An Address ON THE TREATMENT OF GOUT AND RHEUMATISM BY RADIUM.

DELIVERED BEFORE THE BERLIN MEDICAL SOCIETY
ON JANUARY 18TH, 1911.

BY
PROFESSOR DR. WILHELM HIS,
UNIVERSITY OF BERLIN.

GENTLEMEN,—When a substance possessing such striking qualities as radium becomes known, the temptation to test its therapeutic actions is very great. In this particular case there was all the more reason to do this because the substance in question, or at all events some of its derivatives, formed a constituent of certain natural curative springs, the action of which medical men had not been able to explain satisfactorily. Dautwitz, working in Neusser's clinic, first carried out the experiment of treating pathological conditions, which were included in the diseases treated by indifferent thermal springs, with baths to which radium containing uranium pitch ore had been added. Since physicists and chemists in international competition have learnt to recognize whole groups and series of radio-active substances, the primitive experiments of Dautwitz have had to be modified in correspondence with newly-acquired knowledge. As a result, it became apparent that both radium and its primary product of dissociation—gaseous emanation—were capable of producing curative effects, which were especially remarkable in the case of gout and of the various rheumatic affections. About a year ago I was able to report our results to the German Balneological Society. Since then our experience has been considerably extended, and, if you will allow me, I will deal with the results in this place afresh.

We have carried out our investigations with special care, first because we were dealing with diseases which under ordinary circumstances vary greatly in their course and the relation of cause and effect is not always apparent, and secondly, we were using an agent the extraordinary properties of which attract marked general attention, so that it is very difficult to exclude a suggestive action on the patient as well as on the practitioner. In addition, it must be pointed out that both rheumatic processes and gouty attacks are undoubtedly affected to a very considerable extent by all sorts of nervous and psychic influences. We have therefore limited our investigations, as far as possible, to patients whom we could keep under observation for a considerable time in the Charité and in private clinics, or who were under the care of especially astute and competent clinicians. In all 200 patients were treated by us; but only in 128 instances were the above-named conditions fulfilled, including 100 cases of chronic rheumatism and 28 of uric acid gout.

Chronic Rheumatism

Of the 100 cases of chronic rheumatism, 47 were improved, 29 were considerably improved, 5 nearly cured, 13 were uninfluenced by the treatment, and the result was not apparent in 6. The most interesting of these cases are naturally those in which the use of the limbs was almost completely restored by the treatment.

One of these patients was a child, 8½ years of age, who had suffered from symmetrical swelling of nearly all the joints of the extremities for nine months, and who could not use either hands or feet. After eight weeks' treatment the power of walking and the use of the hands returned. This is all the more remarkable in view of the experience that chronic rheumatism in children is prone to be particularly obstinate. Staff Surgeon Eckert, working in Heubner's clinic, has reported this case.

In a girl, aged 20 years, a subacute swelling of both ankles, which had persisted for two months, disappeared in three weeks, and she was discharged cured. In another case a subacute swelling of both astragalo-calcaneal joints was cured in three weeks.

A girl, 19 years of age, had suffered from an exudative poly-arthritis of the joints of the extremities for three years. Several forms of treatment were applied, but none succeeded in arresting the progress of the affection. Treatment with emanation and drinking of radium-containing waters at first produced an increase of the pain—a so-called reaction. The condition then remained stationary for a long time, but eventually yielded to continued treatment. After three months the joints were much less swollen, the patient was again able to use

her hands and to walk, and, according to the latest reports received, she is now even able to dance.

The best result obtained, however, was in a long-standing case of myalgia.

Excellent results of this kind can only rarely be achieved. It is self-evident that no medicament in the world can clear up the numerous and severe anatomical changes which are met with in chronic rheumatism, and which include degeneration and loss of the cartilage, exostoses, indurated thickening of the capsule of the joint, proliferation of the synovial membrane, cartilaginous foreign bodies, contractures and indurated degeneration or advanced atrophy of muscles, and fibrous or cartilaginous ankylosis of the articular surfaces. The best results may be expected in diseases which have not existed for too long a time, and in which the chief changes are swelling and infiltration of the capsule of the joint. This form, which most frequently affects women either at an early age or about the time of the menopause, constitutes the larger contingent of the "considerably improved." In the next place, the dry form, in which the capsule remains unaltered for a long time, while the cartilage is markedly degenerated and the muscles almost always affected, yields very favourable results, in so far as the pain is diminished, the muscular contractures lessened, and the motility increased.

Myalgia.

There were among our cases several of myalgia, an etiologically obscure affection, which is characterized by tender and indurated areas in the muscles. A few of these cases have reacted in a most marked manner to the radium treatment, others were improved, and others, again, were absolutely uninfluenced. This uncertainty in the results of treatment is only too well known to the spa practitioners in Wiesbaden and Gastein. On the whole, it may be said that the younger the individual, the less advanced the illness, the better will be the results, and that even in very long-standing cases alleviation of pain may, at all events, be looked for.

Gout.

The results in gout are much more striking. We were able to observe and treat 28 patients for a considerable period. Of these, 4 remained unaffected, while in 24 a marked improvement in the condition was achieved. Some of the patients have told us that they have remained free from symptoms for a year after the termination of the treatment. The most remarkable effect is noted in the behaviour of the uric acid in the blood. We have learned from Garrod's investigations that gout is characterized by a permanent presence of uric acid in the blood, and numerous recent studies have demonstrated that the uric acid in the blood may be diminished by a rigid diet, but can never be made to disappear entirely. Under the influence of radium emanation the blood loses its uric acid within a few weeks. We were in a position to examine the blood, both before and after the treatment, for uric acid in 18 cases. In 15 the desired result was effected promptly; in a severe case of gout the blood was found to be free from uric acid after 14 days' treatment by drinking water containing radium. On the other hand, uric acid persisted in the blood of 3 patients even after a severe course of treatment. Now, it might be expected that since no salts can be deposited from blood which does not contain uric acid, no attack of gout could occur, and that any deposits which were present would be speedily dissolved. We actually did observe tophi in the ear disappear on two occasions during the treatment. But the clinical improvement did not always run parallel to the uric acid content of the blood. We noted very marked improvement in a patient who was energetically treated, in spite of the fact that the blood retained its uric acid. In another patient, who had gouty nodules all over his body, no uric acid was present in the blood either at the beginning or toward the end of the treatment, and yet the patient had one attack after another during the whole time. Experience, however, has long since taught us that it is not only the deposit of uratic salts which can cause an inflammation; a rapid solution of these salts may do the same. In the majority of cases, at all events, the radium treatment of gout is a very powerful remedy, even if some persons are refractory to the treatment.

Radium Emanation.

Before entering into a discussion of these highly interesting facts, I wish to deal with the methods which enable us to apply radium and its emanation in an effective manner. At first the radio-active material was added to a bath, on the basis of the practice at spas. Further investigations, the most important of which are those of the Brunswick neurologist, Löwenthal, have proved that the active agent is not radium itself, but the emanation which radium produces. Emanation is a gas; it cannot penetrate the epidermis of the body as such, but is readily absorbed by the lungs and by the mucous membranes of the digestive track. Emanation can therefore only act in the bath by passing out of the water into the air and being inhaled. When water containing emanation is drunk, a part of the emanation is taken up in the inspired air and another part is absorbed from the stomach and intestine. Emanation behaves like every other gas which is not a normal constituent of the body. It is excreted to a very slight extent through the kidneys and to a large extent in the expiratory air. When the treatment is carried out by baths, the absorption is only continued as long as the patient remains in the atmosphere laden with emanation from the bath water, and the foreign gas is excreted immediately. On the other hand, when it is carried out by means of drinking waters, the absorption takes place slowly from the intestine, and the body is being constantly supplied with fresh doses of emanation for three or four hours after a single dose. When the patient is given from three to five doses during the day emanation can be detected in the expiratory air at any period of the day. Radium itself behaves in the body like other heavy metals to which it is chemically related—that is to say, it is absorbed slowly, and the absorbed quantity is excreted again through the intestine. As long as it is present in the body, small quantities of emanation are continuously developed from it. It is therefore clear that the most active application of emanation is achieved when the individual is breathing an atmosphere which contains a certain quantity of radium emanation. Under these conditions an equilibrium will rapidly be established between the emanation content of the external air and that of the blood. This equilibrium will be maintained as long as the body remains in this atmosphere. The emanation content of the blood will reach a level in this way which can only be attained by the drinking of exceptionally large quantities of water containing radium. Our experiments have shown that it is usually sufficient for the purpose of obtaining definite curative results, and of ridding the blood of gouty patients of uric acid, to place the patient in an air containing from 2 to 4 "making units" per litre for two hours a day. A better result with larger doses of emanation was only attained in a few cases. "Emanators" have been constructed by Löwenthal and Gudzent on this principle. A stream of oxygen bubbles through a fluid containing a salt of radium and is saturated with emanation. The emanation issuing from the fluid is distributed equally in the air of the room by a ventilator. This method, however, has the disadvantage that it can only be applied when a special emanator is available. For this reason portable inhalation apparatus have been constructed, in which the emanation is liberated from its solution by a stream of air produced by a hand bellows. The air containing the emanation is then breathed. After a few strokes of the bellows the emanation is completely driven off from the water, and a considerable time is required before equilibrium is again established between the insoluble radium salt and the emanation in solution. In other words, the apparatus is exhausted in a few minutes, the inhaled emanation is rapidly exhaled and is diluted to such an extent in the air of the room as to be quite inactive. The portable apparatus, therefore, cannot as yet be regarded as satisfactory substitutes for the emanators.

The body is subjected to the action of emanation equally by these methods of application. If it is desired to concentrate the action on any given point, it is advisable to apply the radium salt directly to the part affected. Experiments undertaken in the Heidelberg Cancer Institute (Ramsauer and Cohn), as well as our own observations, show that a deposition of insoluble radium salts in the body develops emanation for a long period. This can

be demonstrated in the expired air. Added to this action, the rays which are given off from the radium come into play, and when applied in this manner act directly on the diseased area. We have supplemented the general action with marked advantage in certain cases of rheumatism by an injection of insoluble, or repeated injections of soluble, salts of radium in the immediate neighbourhood of the affected joints. Sterile ampoules of these salts are now obtainable from several firms. In other countries, and especially in France, the action obtained by radiation of strong radium preparations has been very energetically employed, and the results which Wickham and Degrais (Paris) have achieved in skin carcinomata and naevi have justly attracted much attention. It has, however, been found necessary to check the too sanguine hopes in respect to the treatment of carcinoma. The results obtained are in some respects so remarkable that further experiments in connexion with internal diseases appear justifiable. This method of application demands special precautions in order to protect the skin from the damaging influence of Alpha rays, which are readily absorbed.

Mode of Action.

There is something unsatisfactory about a therapeutic action the cause of which is unknown and the process of which cannot be controlled. For this reason numerous experiments have been undertaken for the purpose of studying the action of radio-active substances on the processes taking place in isolated portions of the body. These experiments have revealed that the cells may be directly influenced, and under certain conditions the damage may even amount to necrosis. Radium rays, like Roentgen rays, exercise a selective action; for example, when applied to embryos they destroy nervous tissue more especially, and when applied to tumours, the pathological tissue.

The fact, ascertained in our clinic by Fofanow, that the inflammation produced by the introduction of foreign bodies (especially urates) under the skin or into the peritoneal cavity undergoes an extensive change, is of great importance in the interpretation of the curative process under discussion. The inflammatory migration of leucocytes is completely arrested. A further action consists in the activating of ferments. Braunstein and Bergell have demonstrated this in connexion with pancreatin, Bergell and Bickel in connexion with pepsin, Richet with lactic acid fermentation, Löwenthal and Edelstein with autolytic ferments, and Löwenthal and Wohlgenuth with diastatic ferments. It is probable that the same applies to numerous other fermentative processes in the body, but not to all, for, as far as is known at present, the excretion of sugar by diabetics, for instance, is not influenced by the rays, although other metabolic processes are undoubtedly increased thereby. This can be demonstrated in a very clear manner in gout. According to the modern views enunciated by Bloch, Schittenhelm, and Brugsch *inter alia*, the disturbance in gout depends on a retardation of the purin body metabolism; and not only is the formation and breaking down of uric acid slowed, but the mutual relations of the two processes are altered. In the gouty this is evidenced by the fact that when a diet which is free from purin, but which contains nucleic acid, is given, the uric acid formed is not completely excreted within from two to five days, as is the case in healthy persons; the excretion is extended over a considerably longer time, and is not complete. Gudzent and Löwenthal were able to show that after prolonged treatment with emanation the excretion took place as promptly and completely in a gouty patient who had previously shown this phenomenon in a typical manner as in a healthy individual. In addition Gudzent was able to determine another characteristic of radio-active substances. Uric acid exists in the form of monosodium urate in the body. This salt exists in two forms, which differ from one another in respect to their solubility. When freshly precipitated from solution, the readily soluble modification is formed, which, however, spontaneously changes into the less soluble modification in the course of time. This transformation is arrested by the action of certain rays. Gudzent was further able to show that uric acid and its salts are dissociated into carbon dioxide and ammonia under the influence of this action, and he demonstrated in a very ingeniously-

planned experiment that neither radium nor emanation produces this dissociation. It is brought about by a more advanced disintegration product, which is known as radium D. It will thus be seen that very varied actions come into play in gout, all of which tend toward the solution of the gouty deposits and the breaking down of uric acid. In addition to the autolytic action, the action of inhibiting inflammation, and that of alleviating pain, which are affected in the treatment of rheumatism, there is in the treatment of gout a specific action which is directed to the uric acid and its salts, and to the processes of metabolism regulating the quantity of uric acid in the body. This ensures a greater certainty of action.

Selection of Cases.

In selecting cases for radium treatment, the form of disease should be taken into account in the first place. Before the practitioner prescribes a treatment which must be continued for weeks or months, and which will involve the patient in a considerable financial outlay, he must form a clear conception of the results which can be obtained under the most favourable conditions. He must realize that old exostoses and bony ankylosis offer no prospect of cure, and that the chances are most favourable in early stages of the process and when the soft tissues of the joint and its neighbourhood are chiefly affected. It is of paramount importance to know if the attack is due to rheumatism or to gout, because the auxiliary treatment, and above all the diet, must be absolutely different for each of these two groups of disease. I have never been able to satisfy myself that any special diet or the limitation of meat exercises a beneficial influence on the course of rheumatic affections. On the other hand a dietetic treatment of gout is essential, even in conjunction with the employment of the radium treatment. There are two sources of uric acid—the material which has to be got rid of. In the first place there is the body itself, and in the second there is the food. The dissociation of uric acid will be effected more easily and more rapidly if the second source is blocked by the selection of a suitable diet. But the differentiation of gout and rheumatism is by no means as easy as is usually believed. A typical case of gout, no doubt, is readily recognized, but the diagnosis of so-called masked gout is very difficult. A single examination of the urine does not clear the matter up. The interpretation of this form dates back to a time when it was believed that uric acid was formed out of albumen, and when gout was regarded as being due to an increased proportion of albumen persisting in the incomplete oxidation phase of uric acid. On the basis of this assumption it was held that the diagnosis could be made in any sample of urine, from the proportion of uric acid to urea. In the light of our present knowledge this is no longer tenable, since we know that the quantity of uric acid in the urine is not dependent on the quantity of albumen, but is dependent on the amount of purin-containing food taken in. It has been known for twenty years that the gouty patient excretes less rather than more uric acid than the healthy person, when enjoying the same diet, and that the uric acid value may be quite abnormally low, especially just before an attack. If the gouty nature of the illness is to be recognized from the urine, a test must be employed which Bloch, and also Schittenhelm and Brugsch, first described. This consists in putting the patient on a purin-free diet for five or six days, then giving him 10 to 20 grams of nucleic acid, and then examining whether the uric acid is completely excreted within two to five days, or whether the excretion is retarded and incomplete. This tedious test, however, is not reliable, since some gouty subjects in certain stages of their illness react like healthy persons, and, moreover, since non-gouty alcoholics and patients with nephritis also excrete slowly.

We therefore return to Garrod's old suggestion of looking for uric acid in the blood. We know, it is true, that uric acid is present in the blood of patients suffering from nephritis, leukaemia, and pneumonia in the stage of resolution, but these are conditions which can easily be excluded. Garrod employed the primitive thread test, in which a small quantity of blood is acidified with acetic acid and gently evaporated. The uric acid is deposited on linen threads immersed in the blood, and is recognized microscopically. Unfortunately this simple test is un-

reliable. Uric acid can only be detected with certainty by abstracting a larger quantity of blood (80 to 100 c.cm.) by venesection and by analysing it by Krüger and Schmidt's method. Since we have employed this method in doubtful cases, we have experienced a variety of surprises. We have learned that some of the very common myalgias of the neck, shoulder, and lumbar muscles are undoubtedly of a gouty nature, while other are rheumatic. Patients who reveal symmetrical and creeping inflammations of the smaller joints, which give the clinical impression of being rheumatic, have sometimes been shown to be gouty. Neuralgia, and especially sciatica, depends on this cause much more frequently than is usually accepted. It is therefore urgently necessary, in order to secure a prompt and certain result from the treatment, to examine doubtful cases in this way. It must be pointed out, however, that the detection of uric acid in the blood requires some practice and experience, and ought not to be entrusted to the pharmaceutical chemist. It is to be hoped that we shall soon discover a more handy and at the same time more reliable method of examination.

Mode of Application and Dosage.

Once the diagnosis is made, a number of factors have to be taken into consideration in the choice of method of treatment. The form of rheumatism, the duration of the affection and the number of implicated joints must be thought of, and a method of application must be chosen in accordance with the conditions. The susceptibility of the individual in this connexion, as elsewhere, varies greatly, and the physician must be guided as to dosage by the strength of the reaction and the degree of improvement. A certain amount of practice and careful observation of the course of the illness are needed to ensure a proper selection. We have obtained much better results in the Charité patients on the whole than in our private patients, whom we could only see from time to time in the consulting room.

The dosage necessitates a marked individualization. It forms at present a rather weak point in radiotherapy, because we do not possess a uniform and generally accepted system of measurement. In Germany the measurement is made partly by determining the loss of voltage—a value which varies considerably according to the construction of the measuring apparatus—and partly by calculating the "making units," which are also not quite uniform. In France the uranium unit is employed. The International Congress of Radiology in Brussels in 1910 recognized this defect and appointed a Commission, which has accepted as a unit the action issuing from 1 gram of radium. Mme. Curie has undertaken to prepare as pure a sample of radium as possible, and this is to be deposited in Paris as a standard, like the normal metre and the normal kilogram. Exact duplicates of this standard will be placed at the disposal of States interested in this question, and in each of these countries an institution is to be founded, where the standardizing of preparations from the normal measure can be undertaken. The estimation of the value of a radium preparation, even after careful application of the methods of measurement, is not very simple, and a certain industry appears already to be profiting by this uncertainty. It can, however, be carried out with comparative ease, since the content of active substance cannot be calculated by any attribute other than the application of definite methods of measurement.

In spite of the many valuable articles already published, we are still at the beginning of the investigation of the therapeutic action of radium. The extension of the results obtained up to the present, the further studies of the effect on metabolic and secretory processes, and the differentiation of the action of the various forms of rays are all problems of the future. A powerfully radiating member of the thorium group—*mesothorium*—has been prepared in considerable quantities by Professor Otto Hahn, and requires to be tested bio-therapeutically. A large quantity of this substance has just been prepared for the Königl. Akademie der Wissenschaft (in Berlin), thanks to the generosity of Herr von Böttinger. As compared with radium, the want of durability of this preparation is amply compensated by the greater ease with which it can be obtained from raw material. It is extremely probable

that other radio-active substances will be discovered in time, and it is quite possible that they will reveal a variety of peculiarities as regard both their physiological and therapeutic actions, and their selective behaviour. A wide field of activity lies in front of us, and there is urgent need of a special institute which will deal exclusively with these therapeutic biological investigations.

But I must return from the hopes of the future to the actual subject of my discourse. I hope that I have convinced you that in radium and its emanation we possess, not a panacea for all ills, which would restore suppleness and power in the most severe and incurable cases, as by magic, but an extremely valuable and indispensable means of treatment—a means which, in combination with the already known methods of treatment, enables us to achieve highly satisfactory and gratifying results in two groups of disease, which have in the past been a trial of patience both to the practitioner and to the patient, on account of their obstinacy and their persistence.

A FURTHER NOTE UPON THE MECHANICAL EFFECTS OF A RIGHT-SIDED PLEURAL EFFUSION.

By PROFESSOR A. C. GEDDES, M.D.,
ROYAL COLLEGE OF SURGEONS IN IRELAND.

IN THE BRITISH MEDICAL JOURNAL of June 11th, 1910, a note upon the mechanical effects of a massive right-sided pleural effusion was published by the present writer.

More recently, further opportunities of studying the mechanical effects of the accumulation of fluid in the right pleural cavity have presented themselves. In the new case the subject was a male of middle age whose body had been preserved by the injection of 15 per cent. formalin which had firmly fixed all the tissues.

The amount of the effusion had been by no means so great as in the case formerly reported, and though the displacements discovered on section and dissection are less striking than those described by Professor Elliot Smith¹ or by the present writer in cases of massive effusion, they are sufficiently well marked to show clearly the general lines along which the effects of abnormal distension of the right pleural sac manifest themselves. Indeed for purposes of clinical work they are of greater value than those formerly described; for, in this case, the accumulation of fluid had not been so great that it might not well have been met with in normal practice.

GENERAL DESCRIPTION OF THE CONDITION FOUND.

1. The right pleural cavity is full of coagulated fluid. Its capacity is considerably increased. This is due to:

(a) The fixation of the ribs in the position of forced inspiration (see Figs. 1 and 2).

(b) The displacement of the mediastinal structures towards the left (see Figs. 1 and 2). The displacement is most marked at the mid level and least marked at the top and bottom of the mediastinum. In other words the mediastinum is bowed towards the right.

(c) The opening up, to an abnormal degree, of the normal pleural recesses which extend in behind the oesophagus and trachea and in front of the superior vena cava and aorta (see Figs. 1 and 2).

(d) The downward displacement of the diaphragm (see Fig. 4).

2. The right lung is not collapsed and is not adherent to the chest wall nor is there adhesion between the lobes (see Fig. 2).

3. The horizontal curvature of the aorta is somewhat flattened out so that the ascending portion lies almost entirely to the left of the median plane (see Figs. 1 and 2).

4. The trachea is displaced slightly towards the left and is rotated on a vertical axis so that the right bronchus has passed forward (see Fig. 2).

5. The oesophagus is curiously crumpled by the pressure of the distended right pleura, and is slightly displaced to the left (see Figs. 1 and 2).

6. The left lung is compressed, and is, in its lower part, adherent to the chest wall.

7. The superior vena cava is somewhat compressed laterally, and is displaced towards the left. Its lumen is seriously reduced by the pressure exerted upon it, from behind forwards, by the right pulmonary artery, which

has in turn been pushed forward by the right bronchus (see Figs. 2 and 3).

8. The ascending portion of the vena azygos major is pushed into the median plane; the portion which normally arches over the root of the right lung is pulled out to lie in a horizontal plane, and is bent very sharply against the right postero-lateral edge of the trachea at the level of its bifurcation. At the point of bending the lumen is entirely occluded (see Fig. 2).

Fig. 1.—Horizontal section of the thorax at the level of the manubrio-sternal articulation: looking upwards. To show the increased size of the pleural cavity, the flattening out of the transverse arch of the aorta, the crumpling of the oesophagus, and the partial rotation of the trachea.

9. The inferior vena cava is much dragged upon; the caval opening in the diaphragm shows the effects of this by its distortion into a pear-shaped orifice (see Fig. 4). The intrapericardial part is sharply kinked, and its lumen is almost entirely occluded (see Fig. 3).

10. The heart is rotated clockwise round an antero-posterior axis passing through the caval orifice in the diaphragm, so that its apex descends and forces down the cardiac area of the diaphragm (see Figs. 3 and 4). The

Fig. 2.—Dissection of the superior surface of the lower portion of the thorax removed by the section through the manubrio-sternal articulation. On the right side the superior surfaces of the middle and inferior lobes of the right lung are exposed. To show the pushing forward of the right lung root, the rotation of the trachea, the crumpling of the oesophagus, the kinking of the vena azygos major against the right posterior margin of the trachea at its bifurcation, and the pushing over of the superior surface of the heart towards the left.

posterior wall of the right auricle is pushed forward by the lung root and overhangs the opening of the inferior vena cava. The cavity of the right auricle is further reduced by the direct pressure upon its right lateral wall. The left ventricle is fixed in a position of diastole.

11. In the abdomen the liver is depressed and flattened, and the superior aspect of its left lobe is deeply indented by the cardiac depression of the diaphragm; the kidneys, more especially the right, are depressed and deformed by pressure; the suprarenals are also depressed.

The points of greatest interest demonstrated in this dissection are undoubtedly those connected with the