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RECENT ADVANCES IN RADIUM THERAPY*

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The use of radium in the treatment of malignant tumours depends upon the empirical observation that in a large number of instances the cells of malignant tumours are destroyed by an amount of radiation insufficient to destroy the normal tissues. Although it is very doubtful whether the cells of malignant tumours, as such, are specially sensitive to the action of gamma rays, the majority of these tumours have biological characters which render them more sensitive than the cells of most adult tissues.

General Principles of Radium Therapy

Certain biological features have long been recognized as associated with increased sensitivity to radiation. They may be briefly stated as follows:

1. Rapidly growing tissues are more sensitive than slowly growing.
2. Individual cells are specially sensitive at the moment of nuclear division.
3. The chromatin of the nucleus is the most sensitive part of the cell.
4. Those tissues are most sensitive which approach most closely to the embryonic type, and the more specialized tissues are less sensitive.

All malignant tumours grow more rapidly than the tissues in which they lie, and consequently their individual cells are constantly undergoing nuclear division, when their chromatin is especially vulnerable. Moreover, all malignant tumours are of a less highly developed and more embryonic type than are the tissues from which they grow, although there is in this respect great variation. An epithelioma of the tongue, for example, may closely resemble in structure the epithelium from which it is derived, exhibiting in its cell nests the complete structure of the normal skin; or it may consist of a mass of rounded cells which might have arisen from almost any source. But in either event the rapidity of growth and therefore of division is incomparably greater in the tumour than in the normal tissues; both these varieties of epithelioma react to radium, the more embryonic type being far more sensitive. Although of quite a different character the changes in the connective tissues are of equal importance. The most striking is the effect upon the blood vessels, the function of which is slightly but permanently injured. A slowly developed endarteritis is probably accompanied by changes in the walls of the capillaries, affecting their permeability and the nutrition of the tissues they supply. At the same time the permanent connective tissue cells are slightly injured, as is shown by their lessened power of recovery after trauma.

There is a simultaneous development of wandering cells (macrophages) in the connective tissue, and these have a very marked effect on the absorption of the tumour cells.

It will be seen then that so far as our present knowledge extends radium injures both the tumour cells and the tissue cells, and that success in its use depends on obtaining the maximum effect upon the tumour and the minimum effect upon the connective tissue. It is an entire mistake to imagine that any type of radiation can increase the power of the tissues to absorb the tumour. When we expose a tumour to radiation we can only aim at doing as much injury as possible to our enemy, the tumour, and as little as we can to our ally, the stroma. The margin between general destruction of the tissues and selective destruction of the malignant cells which are invading them is very small. It is therefore an essential factor in treatment that every element of tissue throughout the region treated should receive the same amount of radiation. For if at any point there is a defect some malignant cells will survive; while if at any point there is an excess the supporting tissues will be destroyed.

If success is to be achieved radiation must include the whole lymphatic field through which the tumour cells may have spread. Nothing could be more erroneous than to imagine that the tumour itself requires a larger dose of radiation, and that the distant metastases, consisting perhaps of only a few cells, will yield to a milder attack. It is indeed in these distant zones, as was shown long ago by Sampson Handley, that tumour growth is most active: in contrast to human warfare, it is useless to destroy the enemy at his base if we do not at the same time wipe out his outposts.

Every portion of the region under treatment must therefore receive an equal quantity of radiation, but the manner in which this is applied is by no means a matter of indifference. Since the cells are more sensitive at the moment of division we can only be sure that none have escaped when the radiation has extended over a certain period. This requirement we have described as "equality of opportunity." Moreover, distribution of the radiation over a longer period produces less injury to the connective tissues, which have time to recover. On both accounts better results will be obtained if treatment is extended over several weeks than if it is concentrated into a few days.

Problem of the Uniform Field

Success in radium therapy must thus depend very largely upon the solution of the purely physical problem of obtaining a uniform field of radiation. A moment's reflection will show that the first essential for this is

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a radiation of high penetration. Without this, only the surface layers of the tissue can be affected, and they may indeed be destroyed by the radiation long before the deeper cells are aware of its presence. To the short wave-length of gamma rays, and their consequent high power of penetration, we owe primarily the power of radium to destroy tumours, for the penetration of hard gamma rays is at least ten times that of hard α rays, and 50,000 times that of light.

To use gamma rays to their full advantage it is, however, essential that all softer rays should be removed, as can be done by suitable screens. By this means a more or less homogeneous radiation of high penetration is obtained, and we are at least assured that the deep cells of a malignant tumour will not be protected from destruction by the depth at which they lie. We may assume, then, that our radium is screened by an adequate thickness of either platinum or gold to eliminate all but the hard gamma rays, and the problem of producing a uniform field thus resolves itself into that of arranging our radium sources in a suitable manner.

One other factor must be noted and defined accurately if our results are to be at all comparable in different centres—namely, the unit in which our radiation is measured. Without any doubt the r unit is the most ideal, for with it we can compare at once the effects of radium and of α rays. The practical difficulties, however, of measuring r units are considerable, and it has been suggested that the much simpler unit known as the "natural radium unit" is of more practical value. This unit is simply the amount of radiation delivered at a distance of one centimetre by one milligram of radium; but again the complication arises that it takes no notice of screenage.¹ I have suggested that even this difficulty may be got over by appending a suffix to indicate the screenage, and I have drawn up this table for platinum screenage in millimetres, which shows at once how extremely simple the whole matter becomes, while the figures are sufficiently accurate for all clinical purposes.

G(0)	G(0.5)	G(1)	G(2)	G(3)	G(4)	G(5)
hr.	hr.	hr.	hr.	hr.	hr.	hr.
10 r	8 r	6.5 r	5 r	4 r	3.5 r	3 r

Methods of Radiation

NEEDLES

Of the many methods of applying radium one of the most generally useful is the insertion of needles. These are small platinum tubes, ranging in diameter from 1.5 to 3 mm., with a cavity occupying the whole length of the needle except the eye and the point. The cavity is packed with insoluble radium sulphate, and it is essential that the packing should be uniform. The wall of the needle must not be less than 0.5 mm. thick, so as to cut off the whole of the beta and most of the soft gamma rays. The needle is attached to stout silk thread to facilitate removal. The radium content may vary within wide limits, but a very convenient and useful strength is given by one milligram of radium per centimetre of active length.

Such needles provide constant sources of radiation of known value. If they are suitably arranged they can be made to provide a field of radiation of fair uniformity, except in the immediate neighbourhood of the needle itself, where the dose is necessarily excessive and may lead to localized necrosis. In their arrangement, however, there are two golden rules to be observed. They must always be placed in the growing edge of the tumour or actually outside it. If it is at all possible they should be arranged so as to encase the tumour, which is thus subjected to cross-fire from many sides.

RADON SEEDS

These consist of small tubes of gold or platinum, in which are sealed up minute amounts of radium emanation, itself usually sealed in a fine glass capillary. Each seed may be perhaps a millimetre or less in external diameter and from 5 to 10 millimetres in length; it may or may not be attached to a thread for removal.

At first the physical effect is precisely the same as that of a radium needle of corresponding dimensions and content, but as time goes on the emanation decays, so that at the end of four days it is only one-half, and at the end of nine days one-fifth of its original strength. So far, indeed, as the emanation is concerned, the removal of the seed is quite unnecessary, since its action in a fortnight has become negligible.

For accurate implantation some form of introducer is necessary, and the gun which I devised some time ago will be found very convenient. By this means it is possible to introduce even a hundred seeds in a very few minutes, and to deposit them with remarkable accuracy, so that the first condition for a uniform radiation is obtained. The principles described above still hold—namely, implanting the seeds in the growing edge, and surrounding the tumour so as to obtain cross-fire. The accurate introduction of seeds demands some skill, but their small size and the fact that they need not be removed are sometimes advantages of great importance. I have used them with success in such regions as the palate, the tonsil, and even the aryepiglottic fold, in which the introduction of needles is scarcely practicable.

In certain cases I have found another method of introduction most useful, and it presents the advantage of great simplicity. A threaded seed is attached to an ordinary cutting needle; this is passed through the tissues beneath the tumour and brought out through the skin at some convenient point, when the seed can be drawn accurately to the position required. In the tongue and the floor of the mouth the method presents great advantages, since the patient is saved from the inconvenience of threads lying within the buccal cavity. Whether needles or seeds are used their arrangement must be planned so as to give the precise radiation required at every point of the region under treatment. The actual measurement of the radiation from any arrangement may be greatly facilitated by the use of a scale² which I have devised, which gives the radiation in r units per hour at every point from a milligram of radium situated at any other point. It is only necessary to plot the position of each milligram, which may, for practical purposes, be regarded as a point source, to take the scale readings at any point, and to add up the results.

PLAQUES AND MOULDS

Insertion methods suffer from the defect of discontinuity, so that a really uniform irradiation is virtually impossible. This may be avoided to some extent at least by mounting the sources of radiation at a distance from the surface on plaques or moulds. Suppose, for example, that it is desired to treat an epithelioma of the alveolar margin. After removal of all teeth a dental mould is constructed to fit the surface accurately. Upon this needles or seeds are mounted so as to lie at a distance of perhaps 5 millimetres from the surface of the tumour, encircling it so far as is possible. The radium itself is covered by a bulky mass of dental mould material; this holds the other structures of the mouth at a distance from the area under treatment, and thereby protects them from excessive radiation. The method may be equally applied to tumours on the surface—for example, a carcinoma of the scalp. Here, since distance is more easily obtained, a still more uniform radiation can be achieved. We regard

this, indeed, as the most valuable method available for general use.

The calculation of the quantity of radium to be mounted on the plaque and its precise arrangement to obtain the best result, are matters of some difficulty, but we have succeeded in reducing it to a comparatively simple formula. The amount of radium to be used is divided into two equal portions, one of which is distributed uniformly over the surface of the plaque, while the other is arranged round its margin. This arrangement will be found to give the most uniform radiation possible, as regards both the surface and the deeper portions of the tumour.

Given such an arrangement it only remains to discover the amount of radium needed to give the intensity required at the surface. This can be ascertained without any calculation at all by means of a very simple instrument* which I have devised for the purpose. It consists of a chart on which are drawn a series of curves very exactly calculated; each of these corresponds to a certain thickness of plaque—that is to say, a certain radium distance. A sliding rule can be passed across the surface of the chart, the rule being divided into a scale of areas. The area under treatment in square centimetres is read off on the sliding rule, and this is now passed across the chart until this division of the scale lies on the corresponding curve. On a scale at the bottom of the chart is now read the amount of radium required to give 100 r units per hour at each point of the surface under treatment. The method is far simpler to use than to describe, and is capable of a high degree of accuracy. With small modifications it can be applied to most of the conditions met with in clinical practice.

Beam Radiation

Where very large amounts of radium are available a uniform field may be obtained by an entirely different method, which we have described as beam radiation. In a research at present in progress in London, in which I have the honour to collaborate, 5 grams of radium are concentrated in a special apparatus so arranged that the gamma rays emerge through a circular aperture 5 cm. in diameter. The aperture is surrounded by a dense cylinder consisting of a mixture of tungsten and copper. The radium is placed at a distance of 8 cm. from the opening, which is itself closed by a thin metal plate. The radium is contained in fifty small cylinders, closely packed together and so arranged that the rays pass through a primary screen of 3 mm. of platinum, sufficient to cut off a large proportion of the softer rays. The radium itself is surrounded by a huge mass of lead, sufficient to provide adequate protection to those in the neighbourhood of the unit. There is, however, an arrangement by which the radium is withdrawn from the unit, except when this is in actual use, so that all the adjustments of the instrument are made when it is empty of radium.

* The instrument is made by Messrs. Casella, London.

At a depth of 4 cm. the dose is approximately half of that delivered at the surface. By using several portals of entry it is possible to build up a depth dose to any required extent without seriously injuring the skin. By this means a field is obtained more uniform than can be achieved by any other means; owing to the great penetration of the rays it is possible to irradiate uniformly a large volume of the tissue. On the other hand, the restriction of the rays to a more or less definite beam spreading from a circular aperture 5 cm. in diameter limits the radiation to the tissues which actually require treatment, and avoids those general reactions which have, in many cases, proved a serious embarrassment in the use of large units.

Results

As regards the results obtained, it is still too early to speak with confidence, but in the eighteen months during which the apparatus has been in use we have been able to draw certain tentative conclusions from our experience. Our cases have been limited to carcinoma arising in the buccal cavity, the tonsillar region, the pharynx, and the

larynx, this region being chosen for convenience of observation as well as for its known favourable reaction to radium. With a few exceptions the local condition has cleared up rapidly, but this could, in many instances, have been achieved by other means. Of far greater interest and importance has been the effect upon the glands. In almost every case these have responded freely, and in many instances large masses of inoperable glands have

disappeared. The region chosen was particularly favourable for the experiment, since irradiation of the tumour nearly always involved of necessity extensive irradiation of the glandular areas. More recently we have, in fact, concentrated our attention upon the glandular areas, convinced that success in these must carry with it an adequate irradiation of the primary growth. It is much too soon to speak of cures, but one can at least state that the results so far have been encouraging, that we have learnt to use the beam with little risk and no appreciable injury to the patient, and that the research has fully justified the enterprise of those to whom it owes its initiation.

Pneumatic Delivery

One difficulty in using these large masses of radium lies in the risk to those who are operating the apparatus. Their full protection involves huge masses of lead, which render the apparatus unwieldy and difficult of application; even then it is impossible to avoid some degree of exposure. To avoid this I have devised a mechanism by which the radium can be automatically conveyed to and from the apparatus, so that the operator works in absolute safety, while the radium remains at a distance securely protected until its use is actually required. In this model which I have constructed the transference is achieved by pneumatic means, the radium passing from its safe along a flexible pneumatic tube to its position in the apparatus. Its arrival is indicated by the lighting up of a small

FIG. 1.—Long-beam unit, with curved pneumatic delivery, revolving back, and signal lamp.

electric lamp, whilst its position is accurately maintained by the pressure of a light spring.

Such an arrangement eliminates entirely all risk to the operators, since the controls may be placed outside the treatment room, just as with modern x -ray apparatus. It also renders quite unnecessary the great masses of lead usually employed in these units, since all that is required is the protection of the patient. A unit of the size of

FIG. 2.—Short-beam unit. Radium advanced.

FIG. 3.—Short-beam unit. Radium retracted.

this model, if made of lead, could safely accommodate 5 grams of radium, with adequate protection for the patient and for persons at a reasonable distance. The convenience and economy of such a reduction in the size and weight are very obvious. A small refinement is the introduction of the radium along a curved track, eliminating the danger point which might otherwise lie behind the apparatus.

A Short-beam Unit

The methods I have so far described are for the most part well known, apart from the modification which I have indicated. On this very special occasion I should like to deal with the possibilities of the future, and show a model involving principles which I have only recently explored, but which I feel justifies serious consideration. It is based on the principle of pneumatic transference, so that the radium is only in the proximity of the patient when in actual use. It enables one to obtain from 1 gram of radium an effect almost equal to that in an ordinary 5-gram unit, although, of course, over a smaller area.

The body of the unit consists of a rounded cylinder of platinum 3 cm. in diameter and 5 cm. in length, with an axial cavity ending in a conical aperture 20 mm. in diameter. Radiation is effected through this aperture, whilst in every other direction there is an effective screenage of at least 10 mm. of platinum. Since the radium can be placed at will at any point from 15 to 35 mm. from the aperture, considerable variation is allowed in the surface and depth dose and in the dimensions of the beam. The aperture is closed by a glass plate, so as to permit of a visual setting of high accuracy.

The apparatus is sufficiently small to be actually introduced into the mouth, and the aperture placed in contact, for example, with the tonsil; the radiation from one gram of radium in this position is so intense that a few minutes' exposure would suffice. The small aperture of the instrument allows of a large number of ports of entry being employed, while with the varying position of the radium any depth dose desired may be obtained. Although the apparatus has not yet been employed in actual practice I am sufficiently confident of its physical soundness to suggest it to you as a fresh method of attack.

Conclusion

The methods of radium therapy are developing so rapidly that I have only been able to touch upon their broadest features. In combination with deep x rays and diathermy, we now have weapons by which we can attack cancer in almost all its forms, and in many with the certainty of success. But success will depend, above

everything else, upon a precision which is not demanded in any other branch of surgery, and an accuracy which challenges the resources of the physicist. It is upon the combined efforts of the surgeon, the radiologist, the biologist, and the physicist that the future of radium therapy will depend.

REFERENCES

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MYCOTIC INFECTIONS AND THEIR TREATMENT*

BY

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Since the time allotted for this paper is short, I propose to outline as far as possible the salient features of a type of dermatomycosis that has proved to be one of the most troublesome of all skin diseases with which the dermatologist has to deal. Vesicular eruptions of mycotic origin occurring on the feet and hands are often extremely rebellious to treatment of all kinds and, even when beneficially influenced, are frequently characterized by a seasonal recurrence. The condition is frequently encountered in Sydney, and I hope to put forward some helpful ideas on treatment.

Clinical Considerations

The different clinical varieties which are encountered in Sydney are as follows.

1. The superficial vesicular type, which occurs on the fingers, palms of the hands, toes and soles of the feet, and even extends on to the backs of the hands, the forearms, and the dorsa of the feet and legs when the process is severe.
2. The more deeply seated vesicular eruption, which is more limited to the fingers, palms, toes, and soles. Both

* Paper read in the Section of Dermatology at the Annual Meeting of the British Medical Association, Melbourne, 1935.