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THE ETIOLOGY OF HODGKIN'S DISEASE

By

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INTRODUCTION

Hodgkin's disease, according to Cecil, is an affection characterized by painless progressive enlargement of the lymph glands often by fever and in the late stages by cachexia and anemia. CECIL 1933

In writing a thesis on Hodgkin's disease a great deal of difficulty is encountered because of the variety of names under which this disease has been described. During the history of the disease it has been variously designated as Pseudoleukemia, Lymphosarcoma, Adenie, and Generalized Lymphadenoma. In Germany at the present time it is usually called Lymphomatosis Granulomatosa or Lymphogranulomatosis. In England and in this country it is known as Hodgkin's disease or Lymphoblastoma. Therefore, probably in no other subject is there as much confusion in titles as in Hodgkin's disease.

The disease occurs more often in the male than in the female between the ages of twenty and forty, although there have been several cases described in the literature of Hodgkin's disease in children and in the aged. There seems to be no special climate or country in which the disease is more prevalent, but is universal.

Tuberculosis and pyogenic infections often precede Hodgkin's disease and form the basis for arguments about the etiology of the disease as described in this paper.

There is at first no deterioration in general health. The spleen becomes enlarged. The skin may itch or show some dermatitis. The blood smear reveals little or no anemia. There may be a mod-
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erate degree of leucocytosis. (There may or may not be an eosinophilia.) There may be a pyrexia, often of an undulating type called Pel Ebatains fever. There are sweats and loss of weight. Irradiation and arsenic leads to considerable diminution in size of the lymph nodes and spleen. Even without treatment remissions may occur. The skin then takes on a swarthy hue, or is pigmented.

Anemia is more marked and the patient enters the cachectic stage. The patient sinks with progressive cachexia, without further apparent activity on the part of the lymphoid tissues. Death occurs in the majority of cases between the end of the fifth and the end of the seventh year.

The patient may have mediastinal enlargement with intrathoracic pressure; cyanosis, orthopnea, cardiac and respiratory embarrassment, or enlargement of nodes, splenomegaly and hepatomegaly with jaundice and ascites. It may take the form of an acute or generalized infection with fever, sweats, progressive anemia and loss of weight. The nodal swellings may be widespread and the whole process may terminate in three months.

The most common group of lymph glands to become involved is the cervical group. Probably the next most common is in the axilla and then the pulmonary hilum. Lymphadenomatous deposits occur in bones, skin, stomach and in the meninges. Secondary infections may occur with death from this cause. ROSE RESEARCH 1932

In looking over the literature practically every tissue in
the body has been described as being affected in Hodgkins disease. Since it is so widespread, it simulates many other diseases and a biopsy should be done before a positive diagnosis is made.

The treatment as stated above is principally rest in bed, good food, symptomatic treatment and irradiation. Numerous other treatments have had their period of popularity, such as heavy metals, autogenous vaccines, injections of prepared gland filtrate, and other treatments, but none have been found desirable. Irradiation, then is probably the only thing that will reduce the size of the lymph glands. This irradiation is only of value in the early stage because, as pointed out by Rosenthal in 1936, when the lymphocytes in the lymph glands are replaced by connective tissue, the glands will no longer decrease in size. When and if the etiology of the is discovered, it will undoubtedly play a definite role in the treatment of the disease.

At this time there is a great amount of work being done in Germany on Hodgkins disease. My ability to read German has been sadly neglected, so that any mention made in this thesis to the work of German writers has been taken from American articles in which these German writers were mentioned. There are also some very old articles which I did not read that are mentioned in this paper. These have been taken from some of the more recent articles and are of importance in the history and etiology of the disease.
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Almost since the disease has been known, there have been a number of men, both clinical and research, who have been interested in the etiology of the disease. Almost every type of bacteria has been accused of causing the disease. Today there are some men who believe it to be a new growth. Since the etiology as well as the history is the subject of this thesis, I will discuss it in the following pages.

The history is presented here because, in any subject the history is very interesting and in this case etiology and history cannot be separated. In every instance, when a paper has been written, the author has an idea in regard to the etiology. It is interesting to note the change in ideas with the passing years and how some of these same ideas crop up in the later years.
HISTORY

Hodgkin's disease was first described by Morgagni in 1752. He observed that there were some cases which resembled tuberculosis, but in many respects were different from tuberculosis. There was nothing written on the disease then until 1828 at which time Craigie recognized that there was disease which lay midway between carcinoma and tuberculosis. Four years later Thomas Hodgkin presented his noteworthy paper. BURNHAM 1929

Thomas Hodgkin (1798-1866) was a pathologist of Tottenham, England. He was a member of the Society of Friends and always wore their characteristic dress. Because of his eccentric independence of spirit and since he was a philanthropist and reformer by nature, he was driven away from Guy's, says Wilkes. His reputation rests upon his original description of the simultaneous enlargement of the spleen and lymphatic glands or lymphadenoma, which as he himself records, was vaguely outlined by Malpighi in 1665. He also wrote an account of insufficiency of the aortic valve in 1829 which antedated Corrigan's classic paper by three years. His Essay on Medical Education in 1823 is an interesting contribution and his lectures on the Morbid anatomy of the Serous and Mucous Membranes (1836-1840) is one of the earliest treatises on pathology. Being generous to his patients and careless about collecting fees, Hodgkin gradually fell out of practice and devoted the rest of his life to various philanthropies. He died at Joppa, while traveling in the east.
HISTORY

with Sir Moses Montefiore who erected the monument over his grave. GARRISON

In regard to the more specific history of the disease Long states that Thomas Hodgkin was one of that active group at Guy's Hospital in the first half of last century. He prepared his paper, "On Some Morbid Appearances of the Absorbent glands and Spleen", which was presented before the Medical and Chirurgical Society of London by an associate, Dr. Robert Lee on January 10, 1832. Hodgkin had no intention of defining as a pathological entity any single abnormal state characterized by simultaneous involvement of the lymph glands and spleen. He merely wished to reemphasize a frequent association of lesions which as he himself stated must have been observed repeatedly by other pathologists.

In a summary of the seven cases described by Hodgkin every case had in common with the others the finding of enlarged glands either in the neck, axilla, or groin. In some cases there was an enlarged liver. The liver in every case was described as being pale. The kidneys in some of the cases were described as being unhealthy appearing. In some of the cases Hodgkin found evidence of tuberculosis.

After Hodgkin's original paper Sir Samuel Wilkes described thirteen cases in 1865 of which five are homogeneous, three possibly lymphogranuloma and five, questionable. In this paper
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a much better clinical and pathological survey was presented than by any of his predecessors. The disease might easily have been called Wilke's disease because Wilkes published his paper on Lardaceous disease of the Lymphatic System which is superior to Hodgkin's paper. It was unknown by Wilkes at the time that Hodgkin had written a paper on this subject, however, in his second paper Wilkes called the disease Hodgkin's disease.

Long 1929

It was also in this year that Cohnheim introduced the term pseudoleukemia as a fit one to portray the principal objective of this group of diseases.

The histology of the disease according to Gowers was first described in 1867 by Olliver and Ranvier, however, the microscopical characters of the disease were not settled until 1902 by Reed's work which showed by the use of modern staining methods, a uniform histological construction of a disease that resembled tuberculosis, but was not apparently caused by the tubercle bacillus. BURNHAM 1929

I was very much pleased to find an article by Dr. Fox of Guy's Hospital in which he tells of obtaining original specimens of Hodgkin's cases for sectioning and staining by our modern methods. He has made slides of these and I will give the history and his microscopic findings as he gives it in Guy's Hospital Report.
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Case II

A lad of ten had been ill for thirteen months with ever increasing dropsy of the abdomen and scrotum. A large tumor occupied the region of the spleen. Glands in the neck were increased in size. At Autopsy these glands were large smooth and ovoid, connected by loose cellular membranes and minute vessels. Upon cutting there was revealed a firm, light colored cartilaginous surface with feeble vascularity. There was no softening. Some glands were found around the vessels in the chest, while the bronchial and mediastinal glands were greatly enlarged. There was no frank evidence of tuberculosis in the lungs. There was ascites. No nodules were found in the liver. The spleen was enlarged to four times its size.

Microscopic

There is loss of node architecture. The fibrosis as a reticular overgrowth, the presence of scattered large endothelial cells and of occasional Reed giant cells can be clearly recognized. Eosinophilia is absent from both sections. In both occur small foci of necrosis and scarring at first suggesting the presence of Tuberculosis. The lymphoid zone is usually indefinite and often contains poly leucocytes and fragmentary matter mixed with lymphocytes.

The second piece of tissue was not so well preserved as the spleen and its adjacent glands. The section consists of a
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diffusely staining tissue chiefly lightly basophilic, composed of irregular and indefinite strands of connective tissue in a very coarse meshwork. Here and there one sees multinucleated cells that could correspond to Reed cells. The tissue is acceptable as Hodgkin's disease although by no means as convincing as the first section.

Case IV

Thomas Wescott, age 50, was plump, but pale and cachectic. There is enlargement of all glands within reach of examination especially axillae and groin, the average size of a pigeon egg. They are smooth, round and ovoid. A mass may be felt in the epididymus. The abdomen is distended.

Post Mortem Findings

The brain lesions were inadequately described. the deep glands were larger than the superficial. Lungs and pleurae were normal. The heart was dilated on the right side and showed some hypertrophy. The mediastinal glands were enlarged. The superior abdominal and retroperitoneal glands were greatly enlarged. The liver was large pale and granular. The spleen was nine inches by five inches and proportionately thick; firm and redder than normal. Section showed almost infinite number of small white, nearly opaque spots. They appeared to depend upon a deposit in the cellular structure of the organ.
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Microscopic

The tissue cannot be recognized as lymph node. There are irregular and mixed masses of fibrous tissue and cells. The former is both strandwise and mesh like. There are multinucleated cells that correspond in a general way to Reed cells. There are no tuberculous areas. The specimen corresponds therefore with the present conception of Hodgkin's disease.

Case VI

Thomas Black complained of large swellings in the neck and groin. His abdomen was much distended. The disease was of a duration of two years. It followed a fever. Autopsy showed large masses of lymph nodes in the neck and mediastinum. Recent pleuritis with effusion was evident with fluid also in the peritoneal cavity. There were large retroperitoneal masses. Slight cirrhosis of the liver was noticed. The spleen was of moderate size. Glands seemed to be semi-cartilaginous.

Microscopic

This picture is a typical picture of lymphosarcoma as we see it today. FOX 1856

Thus a careful analysis as given above, in the light of modern knowledge makes it clear that Hodgkin was dealing with cases of varied etiology, including generalized tuberculosis, lymphosarcoma, Leukemia, lymphogranulomatosis and perhaps Pseudo Leukemia.
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The etiology of the disease known to us as Hodgkin's disease is unknown. It seems that Sternberg in his publication of studies by him in 1898, 1899, and 1905 started a discussion which has continued up until our present day. A stupendous amount of work has been done on the subject with ever varying results.

In Sternberg's paper he described a peculiar form of tuberculosis of the lymph nodes. The histological picture differed in no important detail from that which was regarded as characteristic of malignant granuloma as portrayed by Dorothy Reed, Longcope, and others. Yet whereas Sternberg was able in fifteen out of eighteen cases to establish a tuberculous etiology either by direct staining of the affected nodes or by animal inoculation Reed, Warnecke, Yamasaki and others were uniformly unsuccessful in proving such an association. BEUFE LD 1918

Bunting and Yates in 1912 isolated a pseudodiphtheroid from glands of a case of Hodgkin's disease and named the organism Baccillus Hodgkinii. Since that time Rosenow and Billings have been also strong adherents to the belief that Hodgkin's disease is caused by a diphtheroid organism which they cultivated from glandular material obtained from their patients. Organisms similar to Bunting and Yates' were isolated from Hodgkin's disease by Rhea and Falconer also, and according to the earlier work of Fraenkel and Much, and de Negri and Miermet were found in similar cases. Fraenkel and Much thought
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that the organism was related to the tubercle bacillus since it was found by them to be resistant to antiformin. This character was shown to be insignificant by de Negri and Hirschot who observed the contrary. YATES 1916

Organisms similar to these can be isolated from normal individuals as well as from a variety of diseased conditions, was well shown by Bloomfield who made a study of the bacterial flora of lymphatic glands. He found avirulent organisms which were correlated with saprophytes on the body surface in cases of Hodgkin's disease, lymphosarcoma and carcinoma. Another group of organisms seemed to possess a relation to oxygen supply. Bloomfield found these in cases of lymphosarcoma, arthritis, carcinoma, and Hodgkin's disease. Virulence tests on rabbits, guinea pigs and mice were negative. He concludes that definitely diseased glands yield a greater number of successful cultures than do normal glands. Saprophytic organisms are filtered out by the glands and become a permanent flora of the same. None of the isolated organisms appeared to be the etiologic factor in this specific disease. BLOOMFIELD 1915

Fox found that no one bacterial variety from definite morphologic and cultural characters were isolated from cases of Hodgkin's disease. That these diphtheroids may be found in enlarged glands in other conditions was mentioned by Fox (1915) and was observed by Eberson who isolated organisms
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morphologically and culturally identical with the so called
Clostridium Hodgkini from an hypertrophied tonsil and from
lymph nodes and other sources. EBERSON 1918

From this time, 1918, there have been numerous articles
written especially by Bunting and Yates setting forth reasons
why they believed that Hodgkin's disease was caused by the
bacillus, Clostridium Hodgkini. Bunting stated that since
the discovery of the diphtheroid in 1912 he was able to
cultivate it from all fresh affected tissue where in the
histological diagnosis was positive or when the blood picture
of the patient was characteristic, unless that tissue had
been contaminated or had been recently actively treated by
xray. However, during the following years they have been
forced to admit the futility of still adhering to their old
stand.

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. Other chickens
were inoculated with material from the first ones and after
killing were found to have tuberculosis with marked envolv-
ment of bones. Cultures of material from reinnoculated chick-
enes gave a pure growth of tubercle bacille of the avian type.
Guinea pigs were inoculated with the original material of
proven Hodgkin's disease and they developed extensive lymph-
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Atrophic tuberculosis. Rabbits after injections were found not to have developed tuberculosis. L'ESPERANCE 1930

These claims were investigated by Rose Research in 1932, Davidson in 1933, Van Rocyen in 1933, and others, all of whom have been unable to reproduce the disease in birds or to isolate the avian tubercle bacillus from human lesions in the disease. Steiner in 1934 wrote a paper in which he says that he has found fewer positive tuberculin tests in Hodgkin's disease than in the average people. He explains this in either of two ways. Patients may be desensitized by the disease, or Hodgkin's disease occurs mainly in that small group of people in whom the normal adult sensitivity to tuberculin fails to develop. This helps in the differential diagnosis of the disease. STEINER 1934

In talking to Dr. Bayliss of the work of L'Esperance I was told that after his work with chickens and guinea pigs a search was made for the cause of his findings. It was found that he had been working with infected animals and fowls before the injections. So at the present time it is generally conceded that the tubercle bacillus is not the causative agent.

In a recent copy of Guy's Hospital Report, however, may be found a report at autopsy of a patient who had enlarged mediastinal glands. Some of these glands were sectioned and found in three adjacent glands the typical microscopic picture
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of tuberculosis, Hodgkin's disease, and lymphosarcoma. There
are numerous reports of tuberculosis of lymph glands associated
with Hodgkin's disease. This fits in with the belief of
Desjardins in his paper published in 1934 which I will mention
at the end of this paper.

Fitchett and Weidman in 1934 stated that their fourth case
of Tuberculosis was associated with Hodgkin's disease. They say
also that in forty-four collected instances there have been
two additional cases in which the histologic picture of Hodgkin's
disease was approached. However, it would be premature, they
say, to regard tubercular infection as one of the causative agents
of Hodgkin's disease. Here as in the case of regarding
Hodgkin's disease as caused by the avian tubercle bacillus,
the agent has not been proven the cause of the disease.

FITCHETT AND WEIDMAN 1934

The Rose Research on Lymphadenoma in their book of that name
has made an exhaustive study of the etiology. They have gone back
into the literature when in 1898 Schenk described first a condi-
tion in which subcutaneous abscesses were according to him
caused by a fungus possibly related to the sporotrichia. So
they have injected the various sporothrixes into experimental
animals and in commenting on the results Pullinger states
that these experimental lesions form a most interesting group
illustrating the kind of reaction which fungi produce in animal
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tissues. The histology shows how these reactions resemble and differ from true lymphadenoma.

Then as mentioned before Sternberg thought that lymphadenoma was caused by the tubercle bacillus and later Twort believed also the Koch's bacillus was the causative factor. So with these works in mind the Rose Research conducted experiments, injecting suspensions of glands from lymphadenoma into guinea pigs with an adequate number of controls. Then search was made for typical tubercles and the tubercle bacillus. The Results may be give best by quoting the summary. "In order to check the results with glands from the forty cases of lymphadenoma, glands have been tested on guinea pigs in the same from 50 control cases." "Among these controls, glands from 10 cases showing histological changes typical of tuberculosis were all positive in the guinea pig while out of 5 glands showing the change known as endothelial tubercle only one gave a positive in the guinea pig." "It would seem from these observations that the incidence of tuberculosis in lymphadenoma glands is much the same as in glands from control cases other than those showing definite histological evidence of tuberculosis."

In 1907 White and Proescher claimed to have demonstrated spirochetes in a case of lymphadenoma by Levaditi and Giemsa stains. However, a close examination of the papers of White
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and Proescher and especially of the microphotographs has left little doubt in the minds of the Rose Research that the bodies which they found and considered to be spirochetes are the same as those pseudo-spirochetal bodies found in the investigation of the Rose Research. This search for the presence of spirochetes has in cases of lymphadenoma given negative results.

As stated before Bunting and Yates found the diphtheroid bacillus in cases of Hodgkin's disease. An examination was made by the Rose Research and they found two types of diphtheroid bacilli; an aerobic and an anaerobic type. Cultures of both categories of diphtheroid bacilli, however, when grown directly from suspensions of lymphadenoma glands and injected into guinea pigs subintradermally and into rabbits intracerebrally, were found to be devoid of pathogenicity and accordingly they were disregarded.

An observation made by Twort while working for the Rose Research was that suspensions of lymphadenomatous glands on injection subcutaneously into guinea pigs are capable of giving rise to a local inflammatory reaction in which bacteria cannot be demonstrated. This has been confirmed by other members of the Rose Research. They say that this pathogenic agent can be demonstrated by injecting suitably prepared suspensions of the gland into the brains of rabbits. When such a suspension
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is injected intracerebrally into rabbits, the disease set up in the rabbit is muscular rigidity and spasm as this is frequently combined with paralysis a condition of spastic paraplegia occurs, accompanied by progressive wasting. Other glands from other diseases of the lymphatic system were found to be inert after preparation when injected intracerebrally in rabbits. TWORT 1924

The pathogenic agent has much the same characteristics of a virus as stated by the Rose Research. It stands dessication better than some of the known viruses, as it does also with heat. However, at the present time it has been found to be inert after passing through a filter.

In 1925 Frei of Breslau discovered that a suspension of the inguinal glands of a case of lymphadenoma inguinale produced when sterilized by heat (60) and injected intracutaneously, a local skin reaction that is specific. In August 1930 Hellerstrom and Wassen Brought forward evidence showing that a suspension of gland from cases of lymphogranuloma inguinale when injected intracerebrally into monkeys produced a fatal meningoencephalitis from which bacteria were absent. The specific nature of this meningoencephalitis was proved by showing that an antigen prepared from the central nervous system of the affected monkeys produced a positive Frei reaction in human cases of lymph-
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Lymphogranuloma inguinale. Further investigation indicated that the pathogenic agent concerned was a virus, and that it excited similar histological changes in the lymphatic glands of monkeys to those seen in human cases of lymphogranuloma inguinale. When introduced intracerebrally into monkeys, this virus was found to produce a characteristic condition in which rigidity was associated with incoordination. ROSE RESEARCH

The test for Hodgkin's disease was discovered by Gordon in 1932 and bears his name. In addition to the test which made Gordon think that the etiological agent in Hodgkin's disease was a virus, there was an incident that came up in which a co-worker received a minor cut on his finger while working with a crushed lymph gland from a case of Hodgkin's disease. In the course of two months this worker developed an adenopathy in the axilla of the same side which was injured. A biopsy was done and the typical picture of Hodgkin's disease was disclosed. This in Gordon's mind was evidence that the etiological agent of Hodgkin's disease was a living thing. GORDON 1933

In 1934, however, Van Rooyen decided that the effects produced in the rabbit were more those of a toxic action than that of a virus infection. He also pointed out that inability to transmit the condition from rabbit to rabbit, the absence of intracellular inclusion bodies, and the absence of
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any immunity reaction rendered it difficult to assign this encephalitogenic agent to the infective viruses. VAN ROOYEN 1934

Friedman in 1934 was also unable to transmit the disease from rabbit to rabbit. He found that the proteolytic enzyme described first by Jochmann in 1908, would give the positive Gordon test. This proteolytic enzyme may be obtained by a special extraction method described by Jochmann and Lochemann, from normal human bone marrow, spleen, and leucocytes, but not elsewhere in man monkeys and to a slight degree in dogs. Jochmann considered that the ferment was peculiar to the leucocytes of certain species and that in these species the occurrence of the ferment in spleen and bone marrow was due solely to the presence of leucocytes in these organs. FRIEDMAN 1934

Friedman is of the opinion that Jochmann's ferment is the same encephalitogenic agent as that in Hodgkin's disease. In his work he extracted lymphadenomatous tissue by the Jochmann Lochemann method and found that the agent was still present. He concludes that a living thing could not survive the drastic treatment demanded by this method. He says that the identity is suggested very strongly by the similarity in species and organ distribution of the two, by the similarity in resistance to heat, and by the similar stability in the presence of alcohol, ether, and alcohol ether. FRIEDMAN 1934
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Van Rooyen found this typical reaction to the Gordon test more marked with a specimen of bone marrow derived from a case of acute myelogenous leukemia in which there were also chloromatos changes. VAN ROOYEN 1934

The question therefore arose, whether the agent present in lymphadenomatous tissue was identical with that in Spleen, leucocytes, and bone marrow, and whether as Friedman pointed out both agents could be identified with the proteolytic enzyme extracted by Jochmann and Lochemann.

Van Rooyen found as Friedman did, that this agent was capable of withstanding the Jochmann Lochemann procedure for the extraction of proteolytic enzymes from tissues. He found also that even though the extract obtained by this procedure was highly pathogenic to the rabbit on intracerebral inoculation, it was devoid of any proteolytic action. Conversely he found that extracts of certain tissues might be markedly proteolytic, containing the so called Jochmann ferment, but quite non pathogenic for the rabbit. He concludes, therefore, that Gordons pathogenic agent found in lymphatic glands affected with Hodgkin's disease could not, therefore, be identified with the Jochmanns proteolytic enzyme. VAN ROOYEN 1934

Lymphatic glands affected with a variety of different pathological conditions have been subjected to the Jochmann
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Lochemann method of extraction, but it was not found possible to derive an encephalitogenic product from those which initially gave a negative Gordon reaction. Experiments have demonstrated that this method of chemical extraction did not destroy all forms of living organisms so this does not contradict the theory that Hodgkin's disease is caused by a living organism. The enzymes, lymphoprotease and leucoprotease, obtained from the dog, and also lieno-b-protease do not appear to be concerned in the production of the encephalitogenic syndrome following the intracerebral inoculation of tissue extracts. VAN ROOIJEN 1934

It is at this time almost universally accepted that Gordon's test is of some value in the diagnosis of Hodgkin's disease. Chapman believes, however, that Gordon's test if positive, is only of supportive aid in the diagnosis of Hodgkin's disease and if negative does not exclude it. Therefore, this test should not replace the routine pathologic examination of tissues for diagnosis. The absence of the encephalitogenic agent in the first four types of lymphoblastoma (lymphosarcoma, reticulum cell sarcoma, Giant follicular lymphoma, and lymphoblastoma, type undetermined) adds support to the belief that Hodgkin's disease is a separate clinical and pathological entity. CHAPMAN 1936

Ginsburg has reviewed the cases observed at Montefiore
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hospital 1922-1932. After observing these cases it is apparent to him that clinically as well as biologically, the malignant character of both Hodgkin's disease and lymphosarcoma is very similar, if not identical. Whatever differences that are observed at times may be regarded as mere variations of the same disease which one would expect to encounter in different individuals with different tissues, organ susceptibility, and resistance. Clinically, both reveal the same marked variation in duration, character, course and selective localization in different regions, tissues and organs in different individuals. GINSBURG 1936

The frequent presence of tuberculosis in Hodgkin's disease and its rarity in lymphosarcoma have been stressed by a number of observers. In the above series of cases tuberculosis was found to be present in almost as many cases as in Hodgkin's disease. This does not favor a tuberculous etiology in either. GINSBURG 1936

The study of the blood pictures revealed no essential difference between Hodgkin's disease and lymphosarcoma. There is no uniformly diagnostic blood picture of Hodgkin's disease. The malignant character was recognized early in the studies of both. Hodgkin's disease carries a somewhat better prognosis although the average duration of either of the two is
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between two and three years. Death in both cases is due to compression syndromes, toxemia, and visceral invasions.

Ginsburg believes that Gordon's biological differential diagnosis test requires a great deal of further study and confirmation before it can be accepted equivocally.

In the radiotherapeutic test there is a more prompt disappearance of the lesions in lymphosarcoma than in Hodgkin's disease. However, this is not always reliable and differentiation between the two is very hard. GINSBURG 1936

Medlar believes that all of the complex picture of Hodgkin's disease can be demonstrated in a single section of bone marrow. In this section of bone marrow he finds a hyperplasia of the marrow with a marked increase of immature cells which probably are the progenitors of megakaryocytes and finds presumptive evidence that the giant cells (megakaryocytes) are the end result of fusion of several premegakaryocytes.

Mitotic figures were observed quite often in the hyperplastic marrow. The majority of mitotic figures were in the small parent cell. Occasionally, there was found a complex multiple mitotic figure in the large megakaryocyte. These observations also hold for the lesions found in other tissues in the body.
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Since the Hodgkin's lesions as seen in the various tissues of the body, differed in no essential respect from those described above in the bone marrow, further description would seem unnecessary. The tumor cells as observed by Medlar were able to wander about in the tissues. This was shown to a striking degree in some of the surgical specimens which were promptly placed in Zender's solution or in 10 percent formalin. So this evidence presented by Medlar leads him to believe that Hodgkin's disease is a malignancy of the bone marrow primarily and involvement of lymph nodes and other tissues outside the bone marrow appears to be metastatic tumor growth, the typical cell being the megakaryocyte. MEDLAR 1931

Clinically, Livingston (1921) and Krumbharr (1931) have both described cases in which the skeleton was envolved and also the spleen with no apparent enlargement of the lymphatic glands.

Burnham has also recognized the similarity of Hodgkin's and lymphosarcoma, but he does not believe that they are the same disease. BURNHAM 1929

Gibbon, Clark, Coley, Oliver, Mallory, and Warthin believe that lymphogranuloma is a new growth. Mallory believes that it is a scirrhus variety of new growth. The type cell is a lymphoblast which occurs in some tumors as cells of large
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size with a large lobulated or multiple nuclei which arise
by mitosis. LANFORD 1928

Symmers believes that Hodgkin's disease is a transition
between an infection and a neoplastic disease. It has charact-
eristics of both processes. It is a systemic disease affecting
the entire lymph-hemolytopoetic system. LANFORD 1928

MoJunkin has found that in his experiments with the Rous
chicken sarcoma no. 1 the round cells of the chicken sarcoma
are much like the Dorothy Reed type of cell of Hodgkin's gran-
uloma. MCJUNKIN 1928

There are men who believe that Hodgkin's disease is not
such a simple thing. They believe that there is a variety of
factors that must be present before Hodgkin's disease can be
produced. Desjardins, a radiologist, after having treated 500
cases of Hodgkin's disease has concluded that the factor imme-
diately necessary for lymphoblastoma hyperplasia of the lymph-
oid structures is chronic infection of some kind. This may be
tuberculous, pyogenic or even syphilitic. It must be an infec-
tion of long duration. If the history of the patients physical
ailments is carefully and persistently inquired into, evidence
of infection of long standing will be obtained in the majority
of cases.

The practically constant association of infection and
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primary lymphadenopathy in the same region and on the same side of the body can hardly be regarded as coincidence. If this were a result of chance the anatomic relationship would not be so consistent.

But even if this etiologic relationship is undeniable, a predisposing factor, also, is required to provide a suitable background for the immediate cause. This additional and essential element is probably to be found in a hereditary predisposition, or tendency transmitted from generation to generation of the lymphoid tissues to react in a certain way to various noxious influences. Lymphogranuloma is not rare in two or more members of the same family. DESJARDINS 1934

Arkin believes also that perhaps heredity plays a part in the etiology of Hodgkin's disease. He describes three cases of proven lymphogranuloma in one family. He states it may require a special constitutional make up. Status lymphaticus may perhaps make a person more susceptible. It may offer a more favorable condition in the tonsils, intestinal mucosa and respiratory tract for the invasion of bacteria. Rosenow says that this may account for the familial tendencies, and that status thymicus may predispose to the mediastinal forms. Arkin is of the opinion that in adults a persistent thymus, largely a lymphoid organ, may make a predilection in the anterior mediast-
ETIOLOGY

Burnham has also recognized the fact that Hodgkin's disease may occur in more than one member of the same family. He described one instance where the disease occurred in five members of the same family. BURNHAM 1929

Other men before this time believed that lymphogranuloma was due to preexisting local disease especially malaria, syphilis, and pneumonia. However, in the opinion of Lanford, there has been no satisfactory evidence that such is the case.

LANFORD 1928
SUMMARY AND CONCLUSIONS

In every paper that I have read there has been no definite established etiology. I have shown that Sternberg thought that Hodgkin's disease was a peculiar form of tuberculosis, and that this was disproved by Reed, Warnecke, and others. Later L'Esperance thought that the avian tubercle bacillus was the exciting cause. After a careful check up, his animals and fowl were found to be already infected with tuberculosis before injection.

Bunting and Yates decided that they had found the etiologic agent in a diphtheroid bacillus. It was then shown by Bloomfield and Fox that a diphtheroid bacillus may be found in a variety of diseases of the lymph glands and also in normal glands.

Then the Rose Research on lymphadenoma started their investigations of every bacteria set forth in the literature as being the etiological agent of Hodgkin's disease. In their research they have found that none of the bacteria would produce in animals the typical picture of the disease. Gordon in his search discovered the so called Gordon's test for lymphadenoma. In comparing this with the Frei test in monkeys it was seen that the reactions were very much alike. Since the etiological agent in lymphogranuloma inguinale is a virus, it was concluded that the etiological agent in lymphogranuloma was also a virus. Some workers in the tests on gland extracts decided that no living thing could exist after going through the various processes.
SUMMARY AND CONCLUSIONS

However, the present belief is that the agent could be a living thing.

At the present time there are some men who believe that Hodgkin's disease is a malignant new growth. Very little work has been done at the present time to prove that this disease is not a new growth.

There is a school of thought at the present time that Hodgkin's disease is a constitutional condition plus some other factor.

At the present time we as readers are confronted with three possibilities of etiology; a virus, malignant new growth, or a constitutional thing with one or more other factors. The other theories set forth have been quite definitely disproved.

In looking at the virus theory, it will be noted that a great many other things such as Jochmann's ferment, leucocytes, bone marrow, spleen, and glands from lymphogranuloma inguinale will give the typical picture of a positive Gordon test. It has not been proven that the disease can be transmitted from person to person. In Gordon's test the encephalitogenic agent cannot be transmitted from rabbit to rabbit. In the experiments there was never an immunity set up in any of the rabbits to the encephalitogenic agent. From this I do not believe that Hodgkin's disease is caused entirely by any living organism.
SUMMARY AND CONCLUSIONS

In regard to the remaining two theories, I believe that these may be linked up together. Certain malignant new growths have been shown to be transmitted from generation to generation in mice. It has also been shown that other new growths are caused by chronic irritation of some sort. It may be in merging the two ideas that we may come out with the etiology of the disease. Clinically members of the same family may develop the disease, and in almost if not in every case, a source of chronic irritation such as chronic infection can be demonstrated. The fact that after this disease has developed there is no hope for complete cure and only retardation, points to the new growth theory. As stated before treatment is irradiation. The only treatment of new growths generally is irradiation. The fact that the histological picture has been so confusing and does not point to a definite etiology also lends support to the new growth theory.

Undoubtedly in years to come there will be a great deal more work done on the subject. So maybe in the next century a definite etiology may be established. Until then we will treat our patients symptomatically and try in a small way to relieve their complaints and perhaps lengthen their life a short while.
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