ANNALS *of* SURGERY

Vol. LXXXVIII OCTOBER, 1928 No. 4

TRANSACTIONS

OF THE

AMERICAN SURGICAL ASSOCIATION

MEETING HELD IN WASHINGTON, D.C., APRIL 30, MAY 1 AND 2, 1928

(Continued)

END RESULTS IN HODGKIN'S DISEASE AND LYMPHOSARCOMA TREATED BY THE MIXED TOXINS OF ERYSIPELAS AND BACILLUS PRODIGIOSUS, ALONE OR COMBINED WITH RADIATION

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In 1915, in a paper on *Primary Neoplasms of the Lymphatic Glands including Hodgkin's Disease,*[1] I reported the end results in 167 cases treated almost entirely with toxins alone. Up to that time radiation had been used with but little success in these cases. While this method (radiation) has since become the generally accepted one in the treatment of lymphosarcoma and Hodgkin's disease, only very recently have the end results in a large series of cases been published. Among the most noteworthy of these publications are the report of Minot and Isaacs,[2] as well as that of Burnam[3] and of Stone.[4] From these data I believe it is now possible to get a fairly accurate estimate of the value of radiation in the treatment of lymphosarcoma and Hodgkin's disease.

It has been found that while radiation has resulted in a marked diminution in size—and in some cases, a complete disappearance—of the enlarged glands, in most cases the disease recurs after a longer or a shorter interval and proves fatal in practically every case. Just how much radiation adds to the duration of life of an individual suffering from lymphosarcoma or Hodgkin's disease is still problematical, at least, in the opinion of Minot and Isaacs. That this method of treatment has resulted in great temporary relief, there can be no doubt.

At the onset it is important to make clear what we mean by the term

[1] Coley: Trans. of American Surgical Association, 1915.

[2] Minot and Isaacs: Jour. Amer. Med. Ass'n, April 17 and 24, 1926, vol. lxxxiv, Nos. 16 and 17.

[3] Burnam: Jour. Amer. Med. Ass'n, October 30, 1926, vol. lxxxvii, No. 18.

[4] Stone: Canadian Practitioner, March, 1924.

"lymphosarcoma" or "Hodgkin's disease". For many years I have held that these two conditions, which are usually regarded as quite different and distinct, are actually quite closely allied etiologically, and bear such a close resemblance to one another that in some instances it is impossible to differentiate them either clinically or histologically. While on the one hand we may have a typical lymphosarcoma with definite clinical and histological features, and on the other, a typical Hodgkin's disease with discrete, freely movable glands, firmer in consistence than lymphosarcoma but not as hard as tuberculous or carcinomatous glands, and histologically containing the typical Dorothy Reed cells, we also have a great number of cases that are more or less atypical and fall between the clear-cut typical lymphosarcoma and the typical Hodgkin's disease. While it may be possible to regard these slightly different atypical conditions as distinct processes with definite etiology, I believe it is far more logical and more rational to regard them as varieties of a single disease. On this assumption we are justified in including them all in a general group, which is just what Minot and Isaacs have done, and to which group they have given the name *lymphoblastoma.*

In their publication referred to, Minot and Isaacs state as follows:

"The views and opinions concerning the nature and relationships of such cases are multiple, and thus students of the problem have utilized a constantly confusing terminology, and not infrequently disagree on the exact diagnosis of a given case. Some apply a term that is synonymous with one used by another, while at other times a special type of case is designated by a name used by others to cover a much broader group. Hodgkin's disease with the pathologic histology described by Dorothy Reed is sharply distinguished by many authorities from two other conditions that they term pseudoleukemia and lymphosarcoma. Others inappropriately include as Hodgkin's disease all, more often some, cases of the latter two conditions, and the terms malignant lymphoma and lymphadenoma have been used for such a group alone. Some contend that two types of lymphoblastoma may occur in one patient. Confusion in the group called lymphosarcoma arises because of differences of opinion as to what constitutes this condition and the lack of appreciation of the difference between the origin of tumors involving structures composed of much lymphatic tissue. Pseudoleukemia and aleukemic lymphocytic or lymphoblastic or lymphatic leukemia are essentially synonymous, as is at times the term aleukemic lymphadenosis. Chronic lymphatic leukemia with a leukemic blood picture is the form of lymphoblastoma most easily separated from others. However, except for the peripheral blood picture, no important distinction, even by pathological examination of tissue, can be made from cases termed pseudoleukemia or aleukemia, and the same case at different times may be given correctly the one name or the other."

While the systemic nature of Hodgkin's disease had been recognized by many writers, and this point fully established by Gowers [5] in his exhaustive paper published in 1879, in which he described the lesions as involving not only the lymph-nodes and spleen, but also the skin, intermuscular tissues, bones, brain, soft palate, pharynx, tonsils, esophagus, stomach, small intestine, large intestine, pancreas, peritoneum, thyroid, thymus, trachea, lungs, pleura, diaphragm, pericardium, heart muscle, suprarenals, kidneys, testes and ovaries, only recently has our attention been called to the fact that the disease involves not only the nervous system, but, as Ginsburg [6] has pointed out, the

[5] Gowers: System of Medicine, Philadelphia, 1879, vol. v, p. 306.

[6] Ginsburg: Archives of Internal Medicine, April, 1927, vol. xxxix, pp. 571–595.

skeletal bones as well. According to the latter, "the impression is still widely prevalent among physicians that the nervous system is so rarely involved in Hodgkin's disease as to be ignored in the differential diagnosis of diseases of the nervous system. Not only did I fail to see Hodgkin's disease mentioned in the standard textbooks on diseases of the nervous system, but even in the excellent recent monograph of Elsberg on *Tumors of the Spinal Cord*,[7] the condition is ignored completely." Ginsburg states that in a series of thirty-six patients with Hodgkin's disease observed at the Montefiore Hospital during the years 1914 to 1925, ten patients, or 27.7 per cent., showed invasion of the nervous system.

In the opinion of Ginsburg, the etiology of Hodgkin's disease still remains obscure, and a specific form of treatment has not been discovered.

In a paper on *The Relation of Hodgkin's Disease to Lymphosarcoma*, Gibbons of San Francisco,[8] discusses the nature of the process as follows:

"Two possibilities as to the nature of the process are apparent, *viz.*, is it a malignant, or is it an infectious process of the character of a granuloma? Most recent writers are inclined to the latter view. Reed is most insistent. Fischer, Clark,[9] and Simmons also hold this view. Longcope seconds it, though guardedly. Recent German publications also favor this view. Yamasaki,[10] regards the condition as a granuloma not of tuberculous but of unknown origin, which, however, may end in sarcoma. Wamecke,[11] although he has clearly recognized that lymphosarcoma cannot be separated from Hodgkin's disease, still adheres to this conception. From the study of my cases I incline strongly to the malignant theory."

Gibbons adds:

"It will be seen at once that many of these facts belong to malignant tumors as well as to infectious processes. We may have a rapidly growing sarcoma or we may have a slow one. We may have it accompanied by fever or we may not; and the fact that the fever of Hodgkin's disease is so variable in character, and sometimes not present at all, rather argues that it is not one produced by a definite infection. We see sarcomas which have existed for a long time, suddenly assume a very much accelerated growth. The mode of spread from diseased glands to adjacent ones is equally characteristic of malignant growths and of infectious diseases. The final stage of anæmia, cachexia, and disturbances of the body functions is very characteristic of the last stages of all malignant growths."

Regarding the nine cases which formed the basis of Gibbons' report, he states:

"Three of the cases were undoubtedly malignant, infiltrating and destroying surrounding structures as does any malignant growth. The only question that remains is, can these be classed with Hodgkin's disease, or are they different and to be classed as lymphosarcoma? Osler asserts that infiltration of the lung, as took place in one of my cases, does not occur in Hodgkin's disease, and that when such an infiltration does take place the disease is true lymphosarcoma. But in the light of the fact that this case, as well as the two other malignant tumors of the neck, present the same clinical features

[7] Elsberg: Tumors of the Spinal Cord, Paul B. Hoeber, New York, 1924.
[8] Gibbons: Amer. Journ. of the Medical Sciences, November, 1906.
[9] Clark: British Medical Journal, 1901, vol. ii, p. 701.
[10] Yamasaki: Zeitschr. f. Heilk., 1904, p. 269.
[11] Wamecke: Mitt. aus den Grenzgeb., 1905, vol. xiv, p. 275.

and the exact histological picture as the twenty-three cases so carefully studied by Reed, Longcope, and Simmons, and as the other six of my series, they must also be regarded as the same morbid condition. This being established, there would be no question as to the malignant character of Hodgkin's disease."

In conclusion Gibbons states:

"1. I agree with Reed, Longcope, and Simmons as to the histological picture presented by the tissues in Hodgkin's disease, but I do not agree that it is necessarily due to an inflammatory process.

"2. I assert that in most cases infiltration of the capsule of the diseased glands can be observed; in many cases an extension beyond the capsule occurs, and in some cases very evident infiltration of adjacent structures.

"3. The study leads me to believe that Hodgkin's disease is a process to be classified with malignant tumors."

One of the most important of recent contributions upon Hodgkin's disease is the Schorstein lecture of 1926 on *lymphadenoma*, (Hodgkin's lympho-granuloma), by Sir Humphrey Rolleston, (Regent Professor of Medicine, Cambridge University). It contains a brief note upon the history of the disease from its first definite description by Thomas Hodgkin and his first published series of cases in 1832; and Samuel Wilks in 1856 and 1865. A lucid discussion of the various theories on the nature and origin of Hodgkin's disease follows. Under the *Nature of Malignancy in Hodgkin's Lympho-granuloma"*, the arguments for and against regarding it as a neoplasm are presented in a most clear and judicial manner.

"That Hodgkin's lympho-granuloma is malignant in the sense that it leads to death is undoubted, and it differs from tuberculosis, which in many respects it closely resembles, in being constantly fatal and not becoming obsolete. . . . But further evidence suggesting malignant characters, such as invasion of adjacent bone and the histological characters of sarcoma, described years ago by Yamasaki and by Karsner, are now established, and Ewing considers this transformation into sarcoma ('Hodgkin's sarcoma') as a tumor *sui generis* and as by no means rare. He describes the new cells as endothelial in origin, but losing this character and appearing as large round cells, so that the term endothelioma is hardly applicable. Such a transformation as the result of long-continued irritation is, of course, well recognized, and Ewing has described it in lymphatic glands affected with chronic granulomatous infection. The occurrence of Hodgkin's sarcoma as a late result of Hodgkin's lympho-granuloma is rather remarkable, as it is very seldom recognized in the other infective granulomas.

"The development of sarcoma in Hodgkin's lympho-granuloma might be explained in one of two ways: (1) that some of the constituent cells of the lympho-granuloma proliferate so vigorously as to become a sarcoma, or (2) that the tissues surrounding a mass of lympho-granuloma are excited by the chronic irritation to a proliferation which eventually becomes sarcoma; this process Ewing compared with the occurrence of cutaneous squamous-celled carcinoma in the site of lupus.

"Prof. H. M. Turnbull, while fully recognizing the existence of the condition which Ewing terms Hodgkin's sarcoma, regards it as the 'lymphosarcomatoid' form of Hodgkin's lympho-granuloma and as inflammatory rather than neoplastic. Lymphosarcoma—the form of growth concerned in the malignant transformation of Hodgkin's disease—he considers as closely allied to it, and like it an inflammatory and not a neoplasm."

I agree with Professor Turnbull in so far as he attributes a common etiology to both Hodgkin's disease and lymphosarcoma, and I will go still

further in regarding them both as infectious processes. But this does not, in my opinion, make it necessary to exclude them from the class of neoplasms, since I believe that both sarcoma and carcinoma are likewise due to the irritation of some infectious agent.

As Rolleston well says, "Gye and Barnard's discovery of an ultra-microscopic virus and specific factor for new growths, and the existence of infective sarcomas make discussion of the *pros* and *cons* of the neoplastic nature of Hodgkin's lympho-granuloma rather an academic exercise than one of practical utility." This was written before later research work had failed to confirm the conclusions of Gye.

Rolleston's paper contains an admirable picture of the more important clinical manifestations of Hodgkin's disease.

Hodgkin's Disease of Bones.—It has long been recognized that the bone marrow was involved in certain cases of Hodgkin's disease. Ziegler [12] believes this occurs in 30–40 per cent. of cases, and Symmers [13] goes so far as to believe the bone marrow is affected in every case. It is only comparatively recently that clinicians have recognized the fact that in certain cases of Hodgkin's disease very definite metastatic tumors of the bone may be found. Symmers found definite bone invasion in 50 per cent of fourteen cases; and Sir Humphrey Rolleston believes that this invasion of bone by lymphadenoma (Hodgkin's disease), is now generally recognized. He states that "among thirty-nine necropsies of the London Hospital, Professor Turnbull found the bone marrow invaded in 49 per cent., the femur most often affected." From a study of the sites affected, he believes that the femur is invaded through the blood stream and the spine by direct extension from the affected retroperitoneal glands. Sir Humphrey Rolleston raises an interesting question whether all bone marrow infection is a part of a widespread reaction to the stimulus of an unknown virus, or whether it is secondary in the same way as a generalized tuberculosis is to an infection from a primary focus. Professor Turnbull concludes it is secondary.

After a careful study of my own cases with bone invasion, I am inclined to agree with Professor Turnbull's views. Here again we find a close analogy to malignant tumors and I believe that the bone invasion and the involvement of other glands and other tissues are closely allied to the metastatic tumors seen in cancer. In nearly all cases it starts in as a primary focus and the multiple tumors result from the infection carried through the blood stream.

Bone invasion may result in paraplegia. I have observed only one case of this kind and in this case the invasion of the spine was probably due to direct extension. The disease started in the glands of the right groin and iliac fossa and was controlled nearly a year by radium and toxins, then recurred and progressed rapidly in spite of further treatment. The lumbar glands were invaded and in a few months the patient developed paraplegia and died about three months later. The diagnosis was confirmed by Doctor

[12] Ziegler: Die Hodgkinsche Kranheit, Jena, G. Fischer, 1911.

[13] Symmers: Am. J. M. Sc., vol. clxvii, pp. 157 and 313, 1924.

Ewing from a microscopical study of the gland removed. I have had one other case with involvement of the lumbar vertebræ from Hodgkin's disease and here also the primary focus was in the inguinal glands.

I have had two other cases of direct invasion of the skeletal bones. One of these is of sufficient interest to warrant a brief citation.

The following personally observed case illustrates this tendency of the disease to metastasize in bones, and is interesting because of the remarkable effect produced by very large doses of toxins given after röntgen-ray had failed to control the disease.

CASE I.—M. G., female, aged forty-eight years. The patient's family history was negative. In October, 1916, she had noticed enlarged glands, the size of a marble, in both sides of the neck. These had gradually increased in size and number and were accompanied by a cough. In September, 1918, a tonsillectomy was performed by Doctor Blake, of Pittsburgh, Pa. Later on, a nodule was removed from the neck, and the pathologist of the Mercy Hospital in Baltimore, Md., pronounced it to be Hodgkin's disease. In February, 1921, the patient was referred to me by Dr. Lawrence Litchfield, of Pittsburgh. At this time she complained of pain, cough, inability to open mouth, and loss of weight and strength. For three years previously she had been treated with röntgen-ray. The disease had been held in almost complete control, but in the latter part of 1920, the glands of the neck became enlarged and masses appeared in both mastoids and frontal region. She was admitted to the Memorial Hospital on February 21, 1921, at which time physical examination showed a patient in fairly good general condition. There was a hard, fixed mass in the left frontal and parietal region, measuring one and one-half inches in diameter, and protruding one-half inch above the normal contour of the skull. In both mastoid regions were large, hard swellings, the size of an English walnut, firmly attached to the bone. In the right side of the neck below and posterior to the mastoid was a mass as big as an egg. Over the occiput was another swelling of the same character as the others. The jaws could be opened only about one-half inch. There was marked telengiectasis.

Increasingly large doses of the mixed toxins were given daily. After one week it was noticed that the masses in the skull were very much smaller, the patient was able to open her mouth wider, and she complained of less pain. By March 15, or after about three weeks' treatment, the pain had entirely disappeared, the masses were very much smaller, and her general condition was considerably improved. By April 26, the patient was practically symptom-free; there was no cough, no lumbar pain, her appetite was good, and the mobility of her jaws was practically normal. The patient was unable to remain in the hospital any longer, and the treatment was continued more or less irregularly and in smaller doses at home. After a few weeks she began to grow worse and in about six months she died.

The foregoing case, while not finally successful, is of the greatest interest for the reason that it is one of the few advanced cases of Hodgkin's disease with extensive bony tumor in both the mastoid and frontal bones. After a failure to control with röntgen-ray, the lesions practically all disappeared as a result of very large daily doses of toxins (25 minims a day—the largest dose I had ever given).

Whether the result would have been otherwise had I been able to keep her longer under treatment, it is impossible to say, but I believe that treatment was begun at a stage too far advanced to expect more than temporary control. If the systemic treatment with the toxins could produce such remarkable disappearance both of the tumor of the bone and soft parts in a few

weeks, it would seem sufficient evidence to justify our making use of this agent in the earlier stages of the disease when there is a greater hope of complete control.

Diagnosis of Hodgkin's Disease.—An entire paper might be devoted to the very difficult question of the differential diagnosis of lymphosarcoma and Hodgkin's disease from the other forms of glandular enlargement, *e.g.* tuberculosis of the glands, chronic or subacute lymphadenitis, or leukæmia but space will permit only a very brief outline of the more important features. The reader is again referred to the admirable paper of Sir Humphrey Rolleston for a lucid discussion of diagnosis and prognosis of Hodgkin's disease. What he has to say on the value and fallacies of biopsies is of especial interest:

> According to Rolleston, *"infiltration of the skin,* by Hodgkin's lympho-granuloma, apart from extension from immediately underlying lymphadenomatous glands, is much rarer than the skin changes of prurigo. In 1924 I could collect twelve cases only. It thus contrasts with mycosis fungoides, which, indeed, has been thought by Ranvier (1869) and K. Ziegler (1911) to be the cutaneous form of Hodgkin's disease, a view difficult to harmonize with the histological appearances. The cutaneous tumors in Hodgkin's lympho-granuloma may be small or large and flat; they grow slowly and seldom, as in Langley and Cole's cases, ulcerate. As a rule, the presence of the tumors has not been associated with pruritus. As they are usually part of the generalization of the disease, they are a late phenomenon in its course."
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> In regard to *"Diagnosis from Sarcomatous Lymphomas",* Rolleston states: "The greatest difficulty is the clinical differentiation of Hodgkin's lympho-granuloma from lymphosarcoma and the closely allied malignant lymphocytoma composed of small lymphocytes, and from endothelial sarcoma. I have seen cases apparently running the clinical course of Hodgkin's lympho-granuloma show these histological appearances finally; the question arises whether, as probably most would consider, these conditions have existed from the start, or whether they have supervened as the result of Hodgkin's lympho-granuloma. Is there any evidence of this change, such as a biopsy early in the course of the disease showing the appearances of Hodgkin's disease, and later a necropsy proving the sarcomatous nature? It does not appear to me that the therapeutic test of X-ray exposures helps in distinguishing them."

The most important clinical signs of Hodgkin's disease are the following: An enlarged gland usually appears first on one side of the neck and is followed soon after by other glands on the same side; after a few weeks or months similar enlarged glands appear on the other side of the neck, and still later, in the axilla and groin. The spleen or liver, one or both, are not infrequently enlarged. The clinical features of the enlarged glands are often sufficiently characteristic to enable one to make a diagnosis of Hodgkin's disease. The glands are freely movable, discrete and very seldom fused as is so often seen in tuberculosis. They are firm in consistence but less hard than a carcinomatous gland and less soft than a lymphosarcoma. In a number of cases, especially after generalization has occurred, there may be an irregular temperature as high as 102° to 103° F. and lasting for weeks. There is nothing of diagnostic value in the blood examination. A severe and progressive anæmia is usually found in the later stages of the disease.

Prognosis of Hodgkin's Disease.—There is no evidence of a spontaneous cure ever having occurred and the universal fatality of the disease has long been recognized. The duration of life varies with the individual case, probably due to variations in the resisting power of the individual and to the variations of the infective agent. It is also very definitely modified by different methods of treatment. Life has been very definitely prolonged by drugs, *e.g.* arsenic, and by röntgen-rays, radium and toxins of erysipelas and Bacillus prodigiosus. In nearly all cases, except a very small percentage, the effect of treatment gradually diminishes and finally becomes nil and the disease goes on to a fatal issue. One case is recorded by Schniffner (quoted by Rolleston), that survived eleven years under röntgen-ray treatment. Some cases run a very acute course causing death within a few months or a year in spite of all treatment.

The following is an example of the difficulty associated with the early diagnosis of Hodgkin's disease especially with a type of Hodgkin's disease which progresses rapidly toward a fatal ending and which shows practically little or no effect from either radiation or toxins.

CASE II.—Mrs. C. W., female, aged thirty-seven years, was referred to me by Dr. Donald Guthrie, of Sayre, Pa., with the following history: The patient had been in good health until February, 1925, when she noticed a small lump in her neck; there were no enlarged glands elsewhere. The gland in the neck was at first believed to be tubercular and was treated for several months with röntgen-ray. In August, 1925, a biopsy was performed by Doctor Guthrie, who regarded the condition as one of tuberculosis. In spite of further röntgen-ray treatment, the glands of the neck continued to increase in size, and on October 13, 1925, Doctor Guthrie performed a second operation. By this time it had become evident that the condition was Hodgkin's disease, in an advanced stage, with involvement of the right cervical region as well. The patient soon began to lose flesh and developed a cough. Röntgen-ray and fluoroscopic examination showed undoubted evidence of thoracic involvement.

When the patient came under my care in November, 1925, there was definite enlargement of the cervical glands on the right side of the neck and extensive involvement of the mediastinal glands, associated with marked dyspnœa. She was losing flesh rapidly. She was immediately started on treatment with the mixed toxins of erysipelas and Bacillus prodigiosus and in addition two radium-pack treatments (9000 mc. hours at 6 cm. distance) were given in December, 1925, and February, 1926. The treatment had practically little or no effect in checking the rapid advance of the disease; the dyspnœa became more and more pronounced, and after suffering intense agony for two weeks, the patient died on February 20, 1926. This was one of the most rapidly progressing cases of Hodgkin's disease that I have ever observed.

Burnam, of Baltimore, in a paper on *Hodgkin's Disease, The Journal, A. M. A.*, October 30, 1926, vol. lxxxvii, No. 18, reports the end results observed in a series of 183 cases of Hodgkin's disease treated at the Howard A. Kelly Hospital between October, 1913, and November, 1925. In his introduction, Burnam states that his original intention "to cover both Hodgkin's disease and lymphosarcoma was abandoned on account of the immensely greater material and the difficulty in analyzing it, and also from the fact that the two diseases are histologically and, in many ways, clinically quite distinct. The first is an infection, in all likelihood, and the second a

neoplasm. I believe that a large number of cases which have been treated and which showed the general distribution in the glands, the fever and the other clinical signs of Hodgkin's disease, may have been Hodgkin's disease. The tissue examinations, however, showed only a lymphoid hyperplasia and, as a consequence, these cases have been classified as pseudoleukæmia, or lymphosarcoma." The latter part of Burnam's statement would lead one to believe that the difficulty in differentiating Hodgkin's disease and lymphosarcoma was somewhat greater than he admits.

Burnam's series corroborates the repeated assertion that Hodgkin's disease is more prevalent in males than in females, his group including 118 males and 55 females.

The age incidence in this group of 173 cases was as follows:

	Per cent.
Up to 10 years	2.45
Between 10 and 20 years	15.33
Between 20 and 30 years	22.1
Between 30 and 40 years	22.3
Between 40 and 50 years	22.1
Between 50 and 60 years	10.4
Over 60 years	5.5

Burnam's series shows that in a great proportion of the cases the disease was apparently primary in the neck. He cites the place of primary gland enlargement as follows:

	Times	Per cent.
Neck	149	86.1
Mediastinum	13	7.5
Abdomen	11	6.1

I believe that a very large number of cases that have heretofore been classed as primary neck cases, should have been classed as primary mediastinum cases; and that failure to take early röntgenograms until after nodules had appeared in the neck has been responsible for the error.

Regarding the course of the disease, Burnam states as follows: "Very acute cases, especially of the intestinal type, last only a few weeks; chronic cases, extending over years, have been long recognized and generally regarded as rare. Two years is the period most authorities give for the average cases, and five years as the extreme limit." The average duration of life in 155 cases of Burnam's series was one year and five months.

In regard to treatment, Burnam believes that surgical removal does no harm in the early localized affections, easily and quickly removed; but extensive operative removals, entailing prolonged anæsthesia, and wide exposures, are unsound theoretically and in practice, and are apparently frequently followed by rapid extensions of the disease. The treatment employed in this series of 173 cases was, with few exceptions, radium alone. A number of the patients had had preliminary surgical removals, but all such showed evidence of disease at the time of treatment. Some had had röntgen-ray treat-

ment, and in some instances it was stated to have been without benefit. Burnam states, "I have recently been engaged in a comparative study of the two agents, radium and the röntgen-ray, and I am not able to state what the comparative ultimate results of the two methods will show. I do find that the reduction of glands, whether deep or superficial, is much more rapid from the radium than from deep röntgen-rays; furthermore, the effects are obtained with much less general upset to the patients. It seems that a very much smaller percentage of gamma rays is effectual than of röntgen-rays in producing similar results." Burnam points out that there are few conditions in which wider differences in susceptibility to radium are encountered than in Hodgkin's disease. He states, "It is obvious that a mass composed of fibrous sclerotic tissue will not reduce so rapidly as one made up almost entirely of cellular tissue and particularly of lymphocytes; but quite aside from differences due to architectural material, there are other and unknown factors, whether in the virulence of the infecting agent or in the defensive forces of the body, which produce striking differences in response to any fixed amount of irradiation. It is of paramount importance to begin with small doses and test out the results in each individual case. When the disease is localized, the dosage may, if it is necessary, be carried to several times that which is, on the average, effectual. In contrast, when the disease is widespread and when incomplete results are obtained by moderate dosage, it is best to go slowly and to recognize that palliation is an end desirable in itself."

The technic which Burnam recommends is "a uniform distance of two inches from the skin, a filter of one millimetre of copper and one millimetre of lead in all the superficial gland areas, and in the deep areas, unless cross-firing is feasible, a distance of from four to five inches. The dosage at the shorter distance is four gram hours, and at the greater from fifteen to twenty-five gram hours. This is about 50 per cent. of the erythema dose."

While Burnam believes that palliation is not to be discredited "and especially when it returns hopelessly ill people for months and even years to normal life, nevertheless I am convinced that certain cases of Hodgkin's disease are not only palliated but cured, from the clinical standpoint at least, and this is as far as one can go with any of the chronic infections, such as tuberculosis, or syphilis, or with any of the malignant new growths. Furthermore, while it is possible clinically to cure very widely spread disease, the percentage of relief is much smaller than when the disease is limited to its original site." Of this series of 173 cases reported by Burnam, 110 patients have died of the disease. Burnam has a group of twenty-eight patients whom he has classified as clinically cured, although two of them are dead, dying in the ninth year, in each instance from apoplexy. The average duration of life in this group was six years and three months.

The importance of beginning treatment as soon as possible after the disease has been recognized is shown by Burnam's end results. Of the entire series of 173 cases, only twenty-four were localized to a single region, and

of these fourteen are in the cured group of twenty-eight cases; twelve of these fourteen cases were cervical, one was mediastinal, and one was splenic. In the remaining 149 cases, only fourteen clinical cures were obtained, and none of these were in the very last stages, although six patients were very toxic and ill at the time treatment was undertaken.

W. S. Stone, of New York, in a report on two hundred cases of Hodgkin's disease treated by röntgen-ray and radium, at the Memorial Hospital, New York, states as follows:

In spite, however, of the extensive literature which has accumulated during the past twenty years, showing the undoubtedly favorable action of these agents, there is little discussion of the curability of Hodgkin's disease. There is also little in the literature to indicate the percentage of cases in which this mode of therapy is effective, the amount of palliation to be expected, and if actual prolongation of life has resulted. Such questions are especially difficult to answer because of the obscure nature of the disease, the location and multiplicity of its lesions and its varied course.

Regarding the permanent curability of Hodgkin's disease by these agents, our records indicate that palliation only can be expected. There are only five living without appreciable lesions or symptoms, one of whom has been well over four years. Three have remained well over three years, one only six months. One patient died after being well for over five years. It is of practical importance, according to the writer's experience, to accept its incurability as a fact in order to obtain the best palliative results. During our early experience a prompt and apparently complete regression of a chain of enlarged nodes led us, in the hope of producing a cure, to give prophylactic treatments over such areas, and also over areas where tumors might be expected to appear. Recurrent tumors, however, developed and new tumors appeared in the fields which had been treated prophylactically, applications to which were found to be less effective than when applied to areas which had not been previously treated. There also appears to be no other disease which requires, even for producing palliation, so many applications to so many areas, demanding, therefore, much consideration of the dosage, the choice of areas and the timing of the applications. The structure of the nodes, also, in Hodgkin's disease, is such that their reaction to these agents causes fibrosis and hardening of the tissues comparatively early, producing pressure upon nerves, blood vessels and neighboring organs, which may cause more distressing symptoms than originally existed. The deleterious effects of repeated and long-continued radiation are seen at autopsy upon these cases to the extent of widespread atrophy of the bone marrow. At present, therefore, we only apply the treatment to tumors as they appear, and often give more consideration to the possible effects upon normal tissues and the general condition of the patient than to the growth activity of the tumors in our timing of the applications.

Stone summarizes his views as follows:

1. X-ray and radium are only palliative agents in the treatment of Hodgkin's disease.
2. Palliation can be accomplished in 60 per cent. of cases, and complete restoration of health with or without complete regression of the tumors may result in about 32 per cent.
3. Restoration of health will often last for a year and rarely two, three or four years.
4. Palliation, if it is to follow, will begin after the first or second treatment.
5. Life may be prolonged one or two years.

DEJARDINS and FORD (J. A. M. A., September 15, 1923, p. 925) report the end results in 135 cases of Hodgkin's disease and fifty-five cases of lymphosarcoma observed at the Mayo Clinic between the years 1915 and 1920. In every case the diagnosis was verified by microscopical examination.

Concerning treatment, they state as follows: "The only form of treatment that

exercises noteworthy influence on such morbid states is irradiation by means of röntgen-ray or radium used either independently or in combination. . . . Even in the presence of extensive mediastinal glandular involvement, with or without pleural effusion, it is often possible for such adenopathy to disappear and the fluid to be absorbed. Unfortunately the improvement is not permanent; it may continue for a number of months or even two or three years, but sooner or later recurrences in the same or other places occur and are usually fatal." Evidently these authors were entirely unfamiliar with the results of treatment of Hodgkin's disease and lymphosarcoma by the mixed toxins of erysipelas and Bacillus prodigiosus reported at the American Surgical Association meeting in 1915.

Of the 135 cases of Hodgkin's disease reported by Dejardins and Ford the date of death was known in seventy-three cases. In these, the average duration of life was two years and seven months. In the fifty-five cases of lymphosarcoma, the average duration of life was found to be two years and three months. Of the entire series of Hodgkin's cases, seven (9.8 per cent.) were well for five years or more; and of the lymphosarcomas, six (11 per cent.) were well for five years.

In conclusion, Dejardins and Ford claim that while it is impossible to state that irradiation prolongs life, it is well known that in many cases it produces complete or partial control of the disease and adds greatly to the comfort and well-being of the patient.

In several instances these authors have noted a certain feature that I myself have observed in my experience with this type of disease, and that is, marked leucocytosis. In one of my cases of Hodgkin's disease, a blood test showed 83,000 white blood cells; and in one case of lymphosarcoma, there was found 247,000 white blood cells. While the latter case clinically resembled one of lymphatic leukæmia, microscopical examination showed it to be a lymphosarcoma.

The statistics of MINOT and ISAACS, already referred to, cover 232 cases admitted to the Massachusetts General Hospital between 1901 and 1925, 225 cases observed at the Collis P. Huntington Memorial Hospital, of Harvard University, between 1913 and September, 1925, and twenty cases seen in private practice since 1916, making a total of 447 cases. Seventy-six patients are living and 401 are known to be dead. Of this entire series, only seven patients were alive ten years or longer after the date of first observation. These seven were classified as follows:

1 female (age group 5–9)
2 males, 1 female (age group 40–44)
1 male in each of the age groups, 45–49, 50–54, 65–69
Total 7; 5 males, 2 females. Of these, 4 were irradiated and 3 were not.

Forty-one patients had lymphoblastoma for six years or more before death, of which 11 per cent. were treated by radiation, and 8 per cent. were not so treated. Of the 401 cases known to be dead, 238 were treated by radiation, and 163 were not irradiated. The latter group includes thirty-three patients who underwent a surgical operation with removal of a considerable amount of diseased tissue. According to Minot and Isaacs, "The patients treated by surgical measures, whether or not they received röntgen-rays or radon, had lymphoblastoma on the average 3.67 years, or 1.11 years longer than the average duration (2.56 years) of the disease in the 334 not undergoing a therapeutic operation. The chances of the former living beyond three years from the time of their first symptoms were greater than for the whole group of irradiated patients. However, the percentage dying a year or less after the onset of disease was the same as for the cases given no especial treatment, and only 10 per cent. less than for the latter group at the end of the two-year period."

The results of Burnam with radium are more favorable than any that have been obtained by other men. The fact that the majority of his series,

well five years, occurred in cases treated in the very early stages of the disease, emphasizes the great importance of early diagnosis and early treatment. It would seem to still further support the view of Professor Turnbull that the disease begins in a single focus and later is carried through the blood stream to other glands and soon becomes generalized. If we wait until this generalization has taken place, we can hope for little more than temporary control. If we can recognize the condition when the disease is limited to a single focus or to a few enlarged glands in a single region, then we are certain to control the disease for a much longer period of time and it is not impossible that we may effect a permanent cure.

This brings up the question of the value of surgery in Hodgkin's disease and lymphosarcoma. From my own experience I am of the opinion that an early biopsy is extremely important in most cases of enlarged glands, especially in young adults and especially when such enlargement cannot be easily accounted for by some adjacent focus of inflammation, *e.g.* in the throat or nasopharynx in the case of cervical glands. One must recognize frankly the fact, that it is extremely difficult to make a diagnosis from a small gland removed at biopsy between Hodgkin's disease or lymphosarcoma or simple hyperplasia. It has been my experience in three or more cases after having removed a gland from the neck in a case of suspected Hodgkin's disease or lymphosarcoma, to receive a microscopical report of chronic inflammation, no evidence of malignancy, and yet in each case the subsequent clinical history showed that it was a case of Hodgkin's disease or lymphosarcoma. In other words, in certain cases we shall still be in doubt after the biopsy report and in a case of negative report we must decide upon our diagnosis and treatment from the clinical evidence alone. Fortunately in the majority of cases of Hodgkin's disease or lymphosarcoma the pathologist will be able to make a positive report and this fact is what prevents us from losing faith in the biopsy and permits us to obtain most valuable help in the majority of cases.

If the biopsy gives positive evidence that the enlarged gland is Hodgkin's disease or lymphosarcoma, what is the best course to pursue? If it was a solitary gland and was completely removed in the biopsy, then it is my opinion that the patient should be put upon a course of röntgen-ray treatment and should receive systemic injections of toxins two or three times a week for a period of six months, in moderate doses that will interfere but little with his ordinary routine of life. If the gland was not solitary, but one of a few regional and well localized glands that apparently can be successfully removed by surgery, then I believe surgery should be performed, followed by prophylactic local treatment by radium and systemic toxins. In the more advanced cases in which several regions and glands are affected and especially if the röntgengram shows the mediastinum to be involved, I believe surgery should not be tried. It can do little good and may do much harm by still further generalizing the disease.

A study of my own cases in which surgery was employed would seem to support the foregoing views.

While I do not go so far as Bunting and Yates do [14] in believing that the disease is strictly local in its origin, at least when the patient first consults a physician or surgeon, and, therefore, should be treated by radical surgical operation, I do believe with Stone as well as Minot and Isaacs, that in a few very early cases when the disease is apparently confined to one or a few glands, and these regional, surgical removal followed by local radiation and prolonged systemic toxin treatment offers the greatest hope of controlling the disease. This group of cases, however, represents a very small percentage of the total.

Stone has pointed out the difficulty of the problem of adjusting the proper dose of radium to the individual case. No two cases are alike; and the dose that might be of great advantage to one patient might do great harm to another. In an advanced case with much fibrosis, radiation is of little value and may do positive harm, increasing the anæmia and lowering the general vitality. Minot and Isaacs and others have pointed out the dangers of too large doses of radiation in the acute highly cellular cases, and in a number of cases the evidence is very positive that radiation has hastened a generalization of the disease.

While I believe that radiation has proved of very great value in the treatment of both lymphosarcoma and Hodgkin's disease, the weight of opinion at present is that this method can be regarded as palliative only, and not curative, in the great majority of cases. It is true that Burnam's results show that in a considerable number of cases of Hodgkin's disease, radiation has kept the disease under control for a long period of time, sufficiently long to warrant classing the cases as cures. On the other hand, the statistics of Minot and Isaacs and of Stone, have not shown these lasting results either in lymphosarcoma or Hodgkin's disease. It is possible that Burnam's series covering, as it doubtless did, mostly private patients, may represent a higher percentage of cases in the early stages of the disease when radiation accomplishes much more than it does in the later stages. Furthermore, being private patients, they were under much better control, and treatment could be carried out much more satisfactorily than was possible in the series reported by Minot and Isaacs and by Stone representing almost entirely cases observed in the out-patient department. In view of these facts, we must admit that the present results in the treatment of lymphosarcoma and Hodgkin's disease are far from ideal; and I believe that the profession should welcome any aid that might be given to radiation, in the way of some systemic remedy or agent.

While this disease (or group of diseases) may be, and probably is, local at the beginning, it is nevertheless true that it is far from being local when its true nature is recognized and treatment is begun. In the majority of cases, instead of finding a solitary enlarged gland, we find a large number

[14] J. A. M. A., vol. lxiv, p. 1953, June 12, 1915.

of glands, and usually these are not confined to a single locality, like one side of the neck, but they involve the mediastinal, axillary, inguinal, and even the retroperitoneal or mesenteric glands as well. If this is true, it becomes apparent that the satisfactory treatment of all these glands, superficial and deep, by a local agent like radiation, becomes a very difficult and often impossible task. While radiation can accomplish much in the way of palliation in most cases, a cure or prolonged control of the disease is rarely obtained. In such cases I believe that systemic injections of the mixed toxins of erysipelas and Bacillus prodigiosus offer a very definite aid to local radiation of all the enlarged glands. That this opinion is based not merely upon theoretical considerations but upon actual results in a large number of cases treated before radiation was employed, has been shown in detail in my paper of 1915. Here we find that upward of 10 per cent. of the cases treated by toxins alone have recovered and have remained well from three to more than twenty years. This would seem to be ample ground for advocating a combination of toxins and radiation.

In his paper already referred to, Burnam has stated that he has used the toxins extensively in Hodgkin's disease and found them to be of no value. It would be interesting to have a more detailed report from Burnam stating in how many cases the toxins were used, in what type and in what stages of the disease, and especially, whether the toxins were used alone or in conjunction with radiation and how long the treatment was continued. If used with radium, it would be extremely difficult to estimate the relative value of either agent. Were my series confined to cases treated by a combination of toxins and radiation, no matter how successful the results were, I should hesitate to say just what part the toxins played in accomplishing these results. However, we have a large group of cases of lymphosarcoma and Hodgkin's disease in which the toxins were used alone and in which it is impossible to attribute the favorable results obtained to any other agent.

If it could be shown that it is possible to obtain equally good results with radiation, there might be some reason for not employing the toxin treatment in lymphosarcoma; but no one has thus far reported any results from radiation that equal the results obtained from toxin treatment, either in regard to the number of successes or the durability of the cures.

While all the successes with the toxins have been obtained by the use of interstitial or intramuscular injections, I believe that it might be possible to obtain far better results from intravenous injections. Some fifteen years ago I tried intravenous injections in two or three cases, but owing to the severe reactions that followed I feared that this method might prove too dangerous and therefore abandoned it. About two years ago, at the suggestion of my son, Dr. Bradley L. Coley, I began again to use the intravenous method and we have used it in a considerable number of cases since. While we have not had any fatalities, we are not yet ready to advocate it as a routine method for the reason that very severe reactions often follow a minute dose (one-twentieth minim). The susceptibility of the different individuals varies

greatly. In one case a dose of one-eighth minim injected intravenously was followed by a temperature of 104° or 105° F., while in another the temperature rose to 105.5° following an injection of one-twenty-fourth minim. I have had a temperature of 104° follow an initial dose of one-fortieth of a minim in an adult. The intravenous method should never be used until the susceptibility of the patient has been ascertained by the use of interstitial injections given over a period of at least one week. The initial dose given intravenously should never be more than one-twenty-fourth minim. A number of cases that have failed to respond to interstitial injections have shown marked benefit from intravenous injections; and I believe that the latter, if given with care, offer greater promise of success not only in lymphosarcoma and Hodgkin's disease but in all types of inoperable sarcoma.

REPORT OF CASES OF SPECIAL INTEREST

CASE III.—*Hodgkin's disease or lymphocytoma, treated with toxins, radium and röntgen-ray. Disease more or less under control for three and one-half years. Death from pneumonia; autopsy.* R. McC., male, aged fifty-two years, came under my care on July 10, 1921, with the following history: In the early part of 1920, while on a sea voyage, he first noticed a swelling under the chin; this lasted for three or four days. It is interesting to note that other members of his family were affected in the same manner. From that time on, the patient claimed that he had never really felt like himself again. In the beginning of 1921, general weakness, which previously had not been so marked, became striking; and he suffered from an attack of lumbago also. In April, 1921, the patient was shocked on noticing for the first time his extreme pallor; soon after this he experienced shortness of breath. On May 13, 1921, he came under the care of Sir Humphrey Rolleston, whose report of the case is as follows: "Patient when first seen had had dyspnœa for a month. Pale aspect at first suggestive of chronic renal disease but urine normal, and blood pressure 165 systolic, 80 diastolic. Enlarged discrete glands on right side of neck; enlarged irregular liver; doubtful mass about splenic flexure; no sore tongue. X-ray report does not suggest carcinoma of stomach or colon. Blood with low color index, otherwise suggests early pernicious anæmia or secondary metastases in bones. On May 30, after rest and arsenic, some improvement of blood and general feeling. July 27, after moderate business activity, worse; glands were enlarged; gland in right groin, also gland in left side of neck. *Röntgen-ray Examination.*—May 17, 1921; report as follows: 'Enlarged glands in root of right lung; heart enlarged.' *Blood Examination.*—May 13, red blood cells, 3,165,000; white blood cells, 4,400; hæmoglobin 57 per cent. May 28, 1921, red blood cells, 3,370,000; white blood cells, 5,000; hæmoglobin 55 per cent. June 27, 1921, red blood cells, 2,710,000; white blood cells, 4,800; hæmoglobin 43 per cent."

The patient came under my care on the day of his arrival from Europe on July 10, 1921. Physical examination at this time showed him to be very anæmic and cachectic, with evidence of marked dyspnœa on the slightest exertion. Enlarged glands, discrete and fairly firm in consistence, were found in the cervical and supraclavicular regions as well as in the axillæ and groin. The spleen was markedly enlarged, and the liver was enlarged to the extent of two finger-breadths below the border of the ribs. My clinical diagnosis was that of Hodgkin's disease, primarily in the mediastinum. Dr. Evan Evans and Dr. Karl M. Vogel, both of New York, who saw the patient in consultation with me, concurred in this diagnosis. I did not believe that he could live more than three or four weeks. Doctor Vogel made a blood examination at this time and reported as follows: Red blood cells 2,500,000; white blood cells 4,400; hæmoglobin 45 per cent. In counting 300 cells, two megaloblasts and eight normoblasts and four microblasts were seen. Abnormal white cells were not seen. The red cells showed considerable

variations in size, very slight poikilocytosis and slight polychromasia. Punctate basophilia was not observed. *Röntgen-ray examination* at this time showed a large tumor in the mediastinum.

The patient was admitted to the Memorial Hospital on July 29, 1921, and a massive dose of radium (9000 mc. hours at 6 cm. distance) was immediately applied over the mediastinum. Four days later another massive dose of radium was applied over the spleen. He showed very little reaction to radium. Röntgen-ray treatment was given over the glands of the neck, axillæ and groin. In addition, he was put upon systemic injections of the mixed toxins of erysipelas and Bacillus prodigiosus, the initial dose being one-quarter of a minim. He proved very susceptible to the toxins and was never able to take a larger dose than three minims.

A gland was removed shortly after the patient's admission to the Memorial Hospital, and submitted to Doctor Ewing for microscopic examination. His report is as follows: "Chronic lymphadenitis; no definite signs of Hodgkin's. The cellular overgrowth is considerable but not enough for lymphosarcoma which it resembles."

As the clinical evidence of Hodgkin's disease or lymphosarcoma was so strong, little attention was paid to the negative microscopical report based upon the examination of a small gland. Seven weeks after the patient's admission to the hospital examination showed changes to have taken place which were very remarkable: all the glands had disappeared, and the spleen and liver had returned to normal. The blood picture, however, was distinctly worse, radiation having caused a fall in the white blood cells to 1,000, and the red blood cells to 2,210,000; hæmoglobin 33 per cent. A blood transfusion was given and was followed promptly by marked improvement. During February, 1922, his hæmoglobin remained stationary, with moderate fluctuations, in the neighborhood of 80 per cent., and his white-cell count was normal. No radiation was given during this period. He received only moderate doses of toxins ranging from 1½ to 2 minims, which produced a slight reaction, temperature of 99.5, but no chill. In August, 1922, one moderate röntgen-ray (low voltage) treatment was given over the axillæ, neck and groin; and he received another transfusion on September 22, 1922.

Physical examination in November, 1922, showed distinct enlargement of the mediastinum. Röntgen-ray examination of the teeth revealed numerous abscesses about the roots, and two of the lower teeth were extracted. The effect of the last transfusion was very much less marked than that of the first, and was more temporary. He was becoming rapidly weaker, even sligh exertion causing dyspnœa; his hæmoglobin had gone down to 45 per cent., his red blood cells to 1,800,000, and his general appearance was very anæmic. No glands could be felt in the neck or axillæ; the inguinal glands were palpable, and enlarged glands could be felt in both iliac fossæ.

He was given another transfusion of blood (750 c.c.). Two days later another radium-pack treatment was given over the iliac fossa and groin. Between November 15 and November 23, four more teeth were extracted. On December 5, 1922, the patient went to Camden, South Carolina. During the next month he showed steady and rapid improvement; he was able to play eighteen holes of golf a day without fatigue. In May, 1923, slight enlargement of the glands was detected in the cervical and axillary regions as well as in the groin; the retroperitoneal glands also were slightly enlarged. In June, 1923, a radium-pack treatment (9,000 mc. hours) was given over the groin, and Röntgen-ray treatment to the other superficial glands; in addition, the toxin treatment was resumed. *Röntgen-ray examination* at this time failed to show any evidence of enlargement of the mediastinum.

During the next eighteen months the patient received a transfusion every four or five weeks by Doctors Coley (B.L.) and Patterson. At first 600 or 700 c.c. were given, but this amount was later increased to 1,000 c.c. (from two donors). The last transfusion was given on December 6, 1924. It was necessary for the patient to travel some two hundred miles, in mid-winter, to get this transfusion, and on the way he caught a slight cold; temperature of 100. He was kept in New York for one week until his

cold had apparently disappeared and his temperature had returned to normal; but on the way home he caught more cold, which developed into pneumonia and caused his death in two days.

An autopsy was performed by Dr. Stanley T. Fortuine and the tissues were examined by Doctor Ewing, whose report is as follows:

"In all the organs from which slides re-submitted (liver, spleen and lung) I find a malignant tumor of the type of malignant small-cell lymphocytoma.

"The spleen section shows a diffuse growth of small lymphocytes obliterating all the normal structures of the organ. In the liver the infiltrations are limited to diffuse lymphomas of the portal canals, while the lobules are free. The lung tissue shows a solid growth of lymphocytes filling the alveoli, but not destroying the framework of the lung.

"This type of tumor is a rather rare but well recognized type of lymphoma, generally called malignant lymphocytoma. It is nearly always systemic, affecting the whole lymphatic system and eventually the organs. It is related to lymphosarcoma and to pseudo-leukemia, but differs from the usual type of lymphosarcoma, in that the cells are small lymphocytes. It is one of the most malignant tumors known. Of the causation nothing is known. I believe all such cases are fatal, without regard to the method of treatment."

This case is of interest from the fact that it shows a far advanced malignant process involving the lymphatic glands to have been kept under partial control for a period of three and one-half years, the patient then dying of pneumonia. According to the autopsy, however, the disease was steadily progressing and, undoubtedly, would have caused death in a comparatively short time even if the patient had not contracted pneumonia. The case further illustrates the importance of paying little heed to a negative microscopical report based upon an examination of sections from a small gland.

CASE IV.—*Round-cell lymphosarcoma of neck and supraclavicular glands, recurrent and inoperable. Patient well twenty-five years after treatment.* A. P., female, aged two years and ten months. This patient was referred to me by Dr. E. J. McKnight, of Hartford, Connecticut, in March, 1902. A primary tumor had been removed by Doctor McKnight at the Hartford Hospital on January 27, 1902. No examination of the specimen was made, but the tumor rapidly recurred, and a second operation was performed in March, 1902. The specimen removed at this time was examined by Dr. W. B. Steiner, pathologist at the Hartford Hospital, who made a diagnosis of small-round-cell sarcoma. The tumor was considered too extensive for removal. The patient was first seen by me on March 8, 1902, at which time I found a series of tumors extending from the clavicle to the mastoid bone on the right side. The submaxillary and axillary glands on the right side were also involved. The clinical appearance of the disease was typically sarcomatous. I advised the toxin treatment, which was carried out by Doctor McKnight for about three months. There was immediate improvement followed by complete disappearance of the tumor.

This patient was shown before the Clinical Congress of Surgeons of North America on November 12, 1912, and at a clinical conference at the Memorial Hospital on November 7, 1918. A letter received from her in 1927 stated that she was married, had four children, and was in excellent health.

CASE V.—*Inoperable melanotic sarcoma of the neck which entirely disappeared under an accidental streptococcic infection. Five years later developed round-cell sarcoma of the cervical glands which was treated with toxins and radium. The disease entirely disappeared and the patient is in excellent health thirteen years after the appearance of the melanoma.* V. B., female, aged seven and one-half years. The patient had always been in good health until February, 1915, when a swelling of the left jaw was noticed. Two weeks later the right side of the neck began to swell and enlargement of the cervical glands was noticed. An examination was made by Dr. W. F. Mercer, of Richmond,

Virginia, who pronounced the throat, nose and ears normal. The patient was then examined by Dr. Robert C. Bryan, of Richmond, Virginia, who found the submaxillary, cervical and supraclavicular glands symmetrically enlarged and matted together. The enlargement was more pronounced on the left side. A provisional diagnosis of Hodgkin's disease was made. The blood examination was negative.

On July 7, 1915, Doctor Bryan made a small incision over the submaxillary gland at the angle of the left jaw and removed two small glands. These were examined microscopically by Dr. S. B. Moon, of the Medical College of Virginia, who made the following report:

"The sections are composed mainly of actively proliferating embryonal connective tissue cells, mainly spherical, but varying widely in shape and size. An occasional giant cell is seen. The vessel walls are thin or lacking, and when present, are intimately associated with the tumor cells. In some areas pigment granules, apparently melanin, are abundant in the cell protoplasm. Fibro-elastic tissue, fat, and striated muscle are definitely infiltrated by the tumor cells in their advance. *Diagnosis.*—Melanosarcoma."

The condition was quite inoperable, and a hopeless prognosis was made. The tumor slowly increased in size until December 25, 1915, when there was also beginning emaciation. On December 26 the neck became red and swollen and continued to increase rapidly in size. The patient's temperature rose to 106° F. and her pulse was 180. There was marked cyanosis, great dyspnœa and evidence of severe infection in the tumor. On December 27, the child became unconscious. On the following day, under primary anæsthesia, a median incision was made under the jaw and a large amount (from two to three ounces), of sero-pus was evacuated. A specimen was examined microscopically by Doctor Moon, who reported as follows: "Pus from neck is streptococcic with various saprophytes."

The infection slowly subsided but the wound remained open for several weeks. The tumors of the neck gradually decreased in size and in a short time entirely disappeared.

Doctor Ewing made a microscopical examination of the sections and confirmed the diagnosis of melanoma.

The patient later came to New York and was placed under my care for observation. She was presented before the New York Surgical Society on March 12, 1919.

In May, 1920, or five years after the appearance of the melanoma, she developed a rapidly-growing sarcoma involving the right cervical glands. A clinical diagnosis of round-cell sarcoma was made. I removed a portion of the tumor and submitted it to Doctor Ewing, who stated that it was a round-cell sarcoma with no pigment.

The toxin treatment was begun and kept up for four months. In addition, she received one radium treatment (2972 mc. hours in the form of a lead tray placed at 3 cm. distance). The tumors rapidly disappeared and the patient made a complete recovery. She was shown at a staff conference at the Memorial Hospital on January 28, 1926, at which time she was in excellent condition, eleven years since the disappearance of the melanoma and nearly six years after the disappearance of the round-cell sarcoma. At the present time, August, 1928, the patient remains in excellent health.

CASE VI.—*Large, inoperable lymphosarcoma of the small intestine treated with toxins and radium. Later metastases developed in the axilla. Patient in good health ten and one-half years later.* R. T., male, aged thirty-four years. The patient's father had died of cancer of the stomach. The patient had always been in good health until July 3, 1916, when he fell from a building, for a distance of eighteen feet striking on a cement floor; he landed in such a position that his upper abdomen received a sharp blow from his doubled-up elbow. Six or seven months later he began to feel pain in the upper left abdomen at the site of the injury. He consulted a number of physicians and surgeons in the State of Washington, who made the following different diagnoses: floating kidney, enlarged spleen, pancreas, sarcoma, tuberculosis of peritoneum, etc. The patient's own diagnosis was "internal cancer". In the middle of December, 1917, he came under the care of Dr. Charles H. Mayo, who made a clinical diagnosis of lymphosarcoma of the small intestine. Doctor Mayo performed an exploratory operation, by a left rectus

incision, revealing a large, inoperable tumor of the mesentery and small intestine. The tumor involved such a large segment of the mesentery that it was deemed unwise to attempt to remove it surgically and the wound was closed. The patient was then referred to me for toxin treatment.

Physical examination on January 7, 1918, showed a recent cicatrix, four inches long, over the left rectus muscle, the upper area of which was not entirely healed. Just underneath this incision was a solid tumor, about eight inches in diameter, deeply attached, but apparently connected with the mesentery or intestine. No enlarged glands could be felt. The patient's general condition was good; he had no pain nor any marked loss of weight. The blood test was negative.

The patient entered the Memorial Hospital and treatment with toxins and radium combined was begun at once. On January 8, 1918, he received his first radium-pack treatment consisting of 20,000 mc. hours applied at 10 cm. distance; on February 7, 1918, a second pack consisting of 16,000 mc. hours was applied at 10 cm. distance; and on March 3, 1918, he received 10,000 mc. hours at 7 cm. distance. He was made very ill by the radium.

On January 15, 1918, the toxin treatment was begun. It was given in small doses and increased very slowly, as the patient proved very susceptible and developed a high temperature, 103°, from a dose of two and one-half minims. After the first week's treatment, the tumor decreased about one-half in size and became much more mobile. The patient's condition steadily improved and he returned to his home on the West Coast, where the toxin treatment was resumed by his family physician.

On July 23, 1918, he again came to see me. Examination at this time showed on palpation, a very small, hardly perceptible mass at the site of the original tumor. As a precaution he was given two applications of radium (18,000 mc. hours at 7 cm. distance, each), and the toxin treatment was continued. During the year 1919 he received further applications of radium, totaling 44,283 mc. hours. The toxin treatment was kept up by his family physician, two or three injections a week being given, in doses not sufficiently large to interfere with his daily routine of life. I saw him again in May, 1920, at which time physical examination failed to reveal any definite mass in the abdomen; there were, however, two very small glands in both cervical regions. The lead tray, containing 3,000 mc. hours of radium, was applied at 3 cm. distance to each area; and the pack, (17,000 mc. hours), was applied over the abdomen. I next saw the patient on November 25, 1920, when he again had the pack, (6,344 mc. hours), applied over the abdomen. The toxin treatment was continued. He received no further radium until August 8, 1921, when the lead tray containing 2,870 mc. hours was applied to the left supraclavicular region, and the pack, (6,344 mc. hours), was applied to the abdomen. In January, 1922, a small nodule was noticed on the left elbow. This was treated with röntgen-rays and disappeared. In January, 1923, he received another pack treatment (18,026 mc. hours), over the abdomen.

The toxin treatment was kept up until November, 1923, after which the patient refused to take it any longer. About two months later, he noticed a slight enlargement of the glands of the left axilla, which steadily increased in size. I again saw the patient on January 20, 1925, at which time physical examination showed enlargement at the site of the old intraabdominal tumor, with apparent involvement of the retroperitoneal glands; the cervical and inguinal glands were normal. In the left axilla was a mass about the size of a large goose egg or a small orange, soft in consistence, movable and extending from some distance beneath the edge of the pectoral muscle. The radium pack was applied as follows: On January 22, 1925, he received 12,000 mc. hours over the abdomen at a distance of 10 cm.; on January 24, he received 10,000 mc. hours over the left pectoral region, at a distance of 10 cm.; and on January 26, he received 10,000 mc. hours over the left axilla, at a distance of 6 cm.

On February 4, 1925, he entered the Hospital for the Ruptured and Crippled, where I removed the tumor of the axilla surgically. Microscopical examination proved it to be a typical lymphosarcoma.

This case is of interest for the following reasons: first, it shows that a rapidly growing lymphosarcoma of the small intestine has been almost completely controlled for a period of ten years, the patient remaining in good health during most of the period; second, it shows that even when metastases have developed, one should not abandon treatment. In this case, the metastatic tumor in the cervical glands completely disappeared under further treatment. The latest and most extensive metastasis in the axilla did not occur until November, 1923, some time after the toxin treatment had been discontinued. While in all probability the disease will prove fatal in the end, I believe there is a reasonable hope of keeping it under control for some considerable time to come. I do not believe this result could have been obtained by toxins alone or radium alone, but was due to the combined treatment with both agents.

CASE VII.—*Lymphosarcoma of neck, or Hodgkin's disease, treated with toxins. Patient well twelve years later, when she died of another trouble.* S. K., female, aged fifty-five years, was referred to me in December, 1913, by Dr. Arpad G. Gerster, with the following history: A tumor had been removed from the right side of her neck at Gouverneur Hospital nine years before. In March, 1913, a second operation was performed by Doctor Erdman for a local recurrence; the tumor removed weighed three-fourths pound and was pronounced lymphosarcoma by the pathologist of Bellevue Hospital. The tumor again recurred in the fall of 1913 and the patient was then referred to me by Doctor Gerster as an inoperable case.

Physical examination at this time (December, 1913) showed several tumors occupying the right cervical region between the mastoid and clavicle, varying in size from a hickory nut to a hen's egg. The tumors were smooth in outline, freely movable, more or less discrete; skin not adherent; consistence only moderately firm; no glands in either axilla or groin. No enlargement of the spleen or liver. The patient was put upon the mixed toxins of erysipelas and Bacillus prodigiosus. She proved very susceptible, the highest dose given being 5 minims. After fifteen treatments, the tumors had diminished markedly in size and became more freely movable, so that I believed it wise to attempt their removal by operation. This was done by my associate, Dr. William A. Downes, on January 15, 1914. Doctor Ewing's report on the specimen, dated January 15, 1914, reads: "Typical Hodgkin's disease; granuloma; giant cells; hyaline and fibrin areas."

The disease recurred shortly after the operation and grew more rapidly than before. She was then put upon röntgen-ray treatment, under which there was marked diminution in the size of the tumor.

After her discharge from the hospital I lost track of the patient and believed she had died. Eight years later I was called in consultation to see her and found her suffering from an acute abdominal trouble (probably gall-bladder). She was removed to the Memorial Hospital, but her condition was too advanced for operation and she died in a few days. There was no evidence of any return of the Hodgkin's disease.

CASE VIII.—*Far advanced Hodgkin's disease; diagnosis confirmed by microscopical examination; disappearance of lesions under toxins and radium. Patient well four and one-half years.* F. A. T., male, aged fifty-seven years. The patient's family history was negative. He had always been in good health with the exception of an attack of typhoid fever thirty-two years previously. His present illness started with a cough in the summer of 1921; for the next seven or eight months he felt very tired and weak. At the end of this time he noticed a lump in the left side of his neck. A diagnosis was not made until March 1, 1922, when a gland was removed and examined by the pathologist of the Buffalo Hospital for Malignant Disease, who pronounced it Hodgkin's disease. In the early part of March, 1922, he received röntgen-ray treatment of his neck. Shortly

afterward the glands in the right side of the neck and supraclavicular region began to enlarge. There was steady increase in size and the patient became weaker. Under further radiation the glands regressed somewhat. He was referred to me by Dr. R. P. Huyck, of Herkimer, New York, and was admitted to the Memorial Hospital on April 24, 1922.

Physical examination at this time showed a well-developed but poorly nourished male. The cervical, axillary and inguinal glands were all enlarged, firm in consistence, discrete and movable. There was a mass of glands on the right side of the neck, the largest just above the clavicle measuring one inch in diameter. The skin was not involved. On the left side of the neck was a similar gland just under the scar. The liver was palpable; and the spleen just palpable.

Röntgen-ray examination by Doctor Herendeen, April 24, 1922: "Plate of chest reveals a diffuse haziness through the right side with some infiltration in the right hilum."

On April 26, 1922, the radium pack (12,750 mc. hours) was applied over the mediastinum, at a distance of 10 cm. In addition, from May 4, 1922, to May 9, 1922, the patient received four exposures (fifteen minutes each) of röntgen-ray to the axillæ and groin. At the same time, treatment with the mixed toxins was begun and continued in gradually increasing doses during his three weeks' stay at the hospital. This was continued at home by his family physician, Doctor Huyck. A few weeks after his discharge from the hospital his general condition became very weak, in appearance he was almost cachectic, and he was strongly opposed to any further treatment. I saw him again and finally persuaded him to go on with the toxin treatment. This was kept up for six months. In early June, 1922, he began to show some evidence of improvement in his condition; this continued until at the end of two months all trace of the disease had disappeared, he had regained his normal health and was able to return to his work. I saw him from time to time and found him in excellent condition. Physical examination in May, 1926, showed apparently no evidence of the disease.

In June, 1926, he developed a tumor in the left hypochondriac region which was regarded by several surgeons, who were not acquainted with the patient's early history, as a tumor of the kidney. This was, undoubtedly, a tumor of the spleen. It increased rapidly in size, his general health began to deteriorate, and in spite of further treatment, he died on August 1, 1926.

In this case I think it is fair to assume that the treatment added four years to the life of the patient, who was in an advanced stage of the disease when the treatment was begun.

My later series of cases personally observed since 1915 includes fifty-eight cases of lymphosarcoma and thirty-nine cases of Hodgkin's disease. In the former group there were thirty-five males and twenty-three females, and in the latter twenty-two males and seventeen females.

Age incidence:

	Lymphosarcoma Cases	*Hodgkin's Disease Cases*
From 1 to 10 years	2	3
From 11 to 20 years	9	1
From 21 to 30 years	11	9
From 31 to 40 years	7	9
From 41 to 50 years	18	4
From 51 to 60 years	4	6
From 61 to 70 years	3	3
Not stated	4	4
	58	39

Locality in present series:

	Lymphosarcoma Cases		*Hodgkin's Disease Cases*
Neck	24	Neck	3
Retroperitoneal region	7	Groin	3
Axilla	3	Neck, axilla and groin	27
Groin	4	Supraclavicular region	1
Mediastinum	2	Cervical region	1
Tonsil	1	Mediastinum	1
Nasopharynx	2	Spleen	1
Multiple	15	Submaxillary region	1
		Multiple	1

Duration of symptoms in present series:

	Lymphosarcoma Cases	*Hodgkin's Disease Cases*
Less than 1 month	3	–
5 weeks to 3 months	7	5
3 to 6 months	13	6
6 months to 1 year	11	12
1 – 2 years	12	4
2 – 3 years	6	4
3 – 4 years	1	2
4 – 5 years	2	2
6 – 7 years	1	–
8 years	–	1
9 years	1	–
Not stated	1	3

An analysis of the cases that have remained well for five to twenty-two years may be of some interest (four others were well for three to five years). Of this group, fifteen were treated with toxins alone and three with toxins and röntgen-ray. This does not include a case of Hodgkin's disease that was treated with toxins alone by Dr. Charles E. Preston, of Ottawa, Canada, my old house surgeon; this case, which was well when last traced, twelve years later, might well be included here, as the treatment was carried out under my direction.

Site of Primary Tumor in Cases of Apparent Cure.

	Cases
Glands of neck	10
Tonsil and neck	2
Axilla	4
Mediastinum	1
Groin	1
Mesentery and small intestine	1
	19

The diagnosis was confirmed microscopically in all these cases with the exception of one, a very large tumor of the mediastinum which disappeared under toxins and röntgen-ray and had not recurred five years later when the patient was last seen.

One case was included in my earlier paper, in which, while not strictly speaking, a lymphosarcoma, was, apparently, a primary malignant tumor of the lymphatic glands.

This patient, the wife of a physician in Louisville, Kentucky, was referred to me in December, 1914, with an inoperable, four-times recurrent tumor that involved the cervical glands on both sides. While a microscopical diagnosis of melanotic sarcoma had already been made, I removed a gland for further study, and it was pronounced a malignant melanoma by Dr. James Ewing. I regarded the prognosis as quite hopeless but decided to give the patient a trial of toxin treatment. The injections were continued for nearly a year at home by her husband. Under this, and no other treatment, she made a complete and uninterrupted recovery. She remained well for more than nine years and then died of an independent trouble.

Of the thirty-nine cases of Hodgkin's disease included in my later series, only three remained well for a period of more than three years, and one of these died of the disease four years after the treatment was begun. Of the fifty-eight cases of lymphosarcoma, six remained well for a period of from three to ten years; two of these died a little over three years later, and the patient who has lived for ten years has marked evidence of the disease and is not expected to live much longer. One other case, No. VII (reported in my earlier paper, at which time the end result was not known) remained well for eight years and then died of another trouble.

A comparison of the results obtained in the later series with those of the earlier series will show the latter—in which treatment for the most part consisted of surgery and toxins—to be considerably better than those of the more recent series, in which treatment consisted of toxins and radiation. I think that the less favorable results obtained in the later series may be accounted for by the fact that most of these patients at the time of first observation were in a much later stage of the disease, the latter having become widely generalized in most cases, and most having been previously treated by radiation.

CONCLUSIONS

1. Lymphosarcoma and Hodgkin's disease should no longer be regarded as absolutely hopeless from any method of treatment.
2. These tumors are as a rule extremely radio-sensitive and are likewise responsive in a remarkable way to treatment with the mixed toxins of erysipelas and Bacillus prodigiosus.
3. It would seem logical to use the combined treatment, thereby securing the advantage of the local effect of radiation (radium or röntgen-ray) and the systemic effect of the toxins which have the power to reach hidden and remote glands beyond the reach of radiation.
4. These patients should be kept under the closest observation for a long period of time; and treatment should be kept up periodically for a number of years, especially in those cases in which the disease was generalized when treatment was begun.
5. Cases of lymphosarcoma so treated should show a cure or at least a

complete control of the disease for a long period (five years or more) in a very considerable number of cases, *i.e.* 10 to 15 per cent.

6. Typical cases of Hodgkin's disease still show a very bad prognosis; and permanent control can be expected in only a very small number of cases.

DISCUSSION: DR. HOWARD LILIENTHAL, New York City, remarked that in the treatment of lymphosarcoma and other forms of sarcoma he had found Coley's fluid to be of especial value in lymphosarcoma. Cases that he had had, for instance, had gotten well with Coley's treatment alone, with recurrence years afterward, and then a second cure by Coley's fluid with eventual apparent permanent cure.

He called attention to the fact that Coley has antedated Blair Bell in giving to the profession something which acts, as we may say, constitutionally instead of locally, as X-ray and radium do. Two years ago a young woman with Hodgkin's disease came to him with an enormous tumor of the mediastinum, which was proven to be Hodgkin's disease by the removal of a lymph-node from the neck. She was suffering from the usual symptoms of intense mediastinal pressure, the dyspnœa, the suffusion of the face and enlarged veins of the head and upper part of the thorax. He advised treatment by X-ray, although she had been given up entirely by the physicians at the Memorial Hospital in New York and had been sent home to die. Nevertheless, under X-ray treatment alone, there was in an astonishingly few weeks a complete disappearance of the symptoms of thoracic malignant disease, so that the chest appeared normal by X-ray and on physical examination. Now, after two years, she remains apparently perfectly well.

DR. CHARLES N. DOWD, New York City, said that he had seen a good many cases of Hodgkin's disease. He had not seen so many of lymphosarcoma of the neck. They usually had come to him with tremendously distended necks. Among these cases he had two who have now lived, one as nearly as he could remember about fourteen years, and the other about ten years.

The surgical operation—which, after all, is not very difficult, because Hodgkin's-nodes come out very easily—has been repeated on one case three times, and there has been very good radiation carried on. The other case was treated also by radiation and by surgery. The fact that he had two of those cases alive after this long period and the fact, as Doctor Coley tells us, that cases who have been treated by surgery have a longer expectation of life than those who have not, would lead him to believe that surgeons ought to endeavor to give these patients the advantage of surgical operation at an early stage in the disease.

The enlargement usually begins in a small group of lymph-nodes on one side of the neck. When one can get hold of them in fairly early stage, one may well believe that surgery offers more than has generally been supposed.

If the palpable nodules are removed and then the locus subjected to such further treatment as seems wise, we are doing the best for our patients.

Dr. Leonard Freeman, Denver, Col., mentioned the case of a man with bleeding from the stomach, pain after eating, loss of flesh, and general disability, upon whom he operated and found two apparently distinct conditions. One was an indurated ulcer near the pylorus and the other an extensive involvement of the distal one-third of the stomach and first part of the duodenum, with a soft, whitish, uniform thickening. There was also enlargement of the glands above and below the stomach, and around the pylorus and aorta—soft, yellowish-white glands as large as the last joint of a thumb.

It did not appear that a resection of the stomach would be of any value as regards cure, but it seemed necessary to relieve him from his symptoms; so the entire pyloric end of the greatly thickened stomach was removed, it being necessary to go directly through the growth, both on the duodenum and the body of the stomach itself. After the operation was done, the recovery was uninterrupted. A pathologic examination of the specimen showed it to be a lymphosarcoma; examination being made not only by the Denver pathologists, but a specimen being sent to Doctor Mills, at the Mayo Clinic, and also to the Columbia University, in New York, and pronounced lymphosarcoma in all instances. The patient was then put upon Coley's toxins and the deep X-ray, but carried out the treatment for a short time only, regarding it as unnecessary owing to his rapid improvement. At the present time he is apparently perfectly well. He has no stomach symptoms whatever thirteen months after he was operated upon. He is virtually normal except that his weight is somewhat less than it was, and there are some enlarged glands in his neck and groins which have decreased in size and seem as though they were about to disappear.

In spite of the diagnosis of lymphosarcoma made by the various pathologists, the question of Hodgkin's disease must be considered, especially in the light of the close connection of the two affections so strongly emphasized by Doctor Coley.

Dr. William B. Coley (in closing) remarked that if one could get early cases of single isolated glands, of the type in which Burnam had most of his successes, and, after removing the glands by surgical operation, give the patient a course of prophylactic toxin treatment, alone or combined with radiation, that a larger percentage of cures will be obtained.

He remembered a case that Dr. Charles H. Peck referred to him some fifteen years ago. Doctor Peck had operated upon a large tumor in the region of the submaxillary gland, performing what he regarded as an incomplete operation, and then turned the patient over to Doctor Coley for toxin treatment. The gland removed was examined by the pathologist of the Roosevelt Hospital and pronounced to be a lymphosarcoma. On reviewing the section later on, after the patient had recovered, the pathologist stated that he was in doubt as to whether it was a lymphosarcoma or Hodgkin's disease. The slide was mailed to Doctor Welch, but, unfortunately, was lost in transit. At

any rate, the patient was alive and well twelve years later; and it does not matter very much which of the two diagnoses was correct.

He had another case, a girl aged eight years, with a glandular tumor of the neck believed to be lymphosarcoma. It was impossible to perform a complete operation, but a portion of the tumor was removed and submitted to Doctor Ewing, who pronounced it to be a round-cell sarcoma. One single dose of radium was given, supplemented by toxin treatment for several months. This patient is alive and well over eight years later. A full history of the case will be found in the text of Doctor Coley's paper.

It is very important to make a diagnosis early, and not wait until the end result has determined the nature of the condition. In order to make an early diagnosis, a gland should be removed at once and examined microscopically.

One of his most remarkable cases of lymphosarcoma of the neck occurred in a child aged two and one-half years. The whole side of the neck was involved, and the condition was pronounced inoperable by Dr. Walter R. Steiner, of Hartford, one of the leading pathologists of Connecticut. Under toxin treatment alone the patient made a complete recovery and is well at the present time, twenty-six years later.

The first illustration of the beneficial effects of the toxins in Hodgkin's disease occurred at the Memorial Hospital some eighteen years ago. The patient had all the clinical earmarks of Hodgkin's disease: markedly enlarged glands of the neck, cervical and axillary regions and groin, with enlargement of the spleen and liver, accompanied by a persistent fever, temperature of 102–03°. In this case he removed one of the glands, which was examined microscopically by Doctor Ewing, and pronounced a typical Hodgkin's (which was the clinical diagnosis of Dr. W. K. Draper). Under six weeks' toxin treatment all the glandular tumors disappeared, the spleen and liver returned to normal size, and the patient gained twenty-six pounds in weight; in fact, he felt so well that he refused further treatment and returned to work. Within less than a year the disease recurred. The patient would not consent to further treatment and died about six months later. If the toxins alone can accomplish what they apparently did in this case, in which there was no doubt of the correctness of the diagnosis, why should they not be employed as a systemic agent in practically all cases of Hodgkin's disease?