THE USE OF RADIUM IN CARCINOMA OF THE BLADDER*

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The views held by urologists and radiologists as to the efficacy of radium in the treatment of bladder tumours vary widely—so widely that an investigator coming new to the subject could not but be impressed by the very marked divergence of opinion even among eminent men who have presumably given radium a fair trial. There are those, for instance, who champion radiation methods so enthusiastically that they use neither excision nor fulguration. Barringer of the Memorial Hospital, New York, is one of these, and all bladder tumours at his clinic have been treated by radiation methods, chiefly radium, for the past eighteen years. There are many others who say that its intervention has been productive of harm rather than good. Among these are many urologists in this country, and radium is used very much less here or on the Continent than in the United States.

In other branches of medicine where there is doubt as to the wisest choice between entirely different methods of treatment it is often found that none of the methods involved is very satisfactory, and it will be admitted, I think, that this is the case in carcinoma of the bladder. This remains true, despite the advances in bladder surgery during recent years, the reason being that surgery still fails in a large number of cases, and that the majority of bladder cancers are beyond the reach of surgery when first seen. It seems reasonable to suggest, therefore, that radium may have something to offer in the treatment of carcinoma of the bladder as it has in other sites, such as the cervix uteri, where surgery, at any rate, has its limitations.

Although radium has been used in the treatment of bladder tumours for years, it is comparatively recently that radium treatment could be discussed and analysed on the same sort of criteria as apply to older and established methods such as surgery. It is true that a comparison of radium treatment with excision is not easy for many reasons, but enough cases have been treated over a sufficient period to enable us to assess its value and to form some idea of what contribution it can make to the solution of a problem which is admittedly a difficult one, and in which advance, even in recent years, has been slow.

Features that Favour Treatment

There are some features of bladder cancers that should favour any form of treatment which has a chance of eradicating the disease. One is that local glandular involvement is late, and, indeed, is often absent even in quite inoperable cases. Another is the rarity of early metastases, although these are present in a high percentage of cases in which the patients die of the disease. Approach to the bladder is easy, and excision in many cases is not a difficult matter. On the other hand, patients with carcinoma of the bladder are past middle life, and are often reduced to poor condition as a result of haematuria or cystitis, or both. The majority of cancers arise on or near the trigone, so that excision is impossible without transplantation of one ureter, or total cystectomy. In addition, there is a large group of cases, varying from 45 to 60 per cent. with different surgeons, which are inoperable when first seen. Faced with such difficulties, radium, if it is an adequate method of attack, is in a

position of advantage, especially with regard to the situation of many growths. It can be used, for example, in cases where the growth is close to the ureteric orifice without grave risk of subsequent stenosis.

Before proceeding further, it must be stressed that, although comparisons are odious here, as in other things, they are in this sort of discussion necessary. A new form of treatment must be judged on its merits, and these can only be assessed in so far as the method of treatment compares favourably or unfavourably with pre-existing methods. And here a difficulty arises at once. It is said, and the view is held by many, that operable cases should be treated by excision, and that radium should only be used for the rest; it is undeniably impossible to compare the methods, because each is dealing with a different type of case. It is important to remember in this connexion that large numbers of malignant bladder growths are inoperable when first seen, by reason of their extent, their fixation, the glandular involvement, or metastases. With regard to operable cases, it is, I think, possible to come to certain definite conclusions as to the use of radium, and these two groups of cases will be discussed later.

Early Radium Methods Reviewed

Early attempts at treatment consisted in the introduction into the bladder, per urethram, of catheters containing radium tubes in the distal end, and this was often combined with external radiation from applicators placed over the suprapubic region. This method resulted sometimes in temporary cessation of haemorrhage and control of symptoms. Later, use was made of ingenious fixing devices, whereby high-content radium tubes could be placed in contact with the growth by vision through a cystoscope. This method had the disadvantages that the time factor could not be prolonged, and that the maintenance in position of such apparatus was a difficult and often painful business.

The suprapubic approach and interstitial radiation were next tried, and glass radon seeds inserted into the growth. As was inevitable, extensive and intractable radium burns rewarded this method, although in a few cases, after much tribulation, the disease cleared up.

The insertion of radium needles gave better results, and this method is still used. The needles are inserted into the base of the tumour, so as to form a field of radiation in the bladder wall deep to it. They have walls usually of 0.5 to 0.8 mm. of platinum, and are of low linear intensity—0.5 to 1. The radiation time extends over a number of days, usually five to seven. The confined space and the irregular bases of many bladder tumours often make it difficult to place needles accurately, so that homogeneous radiation is obtained. In addition, the fact that threads are attached to them makes it easy for them to be displaced, and they have to be removed at the end of the required period of irradiation.

Use of Radon Seeds

Screened radon seeds have none of these disadvantages, and after their introduction by Failla they began to be used extensively by the suprapubic route. In the United States the insertion of screened radon seeds by means of the cystoscope was first carried out by Young and Keyes, and in this country by the late Frank Kidd and Ogier Ward. At the present time radon seeds are being used more and more in carcinoma of the bladder. They have many advantages, not least among which is the fact that they can be left permanently in position, and so, when inserted by the suprapubic route, the bladder can be closed. They are easier to manipulate than needles, and can be introduced, if necessary, by means of a curved cannula. They are suitable for use in tumours

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of irregular outline and base, and, on the whole, are more adaptable than needles. For insertion by the cystoscopic route their advantages are obvious.

The filtration and content of seeds vary, but they are commonly either of platinum or of gold, the thickness being from 0.3 to 0.5 mm. The content ranges from 1 to 2.5 mc. each. The length can, of course, be varied at will, but the standard length is 0.6 cm.

The Suprapubic Route

The bladder is opened in the usual way, care being taken to work in a dry field, and to cover the wound edges to avoid implantation. Many surgeons remove a bulky papillary carcinoma with the diathermy before inserting radium; this avoids haemorrhage during manipulation, and reduces the risk of implantation of cancer cells. If needles are used, these are chosen so that their length is suitable for the growth to be treated; it is wise to have at hand needles of several sizes, because the cystoscopic appearances are often unreliable in giving the exact size of the lesion.

In the case of seeds they are inserted into the tumour base, the area of irradiation being well wide of the tumour limits. In papillary carcinoma with little or no infiltration, the seeds are inserted in the bladder wall in one plane. Judgement as to how deep it is safe to place the seeds is difficult in infiltrating carcinoma, and only comes by experience. The bladder is either sutured without drainage—and it is claimed for this method that a considerable number of such cases heal without leakage, thus avoiding wound infection—or a drainage tube is inserted.

The Cystoscopic Method

The other method commonly used is the cystoscopic, and consists in the introduction of screened radon seeds through a ureteric cystoscope, which must be of the flushing type. The cystoscope was first used in this country by the late Frank Kidd, and certain modifications have been made by Ogier Ward. After inserting the instrument, the flexible introducer is passed into the bladder, having previously been loaded with a seed. The sharp end of the introducer is then plunged into the required place in the bladder wall, and the seed expressed by means of a spring handle of the thumb-press type. At the Radium Institute the seeds for this purpose are made with especially sharp points to render insertion easy.

A minute description of the technique would be out of place here; suffice it to say that seeds are introduced as far as possible beneath the tumour, the point of the introducer being inserted through normal bladder just outside the neoplastic area. The procedure is often a tiresome one, and demands great patience. It is sometimes found that the bladder wall is so tough that it is difficult to make the flexible introducer penetrate the requisite distance. On the other hand, when the instrument has to be inserted into tumour tissue, the latter may prove so friable and soft that the seed drops out as soon as it is introduced.

Bleeding is often a great obstacle to accurate implantation of the total number of seeds. Much of this difficulty can be overcome by the use of the flushing instrument, and in the case of Ogier Ward's introducers, they can be used as electrodes to coagulate the tissue either before or after implantation if the growth bleeds too profusely. If troublesome bleeding occurs and a good view cannot be obtained, it is wiser to insert the remaining seeds at a later date.

At the end of the seeding the base of the bladder should be inspected to make sure that no seeds have dropped out of the growth during the operation. If a seed is found lying on the trigone, it is probably because it has been introduced through a portion of growth, the introducer being, not in the bladder wall beyond the growth, but lying free in the bladder behind it. The delivery of the seed into the wall, however, conveys a distinctive impression to the hand, and this should not happen without the knowledge of the operator.

Radiographs should be taken after forty-eight hours and four days, in order to make sure that all the seeds remain in position, and all urine passed by the patient must, of course, be examined to

make sure that seeds are not included. Seeds left lying free in the bladder are passed painlessly at the first urination, as are seeds which drop out subsequently. The patient need not remain in bed more than four to five days, or in hospital more than a week.

Each of these methods, suprapubic and cystoscopic, has advantages. For the suprapubic method it can be claimed that the growth can be inspected more thoroughly and palpated, that biopsy is made easy, and that the introduction of radon seeds is done by direct vision in a good light, and is therefore more accurate. The cystoscopic method has the advantages that the bladder is not opened, that the patient need not be in hospital more than five to seven days, and that in the case of difficulty of introduction or the desirability of splitting the dose, the insertion of the required number of seeds can be done at more than one sitting. The cystoscopic method is not, however, suitable for the treatment of growths in any part of the bladder. Tumours situated in the anterior wall or vault of the bladder cannot be reached satisfactorily, and must be approached by the suprapubic route.

Surgery in Bladder Carcinoma

Before discussing the use of these methods, let us consider for a moment the surgical aspect of the disease. It is generally admitted that operable cases, including those in which transplantation of one ureter is necessary, are in the minority. In a recent series of cases (Macdonald) the inoperable cases amounted to 60 per

Cystoscope of flushing type (Ogier Ward's modification) and seed introducer. The cystoscope has a valvular attachment so that escape of fluid is avoided while inserting the introducer.

cent., and this figure is given by many workers. Total cystectomy is a very severe operation, and although during recent years a few surgeons have improved the technique so that the mortality has been reduced considerably, it is still a procedure limited to very experienced urologists, and is a malignant operation from the patient's point of view. The mortality remains very high, and the subsequent life of the patient is often a miserable one.

The results of surgical procedures—namely, partial cystectomy with transplantation of one ureter if necessary—can only be seen from figures, and these are not easy to interpret and to compare, because of the differing ways in which the authors set them out. The operative mortality has been steadily decreasing, and is now between 10 and 15 per cent.

Macdonald, in a recent series of representative cases, quoted forty-four carcinomata of different types; operative mortality was 13 per cent., and 31 per cent. were alive for three years or more. Although such figures show that treatment by excision leaves much to be desired, the results are such that any other method has to be very carefully considered before it is substituted. These figures apply to 40 per cent., let us say, of the cases. Of the other 60 per cent. it must be admitted that control by diathermy is all that can be offered them, and that cure is out of the question.

Some Results of Radium Treatment

Leaving out for a moment the 40 per cent. operable cases, what has radium to offer the remaining 60 per cent.? At the Radium Institute, London, we have treated 60 cases of carcinoma of the bladder since 1927. The majority of these have been treated by Ogier Ward, and he was responsible for the cystoscopic technique. I quote them here because they were all considered to be inoperable when first seen, either because of the site, extent, or fixation of the growth, or because of the patient's general condition.

Except in those cases in which the growth had recurred after excision, and in those few which were treated by the suprapubic route, no histological data were available, and diagnosis was made on the cystoscopic findings. This is, of course, an important point, and must be taken into consideration when the results are assessed. It may be that a small percentage of these growths were not malignant, and since papilloma of the bladder is sensitive to radium this factor may be reflected in the results.

Many of the cases are too recent to be of value in this discussion, but thirty-eight of them were treated up to 1931, and I shall only consider these. They are divided into two groups: the papillary and the infiltrating types. Twenty-three were of the papillary type; of these, twenty were treated by the cystoscopic method with seeds, needling by the suprapubic route being the method in the other three cases. Four cases were recurrent after partial cystectomy, and two of these were controlled for periods of two and a half and three years respectively. Of the total number (twenty-three), ten have remained well, five for five years, two for four years, and three for three years after treatment. Of the fifteen infiltrating carcinomata, ten were treated by the cystoscopic method and five by the suprapubic route. Of these, three are alive and well, one for five years, one for four years, and one for three years after treatment. (Three cases in each group were untraced.) These figures are meagre, but they give some idea of the results that have been obtained in a group of cases, all of which were in a very advanced condition when first seen. Of the cases of papillary carcinoma, 43 per cent. were free from disease for three years and more, while 20 per cent. of the infiltrating cases are alive and well after the same period.

Table Showing Results in Thirty-eight Cases of Carcinoma of the Bladder

Type	Number Treated	Cystoscopic Method	Suprapubic Route	Alive over—		
				3 yrs.	4 yrs.	5 yrs.
Papillary... ..	23	20	3	3	2	5
Infiltrating	15	10	5	1	1	1
Total	38	30	8	4	3	6

In the United States, where radium has been used for bladder carcinoma longer than in this country, Keyes, Neill, Young, and Barringer, among others, began to report results as early as 1928. Neill (Baltimore) reported on a series of cases, 168 of all types, treated by radium. Inoperable cases numbered 111, and of these 9.9 per cent. were free from disease for three years or more. The remaining 57 were operable, and of these 35.5 per cent. survived the three-year period without disease. At the Memorial Hospital, New York, all bladder cancers, whether operable or inoperable, have been treated with radium for eighteen years, excision never being used. In 109 cases Barringer reports 43 per cent. three-year cures in papillary carcinoma, and 27 per cent. in infiltrating carcinoma.

Burnam, in 1931, quoted results in 111 cases. In the papillary type 17 per cent. of cures were obtained (of these cases the percentage cure in operable cases was more than twice that in inoperable ones). In the infiltrating type 16 per cent. were cured, and here again the percentage in the operable cases was very much higher. Pfahler, in 1931, reported 19.3 per cent. five-year cures in forty-three inoperable cases of all types by coagulation and radium. Darget, in 1933, reported results in twenty-two cases treated by the insertion of needles by the suprapubic route. Of these, seven were of infiltrating carcinomata, three of which were free from disease eight years, seven years, and four years respectively. The method of treatment is interesting, in that a rubber balloon filled with fluid is placed in the bladder in order to keep the bladder wall away from the radium in the growth. It is claimed that subsequent discomfort is minimized by this procedure, and that post-radiation cystitis is much less. The mortality is low—Barringer claims that in his cases it is 7.2 per cent.—and complications are rare.

The aftermath of treatment may be unpleasant, especially where large doses have been given over a wide area. Radium causes a slough to form, which may take months to separate—very much longer than after fulguration. Phosphatic deposits may be found on the area treated, and slough and deposit sometimes make it difficult to be sure whether there is still growth present or not. From the patient's point of view the prospect is often not a pleasing one, but to say that every patient treated by radium is made miserable for months after his treatment is simply not true. In fact, the after-symptoms vary in severity, from dysuria and frequency of a serious kind to transient discomfort which worries the patient very little. There are many patients who are made worse by radium treatment, chiefly those suffering from infiltrating carcinoma of great extent, where the dosage over a wide field is liable to act on the whole bladder, causing a very severe cystitis; if these patients have received a dose which is insufficient they are made miserable without the disease being eradicated. Experience will, we hope, lead us to avoid these cases.

The results of radium treatment show that papillary carcinoma is sensitive to radium, and that it is amenable to treatment by radium when it is not too extensive, and

when the growth is confined to the bladder. The infiltrating type, on the other hand, is more radio-resistant, and operable cases of this type should, I think, be treated by resection. Inoperable cases must be carefully considered. If they are extensive within the bladder their extravascular spread probably renders them incurable by any means, and widespread interstitial irradiation runs the danger of making the patient more miserable than he was before. Experience with these sixty cases at the Radium Institute seems to show that cystoscopic implantation of seeds should be limited to those cases of papillary carcinoma where the growth or growths are not more than 2 to 3 cm. in diameter, and that larger growths should be dealt with by the suprapubic route; that operable infiltrating carcinoma should be resected; and that great care must be taken in selecting inoperable cases suitable for radium treatment.

ALLERGIC FACTORS IN RHINORRHOEA AND NASAL CATARRH*

BY

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The term "allergic disease" has been introduced into medical literature by American investigators (Cooke and others), to designate a number of conditions which show one common aetiological characteristic—namely, hypersensitiveness to proteins or other substances that are innocuous to normal people. For the most part the patients suffer from acute attacks, while in the interval between two attacks they are in good health. Often, however, especially in the more severe cases, they present symptoms of their illness continuously, and suffer from acute exacerbations.¹

I do not propose to deal with bronchial asthma, skin conditions, or true hay fever, since these are already clinical entities, but I shall restrict myself to allergy as seen by the rhinologist in a rather indefinite form, either complicated or uncomplicated by catarrh of bacterial origin. The following headings may be mentioned: hypersensitiveness to (1) drugs; (2) various pollens; (3) so-called animal proteins; (4) foodstuffs; (5) bacterial products; (6) colloidal substances of unknown composition, the presence of which in the air is due to climatic influences (miasma).²

It is a well-known fact that certain people are hypersensitive to certain drugs, but in one important respect they differ from allergics: the symptoms they exhibit with a small dose of the particular drug are the same symptoms exhibited by normal people with an excessive dose. The true allergic exhibits symptoms which are totally different from any that might occur in persons non-sensitive even on really excessive dosage. I propose to pass over hypersensitiveness to various pollens, to animal proteins, and to foodstuffs, but would like you particularly to bear in mind hypersensitiveness to bacterial products.

It has been thought that there was an anaphylactic element in allergic diseases, but the main arguments against this theory are: (1) Allergic disease is often inherited; anaphylaxis is not. (2) Allergic symptoms are sometimes shown the first time the person comes in contact with the incriminated substance. (3) Allergy cannot be transmitted passively to animals; in anaphylaxis this experiment usually succeeds. (4) The symptoms

of allergy differ largely from those of anaphylaxis, but show resemblance to those of drug idiosyncrasy.

You are all familiar with the typical case of vasomotor rhinitis or paroxysmal rhinorrhoea associated with violent sneezing attacks, and a pouring of clear watery fluid from the nose to such an extent that patients are compelled to use towels instead of handkerchiefs for relief. But I believe, though in many cases I have no definite proof of the statement, that in a large number of so-called chronic catarrhs there is a very definite allergic factor; and I am sure that it is concerning the latter type of case that we should attempt to increase our knowledge.

Factors Operating in Vasomotor Rhinitis

The factors generally found in cases of vasomotor rhinitis are: (1) some personal idiosyncrasy; (2) a sensitive condition of the nasal mucous membrane; (3) some outside irritation; and (4) a supposed nervous element. Of these I consider the first all-important, and the last almost negligible.

As regards personal idiosyncrasy, we know that allergics, whether they be hay fever patients, asthmatics, or persons sensitive to animal emanations, on cutaneous testing, do not only react to their own usually specific protein, but also to numerous others, and that their sensitivity to these various proteins may vary from day to day. According to van Leeuwen, all allergics are sensitive to human dandruff, though varying in their reaction to other proteins. With this fact I will deal in greater detail later.

Our reasons for suspecting increased sensitivity of the nasal mucosa are rather empirical. The nasal mucosa either appears normal, pale, velvety, and slightly congested, or there may be whitish patches on it. This condition may apparently be rendered less liable to irritation by either cauterization or ionization. In certain patients this treatment affords either relief or cure, but it should be borne in mind that the sensitivity is often only to some specific irritant in the allergic person.

It is fully granted that the external irritation, acting on the mucous membrane of the allergic, is the trigger which sets off the attack. The nervous element is, in my opinion, the one most open to doubt. With most patients I consider that the discomfort, nuisance, and distress of repeated attacks of severe rhinorrhoea, which come on at least expected and most inopportune moments, are the cause of the patient's neurosis rather than the result.

Some Causes of Simple Vasomotor Rhinitis

Let us now consider simple uncomplicated vasomotor rhinitis, which is a condition with which we are all familiar. I am not going to deal with its pathology or clinical manifestations, but I would like to suggest one or two causes of the condition. StClair Thomson, in the 1916 edition of his book *Diseases of the Nose and Throat*, stated that vasomotor rhinitis was more common in the young male than in the young female. I am sure you will all agree with me that in these days the disease is much more common in the young woman. I think the reason is, not that there are more allergics, or that the young women are more neurotic, but that practically all women do use face-powder. We are all familiar with the white sheen that is seen on the septum and turbinates of the more heavily made-up woman. Many women are particularly susceptible to orris root, and I am told on good authority that orris root is to be found in certain makes of powder. In fact, one patient of mine told me that she could not use a powder in which orris root was known to be present, as it "was death to her." Quite often the changing of the make of powder is a valuable aid to treatment; it is more than the physician can do to stop its use.

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