and Spleen".

In his opening remarks Hodgkin stated that "The morbid alterations of structure which I am about to describe are possibly familiar to many practical morbid anatomists, since they can scarcely have failed to have fallen under their observation in the course of cadaveric inspection". They have not as far as I am aware been made the subject of special attention, on which account I am induced to bring forward a few cases in which they have occurred to myself".

These remarks were correct for both Carswell had observed a case in one of the Paris hospitals (Wilks 1877) and Morgagni (1761) reports the occurrence of a case in a boy of fifteen years old.

The following form an abstract of the seven cases communicated by Hodgkin in his paper "On some morbid appearances of the absorbent glands and spleen", (Medico/
Case 1. - Boy, aged 9 years. Pains in back last nine months. Terminal ascites. Scrotal oedema. One brother had died recently of phthisis. Patient himself was cachectic.

Necropsy: old pleural adhesions (right), with recent pleuritis; scarring at apex of right lung; a few small nodules scattered in both lungs; bronchial glands enlarged and indurated. Fresh sero-purulent peritonitis (probably secondary, after paracentesis); enlarged mesenteric glands (up to the size of pigeon's egg), of semi-cartilaginous hardness and streaked with black; liver of normal size, containing a few white firm nodules somewhat larger than peas; spleen enlarged, containing numerous nodules; enlarged and indurated para-aortic and pelvic glands.

Case 2. - Boy, aged 10 years, ill for thirteen months, with considerable enlargement of the spleen, which diminished at times and then again increased. Glandular swellings on both sides of the neck. Terminal abdominal distension, scrotal oedema.

Necropsy: greatly enlarged lymph glands in neck, paratracheal, bronchial, and para-aortic, and also in pelvis. These glands were pale, poorly vascularized, of almost cartilaginous hardness, without any areas of softening. Old pleuritic adhesions. Ascites. Liver apparently normal. Spleen four times the normal size; mammillated surface; on section sprinkled with nodules of similar consistence to that of the lymph glands.

Case 3. - Man, about 30 years of age, admitted to hospital because of cachexia and terminal ascites. Previously treated for secondary syphilis with large quantities of mercury. Scrofulous-like ulcers in armpits and neck.

Necropsy: some calcification at the pulmonary aspices; pleural adhesions over right lung. A little ascites. Liver hardened, pale, and permeated with a hard white substance, partly diffuse, partly in pinhead-sized nodules. Spleen twice the normal size, and full of granules like early miliary tubercles, but if anything smaller. Some of the mesenteric glands enlarged and containing firm white material, so also some of the para-aortic, inguinal, axillary, and bronchial glands. The axillary glands were in a condition of suppuration, and partly ulcerated.
Case 4. - Man, about 50 years old, pale, not wasted, but of cachectic countenance. Clinically all the lymph glands were enlarged, especially in the axillae and neck, averaging a pigeon's egg in size. Abdomen distended.

Necropsy: circumscribed whitish infiltration of the peritoneum. Lymphatic glands enlarged, white on section, of rather soft consistence, and having the appearance of morbid hypertrophy rather than new growth. Large retroperitoneal lymph glands. Liver pale, large, and slightly granular. Spleen very large; on section lighter and more reddish than normal, with innumerable small white spots, without nodules. Heart hypertrophied.

Case 5. - Middle-aged man, who had been ill for a long while, especially with chest troubles. In the hospital there were swollen cervical glands.

Necropsy: considerable enlargement of cervical and submandibular glands. Part of one lung was airless and firm, as in white hepatization. Fresh inflammation of one pleura. The liver was more than seven pounds in weight, not much altered on section, like a fatty liver, of dark green to yellowish colour. Spleen four or five times the normal size, firmer than usual, in some parts containing little specks of rather soft consistence. Great enlargement of retroperitoneal glands. Some of the abdominal glands showed ecchymoses. The thoracic duct contained blood.

Case 6. - Man, about 50 years old, fell ill about two years previously with fever; enlargement of the glands on both sides (one side before the other) of the neck, then in the axillae and groins; pallor and ascites.

Necropsy: cervical, axillary, and para-aortic glands greatly enlarged; those on the left side of the neck and in the left axilla were the largest; all these glands were of similar structure, without softening, pale, covered by soft membrane; some were of semi-cartilaginous hardness. Liver rather small, with an irregular and uneven surface, in which there were two or three white nodules. Spleen of moderate size, and free from adventitious deposit. Omentum corrugated. Yellowish ascitic fluid in peritoneum.

Case 7. - Specially communicated under the title, "Cancer cerebriformis of the lymphatic glands and of the spleen." Man, about 30 to 40 years of age, who for three or four months had had enlargement of submandibular, cervical, axillary and inguinal glands. Died in Paris in a few days from difficulty in swallowing.

Necropsy: masses of enlarged glands from chin to axilla, varying/
varying in size and degree of vascularity, each of them enclosed in a capsule; the contents were "brain-like". Similarly altered inguinal and para-aortic glands. Behind the stomach a retroperitoneal conglomerate glandular mass of the size of an adult's head, in the middle of which was a haemorrhage. The vena cava inferior and aorta passed through this mass. Similar alteration in the tonsils. Spleen full of nodules of the brain-like substance, containing fine blood vessels. Apparently there was nothing special in the thorax (not seen by Dr. Hodgkin himself), nor in any other organs.

All these cases were probably not examples of Hodgkin's disease or lymphadenoma as we know it to-day, but it nevertheless illustrates the genius of its describer in his ability to recognise the salient features of the disease in the absence of microscopical examination. Even more remarkable than this should be remembered the fact that Hodgkin's description of the disease was lost sight of for a period of nearly 20 years, and would certainly have been totally ignored had it not been for the work of Wilks, one of his former pupils.

This incident is referred to by Wilks in the following paragraph quoted from Guy's Hospital Medical Reports, Vol. XXII, 1877, p. 272.

"The remarkable fact remains that in spite of Hodgkin's advocacy of the claim of this disease to be regarded as a new pathological entity, it had not penetrated into the text-books of medicine or surgery, and I take credit to myself for having unearthed Hodgkin's paper and introduced it to the profession.

So/
So little, however, was this paper known to me when I took some examples of this glandular disease to the Pathological Society nearly twenty years ago, and so unacquainted were the members at that time with it, that it was received as a novelty, and the 'Lancet', alluding to the fact, said, "Much interest had been evinced amongst the profession by the announcement of Dr. Wilks at one of the meetings of the Pathological Society during its past session that the morbid specimens which he exhibited were taken from a patient whose disease was new and hitherto unnamed"; and a foreign journal spoke of it in the same terms. It was not, therefore, impossible that I might have been fathered with the discovery had I not shortly afterwards alighted on Hodgkin's essay, and so saved the profession from a name even more uncouth than morbus Hodgkini - a patronymic which I must confess to have myself conferred upon the malady now known by the kindlier appellation of lymphadenoma."

**SOME EARLY ACCOUNTS OF HODGKIN'S DISEASE.**

Richard Bright (1838) referred to the condition in the following paragraph "There was another form of the disease which appears to be malignant in character, though it varies from the more usual form of malignant disease, and which has been particularly pointed out by Dr. Hodgkin as connected with extreme disease of the/
the absorbent glands, more particularly those accompanying the blood vessels. The whole of these absorbent glands become larger and firmer with tendency to suppurate, as in ordinary scrofulous disease or to soften as in cerebriform disease, at the same time.

Thereafter, following upon the period of 20 years alluded to above, the condition was noted in Germany by Virchow (1864), Conheim (1865) and Wunderlich (1866). The last named of whom was reputed to have differentiated the condition from lymphosarcoma.

In France, Potani (1861) observed the malady and his account was followed by one from Trousseau in 1865. In Canada and the United States of America literature contains cases reported by Osler (1880) and Bang (1881), whilst in India a case was recorded by Banerjea (1880).

A SHORT SUMMARY OF THE LITERATURE DEALING WITH ITS AETIOLOGY.

Literature on this subject is so voluminous that space does not permit of a fair and accurate survey being made of all views expressed on the aetiology of the condition.

Following the accurate description of its histopathology by Sternberg (1899), Dorothy Reed (1902) and Andrewes (1902), and its clinical features by Greenfield (1878), Zeigler (1911), Butlin (1901), Longcope (1903-4), Weber (1917), Rolleston (1925) & McNalty (1928) much/
much speculative reasoning has been advanced regarding its etiology.

For a detailed account of these views the reader is referred to the work of Simmons (1903), Symmers (1917), MacCallum (1907), Lemon (1924), Utz and Keatinge (1931), Wallhauser (1933) and McGrath (1935). Evidence indicates that the subject of its causation has been a matter of considerable dispute, for opinion is divided into those who maintain that the disease is one or other of the following different conditions:

1. A neoplastic growth.
2. A form of tuberculosis.
3. An infective granuloma.

The first mentioned theory has been dealt with in excellent works of Dreschfeld (1893), Ewing (1913), Adami (1910), Medlar (1931), Levin (1931), Meuller (1928), MacCarty (1930), Coley (1928) and Fraser and Mekie (1933), and their views taken into consideration.

The other hypotheses have been the subject of the writer's own personal observations and the literature pertaining to each of them will be referred to seriatim in parts II and III of this thesis.
PART II.

AETIOLOGY OF HODGKIN'S DISEASE WITH SPECIAL REFERENCE TO B. TUBERCULOSIS AVIS.

The relation of Hodgkin's disease to tuberculosis has been the subject of extensive inquiry, and many workers, such as Sternberg (1898), Ewing (1927), and others, have repeatedly drawn attention to the similarity of tissue changes produced in both conditions. Opinion, however, is divided on the incidence of tuberculosis in patients suffering from lymphadenoma. Ewing says that "tuberculosis follows Hodgkin's disease like a shadow"; Lemon (1924) reports, to the contrary, that out of 191 cases of Hodgkin's disease under observation in the Mayo Clinic only eight showed evidence of tuberculosis. The latter worker further states that out of twenty-six cases of the disease in which the mediastinal glands were involved there was definite evidence of tuberculosis in only one.

 Infective agents other than the tubercle bacillus, such as the diphtheroid organism (Bunting and Yates, 1913), certain monilias (Dias, 1913) and amoebae (Kofoid, Swezy, and Boyers, 1922), have been described in Hodgkin's disease, but such work has lacked confirmation. Stewart and Dobson (1924) attempted to reproduce the disease in monkeys (rhesus and bonnet), but without results.
results. Twort in 1930 published the results of six years' research into the causation of the condition, and arrived at the conclusion that the disease was probably of neoplastic origin, since he was unable to isolate any one organism with constancy or to reproduce the disease in laboratory animals with pathological material.

More recently American workers have advanced two fresh views on the aetiology of the condition. Medlar (1931) maintains that the disease is one primarily affecting the bone marrow, for which he proposes the name "megakaryoblastoma" in view of the particular type of cell involved. L'Esperance (1929-31) claims to have reproduced Hodgkin's disease in birds and "treated" guinea-pigs, from whose tissues she recovered the avian tubercle bacillus. This investigator therefore states that Hodgkin's disease is produced by infection with B. tuberculosis avium. This view has been further elaborated by Utz and Keetinge (1932), who claim to have treated successfully several cases of lymphadenoma by the use of sera obtained from chickens previously immunised with lymphadenomatous tissue. I have investigated the claims of L'Esperance by the inoculation of chickens and other laboratory animals with material obtained at biopsy from three cases clinically and histologically characteristic of Hodgkin's disease, and also with material removed at necropsy from three other cases of the disease, two of which showed mediastinal involvement.
involvement.

The following brief extracts of case and post-mortem notes describe the subjects from which material was obtained.

CASE HISTORIES.

1. Case of Professor Fraser's. - A male, aged 52, had swelling in left axilla of eleven months' duration, with later ulceration and secondary infection lasting three months. There was slight enlargement of the inguinal and infraclavicular glands, with no evidence of mediastinal involvement. Ten per cent eosinophils were present. Histological diagnosis: Hodgkin's disease.

2. Case of Dr. Comrie's. - A female, aged 28, had a swelling of the glands of the neck for eight months, with later involvement of abdominal glands and spleen. These changes were accompanied by extensive bronzing of the skin and intolerable itching. Throughout her illness a fever conforming to the Pel-Ebstein type was present, and the blood picture showed an eosinophilia. At post-mortem the cervical, mediastinal, bronchial and abdominal para-aortic glands were grossly enlarged, together with slight enlargement of the lymph nodes of the lesser omentum. The spleen was enlarged to about three times its normal size, and contained numerous nodules throughout. The heart, liver, and lungs also showed involvement with lymphadenomatous tissue.

3. Case of Professor D. Murray Lyon's. - A male, aged 46, complained of vague symptoms of general illness lasting three months, with loss of appetite and weight, diarrhoea, colic and dyspnœa. Temperature reaction of the Pel-Ebstein type was present, accompanied by enlargement of liver and spleen. At post-mortem there was considerable enlargement of para-aortic, abdominal and mediastinal lymph glands, with commencing enlargement of the cervical and inguinal groups. The bone marrow revealed red patches suggestive of erythroblastic reaction, and microscopically proliferation of bone marrow cells affecting the red cell series was found to be present.

4. Case of Professor Bramwell's. - A male, aged 27, gave a three months' history of loss of weight and appetite, accompanied by distension of the abdomen and bronzing.
bronz ing of the skin. On admission the patient was found to have an enlarged spleen, dullness over the apex of the right lobe, with crepitations and vesicular breathing. Pel-Ebstein type of fever was present. Red blood cells were 4,200,000 per c.mm., and white cells 3,800; differential count was normal, and haemoglobin 70 per cent. Post-mortem revealed typical lymphadenoma of spleen, liver, and para-aortic and cervical glands. Brown atrophy of the heart. No evidence of tuberculosis demonstrable.

5. Case of Professor Fraser's. - A female, aged 31, first noticed lumps on her neck two years before examination, initially confined to the left side, but later involving the right. These painless swellings rapidly increased in size, and later gave rise to pressure symptoms in that region. There was no palpable enlargement of spleen, liver, or lymph glands in inguinal or axillary regions. An intermittent fever accompanied her illness. Red blood cells were 4,540,000 per c.mm., and white cells 9,200: polymorphs, 75 per cent.; lymphocytes, small, 11 per cent.; large, 9 per cent.; eosinophils, 4 per cent.; transitionals 1 per cent. Haemoglobin was 70 per cent.; colour index, 0.08. Histological diagnosis: Hodgkin's disease. Deep x-ray therapy and subcutaneous injections of Coley's fluid over the affected area were employed, which resulted in marked diminution in the size of the glands and considerable general improvement.

6. Case of Dr. Chalmers Watson's. - A schoolboy, aged 8, gave a five years' history of progressive enlargement of submental, supraclavicular, axillary, and inguinal glands, and of the spleen. Increasing weakness and cachexia, severe secondary anaemia, accompanied by cardiac haemic murmurs, commencing integumentary dryness and pigmentation were present. During the last two years patient exhibited a typical Pel-Ebstein pyrexia. The histological diagnosis, clinical manifestations, course of the disease, and reaction to deep x-ray therapy have shown this case to be almost a textbook picture of the disease.

EXPERIMENTAL WORK.

Enlarged lymph glands removed at biopsy, together with liver, spleen, and bone marrow obtained in necropsy, were examined for the presence of avian tubercle/
tubercle bacilli by direct attempts at cultivation on Dorset's egg media, but no such organisms were isolated. It is of interest, however, to state that in both Cases 1 and 6 a small, typical, Gram-positive, aerobic diphtheroid organism was isolated after about ten days' incubation. Both strains subsequently proved to be non-pathogenic to laboratory animals, and so further investigations were discontinued. About 300 histological sections of affected glands and viscera were stained for acid-fast organisms, but none were found.

Animal Inoculation.

Four bantam chickens and four street pigeons were inoculated both intravenously (through the wing vein) and intra-peritoneally with 2 to 3 c.c.m. of a dense emulsion of affected material, comprising enlarged lymph glands, spleen, and bone marrow. Three other chickens were also injected intracerebrally in addition to the preceding routes. Animals were kept under observation for a period of seven to ten months, but no signs of illness were noticed. Two chickens which had been inoculated with emulsions of spleen and lymph gland by the two routes were examined post mortem ten months later, but found to be perfectly healthy.

Grafting/
3. Histological section through a fragment of lymphadenomatous lymphatic tissue after being embedded into the extraperitoneal tissues of a chicken for 3 months. 

(x 12)

4. View showing the dense ring of fibrous tissue formation surrounding the graft. 

(x 700)

5. Observe the absence of infiltration or tuberculous caseation. 

(x 350)
Grafting Experiments.

Five healthy chickens (three buff orpingtons and two white leghorns) were used for these experiments. With strict aseptic precautions small fragments of an enlarged lymph gland (removed at biopsy by Professor Fraser, from Case 5) were implanted into the birds as follows. (1) Extraperitoneally. (2) Intraperitoneally. (3) Intrahepatically: This was carried out by making a V-shaped incision into the free margin of the left lobe of the liver, and inserting into this a wedge-shaped portion of gland, which was then secured by means of catgut sutures. (4) Into shaft of femur: This was done after the manner of an intramedullary graft, and performed by exposing the femur, removing a U-shaped fragment of bone with the aid of bone-nibbling forceps, and then inserting small fragments of lymphadenomatous tissue into the proximal and distal ends of the medullary canal. (5) Intramuscularly: Implantation was in the pectoral muscles. All five birds made a good recovery from the operation, and at the end of a week appeared to be in good health.

Animal No. 1 died after three months, succumbing to accidental injury. Necropsy revealed that the attempted graft had undergone necrosis and subsequent extrusion into the superficial tissues, while the surrounding tissues showed extensive fibrosis and cicatricial/
cicatricial contracture, presumably in the nature of a reaction towards a foreign body. No evidence of tuberculous ulceration or caseation was to be found in the underlying tissues, peritoneum, or viscera. Animal No. 3 was killed after six months and the site of the attempted graft examined both macroscopically and microscopically, but no changes indicative of tuberculosis were evident and no bacterial growth was obtained on culture. The remaining animals are still under observation, and appear to be healthy after seven months.

SUSCEPTIBILITY OF STOCK TO AVIAN TUBERCULOSIS.

In conclusion the susceptibility of the animals used to avian tuberculous infection, was proved by the experimental inoculation of six birds with live cultures of \textit{B. tuberculosis avis}. Every one of these chickens died within four weeks and the organism was recovered from each of them.

DISCUSSION.

In the experiments described above no evidence of infection with \textit{B. tuberculosis avis} was found in material taken from six accurately diagnosed cases of Hodgkin's disease.

Cases of human infection due to the avian tubercle bacillus have already been described by several European/
European workers. Löwenstein (1913) obtained the organism from cases of pulmonary, renal, and dermal tuberculosis. Rabinowitsch (1907) succeeded in isolating the organism from the spleen of a case of generalized miliary tuberculosis, and Janscé and Elfer (1910) also demonstrated organisms of a similar type in the mesenteric glands of a child. It would thus appear that the occurrence of human infection by the avian tubercle bacillus has been proved, and isolation of the causative organisms seems to have been achieved by the usual well-recognized methods. With reference to the claims made by L'Esperance, I have not only failed to produce tuberculosis in chickens by inoculation with lymphadenomatous material, but I have also been unable to demonstrate the presence of avian tuberculosis in affected material, either by direct cultural methods or by examination of a large number of stained histological preparations.

It is noteworthy that in the literature of the cases of human tuberculosis due to avian tubercle bacillus there is no mention that the clinical manifestations of these cases in any way differed from the syndrome produced by infection with the ordinary human or bovine types. Indeed, it is questionable whether the true nature of the causative agent would have been determined had a special search not been made for it.

The/
The feeble pathogenicity of the avian tubercle bacillus to the guinea-pig and its more pronounced effect on the rabbit are well-recognized characteristics (Medlar, 1931) that cannot be lost sight of when one also remembers that the non-pathogenicity of lymphadenomatous material to rabbits and guinea-pigs is a fact of wide acceptance. A notable exception to this is found in the results obtained by M.H. Gordon and co-workers of the Rose Research on Lymphadenome (1932), who have demonstrated that the intracerebral injection of lymphadenomatous tissue into rabbits is followed by ataxia, muscular spasms, and paralysis. Such effects are not produced, however, by the injection of leukaemic, sarcomatous, and carcinomatous tissue. L'Esperance nevertheless claims to have reproduced avian tuberculosis in birds by the injection of lymphadenomatous material into them, without having simultaneously done so in rabbits. The same worker's claim to have reproduced Hodgkin's disease in guinea-pigs which had previously been inoculated with killed cultures of \textit{B. tuberculosis hominis} is also unconvincing.

It should also be pointed out that, according to Griffith (1930), under domestic conditions poultry exposed to infection readily develop tuberculosis, frequently following the ingestion of contaminated food. Organs most commonly involved are the intestine/
intestine, liver, and bone marrow, but the writer has been unable to reproduce avian tuberculosis by the introduction of lymphadenomatous tissue directly into these areas.

SUMMARY AND CONCLUSION.

Pathological material obtained from six accurately diagnosed cases of Hodgkin's disease have been examined by direct cultural methods for the presence of the avian tubercle bacillus, and histological sections examined for acid-fast organisms, but both with negative results. Tissue emulsions have proved to be non-infective to rabbits, guinea-pigs, pigeons, and chickens on intravenous, intraperitoneal and intramuscular administration. Attempts to graft lymphadenomatous material obtained from an acute case of Hodgkin's disease into the bone marrow, peritoneum, liver and muscles of chickens have likewise failed.

No evidence of B. tuberculosis avis can be found in cases of Hodgkin's disease.

Accordingly there is grave doubt as to the therapeutic value of immune chicken serum in the treatment of Hodgkin's disease.
PART III.

A BIOLOGICAL TEST IN THE DIAGNOSIS
OF HODGKIN'S DISEASE.

Recent literature has shed fresh light on many
hitherto obscure factors concerning the nature of
Hodgkin's disease. Thus the workers of the Rose
Research on lymphadenoma have shown, after a careful
search, that neither spirochaetes, yeasts, diphtheroids,
nor acid-fast bacteria have any relation to the con-
dition. Similarly, the finding of L'Esperance
(1931) that the avian tubercle bacillus may be
causally associated with the disease has not been
confirmed (van Rooyen, 1933).

Perhaps the most interesting contribution towards
the study of the problem has been the work of M.H.
Gordon (1932). He showed that the intracerebral
inoculation of rabbits and guinea-pigs with suitable
suspensions of lymphadenomatous tissue was followed
in a few days by spastic paralysis of the hind limbs,
rigidity, ataxia, and muscular weakness. Such effects,
however, were not produced by the injection of simi-
larly prepared suspensions of normal, leukaemic,
sarcomatous, and carcinomatous lymphatic tissue.
It thus appeared that lymphoid tissue affected by
Hodgkin's/
Hodgkin's disease acquires properties which this tissue does not exhibit when affected by certain other pathological conditions. Work bearing on the precise nature of the agent responsible for the syndrome produced experimentally in rabbits is without the scope of the present article, and demands further investigation. It is proposed, however, to draw attention to the possibilities which this phenomenon offers as a means of identifying true lymphadenomatous tissue, and also to its clinical value as an aid in the diagnosis of certain doubtful cases. The following brief abstracts from case and post-mortem reports of patients treated in the Royal Infirmary of Edinburgh describe subjects from which material was obtained. The first six were cases of Hodgkin's disease, the seventh was one of pseudo-leukaemia, and the eighth one of lymphosarcoma. A summary of results obtained with fifty other cases is also incorporated.

Case 1 (H12). A miner, aged 43, under the care of Dr. Goodall, had a swelling on the side of his neck for three to four years, and complained of cough for six months. Enlarged glands were palpable in the neck and axillae, whilst x-ray examination revealed enlargement of the superior mediastinal and bronchial groups as well. The spleen was not palpable. The blood count was as follows: red cells, 4,700,000 per c.mm.; white cells, 6,800 per c.mm. - neutrophils 82 per cent., eosinophils 3 per cent., lymphocytes (large and small) 15 per cent. - haemoglobin 68 per cent.; Wassermann reaction was negative. Histological diagnosis: Hodgkin's disease.

Case 2 (H14). A forester, aged 53, under the care of Dr. Matthew, had noticed progressive enlargement of his right axillary glands for ten weeks before admission. Temperature varying between 102° and 103°F., accompanied the illness. X-ray treatment produced no benefit.
benefit, and death followed shortly.

Post-mortem Appearances. - Glands about three inches in diameter were present in both axillae, together with bilateral enlargement of these occupying the anterior triangles of the neck; the retrosternal, tracheal, para-aortic, and lumbar lymphatic glands were also enlarged. The spleen was about twice its normal size and typical in appearance. The liver was slightly enlarged. The pleural and pericardial seps contained effusions; the heart showed fatty degeneration, and the bone marrow slight haemopoietic activity.

Histology. - The lymphatic glands exhibited extensive replacement of normal glandular architecture with Hodgkin's tissue, numerous giant cells being noticeable. The liver and spleen revealed similar changes. The bone marrow showed some erythroblastic and leucoblastic reaction.

Case 3 (H15). A miner, aged 52, under the care of Professor Murray Lyon, for five weeks had had pain in the abdomen extending into his right leg. Enlarged glands were present in inguinal, axillary, and posterior cervical areas. There were considerable bilateral muscular atrophy and loss of motor power, lateral nystagmus, and weakness of facial movements. Tenderness was elicited over third lumbar vertebra. Fever accompanied his illness. The blood count was: red cells, 4,800,000 per c.mm.; white cells, 3,200 per c.mm.; haemoglobin, 70 per cent.; colour index, 0.7; a film showed slight anisocytosis. Wassermann reaction was negative.

Post-mortem Appearances. - There was considerable enlargement of the para-aortic glands, with some increase in size of those in the right groin; the left inguinal group was slightly enlarged. The spleen was twice its normal size, and contained numerous small patches of yellowish-white tissue scattered throughout its substance. The liver displayed similar deposits, some of which were about one and a half inches in diameter. Both pleural and pericardial seps contained serous effusions, while the left pleura showed deposits of lymphadenomatous tissue and commencing infiltration of the diaphragm. The vertebrae were also affected, and the bone marrow of the right femur showed haemopoietic activity. Histological examination revealed the typical features of an acute case of Hodgkin's disease.

Case 4 (H10). A fisherman, aged 24, under the care of Dr. Goodall, had had cough and pallor of one year's duration, accompanied by swellings in his neck for five to/
to six months. X-ray examination showed enlargement of the mediastinal glands and slight compression of the trachea. The spleen was not enlarged. The Pel-Einstein type of fever was present. The blood count was as follows: red cells, 2,590,000 per c.mm.; white cells, 7,800 per c.mm. - polymorphs 69 per cent., small lymphocytes 20 per cent. and large 8 per cent., eosinophils 3 per cent. - haemoglobin, 85 per cent.

Histological diagnosis: Hodgkin's disease.

Case 5 (H9). A packer, aged 29, under the care of Dr. Chalmers Watson, had had an enlargement of the left side of his neck for sixteen months, followed by swellings in axillae and groins. X-ray examination revealed secondary deposits in the bony pelvis, ribs, and lumber vertebrae. Motor and sensory paralysis was present from the lower costal margin downwards, accompanied by acute backache.

Post-mortem Appearance. - Considerable enlargement of the lymphatic glands existed throughout the body; several of them were hard and tough in consistence. The spleen weighed 500 grams, being greatly increased in size and typical in appearance. The vertebral column showed involvement near the sixth, seventh, and eighth ribs. The brain and meninges were normal in appearance.

Case 6 (H8). One demonstrating the value of Gordon's test in the post-mortem diagnosis of Hodgkin's disease. A married woman, aged 24, under the care of Professor Murray Lyon, took a "cold" in November, 1931, and developed a troublesome dry cough which was accompanied by pain over the sternum. Thereafter she noticed that she was losing weight, and complained of increasing weakness. Early in 1932 a swelling appeared in the right supravacular region. As she could not get rid of the cough she went to her doctor in February. He referred her to the Royal Infirmary, Edinburgh, for X-ray examination, and in consequence of the findings at this examination she was admitted to the Infirmary on May 4th.

She had had several attacks of pain in the right iliac fossa during the past three years. In the family history there was nothing of interest.

Examination. - She was of medium stature, sparely nourished, and looking on the whole fairly healthy. Her temperature was 96°F.; her pulse-rate 74; and her respiration-rate 20. She had a cough, but no sputum or breathlessness; she had had some pain behind the sternum. The thorax was well formed; there was slight fullness on the right side at the root of the neck. In/
In the posterior triangle on the right side some discrete, hard lumps about the size of walnuts were felt. They appeared to be continuous with a mass which disappeared behind the sternum. There were no more lumps on the left side. There was greater dullness than normal over the sternum, and this dullness was also present for 2 in. on each side of the median line in the first, second, and third intercostal spaces. Over the rest of the chest the note was normal. Vesicular breathing was heard all over both lungs, and vocal resonance was not increased. Nothing unusual was noted in the circulatory system, except abnormal faintness of heart sounds in the aortic and pulmonary areas. The lymph glands were enlarged in the right posterior triangle of the neck, but not elsewhere. The alimentary, genito-urinary, and haemopoietic systems showed nothing of note. The urine was normal, and the Wassermann reaction of the blood negative. Radioscopy showed in the upper anterior mediastinum a large shadow of even density and irregular outline. The trachea was centrally situated and not compressed.

Clinical Diagnosis and Treatment. - In view of the clinical and radiological evidence a diagnosis of sarcoma of the thymus gland was made, and a course of deep x-ray therapy instituted. In consequence of this treatment the neoplastic mass underwent a rapid and pronounced diminution in size. The patient was discharged on May 21st and given instructions to attend the radiological department as an out-patient. Her general condition was then good.

State on Readmission. - She was readmitted on Feb. 23rd, 1933, with a history of increasing malaise, weakness, and dyspnoea, giddy turns, cough with little sputum, and loss of weight. Dullness was present below the clavicle to the second rib, and transversely from an inch to the right of the midline to 3 in. to the left. Posteriorly there was a midline area of dullness about 4-5 in. broad. Over these regions vocal resonance and fremitus was greatly increased, and breathing was bronchial in type with no accompaniments. The supraclavicular glands were palpable on both sides, round and shotty, largest on the left. Post-cervical glands were also palpable. One gland in each axilla was enlarged to the size of a big walnut, but none were felt elsewhere. X-ray examination now revealed definite enlargement of the mediastinal mass, together with diffuse opacity of the upper lobe of the left lung.

Termination of Illness. - While in hospital the patient developed a large bilateral pleural effusion. Repeated
Repeated aspiration had no effect in reducing the amount of fluid, which showed numerous red blood corpuscles and lymphocytes with a fair number of endothelial cells and polymorphonuclears, but no organisms. She rapidly became weaker and more breathless, and died on June 3rd.

Post-Mortem Examination and Diagnosis. - Both pleural and the pericardial cavities contained large quantities of greenish serous fluid. In association with the parietal layer of the pericardial sac on the left side, there was, just above the diaphragm, a large mass of nodular, very firm, pale yellowish-white tissue. The peritoneum, larynx, and trachea were healthy.

The pleura of the left lung was smooth and glistening over the upper lobe, wrinkled over the lower lobe. The upper lobe was uncollapsed and more or less uniformly consolidated; the lower lobe was unduly collapsed. Section revealed that the consolidation of the upper lobe was due to extensive infiltration of the tissue by new growth, which seemed to have originated in the region of the hilum and spread peripherally. The margin of the infiltrated zone was irregular, but fairly well defined. The infiltrated area was greyish-yellow in colour, with here and there a congested haemorrhagic patch. The surrounding lung was rusty-red in colour. The lower lobe was congested. The right pleura was unduly wrinkled, and the right lung collapsed, congested, and moderately oedematous.

A group of enlarged glands was present at the base of the neck on the left side. These glands were fairly discrete and very firm, and presented on section pale yellowish-white, more or less homogeneous surfaces; no necrosis or caseation was evident. A few enlarged glands were also present in the anterior mediastinum, and there was a chain along the vertebral column in the posterior mediastinum. Another large mass of glands was present along the lesser curvature of the stomach, and the para-aortic group of glands was markedly enlarged. The heart showed brown atrophy. The liver and spleen showed well-marked chronic venous congestion. The kidneys also showed chronic venous congestion.

The macroscopical findings necessitated a consideration of (1) Hodgkin's disease; (2) carcinoma of lung (bronchial or alveolar); and (3) mediastinal sarcoma. Points in favour of Hodgkin's disease were the age of the patient, the excellent response to irradiation, the widespread lymphatic involvement and the character of the glandular masses (discrete, non-necrotic/
necrotic, non-caseous). Points against this diagnosis were the invasion of the left lung, the presence of a large mass in association with the pericardial sac, and the absence of splenic and hepatic involvement. Bronchial carcinoma was favoured by the character of the growth invading the upper lobe of the left lung. The situation of this apparent neoplasm also suggested the possibility of a sarcoma of mediastinal origin.

Case 7. (H13). A housewife, aged 59, under the care of Dr. Comrie, complained of breathlessness, loss of appetite, and lassitude for one month. A single painless mass of slightly enlarged lymph glands was observed in the right axilla, and there was also some slight swelling in the left groin. The spleen was not palpable. Blood count showed: red cells, 3,640,000 per c.mm.; white cells, 6,400 per c.mm.; haemoglobin, 50 per cent.; colour index, 0.8. A film revealed neither visible abnormality of the erythrocytes nor any alteration in the proportion of leucocytes. Wassermann reaction was negative. X-ray examination showed a large right pleural effusion. Clinical diagnosis: pleurisy with effusion; carcinoma or tuberculosis of the lung.

Post-mortem Appearances. - There was considerable enlargement of the upper abdominal and tracheo-bronchial lymphatic glands, both of which were heavily infiltrated with soft, whitish tissue. The glands in the lesser omentum were similarly affected, the invading tissue extending up the porta hepatis along the larger branches of the portal vein to involve the liver and cause thickening of the wall of the gall-bladder. The kidneys and peri-pancreatic tissue were likewise affected. The spleen was twice its normal size, and exhibited numerous whitish areas about 3 mm. in diameter. In the bone marrow erythroblastic and leucoblastic reaction was present.

Histology. - There was widespread infiltration with small lymphocytes of liver, spleen, lymph glands, and bone marrow, including a subcapsular infiltration of the kidney.

Diagnosis. - The absence of a blood leucocytosis during life, accompanied by the histological appearances as described, indicated that the case was one of pseudo-leukaemia.

Case 8. (H11). A chauffeur, aged 50, under the care of Dr. Goodall, gave a history of seven weeks' enlargement of glands in both axillae and groins, together with a swelling in his right pre-auricular region. Illness was accompanied by progressive enlargement of the spleen, some pain in his side, and a pleural effusion.
effusion. X-ray treatment gave slight relief. Blood count showed: red cells, 4,900,000 per c.mm.; white cells, 7,600 per c.mm. - neutrophils 72 per cent., basophils 0.8 per cent., eosinophils 4 per cent., small lymphocytes 9 per cent., large 14 per cent. - haemoglobin, 85 per cent.

Post-mortem Appearances. - The entire paraaortic lymphatic chain was extensively involved with whitish-looking lymphoid tissue, and also the pelvic, inguinal, supra-clavicular, cervical, and axillary glands. The tracheo-bronchial and mediastinal lymphatic groups were likewise affected, but to a lesser degree. Bilateral permeation from the axillary glands extended into each pectoralis major muscle. The spleen was slightly enlarged, and showed necrotic changes. Both pancreas and suprarenals exhibited secondary invasion.

Histology. - Normal lymphoid tissue was replaced by numerous mononucleated cells, some of whose nuclei displayed mitotic figures and other degenerative changes. The capsule of the gland was invaded.

EXPERIMENTAL WORK.

Enlarged glands removed at biopsy were collected in a sterile test tube and 2 grams of glandular tissue were placed in a sterile mortar, finely minced, and ground in 20 c.cm. of nutrient broth of pH 7.2. This 1 in 10 suspension of material was maintained in a refrigerator at -4°C. for seven days, and was then tested for sterility both aerobically and anaerobically. Post-mortem material was dipped into absolute alcohol, which was burnt off; it was then plunged into boiling water for two seconds and allowed to dry in an incubator at 37°C. The superficial tissues were now cut away, and the central portion prepared for emulsification. This was performed after the manner described above, with the exception that either 3 per cent. ether or 0.5/
6. Dissection of a rabbit's brain view from above. Showing the left frontal and occipital lobes, either of which may be used as the site for inoculation with safety. (½ natural size)

7. Complete exposure of brain. Note how far back the cerebellum is placed.
0.5 per cent phenol was incorporated in the broth as an additional precaution against contamination. After ten days in the refrigerator these suspensions were standardized to approximately the density of a Brown's standard opacity tube No. 2 by the addition of fresh broth, before being used for injection. All the material used was prepared in this manner.

Intracerebral Inoculation of Rabbits.

The procedure adopted was similar to that used by Gordon (1932) and was briefly as follows. Animals were deeply anaesthetized with ether, the hair over the head shaved, and the skin disinfected with absolute alcohol, tincture of iodine, and ether. A short incision was made through the soft tissues of the scalp down to the pericranium at a point situated 2 mm. lateral to the sagittal suture and 1.5 mm. anterior to the lambdoidal suture. The skull was now penetrated with a mechanical drill, or alternatively by means of a trephine. A fine intradermal needle was introduced through the aperture, and about 0.45 c.cm. of tissue emulsion was inoculated into the occipital lobe of the brain to a depth of about 3 mm. The needle was quickly withdrawn to avoid regurgitation, and the skin opening was united with a horse-hair suture and its edges brushed over with collodion. An intravenous dose of 0.5/
8. Rabbit (191) 3 days after intracerebral inoculation with Hodgkin lymphatic tissue. Note body rigidity and undue prominence of the hind limbs.

9. Another animal (R438) also after 3 days, showing the same characteristic spasticity.
0.5 to 0.7 c.cm. of the same inoculum was also administered through the ear vein.

Although the method described above gave satisfactory results, yet access to the frontal lobe of the brain gained by trephining at a point situated 2 mm. lateral to the median plane on an imaginary line joining the two lateral ocular canthi yielded equally good results. This entry was the route of choice in the case of young rabbits from 6 to 8 weeks old. The sites of inoculation into the brain in both methods were situated well behind and in front of the motor area respectively. Deliberate experimental damage to the motor area was, however, inflicted on the brains of six animals. The features of damage to this area, which were characterized by the onset of paralysis within five to twenty-four hours, and its subsequent course were carefully noted.

Results Obtained with Lymphadenomatous Material.

Glandular extracts of varying age were introduced into rabbits (vide supra) and their effects observed.

Case 1. - Suspensions which had been left for periods varying from one hour to seven days were found to be completely inactive, but after ten days in the refrigerator slight activity was noted. Two large rabbits which were inoculated showed, some three to four days later, a trace of stiffness in their hind limbs and some interference with their power of locomotion. At twenty days' broth suspension was next employed, and was found to be highly active. Thus four animals which were injected all showed the typical appearances
10. Rabbit (R 507) 4 days after inoculation, photographed during the act of movement. Observe the awkward attitude of the body and the widespread position of its hind limbs.

11. Also after 4 days showing slight head retraction.
12. R(87). Photographed on the fifth day after inoculation, during the occurrence of the encephalitic syndrome. As the rabbit lies prostrate upon the floor its head is retracted, the eyes exhibit nystagmus and the talons of its fore limbs claw the ground. The back is arched both hind limbs are completely paralysed, sphincter control is lost and grinding of teeth may be observed.

13. R(170). Also depicted during the same phase of the illness. This picture was secured immediately after the animal had recovered from a convulsive seizure. These attacks are attended by violent muscular spasms, body rigidity and temporary cessation of respiration.

Note: To the casual observed these attacks are similar to the signs of meningo-encephalitis following bacterial infection of the brain and cord.

In Gordon's syndrome, however, neither cultivable bacterium nor gross histological evidence of damage are present to account for the manifestations produced (van Rooyen, 1933).
Appearances produced in the moribund rabbit.

Gordon's syndrome may terminate in one or other of the following different ways.

14. R(608) shows an animal lying unconscious with its head retracted and its body muscles in a flaccid condition.

15. R(575). A frequent method of termination seen in the rabbit injected with material derived from an acute case of Hodgkin's disease. Attacks of extreme head retraction, rigidity of the fore limbs and arching of the back together with convulsive movements may be noted prior to death.

16. R(609). Appearances seen in the chronic type of lesion produced in the rabbit, after 4-6 weeks. Complete paralysis of hind quarters, muscular atrophy, and loss of sphincter control becomes evident.

Note: From the observations recorded, it would seem evident that either the brain or spinal cord may be principally affected. Thus in the acute type of lesion produced in the rabbit, the brain is more usually affected than the cord.

17. Place a roller towel 36 ins. long on the floor of the room and lay the rabbit at one end of it.

18. Wrap the end of the towel round the body of the animal.

19. And roll the towel completely around the animal by gently rotating it upon itself, until completely surrounded by the fabric.

20. Next, release the rabbit by grasping the free end of the towel in your right hand and drawing it sharply towards yourself.

Note: The normal rabbit after such rotation exhibits no characteristic movements, but the animal showing signs of the encephalitic syndrome displays numerous inco-ordinated movements with marked ataxia. Several of the peculiar attitudes assumed by these animals immediately after the application of this test have been depicted in the preceding photographs.
A method for the demonstration of spastic paraplegia in the rabbit – van Rooyen’s "Plumb" test.

The normal rabbit when suspended in mid air by the ears retains sufficient muscular power in its hind legs to avoid these from hanging downwards.

The animal which suffers from the encephalitic syndrome on the contrary is unable to do so.

21-22. Fig. (21) and (22). Test elicited by two different assistants.
- **Left.** Note the attitude of the normal animal and particularly that of its back and hind legs.
- **Right.** The paralysed animals. Note the undue rigidity of its body, the arched back and outstretched hind limbs. (4th day after inoculation).

23. Fig. (25).
- **Left.** Animal which had been paralysed for 14 days. Note excessive wasting and flaccid paralysis.
- **Right.** Normal rabbit after 5 minutes suspension.

**A Fallacy.**

A normal rabbit suspended continuously for 5 minutes in mid air may occasionally show drooping of its hind legs. This test must therefore not be repeated at short intervals if found to be negative on the first occasion. Repeat only at 15 minute intervals.
24. Close up view of No. 22, illustrating the "plumb" test.  
Left: negative animal. Right: positive animal.

25. Two rabbits placed upon the floor.  
Left: animal affected with encephalitic syndrome, showing spasticity of rear legs.  
Right: normal rabbit.

26. Another animal exhibiting the rigidity and spasticity evident in Gordon's syndrome.

27. Two further rabbits in the same condition.  
Left: slightly affected.  
Right: to a greater degree.
gland tissue could not, therefore, be prepared, since it did not readily emulsify or disintegrate after standing in the refrigerator. Twelve animals were injected at weekly intervals for six weeks with this material, while the suspension was left in the refrigerator, but no results followed. In view of these findings it is suggested that the test is not applicable in the case of tough fibrotic glands which do not readily emulsify, disintegrate, or undergo autolysis after standing at low temperatures for several weeks.

Case 6. In order to avoid superficial contamination, enlarged glands removed from both neck and abdomen were flamed in absolute alcohol and plunged into boiling water for two seconds. The superficial loose tissues were then clipped away, and the central portion prepared for emulsification. About 2 g. of tissue were then ground in 20 c.cm. of broth (pH 7.1) and a part of it used for the immediate inoculation of rabbits, whilst the remainder was stored at -4°C. in the refrigerator for later use.

Three rabbits were prepared for intracerebral inoculation, and approximately 0.35 c.cm. of the suspension was introduced into the occipital lobe of each animal to a depth of 3 mm., accompanied also by the administration of an intravenous dose of 0.5 c.cm. into the auricular marginal vein, conducted after the manner described by van Rooyen (1933).

The animals withstood the operation satisfactorily and were apparently in good health after 36 hours. At the end of 48 hours, however, all three rabbits showed slight signs of impaired locomotion. This was followed next day by spastic paralysis of the hind limbs and marked ataxia with incoordination on attempted movement. The last-named features were more readily demonstrable by the application of Gordon's Romberg test for ataxia and van Rooyen's "plumb" test for spastic paraplegia in rabbits.

Tissue suspensions which had been allowed to stand at -4°C. in the refrigerator for varying periods of time up to three weeks were used for the inoculation of 12 additional rabbits. Eleven of these developed the characteristic syndrome described by Gordon within three days. Four rabbits succumbed to the illness, three recovered completely, and four passed into a chronic condition characterised by muscular atrophy of the hind-quarters, loss of weight and hair, and incontinence of urine and faeces.

Bacteriological examination by aerobic and anaerobic methods of cultivation failed to reveal the presence of any organism in the brains of animals which had died from the condition. Media were kept under observation and remained sterile for four weeks.

The/
The above results favoured the conclusion that the case from which the glands had been taken was one of Hodgkin's disease.

**Action of Tuberculous, Leukaemic, Sarcomatous, and other Tissues.**

A suspension of an enlarged cervical tuberculous lymphatic gland, prepared as in the case of lymphadenomatous tissue, was repeatedly introduced into five animals without any sign of appearance of the syndrome in question. Animals were observed for four weeks only, and then destroyed prior to the development of tuberculosis.

Similarly, glands removed from cases of pseudo-leukaemia (Case 7) and lymphosarcoma (Case 8) yielded consistently negative results throughout, suspensions varying in age from one hour to six weeks being unsuccessfully employed.

During the course of the work a variety of tissues other than enlarged lymphatic glands were introduced intracerebrally into rabbits, but with the exception of the result obtained with bone marrow (see page 77) no other significant findings were observed.
Reinoculation with Lymphadenomatous Material.

Four rabbits unaffected after inoculation with non-lymphadenomatous material were reinoculated with Hodgkin's tissue obtained from three separate cases described. After an incubation period of four days all the animals showed the characteristic syndrome.

DISCUSSION.

From the results described above it will be noted that lymphadenomatous tissue, when ground, suspended in broth, and kept at -4°C. for over ten days, produces striking effects when introduced into the brains of rabbits. It is also evident that these effects appear to be specific in character, for it has been shown that similarly prepared suspensions of lymphoid tissue removed from cases which clinically resembled Hodgkin's disease yielded negative results on test. Such cases have included glandular tuberculosis, lymphosarcoma, and leukaemia, all of which perhaps may be regarded as the commonest forms of lymphatic enlargement that may simulate Hodgkin's disease in temperate climates.

Colvert and Sanguinetti (1933), in their description of a case of Hodgkin's disease with relapsing pyrexia, have drawn attention to the extraordinary difficulties which may occasionally confront the clinician and pathologist alike when attempting to arrive/
arrive at a diagnosis in certain atypical forms of lymphadenoma.

In case 6 microscopical examination of tissue from cervical and para-aortic lymph glands, pulmonary growth, and pericardial mass was carried out a week after the autopsy. The histological appearances were in all cases similar. The tissue consisted in the main of a mass of reticulo-endothelial cells of all sizes up to small giant-cells of the typical Hodgkin type. Among this heterogeneous mass of cells were scattered numerous lymphocytes. The background consisted of finely granular, eosinophilic, necrotic-looking material. Here and there fairly large areas of tissue had undergone complete necrosis. This was especially so in the case of the pulmonary growth. Occasionally evidence of slight fibrosis was apparent, but this was not at all an outstanding feature. The condition was histologically one of acute "malignant" Hodgkin's disease.

Thus the biological test was applied to a case in which the clinical and post-mortem naked-eye findings were not conclusive of Hodgkin's disease. The test gave a positive result in 48 hours and thus substantiated a diagnosis of lymphadenoma. This was corroborated a week later by microscopical examination of the tissues.

Dr. /
Dr. Goodell's case (Case 8) illustrates a somewhat similar example. This patient's clinical history was suggestive of Hodgkin's disease, and clinical examination revealed the presence in both axillae and groins of enlarged glands whose size, consistence, and feel were not unlike those of a lymphadenomatous gland. The case, however, presented difficulties, since the histological appearance of these glands was not characteristic of lymphadenoma. Professor Drennan and Dr. James Davidson, however, regarded the condition as being one of lymphosarcoma, and were proved to be correct at necropsy. The case under the care of Dr. John Comrie (Case 7) illustrates another such example, for the diagnosis of pseudo-leukaemia was only first accurately established at post-mortem examination. In both these cases the Gordon biological test repeatedly yielded uniformly negative results throughout.

Space does not permit of a detailed account of experiments which have been directed towards ascertaining the precise nature of the agent responsible for paralysis, ataxia, and muscular wasting in rabbits. The results obtained so far indicate that the autolysis, disintegration, and cellular destruction of lymphadenomatous tissue liberates a product which is capable of producing an encephalitic syndrome in rabbits.
rabbits and guinea-pigs. Neither the inoculum nor the brain of an animal which succumbs to the condition shows the presence of bacteria after lengthy periods of observation.

The encouraging results given by this biological test are worthy of great attention, and we would suggest that glands removed at biopsy in suspected cases of Hodgkin's disease should not only be examined histologically and bacteriologically, but should also be subjected to Gordon's biological test.
FURTHER RESULTS OBTAINED WITH THE BIOLOGICAL TEST.

TWO CASES ILLUSTRATING ITS VALUE IN THE DIAGNOSIS OF MEDIASTINAL HODGKIN'S DISEASE.

The following two cases quoted from Ogilvie and van Rooyen (1934) illustrate the practical value of this test to the morbid anatomist. The first of these, Case 9 (H40) is almost identical with Case 6 (H18 - see page 45) which has been reported by Ogilvie and van Rooyen (1933). The second Case 10 (H38) is an example of a case of true bronchial carcinoma which yielded a negative biological test.

Case 9. (H 40).

Clinical History.

The patient was an unemployed miner aged 59 years who was admitted to the Royal Infirmary, Edinburgh, on 15th November, 1933, complaining of weakness and loss of weight (9 weeks' duration), dyspnoea and cough (6 weeks), anorexia and sweating (3 weeks). The patient was well until about 9 weeks before admission when one day he had a shivering attack and went home to bed. But he did not stay in bed and during the next three weeks he had repeated slight shivers, sometimes two or three in a day. He felt himself getting weaker and people remarked that he was not looking well. Six weeks before admission he was compelled to take/
take to bed because of weakness and about the same time he began to have a cough and to be short of breath. He never saw any blood in his sputum which was yellowish in colour, scanty and difficult to expel. He was constipated and during this time he lost weight rapidly. His appetite was poor. During the three weeks prior to admission he sweated profusely when asleep and latterly his sleep was disturbed.

Two years before he had had a swelling removed from the left side of the neck. This swelling had been present for four years during which time it had enlarged slowly and latterly it had been red. About a year ago he had noticed further swellings in the right side of the neck, but he did not think these had grown much larger lately. They had never been painful or tender.

Previous illnesses included enteric fever and rheumatic fever. There was no family history of tuberculosis, but the patient lived in a small, insanitary and overcrowded house. He used to take a fair amount of alcohol.

Physical Examination.— The man looked ill, pale, and emaciated, but was cheerful and optimistic. There was considerable myotatic irritability. His skin was loose and atonic, his hair shabby and dry. His temperature was 101.4°F. His breathing was mainly abdominal and/
and at the rate of 32 per minute. Chest was well-formed, but poorly clothed and moved equally on both sides. There was no definite impairment of the percussion note, but a suggestive area of dulness was present over the middle zone of the right lung. The breath sounds on both sides were harsh vesicular with sibilant rhonchi towards the end of inspiration and some during expiration. Sputum was negative for the tubercle bacillus. X-ray of chest revealed slight deviation of heart and mediastinum to right side with infiltration of medial part of upper, middle and lower zones of right lung: there was also thickening of the pleura in the lesser and greater fissures. Pulse was 136 per minute, regular in time and force. Blood pressure: systolic 119, diastolic 65. Heart sounds were pure, but feeble. Abdomen was rather prominent. On the skin of the abdomen and lower chest there was a yellow, scaly lesion which had been present since the Boer War. There was no abdominal rigidity or tenderness. No abnormal swellings were present and there was no enlargement of the liver or spleen. Many enlarged glands were present in the neck and axillae. Wassermann Reaction negative. There was nothing to note in the nervous system.

Clinical Diagnosis and Termination of Illness.

In view of the clinical and radiological evidence a diagnosis of pulmonary tuberculosis was made. The patient/
patient unfortunately went rapidly downhill and died six days after admission.

Post-Mortem Examination.

Macroscopical.— The body was that of a somewhat emaciated, middle-aged male. The pericardial sac contained a small quantity of clear serous fluid. The left pleural sac contained half-a-pint of slightly blood-stained fluid: the right contained a few ounces of similar fluid. The peritoneal cavity was healthy. In the right bronchus just beyond the bifurcation of the trachea there was a new growth in the shape of firm, whitish, slightly raised plaques. The growth extended down into the main branch of the right lower lobe and had actually spread for a short distance into the substance of this lobe. It extended upwards into the trachea for 2 or 3 inches and also down the left bronchus and its larger branches. Both lungs were voluminous and emphysematous and showed marked carbon pigmentation. Numerous deposits of white tissue were scattered over the surface of both lungs. Patches of broncho-pneumonia were present in the upper lobe of the right lung. The rest of the lung and also the left lung showed congestion and the bases of both lungs were oedematous. Large masses of glands were found at the roots of the lungs. These extended up the trachea and communicated with similar large glands in/
in the anterior triangles of the neck. Masses of glands were found in both axillae, along the aorta and common iliac vessels, at the porta hepatis, and along the superior border of the pancreas. In all these situations the glands were discrete, firm and elastic in consistence, and on section showed a whitish marbled surface. The heart was globular in shape owing to dilatation of all chambers. The myocardium was very pale and soft. Coronary vessels and aorta showed slight atheroma. Oesophagus, stomach and intestines were free from pathological change. Liver was of average size but pale. It was dotted throughout by small white deposits, the largest of which was a centimetre in diameter. Spleen was three times its normal size and nodular on the surface. On section it presented a dark red surface throughout which were scattered nodules of white tissue. Pancreas showed nothing of interest. The genito-urinary system beyond abnormal pallor of the kidneys was normal. A large deposit about $2\frac{1}{2}$ centimetres in diameter was found in the left parietal bone towards the vertex. It was similar in appearance and consistence to the glandular masses elsewhere. It involved the whole thickness of the skull, but the underlying dura was not affected. Other deposits were discovered in several of the vertebrae (T 3, 4, 10, 12, L 1 and 2). The brain
and its meninges were healthy, but the cerebral vessels were markedly atheromatous. The yellow marrow at the middle of the femur was replaced by whitish tissue.

Microscopical.- Tracheal and pulmonary growths consisted of polyhedral cells with a moderate amount of clear cytoplasm and a nucleus varying in size and chromatin content. These cells were for the most part distributed indiscriminately, but occasionally, especially in the pulmonary growth, they tended to assume a palisade arrangement, though no actual acini were formed. In the tracheal growth cells were occasionally seen larger than the others with a single lobulated nucleus or with 2 to 6 nuclei irregularly arranged toward the centre of the cell. No such cells were observed in the pulmonary growth. Special staining revealed the presence between the cells of a fine supporting reticulum. This malignant-looking tissue was actively invading the mucosa of the trachea on the one hand and the alveoli of the lung on the other. Many mitotic figures were present throughout the tissue of both lesions.

In one of the lymph-glands examined only a few small foci of lymphoid tissue were left. The remainder of the tissue presented appearances similar to those of the tracheal lesion though small giant-cells with single lobulated or several nuclei were rather more numerous.
numerous and there was no palisade arrangement. Between the cells was a very definite fine reticulum. In another gland widespread necrosis had occurred with haemorrhage and the formation of haemosiderin.

In the liver small foci of new growth had developed in relation to some of the portal tracts. The histology of these and also of the growths in the spleen, marrow, skull and vertebrae was similar to that of the trachea and lymph-glands above described.

**Biological Test.**

A large gland removed from the left axilla was freed from superficial contamination by flaming with absolute alcohol, immersion in boiling water for 2 seconds, and subsequent removal of loose surrounding tissue. The gland was then divided with a knife and a portion (about 1 gram) was removed from the centre. This was finely divided, and thereafter emulsified with pestal and mortar in 20 c.c. broth of pH 7.1. The emulsion was divided into two parts: one of these was used for immediate intracerebral inoculation of 3 rabbits; the other was allowed to stand for 7 days in a refrigerator at -4°C and then used for inoculation of 3 additional rabbits. Inoculation consisted in the injection of 0.35 c.c. of the suspension into the occipital lobe of each animal to a depth of 3 mm. This/
This was accompanied by the administration of an intravenous dose of 0.5 c.c. into the auricular marginal vein.

The three animals which were inoculated immediately with gland emulsion showed after 4 days signs of only slight ataxia from which they rapidly recovered. The other three rabbits injected with emulsion which had been refrigerated for a week showed signs of gross nervous damage. These signs consisted of ataxia and incoordination setting in on the third day and progressing rapidly during the next few days to complete paralysis of the hind quarters with head retraction and nystagmus. On examination by aerobic and anaerobic methods of cultivation the brain and meninges of these animals yielded no growth. The test was, therefore, regarded as positive in favour of Hodgkin's disease.

Discussion.

The diagnosis of this case remained in doubt even after naked-eye study of the organs and histological examination of the various lesions. The main interest centres round the biological test and the help it gave in determining the diagnosis.

The clinical diagnosis was pulmonary tuberculosis. Post-mortem the diagnosis lay between (1) bronchial carcinoma and (2) lymphadenoma. The former was favoured by (a) age of patient (60 years): (b) the presence of tracheal and bronchial lesions invading the right lung: (c) the presence in the pulmonary growth/
growth (right lung) of more or less columnar cells arranged in rows in the midst of an otherwise spheroidal-celled tissue: (d) the indeterminate histology of the lesions in other organs. Points in favour of lymphadenoma were (a) a history of cervical glandular swellings for six years: (b) widespread lymphatic involvement (post-mortem) and the character of the glandular masses: (c) involvement of liver and spleen: (d) the presence in all the lesions of a fine but definite supporting reticulum: (e) the occurrence in most lesions of cells like Hodgkin giant-cells.

Although the weight of evidence was undoubtedly in favour of lymphadenoma there yet remained an element of doubt. Consequently the result of Gordon's Test was anticipated with interest and as already indicated it was positive. Since, moreover, bronchial carcinoma yields a negative biological test (see Case 2) the lymphadenomatous character of this case seemed definitely established.

To complete the history it should be stated that the gland which had been removed from the neck 2 years before death (1931) and examined elsewhere was later traced. It showed lymphoid hyperplasia with loss of gland-architecture and in places proliferation of endothelial cells amongst which were a few single giant-cells with single convoluted nucleus, or two or/
or three nuclei. The condition was histologically one of early Hodgkin's disease. The case is thus also noteworthy as illustrating how the lymphadenomatous lesion from being more or less characteristic may in the course of time develop very atypical features and assume malignant characters.

**Case 10 (H 38).**

**Clinical History.**

A railway ported aged 61 years was admitted on 17th November 1933 with a history for the past six months of pain in the upper part of the left chest anteriorly. For the past two months there had been a painful, tender swelling about 3.5 cm. in diameter over the second left costal cartilage. Until a fort-night before admission he had been in good health except for the painful swelling, but since then he had felt weak and breathless on exertion and had noticed that his ankles were swollen, particularly in the evening. He had had a slight cough for years.

**Physical Examination.**—The patient had an ashen complexion with a cyanotic tinge. Two firm, tender lumps each about 3 cm. in diameter were present under the skin over the second left rib. Chest expansion was diminished. In the lower part of the right lung there were areas of low-pitched bronchial breathing with moist accompaniments and in the left lung there was/
was dulness with high-pitched bronchial breathing and whispering pectoriloquy. Cardio-vascular, alimentary, genito-urinary and nervous systems showed nothing of interest. There was a slight degree of secondary anaemia.

Post-Mortem Examination.

The lungs were moderately emphysematous and showed some basal congestion. The right lung was otherwise healthy. In the left bronchus just beyond the bifurcation of the trachea there was a nodule of neoplastic tissue in process of invading the adjacent lung substance. The nodule was continuous in the anterior mediastinum with a large, firm, creamy-yellow new growth consisting apparently of enlarged lymphatic glands. The upper part of the lung was collapsed and heavily infected owing to bronchial obstruction. The mediastinal mass also extended through the intercostal spaces to form two nodules below the left pectoralis major. The right kidney contained a single large mass of tumour tissue similar to that described. The left lobe of the prostate gland had in it a nodule which superficially resembled the tumours elsewhere. Liver showed marked chronic venous congestion. Spleen exhibited no noteworthy abnormality. The abdominal lymphatic glands with the exception of one on the right renal vein showed no malignant involvement.

Microscopical/
Microscopical examination of the thoracic mass proved it to consist of adeno-carcinomatous tissue. Much of the tumour was very undifferentiated, but acini occurred here and there. The neoplasm had induced the formation of fairly abundant stroma. Lymph-glands and right kidney showed invasion by similar tissue. Prostatic nodule was adenomatous in character and microscopically did not resemble the other neoplasms.

Macroscopical and microscopical findings together indicated a Bronchial Carcinoma.

Biological Test.

3 rabbits were inoculated after the manner above described with tissue taken from enlarged lymph-glands - one immediately on 9th October (day of autopsy), a second on 1st November, and a third on 8th November. The material used to inoculate the last two rabbits was kept in a refrigerator at -4°C. All of the animals remained normal and the test was, therefore, regarded as negative.

Summary.

Two cases are described. In Case 9 the clinical and post-mortem (macroscopical and microscopical) findings while favouring Hodgkin's disease did not conclusively support such a diagnosis. Gordon's biological/
biological test was applied to the case. The test gave a positive result, thus supporting a diagnosis of lymphadenoma. Case 10 is one which macroscopically resembled Hodgkin's disease: it yielded a negative biological test and was ultimately proved by histological examination to be a typical bronchial carcinoma.

These cases illustrate the value of Gordon's test as a diagnostic procedure in circumstances where Hodgkin's disease is suspected in the mediastinum.

SUMMARY OF RESULTS OBTAINED WITH THE BIOLOGICAL TEST.

The following are a list of results obtained with material derived from cases situated in different parts of the country.
### BIOLOGICAL DIAGNOSTIC TEST (GORDON).

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Patient's Initial</th>
<th>Specimen supplied by</th>
<th>Institution</th>
<th>Histological Diagnosis</th>
<th>Result of Test</th>
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<tbody>
<tr>
<td>* H9</td>
<td>T.</td>
<td>Dr. Chalmers Watson.</td>
<td>Royal Infirmary,</td>
<td>Hodgkin's Disease.</td>
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<tr>
<td>* H10</td>
<td>J.</td>
<td>Dr. Goodall.</td>
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<td>* H12</td>
<td>R.</td>
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<td>F.</td>
<td>Dr. Matthews.</td>
<td>&quot;</td>
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<td>* H15</td>
<td>L.</td>
<td>Prof. Murray Lyon.</td>
<td>&quot;</td>
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<td>** H18</td>
<td>H.</td>
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<td>&quot;</td>
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<td></td>
<td></td>
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<td>&quot;</td>
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<td>H32</td>
<td>C.</td>
<td>Dr. Goodall.</td>
<td>Stobhill Hospital,</td>
<td>&quot;</td>
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<td>C.</td>
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<td>&quot;</td>
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<td>Royal Infirmary,</td>
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<td>H.</td>
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<td>G.</td>
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<td>Royal Sick Childrens</td>
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<td>Hospital, Aberdeen.</td>
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<td>B.</td>
<td>Dr. Larks and Dr. McConaghy.</td>
<td>City Hospital, Plymouth, England</td>
<td>Hodgkin's Disease</td>
<td>Positive.</td>
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<td>* H11</td>
<td>A.</td>
<td>Dr. Goodall.</td>
<td>Royal Infirmary, Edinburgh</td>
<td>Lymphosarcoma.</td>
<td>Negative.</td>
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<td>* H13</td>
<td>McI.</td>
<td>Dr. Comrie.</td>
<td>Royal Infirmary, Edinburgh</td>
<td>Pseudoleukaemia.</td>
<td>Negative.</td>
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<td>H20</td>
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<td>Dr. Goodall.</td>
<td>Royal Infirmary, Edinburgh</td>
<td>Lymphosarcoma.</td>
<td>Negative.</td>
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<tr>
<td>H22</td>
<td>McH.</td>
<td>Mr. Stewart.</td>
<td>Royal Infirmary, Edinburgh</td>
<td>Gumma ? Tubercle.</td>
<td>Negative.</td>
</tr>
<tr>
<td>H29</td>
<td>R.</td>
<td></td>
<td>Royal Infirmary, Edinburgh</td>
<td>Acute Lymphatic leukaemia.</td>
<td>Negative.</td>
</tr>
<tr>
<td>H44</td>
<td>McI.</td>
<td>Dr. Cruikshank.</td>
<td>Royal Infirmary, Glasgow</td>
<td>Lymphatic leukaemia.</td>
<td>Negative.</td>
</tr>
<tr>
<td>H36</td>
<td>H.</td>
<td>Mr. Chiene.</td>
<td>Royal Infirmary, Edinburgh</td>
<td>Lymphosarcoma.</td>
<td>Negative.</td>
</tr>
<tr>
<td>H27</td>
<td>L.</td>
<td>Prof. Wilkie.</td>
<td>Royal Infirmary, Edinburgh</td>
<td>Leukaemia.</td>
<td>Negative.</td>
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<tr>
<td>H8</td>
<td>A.</td>
<td>Prof. Murray Lyon.</td>
<td>Royal Infirmary, Edinburgh</td>
<td>Tuberculosis.</td>
<td>Negative.</td>
</tr>
<tr>
<td>H30</td>
<td>G.</td>
<td>Dr. Eason.</td>
<td>Royal Infirmary, Edinburgh</td>
<td>Carcinoma (Bronchial)</td>
<td>Negative.</td>
</tr>
<tr>
<td><strong>H38</strong></td>
<td>C.</td>
<td>Prof. Ritchie.</td>
<td>Royal Infirmary, Edinburgh</td>
<td>Leukaemia.</td>
<td>Negative.</td>
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<tr>
<td>H39</td>
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<td>Mr. Stirling.</td>
<td>Royal Infirmary, Edinburgh</td>
<td>Lymphosarcoma.</td>
<td>Negative.</td>
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<tr>
<td>H42</td>
<td>McQ.</td>
<td>Dr. McCrie.</td>
<td>Royal Infirmary, Edinburgh</td>
<td>Lymphosarcoma.</td>
<td>Negative.</td>
</tr>
</tbody>
</table>

* Previously published see van Rooyen, (1933).
** Submitted for publication see Ogilvie and van Rooyen (1933).
*** Submitted for publication see Ogilvie and van Rooyen (1934).
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Patient’s Initial</th>
<th>Specimen submitted by</th>
<th>Institution</th>
<th>Histological Diagnosis</th>
<th>Result of test</th>
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<tbody>
<tr>
<td>H46</td>
<td>F.</td>
<td>Dr. Comrie.</td>
<td>Royal Infirmary, Edinburgh.</td>
<td>&quot;</td>
<td>&quot;</td>
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</table>
Gordon's test has been applied to clinical and post-mortem material derived from 20 separate cases of Hodgkin's disease, and 15 of these were found to give a positive result.

Other cases of lymphadenomegaly due to a variety of different pathological conditions have likewise been submitted to the test but found to be negative.

The test is exceedingly helpful as an aid to the diagnosis of Hodgkin's disease when the histological appearances are not entirely typical of the condition. For example, in Case 9(H40), death appeared to be due to bronchial carcinoma with secondary metastasis in the lymphatic glands and elsewhere. Microscopical findings, however, led to considerable diversity of opinion with regard to the diagnosis and there was much speculation in regard to the nature of the condition. The case however gave a strongly positive reaction in the rabbit and was ultimately proved to be one of Hodgkin's disease, for this patient had already been some years previously, under the care of an institution elsewhere, at which biopsy had been performed and the histological section found to be typical of Hodgkin's disease. This is the second case I have encountered in which the test has proved to/

*see page 51.
to be of great value, the first of them has been recorded, Ogilvie and van Rooyen (1933), and it is hoped that these findings may prove of interest to other workers.

It will be observed from the above table that certain specimens of glands produced more severe lesions in the rabbit than others. For example, Cases H33 - H40 - H15 and H18 all produced a strong reaction in animals injected with emulsified glands soon after their excision from the patient. The remainder however had to be emulsified in broth (pH 7.1) and stored at -4°C for 7 days (at least) before a satisfactory result could be obtained in the animal. A few were entirely negative and preliminary treatment did not influence the results.

In view of this marked variability in pathogenicity exhibited by different specimens, an attempt was made to ascertain whether the reaction was dependent on the predominance of any particular type of cell present in the lymphatic gland. Sections were therefore made from glands which gave strong, weak and negative reactions respectively in the rabbit and these were examined microscopically in order to detect any demonstrable differences in histopathological appearance. No significant changes could however be found and attempts to correlate/

* page 45 Case 6 (H18).
correlate the syndrome with the presence of any particular type of cell seen in the histological picture described by Sternberg and Reed, were unsuccessful.

The syndrome does not depend on the presence of lymphocytes or immature forms of haemopoietic cells, for enlarged glands removed from cases of lymphosarcoma and leukaemia give negative results. It is not related to Sternberg-Reed giant cells for glands containing large numbers of them appeared to be no more toxic to the rabbit than those which contained only a few. This point is well illustrated in two cases of Hodgkin's disease, H9 and H40 respectively. The former of these revealed histologically numerous giant cells, but nevertheless repeatedly yielded a negative result (glands being excised both at biopsy and necropsy). The latter on the contrary exhibited only a few of them but gave a strongly positive result.

The presence of eosinophilia does not appear to be of any consequence either, for the syndrome has been reproduced with tissue revealing only occasional eosinophil cells on histological section.

The result noted with bone-marrow may help to throw some light on the problem but the subject requires further study.
SUMMARY AND CONCLUSIONS.

Enlarged lymph glands removed from 20 cases of Hodgkin's disease have been subjected to the test devised by Gordon, and 15 positive, and 5 negative results were obtained.

The syndrome produced in rabbits by Hodgkin's tissue cannot be elicited by the introduction of normal, lymphosarcomatous, leukaemic, or tuberculous lymphatic tissue.

Gordon's biological test affords an easy method whereby lymphadenomatous tissue may be differentiated from lymphosarcomatous, leukaemic, and tuberculous tissue. In consequence of this it may be utilized as a laboratory aid to the diagnosis of Hodgkin's disease.
28. Inflammatory nodule produced in the subcutaneous tissues of a guinea-pig after 4 days, following inoculation with Hodgkin lymphatic tissue. (Twort, 1930).

29. A close up view of the nodule showing the circumscribed area of congestion and redness.

Note: Twort claimed no specificity for the occurrence of such a nodule since a similar type of reaction was produced by injecting tissue derived from burns and other clinical conditions. The occurrence of the phenomenon, however, in association with Hodgkin's disease is nevertheless of importance. Such a nodule as this neither reveals the presence of bacteria within it, nor does it appear to be readily transmissible.
PART IV.

AN INVESTIGATION INTO THE NATURE OF THE PATHOGENIC AGENT CONTAINED IN HODGKIN LYMPHATIC GLANDS.

Recent work on the aetiology of Hodgkin's disease has served to bring fresh interest to bear on the nature of this condition.

In 1930 L'Esperance reported having isolated the avian tubercle bacillus from cases of Hodgkin's disease and claimed to have reproduced the condition in chickens. These claims have been investigated by Davidson (1933), the workers of the Rose Research on Lymphadenoma (1932), van Rooyen (1933), and others, all of whom failed to reproduce the disease in birds or to isolate the avian tubercle bacillus from human lesions in the disease. In 1930 Twort found that the subcutaneous inoculation of a guinea-pig with a suspension of Hodgkin lymphatic tissue produced after three to four days a swollen inflammatory nodule, in which no bacteria could be demonstrated by the application of ordinary methods. The workers of the Rose Research on Lymphadenoma (1932) next published an extensive series of observations on the pathology of the condition, showing that neither spirochaetes, yeasts, diphtheroids, nor acid-fast organisms were responsible/
responsible for the causation of the disease.

THE ENCEPHALITIC SYNDROME IN RABBITS.

Among the many findings of the last-named workers those of M.H. Gordon were perhaps of the greatest significance. He found that the intracerebral inoculation of rabbits with suitable suspensions of lymphadenomatous tissue was followed in three to four days by highly characteristic changes affecting the central nervous system of the animal. The sequence of events was: initially, slight impairment of locomotion, this being followed by progressive ataxia, muscular incoordination with spasm, spastic paralysis of the hind limbs, and frequently accompanied by incontinence of urine and faeces. The severity of these lesions produced in the rabbit were to some extent dependent on the acuteness of the case from which material was derived. Thus tissue from an acute case of Hodgkin's disease produced, in addition to the foregoing changes, violent convulsive movements, head retraction, opisthotonos, and grinding of the teeth. Animals affected to such an extent inevitably died, but in the less severe type of lesion several recovered completely, and a few passed into a chronic state in which severe muscular atrophy and wasting were much in evidence.

This "encephalitic" syndrome, as described by Gordon/
Gordon (1932), was found to be highly specific in character, and could not be elicited by the intra-cerebral inoculation of rabbits with material derived from cases other than those of Hodgkin's disease. This fact has been utilized by the writer (1933), who attempted to use this finding to form the basis of a biological test for the more accurate diagnosis of Hodgkin's disease.

The test has proved of value as an aid to the clinical and post-mortem diagnosis of this disease, particularly when the appearances presented are not entirely typical of the condition. In view of the satisfactory results obtained from the Gordon biological test, it has been proposed that material removed at biopsy and necropsy from suspected cases of Hodgkin's disease should be subjected not only to histological examination, but also to this animal inoculation test. It must be emphasized, however, that a rabbit which exhibits the encephalitic syndrome reveals no cultivable bacterium in either its brain or meninges. Hence, prior to the acceptance of a positive result in any animal, the possibility of bacterial infection being responsible for the effects manifested should first be excluded by appropriate methods of bacteriological examination.

ITS AETIOLOGY.

From/
From the theoretical standpoint one or other of the following causes might be responsible for the production of the condition.

(a) Trauma following damage by mechanical irritation.

(b) A specific neurotoxin present in vivo in lesions of Hodgkin's disease, or produced in vitro by changes in the tissue of the lesion after removal from the body.

(c) The action of a virus specifically associated with the disease and producing an effect on the nervous system of the rabbit.

The complexity of this problem, combined with the incomplete state of our knowledge regarding diseases produced by ultra-microscopic viruses in general, render it extremely difficult to express a dogmatic view regarding the nature of the pathogenic agent under discussion. I propose, therefore, merely to discuss the arguments relative to the above-mentioned hypotheses, guided by the experimental evidence so far advanced.

TRAUMA.

Efforts to Reproduce the Syndrome by the Intracerebral Inoculation of Toxins, Proteins, and Chemical and Mechanical Irritants.

In an endeavour to reproduce this encephalitic syndrome by other means the following substances were inoculated intracerebrally: 0.2 c.cm. of an active streptococcal.
streptococcal toxin; 0.4 c.cm. of a killed emulsion of
*P. typhosus* (916 million organisms); 0.7 c.cm. of
sterile milk; 0.4 c.cm. of 5 per cent sodium nucleinate
with 5 per cent aleuronat; 0.2 c.cm. of a mixture of
1 per cent solution of quinine hydrochloride and 2 per
cent urethane; 0.4 c.cm. of 1 per cent peptone water;
0.2 c.cm. of 1 per cent turpentine oil; and 0.3 c.cm.
of a sterile suspension of powdered glass in gum
tragacanth. In each case, excepting the last, an
intravenous dose of 0.4 c.cm. was also given.

Rabbits injected with turpentine and powdered
glass showed signs of cerebral irritation accompanied
by increasing restlessness after forty-eight hours,
followed by sudden collapse and death three to four
days later. The remaining animals were kept under
observation for periods varying from seven to fourteen
days and then examined for histological changes at the
site of inoculation in the brain, but on no single
occasion was it found possible to reproduce effects
which bore the least resemblance to the syndrome
under discussion. Indeed, some of these irritant
substances could be introduced into the brains of
rabbits as young as six weeks old without the slightest
visible effects being produced.

From the results indicated above it was concluded
that the inability of irritant substances to produce
paralysis
Histological Changes produced in the Brain of a Rabbit injected with Hodgkin Lymphatic Tissue. (Case No. H18 Professor Murray Lyon, Royal Infirmary, Edinburgh.)

30. Site of inoculation showing the needle track occupied by a few erythrocytes and a surrounding area of lymphocytic infiltration. (x 55)

31. Above, under higher magnification showing lymphocytic infiltration. (x 312)

32. View of adjacent brain tissue showing changes around the capillaries. (x 40)

33. Oblique section of blood vessel in this area viewed under x magnification, exhibiting perivascular lymphocytic infiltration or "cuffing". (x 280)
paralysis, ataxia, and muscular wasting in rabbits strongly supports the view that the changes following the introduction of lymphadenomatous material cannot be attributed to the outcome of simple traumatic and inflammatory changes produced in the brains of these animals. It would thus appear that the symptoms are the result of the action of a diffusible agent present in suspensions of lymphadenomatous glands when kept at -4°C for ten days or longer.

**HISTOLOGICAL CHANGES IN THE RABBIT'S BRAIN.**

Below is a discussion on trauma and the histological changes produced experimentally following intracerebral inoculation with Hodgkin's tissue and other substances described above.

The chosen site of inoculation lies in the occipital lobe of the rabbit, and is situated well behind the motor area of its brain. Histo-pathological changes following the inoculation of Hodgkin tissue into this area were relatively slight in character. They revealed the occurrence of some localized haemorrhage occupying the path of the needle, and surrounded by a zone of lymphocytic infiltration. Occasionally similar infiltration of the meninges overlying the point of inoculation was also noticed, but this finding was too inconstant to be regarded as a regular feature. It may be stated that the slight histo-pathological changes/
Photographs supplied by courtesy of Dr. M.H. Gordon, St. Bartholomew's Hospital, London, illustrating:

Histological changes produced in the brain and meninges of the guinea-pig after injection with Hodgkin lymphatic tissue.

34-35. Meningeal infiltration.

36. Site of inoculation showing lymphocitic infiltration.

37-38. Longitudinal sections of blood vessel showing perivascular infiltration and "cuffing".
Two rabbits 7 days after intracerebral inoculation with powdered glass and 1 per cent turpentine oil respectively. Neither animal showed any apparent signs of disease up to the time of taking this photograph. (R83 and R213).

Histological section made from the brain of R83 showing gross evidence of damage. Haemorrhage, lymphocytes and wandering mononuclear cells are present together with a few polymorphonuclear leucocytes. (x 50)

Section made from the brain of R213. Note extensive damage produced by turpentine oil. Widespread haemorrhage occupying the major part of the field is accompanied also by cellular infiltration and necrosis of brain parenchyma. (x 50)
Section of rabbit's brain showing the site of inoculation after the introduction of 0.4 c.c. of 5 per cent Sodium Nucleinate and 5 per cent aleuronat. There is considerable congestion, capillary dilation and much diffuse haemorrhage.

(x 50)

High power view of above showing an area of haemorrhage which has undergone hyaline degeneration.

(x 250)

Also a view of the same tissue showing the intense infiltration with lymphocytes and wandering mononuclear cells.

(x 312)

Note: A mixture of 5 per cent Sodium Nucleinate and Aleuronat when introduced into the tissues of a rabbit (e.g. pleura) give rise to the production of a considerable cellular inflammatory exudate. (See Mackie and van Rooyen, 1934). Although such extensive damage was present, two animals injected, remained well and healthy up to the time of autopsy 10 days later.
non-specific irritant substances into the brain of that animal.

TOXIN OR VIRUS?

The only unequivocal proof of the existence of a living virus is by means of its demonstration in vivo and in vitro, the former by serial propagation in the living animal and the latter as evidenced by its multiplication in artificial culture.

Neither condition has been fulfilled in the case of this pathogenic agent. The weight of experimental evidence so far advanced is equally capable of indicating the cause of the encephalitic syndrome to be the outcome of specific toxic activity or to its substance to withstand desiccation, to resist 73°C for half an hour, to be annulled by the action of weak antiseptics, and occasionally to give rise to immunity phenomena (Gordon, 1932-3) is a common property of both a virus and a toxin. This agent has been further stated by Gordon to be non-filterable, but the writer has latterly been able to demonstrate in a series of preliminary experiments that filtration could be effected under certain conditions. He also observed that tissue suspensions appeared to be most active when suspended in broth ranging from pH 6.2 to pH 7.2. This/
This aspect of the subject is under course of investigation and will be dealt with later.

CONCLUSION.

It can be stated that the encephalitic syndrome produced in the rabbit is specific for Hodgkin lymphoid tissue, and may consequently be utilized as a biological test for the diagnosis of the condition. The precise nature of the syndrome produced in the rabbit is not the outcome of a simple traumatic and inflammatory change produced in the brain of the animal, but is probably due to the action of either a specific toxin or a filterable virus, derived from the human subject suffering from Hodgkin's disease. The present available data regarding the nature of this pathogenic agent neither confirm the possibility of these effects being the results of a specific toxic activity nor exclude them from being due to the action of a filterable virus.
AN OBSERVATION ON THE BONE MARROW FROM A CASE OF ACUTE MYELOGENOUS LEUKAEMIA.

During the course of this work different tissues derived from various pathological conditions have been introduced into the brains of rabbits, including bone marrow derived from two cases of Hodgkin's disease. Only one result of any significance was obtained and this is recorded below.

It concerns the bone-marrow removed from the femur in a fatal case of acute myelogenous leukaemia. The specimen was one which exhibited chloromatous change and contained little or no visible fat. The following clinical and post-mortem notes describe the subject from which the specimen was procured:

C.F., female, set. 35, under care of Professor Bramwell at the Royal Infirmary, Edinburgh. Complained of progressive anaemia for several weeks, bleeding, ulceration and swelling of gums. Metrorrhagia and menorrhagia during last 10 days. Ecchymosis on trunk and legs.

R.B.C. 1,900,000 per cm. HB 33%. C.I. 0.8.
W.B.C. 7000 per cm. Reticulocytes 1%. Polymorphs few. Small lymphocytes increased. Myelocytes and megaloblasts numerous.

Post-mortem revealed leucoclastic reaction and deposit of chloromatous pigment in marrow. Cloudy swelling of myocardium, liver and kidneys. Petechial haemorrhages into epicardium and gastric mucosa. Spleen was slightly enlarged and gave a positive prussian blue reaction.

Of 8 rabbits injected intracerebrally with this tissue after 3-4 days all developed a spastic condition.
dition of their hind limbs which closely resembled the encephalitic syndrome of Gordon. On the other hand a lymphatic gland removed from the same patient gave a negative result in the biological test.

Whether the encephalitogenic agent in bone marrow described by Friedemann and Elkeles (1933) and also by the writer of this paper, are identical with that present in lymphadenomatous tissue, can only be decided after further investigation. It is hoped that information supplied in this paper concerning some physical properties of the latter might offer help towards a solution of the problem.

SOME PROPERTIES OF THE ENCEPHALITOCGENIC AGENT PRESENT IN LYMPHATIC GLANDS AFFECTED WITH HODGKIN'S DISEASE.

The optimum conditions necessary for the activation of the pathogenic agent from tissue, - influence of pH.

Some earlier results showed that the pH of broth used for the emulsification of tissue appeared to influence the pathogenicity of suspensions to the rabbit's brain. Accordingly in these experiments an endeavour was made to discover the optimum hydrogen-ion concentration necessary for the activation of the pathogenic agent from lymphadenomatous tissue.

It has previously been noted by van Rooyen (1933) that material procured from different cases of this disease/
disease showed marked variation in their pathogenicity to the rabbit. Hence it was necessary to estimate the degree of activity possessed by each specimen of gland by the preliminary inoculation of rabbits with varying dilutions of tissue-suspensions. An approximate estimation of the minimum pathogenic dose to the rabbit could thus be arrived at for each specimen employed. The proportion of tissue present in each emulsion varied from 1:20 to 1:40 parts per cc. of which the dose administered was 0.4 cc. intravenously and 0.4 cc. intracerebrally.

Dessicated material derived from different cases of Hodgkin's disease was weighed, emulsified and diluted in broth varying in range from pH 5 to pH 10 and then used for intracerebral inoculation, (vide supra). Animals were injected both immediately after each suspension was prepared and after it had stood for periods varying from 3 to 25 days in a refrigerator at -4°C.

The latter procedure was adopted in order to elicit further information concerning the nature of changes which occurred in these tissue suspensions when maintained at low temperatures, for varying periods of time as in Gordon's original technique.

Technique of pH estimation.

The method adopted was to obtain varying degrees of/
of pH by adding $\frac{N}{20}$ NaOH to 5 c.c. of buffered phosphate broth, 0.5 c.c. of a 0.01 per cent aqueous solution of phenol red was used as indicator and by comparison with a standard set of indicator tubes readings were made over the range pH 6.6 to pH 8.

Above and below these figures a Universal indicator and Brom-thymol blue were used for indicators.

The above method could not be used when working with smaller quantities of fluid and the pH of these had to be ascertained by means of a B.D.H. capillitator outfit. Phenol red, Brom-cresol purple and thymol blue being used as indicators in order to obtain the desired pH range.
## EFFECT FOLLOWING VARIATIONS IN THE pH OF TISSUE SUSPENSIONS.

<table>
<thead>
<tr>
<th>Animal Number</th>
<th>Gland Tissue used</th>
<th>pH of broth used for Suspension</th>
<th>Concentration of tissue</th>
<th>Duration of maintenance at -4°C</th>
<th>Results Following inoculation of Rabbit</th>
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</thead>
<tbody>
<tr>
<td>R 354</td>
<td>EDH18</td>
<td>5.6</td>
<td>1:20</td>
<td>3 days</td>
<td>Negative</td>
</tr>
<tr>
<td>R 345</td>
<td>EDH18</td>
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<tr>
<td>R 350</td>
<td>EDH18</td>
<td>6.6</td>
<td>1:20</td>
<td>4 days</td>
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</tr>
<tr>
<td>R 351</td>
<td>EDH18</td>
<td>6.8</td>
<td>1:20</td>
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<tr>
<td>R 352</td>
<td>EDH18</td>
<td>7.0</td>
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</tr>
<tr>
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<td>7 days</td>
<td>&quot;</td>
</tr>
<tr>
<td>R 369</td>
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<td>1:20</td>
<td>8 days</td>
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<tr>
<td>R 364</td>
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<td>R 349</td>
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<tr>
<td>R 353*</td>
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<td>1:20</td>
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<tr>
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<td>EDH18</td>
<td>7.6</td>
<td>1:20</td>
<td>3 days</td>
<td>Negative</td>
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<tr>
<td>R 353/1</td>
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<td></td>
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<tr>
<td>Animal Number</td>
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<td>Concentration of tissue</td>
<td>Duration of maintenance at -4°C</td>
<td>Results following inoculation of rabbit</td>
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<tr>
<td>R 353</td>
<td>EDH18</td>
<td>7.6</td>
<td>1:20</td>
<td>4 days</td>
<td>Negative</td>
</tr>
<tr>
<td>R 379</td>
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<td>1:20</td>
<td>8 days</td>
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<tr>
<td>R 367</td>
<td>EDH18</td>
<td>7.6</td>
<td>1:40</td>
<td>3 days</td>
<td>Negative</td>
</tr>
<tr>
<td>R 365</td>
<td>EDH18</td>
<td>7.6</td>
<td>1:40</td>
<td>7 days</td>
<td>Positive</td>
</tr>
<tr>
<td>R 516</td>
<td>LD Et.</td>
<td>6.0</td>
<td>1:40</td>
<td>inoculated immediately</td>
<td>Positive</td>
</tr>
<tr>
<td>R 526</td>
<td>LD Et.</td>
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<td>1:40</td>
<td>inoculated immediately</td>
<td>Negative</td>
</tr>
<tr>
<td>R 517</td>
<td>LD Et.</td>
<td>7.0</td>
<td>1:40</td>
<td>inoculated immediately</td>
<td>Negative</td>
</tr>
<tr>
<td>R 518</td>
<td>LD Et.</td>
<td>8.0</td>
<td>1:40</td>
<td>3 days</td>
<td>Negative</td>
</tr>
<tr>
<td>R 520</td>
<td>LD Et.</td>
<td>10.0</td>
<td>1:40</td>
<td>7 days</td>
<td>Positive</td>
</tr>
</tbody>
</table>
The above results strongly indicate that the agent present in Hodgkin lymphatic tissue only exhibited maximum activity within a comparatively narrow pH range (6.8 - 7.3). Thus for example, whilst a 1:40 suspension of gland tissue emulsified in broth of pH 7 was found to be active both immediately and after 3 days, yet tissue suspended in broth of pH 5.6 or pH 8, produced no effect in the rabbit, when tested under identical conditions.

The same common characteristic has been demonstrated in tissues derived from 3 different cases of Hodgkin's disease.

Efforts made to reactivate tissues which had been previously rendered inactive by suspension in broth of pH 5 or pH 8 (vide supra), by the addition of fresh alkali or acid, were without success. It was therefore concluded that this inactivation was an irreversible reaction.

Reduction in the Pathogenicity of Tissue Emulsions to the Rabbit by the action of Sodium Hydroxide, Sodium Bicarbonate, Ammonia and Ammonium Carbonate.

In view of the preceeding experiments concerning the influence of pH on this agent, attention was next paid to the effect of treating highly pathogenic suspensions of Hodgkin lymphatic tissue with certain alkalis, prior to the intracerebral inoculation of rabbits.
The difficulties encountered in attempting to arrive at an accurate standard of dosage for the rabbit have already been alluded to. Accordingly it was possible only to compare the relative severity of changes produced in 2 rabbits the one inoculated with normal material and the other with the same tissue after it had been treated with alkalis.

Thus it was observed that the treatment of a highly pathogenic suspension of tissue with 1 per cent NaOH for 24 hours at -4°C resulted in considerable loss of pathogenicity for the rabbit. The effect was even more noticeable with less active tissue which could be inactivated by 0.5 per cent liquid Ammonia or Ammonium carbonate within 12 - 24 hours.

The effect appears to be quantitative in nature for it depends on the activity of the tissue, the concentration of alkali and duration of its action. As previously, attempts to reactivate inactive material by neutralisation with acid were unsuccessful.

Filtration Experiments.

Previous experiments to demonstrate the filterability of this pathogenic agent were unsuccessful. Since the writer's findings have suggested that a comparatively narrow range of hydrogen-ion concentration is necessary for the satisfactory demonstration of this pathogenic agent, it is probable that/
that variations in pH resulting from the act of passage through an earthenware candle may have been sufficient to account for the inert filtrates reported by Gordon (1932-3).

He has overcome this difficulty by the employment of specially treated filter candles and has been able to demonstrate the filterability of Gordon's pathogenic agent to the rabbit.

Technique of Filtration.

Two types of filters were used, the one a Berkefeld (British) and the other a Seitz (EK) fine pore asbestos disc of 1/4" diameter. The candle of the former and the disc of the latter were first treated with buffered phosphate broth of pH 6.7 by allowing the fluid to act on the two elements for 12 hours at 26°C, and then put into use.

Material used for filtration was a desiccated of lymphatic tissue derived from a typical case of Hodgkin's disease that had previously yielded a strong positive biological reaction. 1 gm. of tissue was emulsified in 10 c.c. of sterile broth of pH 7.1 and then placed in a refrigerator at -4°C for 7 days. Thereafter it was centrifuged at 1500 R.P.M. for 12 minutes and the supernatant fluid withdrawn with a sterile pipette. To this was added 0.5 c.c. of an emulsion of B. prodigiosus prepared in broth of pH 7.1 standardized to approximate the density of Brown's opacity tube No.1 and 0.5 c.c. of a similar suspension of B. melitensis which was also added. The mixture was then divided into 2 equal parts of 5.5 c.c. and passed through each filter, a negative pressure of 350 mm. of Hg. being applied for a total duration of 12 minutes at a room temperature of 20°C. Both filtrates were clear in colour, contained neither B. melitensis nor B. prodigiosus and 0.4 c.c. of each were accordingly introduced intracerebrally and intravenously into 4 rabbits.

Animals recovered from the operation and remained in good health for a period of 4 days after which they/
they all developed the typical encephalitic syndrome. The brain of each animal was then removed and subjected to bacteriological examination. As no growth could be obtained from these by aerobic or anaerobic methods of cultivation after 3 months, it was concluded that the pathogenic agent was definitely filterable and could pass through both a Berkefeld (British) and the finest pore asbestos disc of a Seitz (EK) Grade 3 filter.

This experiment was repeated thrice with material procured from three different cases of Hodgkin's disease. The most active filtrates were obtained from lymphatic tissue that normally gave a strong positive biological test in the rabbit (van Rooyen, 1933), the material being suspended in high concentration in buffered phosphate broth of pH 7.1 and the pH of the filtrate being kept below pH 7.1.

The Action of Adsorptive Agents, e.g. Keiselghur, Carbon Particles, Calcium Sulphate, Dead Bacteria and Normal Rabbit Brain.

In these experiments emulsions of Hodgkin lymphatic tissue were first treated with the adsorptive agents named, and then injected into rabbits. Some interesting facts have been obtained but these are of limited value for only the behaviour of the agent at pH 7.1 could be investigated. This has been unavoidable because the range of pH over which this agent exhibits/
exhibits activity is small (pH 6.8 - 7.3) and consequently it was not possible to conduct experiments on the effect of adsorbents at different H-ion concentrations.

**Technique.**

2.5 c.c. of a 1:20 emulsion of Hodgkin lymphatic tissue prepared in broth of pH 7.1 containing 0.25% phenol, was added to each of four different flat-bottomed conical flasks containing 0.2 gm. of sterile keiselguhr, pulverised vegetable carbon particles, calcium sulphate and emulsified normal rabbit's brain. Also a fifth flask containing 45770 millions of dead *B.* typhosus, a sixth with 37870 million dead *B.* coli, and a seventh empty one which acted as the control. The number of bacteria were calculated as follows: 12 twenty-four-hours agar slope cultures of each organism were heated to 65°C for 30 mins., emulsified in 10 c.c. of 0.86 per cent physiological saline solution of pH 7.1, standardised to approximate the density of Brown's opacity tube No. 10 and 10 c.c. of the emulsion centrifugalised to yield the desired number of organisms. All seven flasks were mounted on a slowly oscillating electrical shaking machine and placed in an incubator at 37°C for 4 hrs. Thereafter the contents of each flask was transferred with a sterile pipette into separate test tubes, centrifugalised at 2100 R.P.M. for 12 mins., the supernatant fluid withdrawn from each tube, divided into two equal parts and injected into two rabbits after the usual manner.

Of the 14 animals injected, the two inoculated with control material developed the syndrome and died after 5-7 days. Likewise also did those injected with material treated with *B.* typhosus, *B.* coli, and calcium sulphate respectively. Slight loss of pathogenicity followed adsorption by normal rabbit brain, for animals developed a less severe lesion than did the controls. Greater loss was observed after/
after treatment with carbon as only one of the rabbits developed a slight illness lasting two days and the other escaped completely. After treatment with kieselguhr, however, tissue suspensions of Hodgkin lymphatic tissue appeared to be completely non-pathogenic to the rabbit for they failed to reproduce the syndrome in rabbits.

The above experiment was repeated thrice with clinical material supplied from institutions in Edinburgh, Glasgow and London and in each case the same result was obtained.

It was therefore concluded that the pathogenic agent contained in these glands, could be readily adsorbed in neutral solutions by treating with kieselguhr, less so by treating with carbon particles and least of all by normal rabbit brain.

The Effect of Dessication.

Gordon (1932) stated that the agent was capable of withstanding dessication and might be concentrated and rendered more active in glands by first drying them. This finding has been confirmed by the writer in the case of material from case H28, which showed increased pathogenicity to the rabbit's brain after it had been dessicated in vacuo over P₂O₅ at 0°C for 4-6 weeks.

In consequence of these results a number of
lymphatic tissues removed from cases of pseudoleucaemia, lymphosarcoma, and two cases of Hodgkin's disease (e.g. H9 and H10) which gave a negative result in the rabbit (even after prolonged refrigeration) were dessicated, re-emulsified and then used for inoculation, but with negative results throughout.

It was therefore concluded that the pathogenic agent, when present in Hodgkin lymphatic tissue, may be concentrated therein by preliminary dessication.

The Effect of Freezing Tissue Emulsions to 190°C below Zero.

In order to gain information concerning the action of extreme cold per se on this neurotoxic agent, material derived from four different cases of Hodgkin's disease were investigated in the following way:

**Technique.**

Tissue suspensions were put up in hard glass test tubes and then placed in a small Dewar vacuum flask. A pure specimen of liquid air was next syphoned off from its container into the flask. After 12 minutes immersion in the fluid suspensions were withdrawn and set aside to melt at 17.4°C.

On one occasion a dessicate of Hodgkin lymphatic tissue was frozen to -190°C for 12 hours, after which it was emulsified in broth of pH 7.1, allowed to stand at -4°C for 7 days and then used for inoculation.

The material appeared to be unaffected by such a degree of exposure to cold. It still retained its pathogenicity to the rabbit and reproduced the characteristic/
characteristic syndrome after the usual incubation period of three days.

In Vitro Effect of X-rays on the Pathogenic Agent.

Investigations were conducted towards ascertaining whether these rays produced any destructive effect on the agent in question.

Small fragments of dessicated tissue weighing from 230 to 350 mgms. were placed in a quartz glass test tube (98% SiC in composition), and then exposed for 35 mins. at a distance of 26 cm. to the rays emitted from a Muller W anticathode, utilising 5mA at 80kV. A variety of different dosages were employed in the tests and the greatest of them was an exposure of 4545 r, approximately equivalent to 10 U.S.D.

As far as could be gathered from the results following rabbit inoculation, it did not appear that irradiation produced any diminution in the pathogenicity of the material to the rabbit. It was therefore concluded that the agent in these glands responsible for the encephalitic syndrome in rabbits, was capable of withstanding considerable doses of X-rays.

Susceptibility of Rabbits recovering from the Syndrome to Re-inoculation.

Several animals which had recovered from the syndrome were allowed to regain their normal health and weight and then re-inoculated with the same material as was used for their first injection. The period which elapsed between the two operations varied from a fortnight in some cases to three months in others.
On no occasion, however, was it possible to demonstrate immunity to the second dose; indeed, so far as could be observed it appeared that the rabbits were even more susceptible to it than before.

Histological Changes in the Brains of Affected Rabbits.

As previously stated, rabbits affected with the encephalitic syndrome only showed a slight leucocytic infiltration at the site of inoculation, and occasionally similar changes in the meninges overlying this area. The specificity of the latter was dubious as its presence was comparatively infrequent and was sometimes met with in normal rabbits. In a few animals, however, in addition to the foregoing changes, marked perivascular, round cell infiltration and "cuffing" was found to occur around blood vessels. The response appeared to be evanescent in type, for these changes were usually best demonstrable about the 7-10 day after injection and thereafter disappeared rapidly, irrespective of the state of the animal. No evidence of *Encephalitozoon Cuniculi* infection could be found and consequently the changes were not regarded as being of a spontaneous character.

A search for inclusion bodies was carried out by removing the brains of rabbits which had been paralysed for 3-6 and 12 days respectively, fixing these in Bouin's solution and staining them by Mann's method,
but none were found. A few animals which had recovered from the syndrome were examined after 6-8 weeks, but the results were negative.

Intracerebral Inoculation of Cats, Dogs and Ferrets.

Five kittens and two puppies were injected intracerebrally and intraperitoneally with suitable suspensions of lymphatic tissue, but no results were observed to follow after three months observation. Fifteen ferrets were injected intracerebrally, intraperitoneally and intraconjunctivally with similar material. Twelve of these animals died within 2-4 weeks and some of them showed signs of encephalitis prior to death. The animals, however, had not been quarantined before the test in order to exclude ferret distemper and no definite statement can be made yet regarding the significance of the results. It was also noted in some of the ferrets that had been injected intracutaneously, a small inflammatory nodule developed at the site of inoculation after 5-6 days, similar to that described by Twort (1930), in the guinea-pig. This part of the work is in course of progress.
Extended observations on Gordon's test have again proved it to be a reliable laboratory method for the diagnosis of Hodgkin's disease. The specificity of the reaction with lymphatic tissue obtained from this condition appears to be a well established fact, but the precise nature of the agent — whether a virus, toxic substance or enzyme, responsible for the syndrome in rabbits is quite obscure. The effects are not due to trauma (van Rooyen, 1933), but seem to result from some pathogenic entity present in lymphoid tissue affected with Hodgkin's disease, and demonstrable experimentally by the intracerebral inoculation of rabbits. In his earlier work Gordon (1932), found it was necessary to place tissue emulsions in a refrigerator at -4°C for several days before they showed pathogenicity. Since then a great many other cases of Hodgkin's disease have been investigated and several have been encountered both by Gordon (1933) and the writer, in which tissue has been found to be active when immediately emulsified. This may be due to the fact that the quantity of the agent present in different pathological specimens varies greatly; thus, when present in large amount in any one case, the immediate titration and emulsification of the tissue may liberate a sufficient quantity to produce lesions in/
in the rabbit. This presupposes that the pathogenic principle is intracellular either in origin or distribution; thus it has been observed that feebly pathogenic emulsions of tissue may be rendered more active by allowing rapid cytolysis to occur, e.g. by maintaining it at 37°C for 2-3 days, or by intense freezing in liquid air followed by rapid thawing. The fact that fresh tissues may prove active excludes the possibility that the agent is a product of in vitro autolysis. The diffusibility of the agent is indicated by the positive results obtained with centrifugalised and cell-free suspensions and should it be of particulate nature, then the particles must be of ultramicroscopic dimensions.

The work of Friedemann and Elkeles (1933), on bone-marrow may throw some light on the problem and it is of considerable interest since Medlar (1931) has regarded Hodgkin's disease as a megalaryoblastoma and a tumour having its origin in bone marrow.

This might suggest that the pathogenicity of lymphatic tissue is related to its cellular content but so far no such correlation has been found to exist. Moreover, further work is required to ascertain whether the encephalitogenic agent in bone-marrow is identical or not with that demonstrated in Gordon's test.

Another question for consideration is the aetiological relationship of this encephalitogenic agent/
agent to the clinical condition, but no evidence is available at present which affords any definite indication that it is causally related to Hodgkin's disease, except for its striking association with the disease.

Meanwhile the demonstration of such an agent in bone-marrow (normal and pathological) limits the significance to be attached to the encephalitogenic property of lymphadenomatous tissue.

In conclusion there remains the problem concerning the exact nature of the pathogenic principle in lymphatic tissue and some information has been obtained on its characters by a study of its behaviour and susceptibility towards certain physical effects.

Thus it exhibits great resistance towards cold, and X-rays, displays maximum activity in solution at pH 7.1, can be readily adsorbed by keiselguhr, carbon particles and normal rabbit brain and is also filterable. It has also been shown by Gordon to be capable of withstanding temperature up to 70°C for half an hour.

The significance of these facts cannot readily be assessed because many of the features alluded to above, are those which are common to both viruses and toxins, though the peculiar nervous syndrome produced in the rabbit by analogy with other virus diseases of the central nervous system, tends to favour the virus hypothesis.

Finally,
Finally there is the possibility that the substance may be of the nature of an enzyme producing specific damage to the central nervous system.

The problem is one of the greatest interest and practical importance and the data given in this paper are put forward as a further contribution towards its study. Whether or not the encephalitogenic agent is directly related to Hodgkin's disease, the fact remains that it is of clinical importance in the diagnosis of the condition and as a new pathogenic principle merits the most careful investigation.
CONCLUSIONS.

(1) 20 cases of Hodgkin's disease and 13 other conditions of lymphadenohypertrophy have been investigated: Gordon's biological test gave positive results in 15 (75%) cases of Hodgkin's disease, and was found to be negative in the others.

(2) The occurrence of a reaction in the rabbit closely simulating Gordon's encephalitic syndrome has been observed to follow intracerebral inoculation with bone-marrow derived from a case of acute myelogenous leukaemia.

(3) The encephalitogenic agent in Hodgkin's disease has been found to exhibit the following properties:
   (a) The maximum quantity is liberated from Hodgkin lymphatic tissue when buffered phosphate broth of pH 7.1 is used for its emulsification.
   (b) Alkalis such as sodium hydroxide, sodium bicarbonate, ammonia or ammonium carbonate may all cause considerable reduction in the pathogenicity of active material.
   (c) Tissue emulsions have been frozen to -190°C for 10 minutes and tissue dessicates for 12 hours, without inactivation.
   (d) Resists exposure to 10 Unit Skin Doses of X-rays.
   (e) Can be readily adsorbed in neutral solutions by keiselguhr, less so by carbon particles and least of all/
all by normal rabbit brain.

(f) Can be passed through Herkefeld (British) and Seitz (EK) filters.
GENERAL CONCLUSIONS REGARDING THE AETIOLOGY OF
OF HODGKIN'S DISEASE.

The Neoplastic Theory.

A review of the literature has convinced the writer that the evidence submitted in favour of its neoplastic origin is as yet inconclusive. Many such views have been founded on the tendency of Hodgkin's disease to invade various tissues after the manner of true tumour formation. However suggestive these appearances may be it should be pointed out that the property of invasion is an equally well-known attribute of granulomatous tissue, and in consequence cannot be regarded as furnishing proof of malignancy.

The relationship of Hodgkin's disease to lymphosarcoma has been the subject of extensive study and although certain observers conclude that the former may be transformed into the latter, the bulk of evidence points to the fact that Hodgkin's disease is a granulomatous process which is entirely separate from lymphosarcoma. The writer ventures to suggest that the introduction of the Biological Test will further help to differentiate between these two conditions.

The Tuberculous Theory.

In 27 cases of Hodgkin's disease (12 of which were/
were examined post-mortem) the author has never seen signs of active tuberculosis in any of them. Furthermore, efforts to isolate \( B.\) \textit{tuberculosis avis} from suitable subjects has likewise failed, and these findings have been confirmed by the work of others who have obtained similar results. He is therefore of opinion that Hodgkin’s disease has no relationship whatsoever to infection with \( B.\) \textit{tuberculosis hominis, bovis} or \textit{avis}.

**Is the Disease an Infective Granuloma?**

It is probable that this disease is an infective granuloma of unknown origin. The work of Gordon and the significance of the encephalitogenic agent in lymphadenomatous tissue has already been discussed. It has further been shown that this agent possesses properties which call for its classification as a new type of pathogenic principle. Under the circumstances it is necessary to reconsider our views with regard to the aetiology of Hodgkin’s disease. We must take into consideration the fact that the disease may be due to infection with an ultra microscopic filterable virus which exhibits a high degree of specific affinity for human lymphoid tissue, and which cannot be satisfactorily propagated in the usual experimental animal.

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