Remarks on Hodgkin's disease / by the late Sir James Galloway, K.B.E., C.B., M.D., consulting physician to Charing Cross Hospital.

Lady Galloway's Compliments. 16

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Remarks

ON

HODGKIN'S DISEASE.*

BY

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ENLARGEMENT of visible lymphatic glands is a sign of disease quickly noticed by the sufferer and usually a cause of anxiety to him. In many cases it is also a cause of anxiety to the physician. It is true we are often able to reassure the patient—for instance, when it is recognized that the enlargement is due to septic infection within the lymphatic drainage system of the affected glands. Unless too far advanced, the cure of the original infective focus will cause the enlargement of the glands to disappear. In other cases we may be able to discover that the enlargement is due to a chronic infective process, such as tuberculosis, or to the occurrence of new growth, either primary or secondary in character. In such cases there is sufficient cause for alarm, but we have the advantage of understanding something of the nature of these enlargements and the satisfaction of knowing how much can be done and what should be avoided. But there are still other instances in which we are quite ignorant of the cause of the enlargement, but we do know the progressive nature of the disease. The most important example of this class is

* Sir James Galloway, whose death on October 18th has been so great a loss to clinical medicine, left behind him notes he had prepared for a post-graduate lecture he was to have delivered before the Fellowship of Medicine and Post-graduate Medical Association on October 11th. They have been put in order by Sir William Hale-White and are here published. It is probable that Sir James Galloway would have made the lecture longer had he survived.

Hodgkin's disease. A recent writer has stated that this disease "presents the most hopeless condition in the whole domain of medicine." It cannot be denied that there is much truth in such a statement; it may, we trust, prove to be too emphatic. In this lecture I propose to draw your attention to certain manifestations of this disease in the hope of stimulating interest and investigation.

It is clear that the serious nature of the malady and the mystery of its occurrence must have made an impression on the mind of Dr. Thomas Hodgkin when he wrote his paper on "Some morbid appearances of the absorbent glands and spleen"[1] in the year 1832. In the series of cases he describes he saw and noted the association of prolonged illness with enlargement of the lymphatic glands and the formation of new tissue resembling the lymphatic glands in the spleen. It cannot be said that his observations are presented in a very attractive form. Hodgkin apparently did not proceed with his investigation of the subject, and the record of his discovery appears to have been almost forgotten. Dr. Richard Bright[2] referred to Hodgkin's cases in his description of certain abdominal tumours, but with this exception Hodgkin's observation seems to have been lost sight of until Sir Samuel Wilks[3] once more drew attention to the subject of "Enlargement of the lymphatic glands combined with a peculiar disease of the spleen" in 1856, and, recognizing the priority in discovery, spoke of "Hodgkin's disease." Wilks strangely had been in ignorance of Hodgkin's description during his earliest work on this subject, but at the end of his paper he writes: "It is only to be lamented that Dr. Hodgkin did not affix a distinct name to the disease, for by so doing I should not have experienced so long an ignorance—which I believe I share with many others—of a very remarkable class of cases, the recognition of which would have guided both myself and others to an explanation of some more recent cases coming under our notice." If Sir Samuel Wilks could now look back on the record of descriptions and investigations of this disease he would sympathize with the difficulty of affixing a "distinct name to the disease."

Since those days the disease has been carefully studied, using all the means at the disposal of modern investigation; its possible association with tuberculosis has been discussed—many have held that it is in reality an unusual manifestation of tuberculosis infection, an opinion probably now held by but few; the peculiar fever associated with the disease has been noted and looked upon as evidence that the disease is an unrecognized form of relapsing fever. Its relations to disorders of the blood, especially the varieties of leukaemia, have been investigated, and still we are unaware of the cause of the disease or its exact morbid relationships. The various synonyms which have been suggested are in some cases useful in laying stress on features of the malady; but it appears to me best still to adhere to the name of "Hodgkin's disease," especially as new "distinct names" do not take into account sufficiently the fact which becomes more evident—that we are dealing with a general specific disease associated with progressive infection of susceptible structures.

A very interesting chapter of medical bibliography could be written respecting Hodgkin's disease, especially if note were made of some of the distinguished writers.

The disease is so widely distributed, and its main features are now so well given in many textbooks, that it is unnecessary as well as inopportune for me to describe them in this place. I propose to illustrate points in its symptomatology, using for this purpose cases recently under my own observation. I think that the cases will support the conception of the malady which I have stated.

The Occurrence of Unusual Protein in the Urine.

Apart from the complication produced by true nephritis, I believe that the occasional or temporary occurrence of albumin in the urine in small quantity is not uncommon in Hodgkin's disease, just as in many other chronic maladies, and is probably not of special significance; but the incident I am about to relate is in a different category. I have had recently under close observation, until the time of his death in Charing Cross Hospital, a case of the disease in a man. Early indications of the disease, such as enlargement of the cervical and inguinal glands, appear to have been noticed in the early part of 1919. He came under my close observation in 1920, and was then in fair health, although the nature of his malady was clear. In July, 1920, I examined his urine carefully; it had a specific gravity of 1.016, and contained no albumin and no sugar. I again saw him in the early part of 1921, when he told me that something unusual had happened; at night-time, he said, he was troubled by having to pass urine in large quantities, although during the day-time he was little disturbed in this way. On examining his urine on this occasion I found the specific gravity to be 1.014. On proceeding I saw the faintest possible cloud after acidulating the urine and heating. To my surprise this cloud disappeared on heating still further, and showed itself again on cooling. Treating the urine with picric acid saline I obtained a heavy flocculent precipitate estimated in an Esbach's tube to be about 14 parts per 1,000. It was now quite clear that the urine contained a protein of unusual character, and I suspected that it might be an example of "Bence-Jones albumin." Careful and repeated examinations showed that this peculiar protein was constantly present. It occurred in large quantities, varying from 1 to 2 up to 10 to 15 parts per 1,000 by Esbach's method. This peculiar protein remained present during the rest of his life: the symptom of polyuria gradually diminished, and in the later stages the amount of this protein present was considerably less than when first observed. Fortunately, when the patient had to be admitted to hospital I had the co-operation of my colleague Mr. Sydney W. Cole. The characters of the precipitate have been carefully investigated, both at Charing Cross Hospital and in the Biochemical Laboratory, Cambridge. I hope that Mr. Cole will publish shortly a full description of this unusual substance. In the

meantime, by way of identification, I can give the following description sent to me by Mr. Cole :

The protein is similar to the "Bence-Jones albumin" in that it is coagulated on heating, redissolves on further heating, and reappears on cooling. It differs in several respects :

Bence-Jones Protein.	*New Protein.*
Coagulates at temperatures under 55° C.	Under the most favourable conditions it does not coagulate under 75° C. Full coagulation at 79° to 82° C.
Coagulates at 55° C. in the presence of a minimum amount of salt and acid.	Only coagulates in the presence of a considerable amount of acids, and salts like sodium chloride or ammonium sulphate.
Difficult to coagulate.	Becomes quite insoluble if kept at 80° C. (in the presence of acid and salt) for some minutes.
Even when highly diluted exhibits a white ring of precipitate when poured upon strong HCl (Bradshaw's test).	Not precipitated by HCl under any conditions.

The new protein is best detected by noting the precipitate in the cold with sulpho-salicylic acid—the urine itself failing to give a heat coagulum under optimum conditions of reaction (that is, just acid to brom-cresol-purple). The new protein often separated in flocculi as the urine cooled.

Microscopic and other investigations of the urine were frequently carried out, and gave no evidence of true nephritis. The autopsy completely confirmed the diagnosis of the case. The kidneys were unusually affected ; the capsules were greatly thickened, but stripped off easily. There were cysts in both kidneys; microscopical examination showed that the cortices of the kidneys contained small areas of the characteristic overgrowth of the disease.

The Fever of Hodgkin's Disease.

In all cases of this disease the body temperature is raised at some time. On looking over many temperature charts the occurrence of fever seems often to be irregular and comparatively mild in degree. But in a few cases the course of the temperature is extraordinarily regular, both in its exaggerations and in its relapses. In a characteristic case the chart is one of the most remarkable within medical knowledge.

The temperature of other cases, which appears at first sight to be irregular, on closer examination gives evidence of a definitely periodic course. The peculiar character of the temperature has attracted the attention of many observers; its occurrence was emphasized by Pel[4] of Amsterdam, and by Ebstein[5] of Göttingen, who described such cases as examples of an unusual type of relapsing fever.

I have recently had under my observation a patient whose temperature was a very perfect example of this relapsing type. I have a complete record of his body temperature during a period of five months preceding his death. After being nursed at home, and later in a private nursing home, he was admitted to Charing Cross Hospital under the care of

my colleague Mr. Peter Daniel. I had therefore frequent opportunities of seeing the patient during the last two months of his life.

On examination little could be made out in the way of physical signs. None of the easily palpable lymphatic glands were enlarged, although I suspected that the retroperitoneal lymph glands might be. These, however, were not easily palpable. After death the glands extending along the whole of the left side of the lumbar vertebrae formed a large mass, the glands in the groin were also enlarged, and there were white nodules in the spleen.

During the relapses of the fever he was deeply unconscious, with low delirium, and resembled a severe case of typhoid fever about the third or fourth week. When the temperature remitted he recovered consciousness to a very marked degree and improved greatly in general appearance. But even in the afebrile periods the patient was obviously seriously ill.

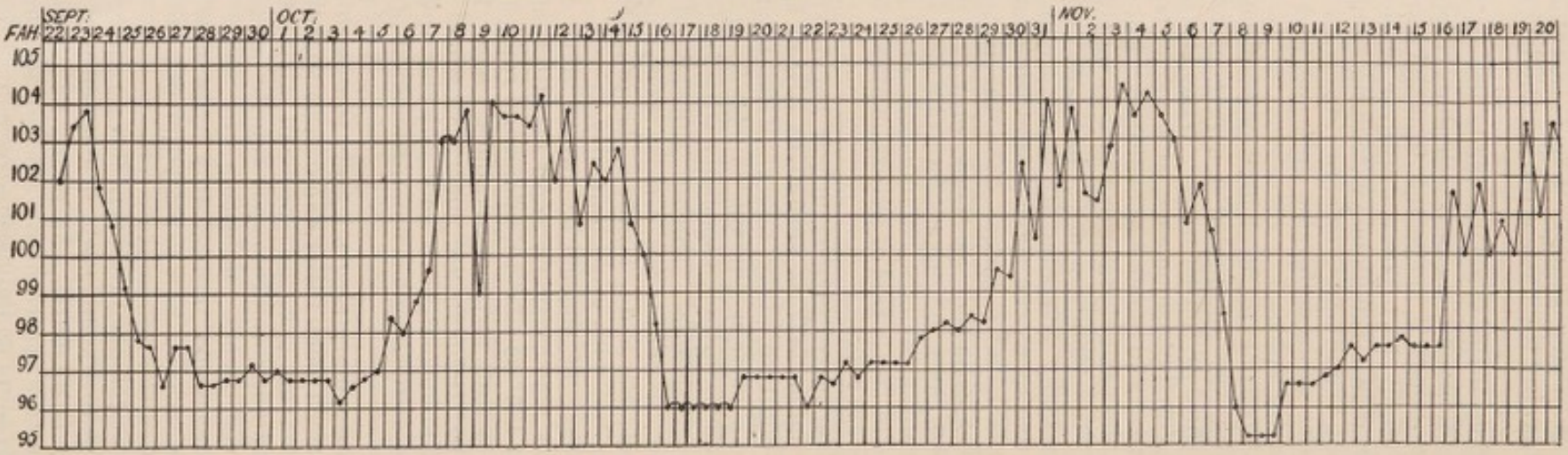
On studying the temperature chart we observe that the fever is markedly relapsing in type; there are febrile periods of from five to eleven days in duration, succeeded by periods of pyrexia usually longer than the periods without fever. The pyrexial period in what may be regarded as atypical outbursts lasts for about twelve days; the cycle of the disease, reckoning from the commencement of the afebrile period to the end of the period of pyrexia, appears to be on the average about twenty days.

The rise of the body temperature is rapid, reaching an elevation from subnormal or normal to 104° or 105° in the course of forty-eight to sixty hours. This rapid rise was associated with a certain amount of shivering and other evidences of a febrile attack, especially with rapidly increasing and severe toxaemia. During the period of raised temperature the patient was almost unconscious, as if severely poisoned; he could, however, be roused to answer simple questions, but with great difficulty.

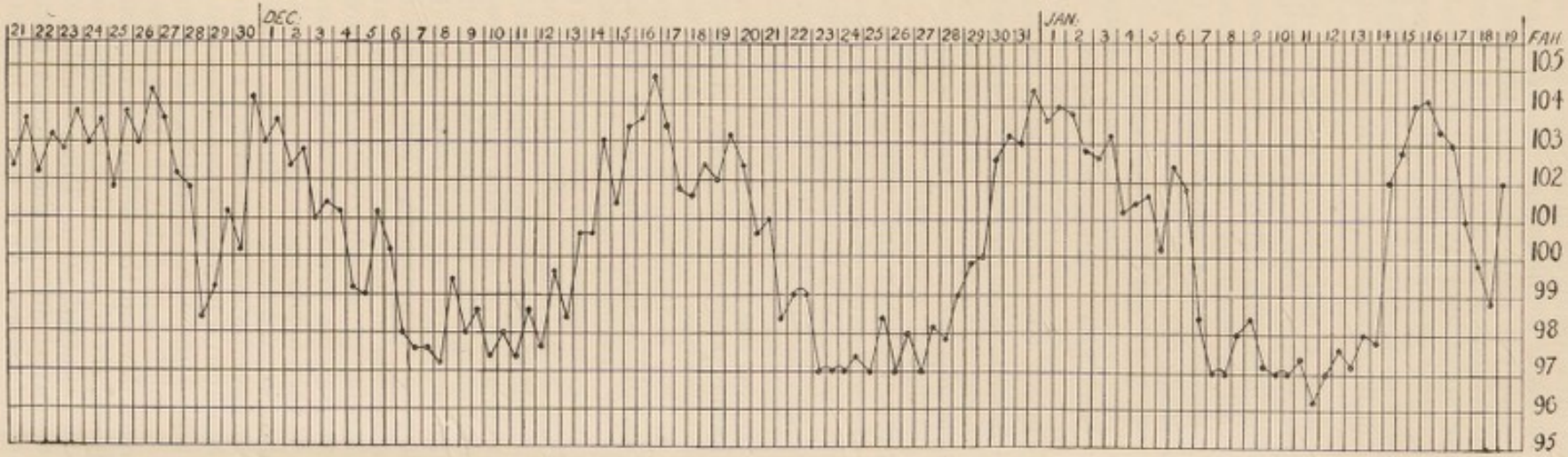
After the period of eleven or twelve days the fall of temperature took place, usually more rapidly than the rise. Thus a fall from 104° or 105° to subnormal ranges of 96° and 97° would occur within forty-eight hours. After four or five days of subnormal temperature the curve would again rise slowly towards the normal, then suddenly the upward curve would show itself, indicating the commencement of the period of relapse.

This temperature chart also suggests that two attacks of fever might succeed each other rapidly, so that there would be an unusually long pyrexial period of about twenty-one days, but during such a prolonged febrile attack definite remission of fever occurs, indicating the usual limit of a febrile period, succeeded immediately by a new access of fever. It was remarkable how rapidly the patient recovered consciousness when the temperature fell.

I have had this prolonged record of fever reduced from the four-hourly charts to a small scale of one-tenth of an inch to each observation (see Chart). As nearly as possible I have taken the temperature record of 8 o'clock in the morning and 8 o'clock in the evening as indicating the course of the fever.



TEMPERATURE CHART.



CONTINUATION OF TEMPERATURE CHART

The reduction has brought about the appearance ot exaggeration of the variations of temperature relatively to the time. Bearing this in mind the reduced chart demonstrates very well the peculiar relapsing nature and the severity of the fever. I owe to my friend Professor Arthur J. Hall[6] of Sheffield the suggestion of arranging such prolonged temperature curves in the way described. Professor Hall showed me a chart arranged in this manner in a similar case of prolonged Hodgkin's fever.

On examining such a temperature curve we get a strong impression that the disease characterized by this fever is caused by a specific poisoning; also that this poisoning is of infective and in all probability of parasitic nature; and further, that the periodicity of the temperature depends on some such event as the life cycle of a parasite. It is a facile suggestion to make—that the infective agent may be a protozoon. Unfortunately, as yet we have no definite evidence that a parasite is the cause of Hodgkin's disease.

The Cutaneous Signs of Hodgkin's Disease.

Probably in all infections certain tissues are more susceptible to the morbid influence than others. This is very clearly the case in Hodgkin's disease. The lymphs glands and allied structures are peculiarly susceptible. It might at first be thought that as the skin does not contain obvious lymphoid structures, with the exception of the all-pervading lymphatic channels, it would not usually show signs of the malady, but the observation of patients teaches that the skin not unusually gives evidence of the disease. These manifestations fall into two categories. By far the most important is the appearance of small erythematous points or macules on the skin of the body and the extremities. Sometimes these become distinctly papular, raised a little above the surface; usually they disappear, leaving a faint staining of the skin. Very rarely these papular lesions become slightly vascular. In association with the enlargement of the lymphatic glands, the cutaneous condition closely resembles the severer forms of prurigo. As the result of these lesions, aggravated by friction and scratching, wide areas of the skin may become thickened and swollen, producing an exaggeration of the natural texture of the skin, emphasizing the folds and wrinkles, and giving an elephantoid appearance. This condition of the skin closely corresponds in appearance with what has been named lymphodermia. Coexisting with the above state the surface of the skin may be dry in some cases, desquamating in fine scales, and very often showing widespread pigmentation of a pale yellow-brown colour. But the most important of all the cutaneous symptoms is pruritus. I believe that the misery experienced by the itching in some cases of Hodgkin's disease is unexampled in other maladies. It seems to occur very commonly in mild degree, bnt in those cases in which the papular lesions develop the itching is intense and most exhausting. Nothing seems to be able to control the desire to scratch and rub the affected skin. The patients scratch open the papules, and only then will they admit that they have a certain amount of relief. Anyone who has to deal with

a severe case of Hodgkin's pruritus will not fail to remember the misery of the patient and the difficulties experienced in advising treatment.

The histological examination of the skin in such cases shows two sets of lesions. In the first there are the usual changes occurring in severe non-pyogenic dermatitis. Such changes might arise from the specific poison of the disease itself or as the result of absorption from the newly formed tissues of the disease. Secondly, in some cases the formation of new cells in the neighbourhood of the blood vessels and lymphatic channels seems to be of a special character and to resemble the characteristic overgrowth of the disease.

In addition to these generalized cutaneous conditions, which are not very uncommon, there occurs much more rarely the formation of small tumours and nodules in the skin. They are often numerous, small, up to the size of a broad bean, flattened rather than definitely raised from the surface, and pale pink or brownish in colour. The histological examination of these nodules shows that they are composed of the characteristic Hodgkin's "granuloma." These nodules may occur apart from the other indications which I have mentioned.

These cutaneous lesions are not only important in themselves, but they have a close resemblance to the skin manifestations of other diseases. The most striking of these is the distressing malady known as mycosis fungoides. Just as in Hodgkin's disease, mycosis fungoides seems to be caused by a general infection of the body. The cutaneous manifestations fall into two groups: a widespread inflammatory change in the skin, and the formation of tumours. The histology of the tumours closely resembles the histology of the granuloma in Hodgkin's disease, so much so that certain very competent observers have come to the conclusion that mycosis fungoides is but a special manifestation of Hodgkin's disease, affecting mainly the skin. It is very important as well as interesting to note that the cutaneous manifestations in the varieties of leukaemia also resemble in many of their features the conditions mentioned. There may occur a widespread pruriginous dermatitis on the one hand, and the formation of nodules composed of characteristic cellular elements on the other.

Treatment.

As we are yet ignorant of the cause of this disease, its treatment is unsatisfactory. There is still too much truth in the opinion that there is no recorded case of cure or recovery. There are, however, methods of alleviation.

Arsenic seems to be the only drug which has any beneficial influence. A considerable amount of evidence shows that the drug is of value, at any rate in certain cases. It has been used in various ways—by the mouth, subcutaneously, and, since the introduction of the salvarsan group of preparations, by intravenous injection. I have used the drug in a considerable series of cases, and have come to the conclusion that benefit is most conveniently obtained by its administration in the form of sodium cacodylate. The plan I usually follow is to prescribe the cacodylate in quarter-grain doses by the

mouth, repeated during the day till as much as a grain or a grain and a half is administered daily. The patients bear this preparation well, with little intestinal discomfort. It is usually an indication to stop administering the drug, temporarily, when the characteristic garlic-like odour can be appreciated on approaching the patient closely. As a result of the administration of the drug, I believe that I have seen the glands diminish in size and the patients become more comfortable. A point of some interest has to be borne in mind. It appears that in some of the cases who have developed the characteristic pruritus of the disease, arsenic, at any rate after a time, seems to increase the pruritus. On stopping the drug I have known the pruritus diminish in degree.

A second method of treatment of undoubted value in certain cases of the disease is the use of *x* rays. The most distressing and dangerous complications of the disease occur when the glands within the thorax are affected. They may increase in size, producing at first discomfort, then symptoms of serious dyspnoea with stridor, owing to the pressure of the tumours on the trachea, bronchi, and other structures. A good many cases are now on record showing that the careful use of *x* rays in such cases of mediastinal Hodgkin's disease has brought about a great improvement in the symptoms and much comfort to the patient. Not only so, but repeated *x*-ray examination of the chest in these cases shows very clearly that, at any rate, the shadow produced by the tumour is greatly shrunken, no doubt owing to diminution in size of the glandular masses.

I have under observation at the present time a lady who was brought to me with clear evidences of Hodgkin's disease. There were enlarged glands in the axilla and in other parts of the body, but the main seat of the disease seemed to be those in the right side in the mediastinum. The patient suffered from dyspnoea with severe exacerbations and much stridor, so that her life was in immediate danger. She was treated by my late colleague Dr. Ironside Bruce, more than two years ago, with very satisfactory results. The patient improved, the dyspnoea and other discomforts almost disappeared, and she was able again to undertake her duties in her house. More than a year after a recurrence of the symptoms took place and she was once more treated by Mr. Stanley Melville. The favourable results, with relief of the symptoms, once more occurred. The patient after two and a half years still remains free of her symptoms and is able to carry on her duties. (See Figs. 1 and 2.)

In this case an enlarged gland was removed from the right axilla and shows the characteristic histological structure of the disease. I am glad to be able to demonstrate the *x*-ray photographs in this case, before and after treatment, and I have also had the advantage of comparing with these the *x*-ray photographs in a very similar case with similar results treated by my colleague Dr. Russell Reynolds.

There is one observation I should like to make with respect to *x*-ray treatment of this disease—the lesson was strongly impressed upon me when treating some cases with the help

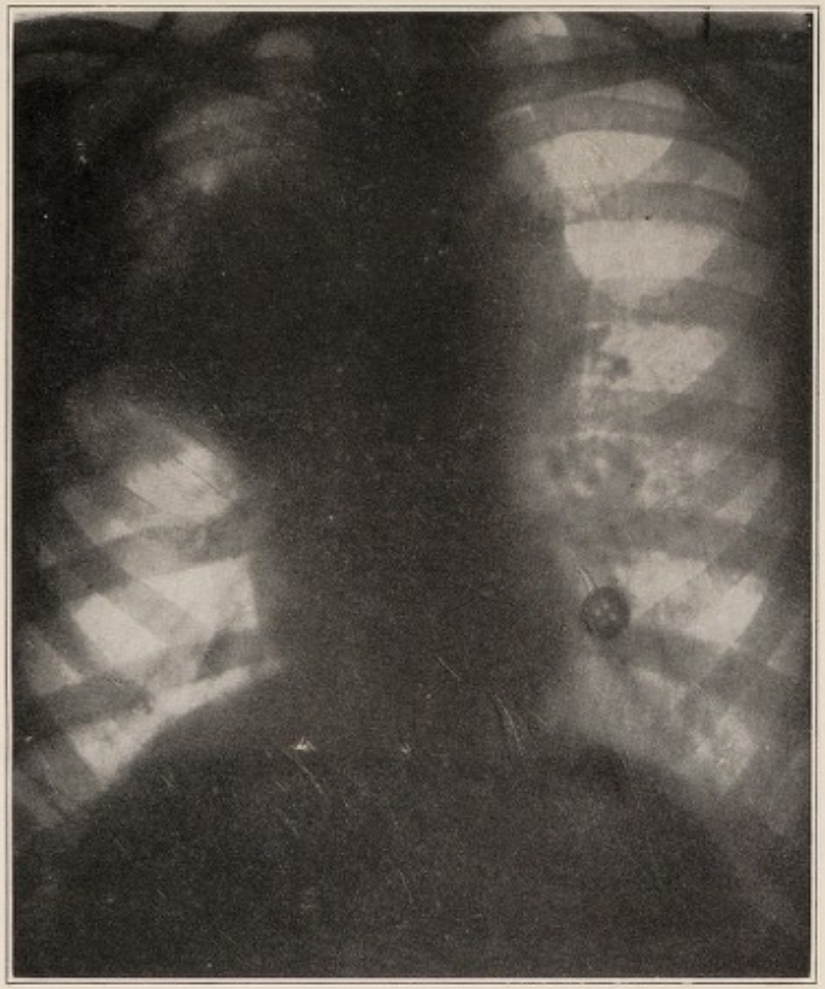


FIG. 1.—Photograph of chest on November 30th, 1921, showing the mass in the mediastinum before treatment by *x* rays.

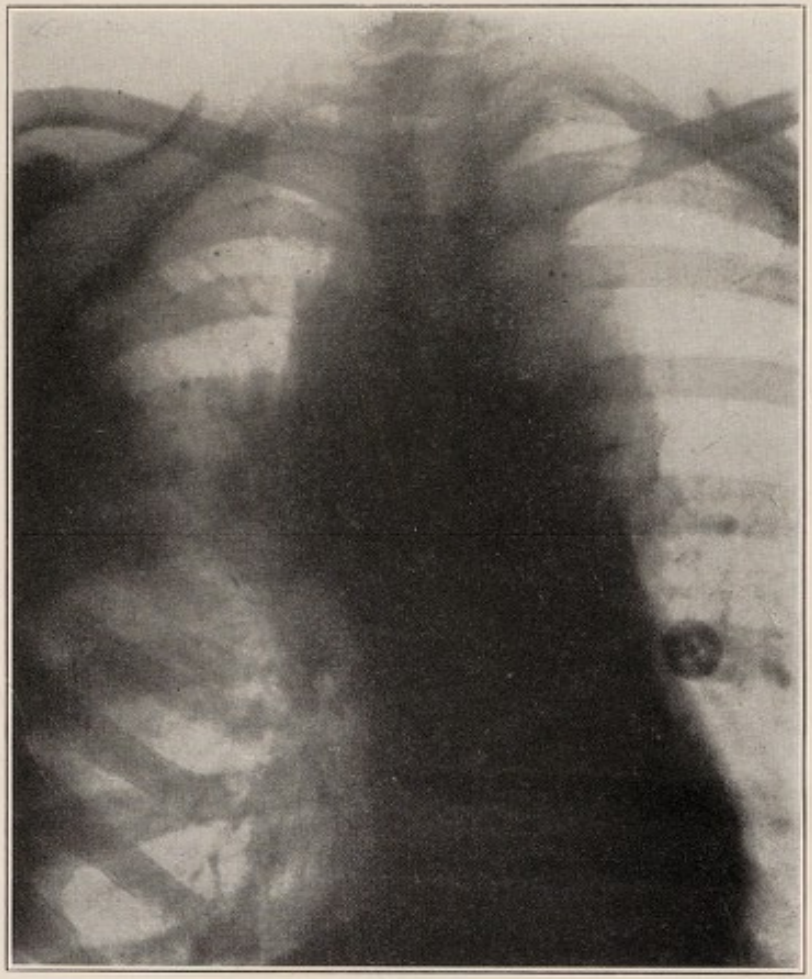


FIG. 2.—Photograph of chest, January 11th, 1922, showing diminution of the mass under *x*-ray treatment carried out since November 30th, 1921.

of my late colleague Dr. Ironside Bruce. It seems to be possible in certain cases, and apparently when too rapid resolution of the lymphoid masses takes place under *x* rays, that very severe reactions with serious rise of temperature and other untoward results may follow the *x*-ray exposures. This phenomenon suggests that alien protein poisoning occurs as the result of the breaking down and absorption of the newly formed cells. It must, however, be stated that the tumours of Hodgkin's disease do not always diminish under *x* rays. In some cases the application has little or no beneficial effect; it is possible that in these cases much fibrous change has taken place in the glands, so that little beneficial effect from *x* rays can be expected.

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[EDITORIAL COMMENT.]

A SAD interest attaches to the article on Hodgkin's disease published this week (p. 1201). Sir James Galloway was preparing a post-graduate lecture on the subject at the time when he was taken ill, and it was in his mind at the last. The notes he left have, as an act of piety to his friend, been put together by Sir William Hale-White, who has little doubt that the lamented author had intended perhaps to expand the lecture and almost certainly to complete it by some further discussion of the observations and theories he recorded. Even as it stands now it well illustrates Galloway's qualities as a physician and his attitude towards the more modern methods of studying disease. While he put first clinical observation, coupled in any particular case before him with a consideration of the individual patient, he always had in mind the institutes of medicine, and was ever ready to study the suggestions continually flowing from physiology and pathology into the broad stream of medicine. The lecture affords more than one illustration of this. The discovery that the urine in the first case he relates contained a peculiar protein at once aroused his attention. He recognized that it resembled Bence-Jones's albumin, and sought the expert help of Mr. Sydney W. Cole, who established the fact that the substance was a new protein, differing from Bence-Jones's albumin in the respects briefly stated in the lecture. We may express the hope that Mr. Cole may shortly publish a fuller account of it, and that other physicians will look out for it in similar cases. Early in his career Galloway had given special attention to diseases of the skin, and the descriptions in this lecture of the cutaneous manifestations to be observed in Hodgkin's disease are of great value; commonly these manifestations are mentioned only briefly in text books, and yet they may be of very considerable importance. That the pruritus occasionally observed may be so intense as gravely to

affect the patient's general condition is a valuable observation. The further statement that arsenic, a favourite remedy in the disease, may increase the pruritus, is a useful clinical point. The etiology of Hodgkin's disease is still obscure; Galloway, in pointing out that it is a general specific disease associated with progressive infection of susceptible structures, ranged himself with those who hold that the poisoning is of an infective and, in all probability, a parasitic nature. This view is supported by the occurrence of pyrexia, of which a very good example is given, the temperature being plotted in the way recently suggested by Dr. Arthur Hall in the *Quarterly Journal of Medicine*. The periodicity of the temperature may depend on the life cycle of the hypothetical parasite. Finally the observations on the value of *x*-ray treatment are worthy of note: others also have seen the treatment do great good, and it seems clear that its application to the glands of the chest may relieve urgent symptoms.