Observations

ON

THE USE OF RADON SEEDS IN THE
TREATMENT OF CARCINOMA.

BY

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THE use of radium emanation in the form of seeds presents very considerable advantages in practice, and for nearly two years I have adopted it whenever possible, to the exclusion of other methods. In the course of that time I have developed certain modifications in technique which I have found advantageous, and although it is obvious that observations on cases treated over so short a period can only be of a tentative nature, I feel that they may not be devoid of interest.

Radon, or radium emanation, is a heavy gas of atomic weight 222, and it is formed by the decay of radium at an absolutely constant rate, which is independent of the physical condition of the radium, its solution, temperature, or pressure. Radon itself decays, but by the end of a month, if undisturbed, the radium and its emanation have virtually reached a state of equilibrium, when the production of radon is balanced by its decay and no further accumulation can take place. The amount of radon in equilibrium with one gram of radium is defined as one curie, and the volume of this very potent source of energy, the physical equivalent of 1,000 milligrams of radium, is only 0.6 of a cubic millimetre. It will thus be seen that we have here the means of packing an extremely powerful source of radiation into a very small compass.

From a surgical standpoint the radiation produced by radon is identical with that of radium, and indeed it is only from its accumulated store of radon that radium itself derives its power. Stripped of its emanation radium is for the moment entirely inert. There is, however, this very important distinction: that radium, giving off a

constant stream of radon gas, furnishes through this a constant and unvarying source of radiation; but radon, separated from its parent, steadily decays. Commencing with 100 millicuries of radon, we have left at the end of 3.82 days only 50 millicuries, in 9 days only 20, and at the end of a month practically the whole has gone. If, then, we use radon we must recognize that we are using a diminishing source, and make a corresponding allowance in the amount we apply.

This steady decay in power might be a fatal objection to the use of radon in surgery, but this is not in fact the case. All the evidence at present available goes to show that the effect produced upon a tumour is proportional to the total energy delivered, and that it is a matter of apparent indifference within certain limits whether this energy is produced slowly or rapidly, or whether its rate of production is constant or diminishing. It may, indeed, eventually prove that a powerful attack gradually withdrawn is more effective than a continuous bombardment at constant pressure.

It is usual to collect the radon in fine glass capillaries, but these must be screened by metal sheaths to cut off beta

rays, which have no selective action on the cells of carcinoma and produce a general local necrosis of the tissues. The most effective screen is platinum, and with a platinum sheath whose wall is 0.3 mm. in thickness, all but a very small fraction of the beta rays are absorbed. I have found, however, that with such small amounts of radon as are used in seeds—usually from 1 to 2 millicuries—silver of the same thickness forms a perfectly satisfactory screen at a fraction of the cost, whilst it is an old observation that silver, owing to its slight antiseptic properties, is better tolerated in the tissues if left in permanently. The only exception is in the case of a growth close to a mucous or cutaneous surface, and here platinum should be used, as these surfaces are peculiarly sensitive to beta rays. The seeds may be attached to fine silk threads to be removed, but personally I only adopt this course in such special regions as the eyelids. In most regions the seeds may be left in permanently without any ill effect. The seeds I use are of one standard size, 5 mm. in length and 1.1 mm. in diameter. The wall is 0.3 mm. in thickness, so that a lumen is left 0.5 mm. in diameter, allowing ample room for the glass capillary. The seeds contain 1, 1.5, or 2 millicuries of radon, and they may be inserted in large numbers. Thus for a breast case 50×2 mc. seeds would be used, unless the patient were very stout or very thin, or the tumour exceptionally large, in which case the number or strength of the seeds might be modified. In a tongue one might use 10×1.5 mc. (preferably platinum), but a similar or larger quantity might be required for secondary glands in the neck. In the oesophagus I should use 12×1.5 mc. seeds in an ordinary case; in the rectum perhaps 30×2 mc.

These examples will serve to show the adaptability of seeds to various conditions and the flexibility of these small standard units to meet varying requirements as to dosage. In general, the aim in view is to produce a nearly uniform radiation of the region under treatment by as accurate a "random" distribution as it is possible to obtain. It is obvious that the smaller the unit the more easy will it be to obtain a true "random" distribution. In such a distribution it is obvious that the effects of crossfire will be important, but it is not usually realized how considerable this effect may be.

It is a generally accepted standard of dosage that one millicurie of radon during its decay will produce a gamma radiation sufficient to destroy all carcinoma cells within a distance of 0.5 cm. This is, of course, a very rough estimate, for no account is taken of the considerable variation in the sensitivity of various types of cancer. Taking it, however, as a rough basis of calculation, it would suggest that the correct dose would be 1 millicurie for each sphere of tissue 1 centimetre in diameter, and that a tumour 8 cm. in diameter would require 512 millicuries, since its volume is 512 times that of the unit sphere. Let us see how this estimate is affected by crossfire.

Let us represent the density of radiation at any point P by the letter R, taking as unity the density of radiation produced by 1 mg. of radium at a distance of 0.5 cm. Suppose the space around P to be filled by radium at a uniform density δ , so that every cubic centimetre of space contains δ milligrams of radium.

Consider a spherical shell described about P as centre, of radius r and thickness dr . The area of this shell is $4\pi r^2$, and its volume $4\pi r^2 dr$, so that in this shell are contained $4\pi r^2 dr \delta$ milligrams of radium, all at a distance r from P. The density of radiation dR at the point P due to the spherical shell is proportional to this and to the inverse square of the distance, and we therefore have

$$dR = 4\pi r^2 dr \delta \times \frac{1}{r^2}$$

since the radiation of 1 mg. at a distance of 0.5 cm. is taken as unity. Thus $dR = \pi \delta dr$, and hence on integration we have $R = \pi \delta r$.

In the case, then, of a spherical tumour 4 cm. in radius the density of radium required to produce unit radiation at the centre is given by $\delta = \frac{1}{4\pi}$. The total amount of

radium required is therefore $\frac{1}{4\pi} \times \frac{4}{3} \pi \times 4^3$, or 21.3 mg. If we are using radon the amount required is 21.5 mc.

The contrast between this and the original estimate of 512 is a striking example of the remarkable effects of cross-fire. It is, of course, true that the effect is greatest at the centre, that we have taken no account of absorption, and that such a distribution is unattainable in practice. The argument is, however, perfectly sound in demonstrating the value of an even distribution and the enormous increase in effective radiation which results, and incidentally it provides a substantial reason for the use of seeds by which an even distribution can most readily be obtained.

The seeds are introduced by means of a fine cannula 15 cm. in length and provided with a breech at the proximal end by which the seeds may be introduced. The seed is pushed down the cannula by means of a plunger, and is extruded at the distal end. The cannula is now withdrawn a short distance, say, 2 cm., and another seed is introduced. In this way a linear distribution of the seeds can be made with great accuracy and with no further trauma than is involved in the first introduction of the cannula. Further parallel rows of seeds can be similarly introduced, or several rows may be arranged to radiate from one puncture. The actual number of punctures in the skin required is very small, and we have usually found that for the breast six punctures will be ample, whilst for a full infiltration of the pelvis for a carcinoma of the rectum two punctures in the perineum may suffice. The resulting absolute elimination of sepsis is no small advantage of the method.

The best results are undoubtedly obtained by the introduction of large numbers of seeds, so that the total amount of radon is distributed as evenly as possible. The introduction of fifty or sixty seeds down a simple cannula is a tedious process, and I have therefore devised a magazine introducer, with a detachable magazine carrying ten seeds. The introducer is held in the left hand, and the magazine is rotated by the thumb, whilst the plunger is pushed home with the right hand. The saving of time is considerable, but perhaps even more important is the gain in precision of distribution of the seeds.

In the oesophagus this method is not applicable, and a special instrument is required. This takes the form of a long wire carrying a fine tube laterally at the distal end. A parallel wire running in guides can be pushed through this tube as a plunger. A seed is introduced into the distal end of the tube, which is bevelled off to a blunt needle point, and is fixed there with a little vaseline. The introducer is passed down the oesophagoscope under full visual control, and is advanced directly into the substance of the growth, the plunger is pushed home, and the seed deposited.

THE USE OF SEEDS IN SPECIAL REGIONS.

The application of these general principles to tumours in various regions involves in each case special considerations, and we propose to illustrate these by discussing in turn the treatment of tumours in the tongue, the breast, the rectum, and the oesophagus.

The Tongue.

The tongue is particularly adapted to the use of seeds, since their introduction is such a simple matter and their removal is quite unnecessary, whilst the patient is saved from the annoyance of the threads which must be used to secure radium needles. As in the case of all tumours, an endeavour is made to infiltrate the growing edge of the tumour with a uniform barrier of seeds. The definition

of this growing edge is the most difficult part of the problem, and can only be judged after considerable experience. In this surface of growth the seeds are deposited so as to lie about 1 cm. apart, and a few additional seeds are then introduced into the tumour itself superficially to the deep growing surface. The total amount of radon used and the number of the seeds will, of course, vary with the nature of the case, but in an average case from ten to sixteen 1.5 mc. seeds will be required. They should be screened with platinum, as it is of importance that the mucous membrane of the tongue itself and of the palate should be absolutely protected from the action of beta rays.

The actual introduction of the seeds is a simple matter. Even in tumours situated at the base of the tongue it is quite easy to guide the cannula by means of a finger placed upon the ulcerated surface, and to judge of the depth at which it lies within the substance of the tongue. The

needle is introduced through any convenient site, whether from the dorsal surface or from beneath the tongue, whilst in growths which extend on to the floor of the mouth the seeds may even be introduced with advantage from the neck beneath the jaw. Uniformity of arrangement so as to obtain a uniform

crossfire is the chief object to be aimed at, and one should not allow oneself to be tempted to concentrate groups of seeds in the substance of the tumour where they will merely have a destructive action and produce a slough. I feel convinced that many of our failures are due to a too localized distribution of radium, and that some, at least, might have been converted into successes if a primary layer of seeds had been distributed far beyond the apparent region of the growth and not within its margins.

The course of events to be expected in a successful case is somewhat as follows. Within forty-eight hours it will be noted that the induration is diminishing, and in a week it has almost disappeared, whilst the growth is definitely smaller. At the end of two weeks the growth itself, and sometimes the adjoining mucosa, is covered by a smooth white layer of lymph, absolutely characteristic of a successful reaction. Beneath this the epithelium spreads in from the margins, and at the end of three weeks the growth has disappeared completely, the surface is healed, and only a pucker may remain. Where the growth is very large the process may take longer, and some deformity may result, but it is never in any way comparable with that produced by any form of operative removal.

The cervical lymphatic glands form one of the most difficult problems in carcinoma of the buccal cavity. It has long been recognized that in carcinoma of the tongue recurrence in the cervical lymphatics is almost invariable unless these have been removed, even where no local recurrence has taken place, and it is quite commonly bilateral. We have no doubt at all that at the present day the proper treatment of a primary carcinoma in the buccal cavity is irradiation; we cannot, however, speak with the same confidence of the cervical glands, and it still remains a question whether these should be dissected out completely, or whether we should depend on irradiation, or whether complete dissection should be followed by surface irradiation.

The method we are at present adopting is to treat the glands in precisely the same way as the primary growth, infiltrating the whole of the cervical region on the affected side with seeds, and following this up if necessary with a similar irradiation of the opposite side of the neck. In almost every case where the glands were already enlarged

this has been followed by a rapid diminution in their size, or even by total disappearance, and the fact that recurrence has in some instances occurred in more distant groups does not invalidate the local effectiveness of the seeds. It rather tends to show that the seeds must be distributed on a much wider scale, or that their action should be backed up by the more diffuse form of radiation which can be obtained from a collar.

The Breast.

The breast is a site so easily accessible for the introduction of needles that it might be thought that seeds presented few advantages. This is, however, far from being the case. The seeds can be introduced through a few minute punctures, not more than six being required in even the most extensive case. With the introducer which I have described their distribution can be controlled with mathematical precision, and x-ray photographs have convinced me that they do not wander from their site in any reasonable time. The punctures through which they are introduced heal almost immediately, so that there is no possibility of sepsis to complicate the treatment, whilst the patient is saved from the considerable annoyance caused by threads and the removal of needles.

The seeds are introduced according to the very satisfactory plan worked out by Gask and Keynes for the introduction of radium needles. The region just beyond the growing edge of the actual tumour itself is infiltrated with long columns of seeds, perhaps five rows with five seeds in each row, and above this into the base of the tumour itself further rows of seeds are inserted at right angles to the original set. Thus, the first layer of seeds will probably lie in the pectoral fascia, while the second lies in the substance of the tumour, assuming that the latter is of considerable dimensions. The cannula is now introduced through a puncture in the axilla and passed up beneath the pectoral muscles along the axillary vein, until it can be felt just below the middle of the clavicle. A long line of seven or eight seeds is now deposited, and this line is duplicated by another at a somewhat lower level, which really lies, for the most part, in the pectoralis major. Through the same puncture a line of seeds can be introduced along the axillary border of the pectoralis minor and upon the surface of the serratus magnus just behind this. Finally separate seeds are introduced, one in each of the intercostal spaces just outside the sternum, and two into the sheath of the rectus.

Although this is the general arrangement of the seeds, it may have to be modified to suit special circumstances. On occasions I have had to deal with tumours so large that I felt obliged to concentrate the whole of the seeds upon the tumour itself, leaving the lymphatic infiltration to a later date. One has to remember that the exposure of a patient to too large a dose may have serious constitutional results.

The Oesophagus.

The treatment of carcinoma of the oesophagus by means of radium presents very considerable difficulties. There is the difficulty of obtaining access to the tumour, secondly of forming any estimate of its dimensions, and thirdly of introducing radium. The last difficulty is to a large extent overcome by the use of seeds, whilst access to the upper end of the tumour can be obtained fairly readily by a properly designed oesophagoscope. Some idea of the length of the tumour can be formed from a radiogram after the swallowing of a bismuth emulsion, but it must be admitted that it is impossible to form any but a very vague idea of the extent of the growth. It has been suggested that freer access and more complete information would be gained by thoracotomy, but few of the patients with this disease are in a condition for such a formidable procedure, whilst there is so far no evidence to show that the results would be at all improved by its use.

My present method of procedure is as follows. Using the largest possible tube of my own oesophagoscope with proximal illumination, an excellent view of the upper end of the growth can be obtained. By means of a special introducer the seeds are passed down the lumen of the tube and implanted in the growth under the full control of vision.

The introducer consists of a short cannula carried at the end of a long wire, with a plunger which can be operated from the proximal end. Each seed is placed separately into the distal end of the introducer and secured with a little vaseline. The instrument is inserted into the growth, and on pushing home the plunger the seed is deposited. By deflecting the oesophagoscope in different directions, and by inserting the introducer to different depths, the seeds may be deposited through the growth with much greater uniformity than might be imagined. About twelve seeds of 1.5 mc. each are inserted. There is no reaction, but in about a week improvement in swallowing may be expected to commence, and in a favourable case the patient should in three weeks be able to swallow ordinary soft food without difficulty.

This method of treatment has the advantage of simplicity and apparently of safety, for I have never so far seen any untoward result. An obvious criticism is that there is no guarantee that the seed will not be implanted in the mediastinum or elsewhere outside the growth. As, however, it is impossible for organisms to grow in the neighbourhood of an active seed the risk is more apparent than real. The great advantage over intubation is that there is no need to pass a bougie through the lumen, always a difficult and dangerous procedure.

The Rectum.

The rectum is a region peculiarly adapted to the use of seeds, especially if the growth is situated within reach of the finger. In this case the growth itself and the whole of the pelvic tissues around it can be easily infiltrated with seeds through two small punctures in the perineum, and the simplicity of the procedure and the absence of sepsis are then very valuable. I shall describe the method as it was applied with complete success to a carcinoma on the posterior wall of the ampulla involving the sacrum. With the patient in the lithotomy position two small punctures were made in the perineum, one on each side of the tip of the coccyx, and thirty seeds of 2 mc. each were introduced in long columns so as to be deposited as uniformly as possible in and around the growth. The magazine introducer was used and its position was controlled by means of a finger in the rectum in contact with the growth. Care was taken to establish a substantial barrier of seeds in the hollow of the sacrum behind the rectum in order to irradiate both the base of the growth and the rectal glands.

Where the growth is situated at a higher level it will be necessary to expose the growth by laparotomy and to introduce the seeds across the peritoneal cavity. As a full view of the growth is thus obtained there is no difficulty in the operation, nor is the introduction of the seeds accompanied by any special risk. In these cases, however, the growth has usually encircled the bowel, producing obstruction, so that a permanent colotomy is almost essential.

The rapidity with which a tumour of the rectum may disappear is remarkable, and even in advanced cases the insertion of radium may make possible the removal of a growth previously inoperable. It is obvious, however, that it is impossible to ensure the irradiation of a growth of the rectum with the same completeness as in the case of the breast or the tongue, and it is probably safer to excise the rectum from the perineum three months after the introduction of the radium whenever this is possible.

Sections of tumours removed under these conditions certainly support this view, for although they show that the vast proportion of the carcinoma cells have been destroyed, a few still remain as a possible source of recurrence.

CASES TREATED WITH RADIUM.

The following series of eighty-five cases includes those which we have treated up to the commencement of the present year, excepting a few cases which it was impossible to trace or in which for some reason the record was unsatisfactory. With very few exceptions these cases have been treated by the methods we have described, but a few early cases in which radium itself was used have been included for the sake of completeness. We feel that direct

presentation of actual cases is the only sound foundation upon which to build at the present time, for only in this way can the powers and the limitations of radium be shown.

The following notes have been suggested by a study of the cases, and express concisely the conclusions which may be drawn.

The Skin.—The skin is undoubtedly the most successful situation for the application of radium. Both basal and squamous carcinomas respond readily, and although in the former case the absence of secondary deposits is an advantage, this is somewhat balanced by a more marked tendency to local recurrence. Of the 11 cases under review, the tumour has disappeared in all, and there has been no recurrence, local or otherwise, after periods extending up to seventeen months.

The Lip.—In every instance there was a rapid local response, and 3 out of the 5 cases have remained well for six, thirteen, and fifteen months. The one fatal case was really untreatable when first seen.

The Tongue.—These were all advanced cases, untreatable by any other method. In every instance, however, there was a rapid local response, with, in every case but one, a total disappearance of the primary tumour. In the 4 cases where the glands were treated by radium they responded at once. In 5 of the 7 cases distant secondary deposits appeared, and in

only one (21) is there any possibility of a permanent cure. This also was, however, a totally inoperable case.

The Mouth.—These were all entirely inoperable cases, 5 of a very advanced and extensive nature. In the only case where the growth was limited (26), although surgically inoperable, there has been no recurrence after two years. In 4 of the other cases the local growth disappeared, but recurred later. In 1 there was a local reaction of quite unexpected severity, masking the immediate effect upon the growth.

The Breast.—The 24 cases have been classed as early, advanced but operable, and inoperable. Of the 11 cases in the first group all but one have been followed up to date, and these all remain free from recurrence at periods of from six to twelve months. In 4 cases the tumour was first excised locally from doubts as to the diagnosis, but in the other 7 cases the disappearance of the tumour was entirely due to radium. Of 7 cases classed as advanced but operable, 1 was not traced, 1 was amputated after fifteen months for local recurrence, and 5 remain well after periods of from six to sixteen months. Of 6 cases which were totally inoperable, 1 died five months later from general dissemination, 1 remains locally well but has probably a thoracic deposit, and 4 remain well after periods of from six to eleven months. Out of 24 cases local recurrence has so far appeared in one case only. In 2 cases, however, the tumour did not respond, but in one of these removal of the tumour showed dense fibrosis with scattered groups of carcinoma cells.

SKIN.

No.	Age and Sex.	Duration.	Characters of Growth.	Dosage.	Result.
1	F. 74	5 weeks	Small ulcer below outer canthus left eye. Squamous carcinoma.	2 × 2 mc.	Disappeared in 5 weeks. (9 months.)
2	M. 44	13 years	Circular ulcer 2 cm. diameter in front of left ear. Squamous carcinoma.	12 × 1.5 mc.	Disappeared in 4 months. (6 months.)
3	M. 67	42 years	Recurrent basal-celled carcinoma invading voluntary muscle of cheek.	4 × 1.5 mc.	Disappearance of local recurrence. (6 months.)
4	F. 68	6 months	Ulcer 2 cm. diameter outside external canthus right eye. Enlarged pre-auricular glands. Squamous carcinoma.	6 × 2 to ulcer; 7 × 2 pre-auricular glands; 7 × 2 upper cervical glands	Rapid healing of ulcer and disappearance of glands. (4 months.)
5	F. 63	10 months	Hard ulcerated mass size of pea upper margin left pinna. No secondary glands palpable.	2 × 2 mc.	Disappeared in 4 months. (17 months.)
6	M. 83	6 months	Ulcer 3 cm. diameter left cheek. Squamous carcinoma.	10 × 2 mc.	Disappeared in 1 month. (12 months.)
7	F. 61	14 years 6 months	Carcinoma of skin. Secondary in gland of groin.	14 × 2 mc. into gland	Disappeared in 5 months. (9 months.)
8	M. 80	2 months	Ulcer 1 in. diameter behind left mastoid. No enlarged glands. Squamous epithelioma.	10 × 2 mc.	Rapid healing.
9	F. 79	Many years	Infected ulcerated mass 3 cm. diameter over left parietal region. Section: sebaceous carcinoma.	6 × 2 mc.	Complete healing in 4 months. (7 months.)
10	F. 76	7 years	Large vascular tumour 3 in. long, 1 in. wide, upper part of left neck reaching as high as the ear. No secondary glands. Probably a basal carcinoma.	15 × 2 mc.	Two months later tumour had entirely disappeared without ulceration. (5 months.)
11	M. 72	37 years	Extensive scarring from recurrent rodent ulcer. Nodule in left lower eyelid, one year.	2 × 1.5 mc.	Perfect result locally. (2 years.)

LIP.

No.	Age.	Duration.	Characters of Growth.	Dosage.	Result.
12	68	12 months	Huge fungating growth 4 in. × 2 in. with indurated base completely replacing lower lip and extending almost to point of chin. Squamous carcinoma.	32 mg., radium 5 days	Rapid disappearance of growth and reappearance of lip. Death after 10 months from secondaries in lungs.
13	61	6 months	Typical epitheliomatous growth 1 in. diameter in centre of lower lip.	5 × 1.5 mc.	Healed in 8 weeks. (15 months.)
14	47	9 months	Indurated ulcer 2 cm. diameter just above upper lip on right side. Section: squamous carcinoma.	12 mg., radium 5 days	Healed in 10 weeks. (13 months.)
15	68	8 months	Fungating epithelioma 3 × 1 cm. on right side of lower lip.	10 × 1.5 mc.	Healed in 4 months. (6 months.)
16	86	5 months	Fungating epithelioma in centre of lower lip.	8 × 2 mc.	Rapid disappearance of growth.

TONGUE.

No.	Age.	Duration.	Characters of Growth.	Dosage.	Result.
17	59	12 months	Extensive leukoplakia with deep carcinomatous ulcer on dorsum, extending to epiglottis. Fixation and swelling of tongue. Secondary glands on both sides.	9 mg. radium 16 days	Ulcer disappeared and tongue became mobile. Healing complete in 6 weeks. Glands removed later. Died 4 months, distant secondaries.
18	49	3 months	Tumour involving whole of left side of tongue. Deep ulceration and complete fixation. Secondary glands beneath jaw.	30 mg. radium 6 days, tongue and glands	Rapid disappearance of tumour and healing of ulcer. Died 2 months, distant secondaries.
19	70	12 months	Deeply ulcerated carcinoma occupying posterior half of right side of tongue and extending to epiglottis. Glands in neck. Squamous carcinoma.	8 × 1.5 mc.	Rapid local improvement. Glands removed later and 8 × 1.5 mc. inserted. Died 6 months, distant secondaries.
20	72	6 months	Large ulcer on right side of tongue, extending to epiglottis. Glands in anterior triangle. Squamous carcinoma.	21 mg. radium 5 days	Rapid healing of ulcer. 8 months later new carcinoma on left tip of tongue, 8 × 1.5 mc. Healed but recurred. Died 11 months, distant secondaries.
21	64	3 months	Indurated ulcer on left side of posterior surface of tongue, extending to epiglottis and on to the fauces. Polygonal carcinoma, not squamous. Glands behind angle of jaw.	20 × 1.5 mc. tongue and glands	Rapid disappearance of ulcer and of glands. Well after 8 months.
22	43	4 months	Indurated ulcer in right border of tongue and floor of mouth. Glands in angle of jaw. Squamous carcinoma.	12 × 2 mc. tongue 28 mg. radium 6 days glands and floor of mouth	Rapid healing of tongue and disappearance of glands. Recurrence after 5 months in more distant glands. No recurrence in tongue or glands.
23	63	4 months	Deep ulcer between root of tongue and jaw on right.	12 × 2 mc.	Three months later cavity persisted. Radon again inserted. After 9 months no evidence of carcinoma in tongue. Secondaries in glands dissected out.

MOUTH.

No.	Age.	Duration.	Characters of Growth.	Dosage.	Result.
24	62	3 months	Indurated tumour at back of floor of mouth on left side. Mass of hard glands behind and below jaw on left. Trismus so that teeth could only be separated 1/2 in., but extensive ulceration over fauces on left side could be made out. Squamous carcinoma.	Access obtained to tumour by resection of left angle of lower jaw. 6 × 2 mc. Removal of glands	Rapid improvement. Softening of tumour and disappearance of ulcer. No recurrence discovered after six months.
25	63	18 months	Floor of mouth covered by fungating growth, which has penetrated tongue and appears on dorsum. Tongue enormously enlarged by growth. No glands. Squamous carcinoma.	6 mg. radium 6 days, 8 × 1.5 mc. seeds	Rapid disappearance of growth and reduction in size of tongue. Died 4 months, secondaries in glands.
26	55	3 months	Fungating carcinoma of posterior end of hard palate on right side, extending on to alveolus.	6 × 1.5 mc.	Entire disappearance of growth in 14 days. Well after 2 years.
27	72	15 months	Ulcerating carcinoma covering whole of hard palate on right side.	9 × 1.3 mc.	Oral part of growth disappeared, revealing perforation of palate. Died 5 months, local recurrence and secondaries.
28	69	3 weeks	Indurated ulcer in floor of mouth beneath tip of tongue, extending through jaw into substance of chin.	16 × 2 mc.	Complete disappearance of growth in 6 weeks. Well after 6 months.
29	63	2 months	Indurated tumour involving fauces and root of tongue on right side. Enlarged glands.	20 × 2 mc.	Severe reaction with great swelling and pain. Result doubtful.

BREAST.

EARLY CASES.

30	41	3 months	Small tumour in axillary quadrant of right breast. No enlarged glands. Tumour excised. Polygonal carcinoma.	77 mc.	Normal reaction. After 5 months an enlarged gland was felt in axilla. Remained stationary, 3 months later radon inserted as precaution. Well after 12 months.
31	51	1 month	Small hard irregular tumour in axillary quadrant of left breast. Tumour excised. Spheroidal carcinoma.	65 mc.	Normal reaction (12 months.)
32	51	2 months	Small hard tumour in axillary quadrant of right breast.	78 mg. radium 6 days	Disappearance of tumour in 2 months. (12 months.)
33	63	4 months	Small hard tumour in axillary quadrant of left breast. No glands.	78 mg. radium 6 days	In 2 months tumour much smaller. Later replaced by small soft swelling. (10 months.)
34	62	5 weeks	Tumour size of small orange in axillary tail of left breast.	40 × 2 mc. seeds	Rapid diminution in size. (Not traced.)
35	63	3 months	Small hard tumour in outer portion of left breast, adherent to skin.	50 × 2 mc.	Rapid disappearance of tumour. (11 months.)
36	34	3 months	Small hard nodule above right nipple. Local removal. Spheroidal carcinoma.	50 × 2 mc.	Normal reaction. (10 months.)
37	48	2 months	Early scirrhus carcinoma in outer portion of right breast.	50 × 2 mc.	In 2 months tumour replaced by soft indefinite swelling. Disappeared later. (11 months.)
38	44	18 months	Tense elastic tumour in upper inner quadrant of left breast. Removed locally. Carcinoma containing few cells.	50 × 2 mc.	Local result perfect, but followed by severe pain in shoulder. (8 months.)
39	74	6 months	Tumour 2 in. diameter in lower outer quadrant of left breast. Attached to skin.	50 × 2 mc.	Rapid softening of tumour. Local denudation of skin. (6 months.)
40	64	1 week	Small hard tumour below left nipple, attached to skin and deep fascia.	50 × 2 mc.	Rapid disappearance of tumour. (6 months.)

ADVANCED BUT OPERABLE CASES.

41	66	2 months	Indurated tumour attached to nipple, skin, and fascia, in lower half of right breast.	60 mg. radium tumour 5 days; 23 × 2 mc. seeds glands	In one month disappearance of tumour. Well after 16 months.
42	64	18 months	Ulceration of left nipple, which has now completely disappeared, and is replaced by an ulcer 1 in. diameter. (Paget.) Tumour in upper part of breast about 2 in. diameter attached to skin. Secondary glands in axilla.	64 mg. radium 9 days	In 3 months ulcer healed, glands disappeared, tumour soft but still present. Gradual disappearance. (15 months.)
43	61	6 months	Hard tumour 2 in. diameter in upper portion of left breast attached to skin. Enlarged axillary glands.	88 mg. radium 5 days	Tumour diminished in size. Not traced.
44	63	2 years	Hard irregular tumour in axillary quadrant of right breast attached to skin and fascia.	50 × 2 mc.	Rapid disappearance of tumour. Skin broke down from excessive reaction. (9 months.)
45	55	1 year	Rounded tumour in upper and inner quadrant attached to skin and fascia. (R.)	50 × 2 mc. seeds	Tumour did not respond. Removed 4 months later. Sections showed dense fibrosis and scattered areas of carcinoma cells. Denudation of skin showed that failure was not due to inadequacy of dose. (8 months.)
46	75	7 weeks	Large irregular mass in inner lower quadrant of right breast, attached to skin and fascia.	126 mg. radium 5 days	Tumour remained stationary in size. Skin over it broke down. (No change.)
47	44	2 months	Small hard nodule in lower outer quadrant of left breast, attached to skin and fascia.	30 × 1.5 radon seeds (gold)	Rapid disappearance of tumour, replaced by deep pucker of skin. Well for 15 months. Then local recurrence, and breast amputated.

INOPERABLE CASES.

48	50	2 years	Ten years ago complete Halstead of right breast. Recurrence over fourth and fifth right costal cartilages. Hard irregular tumour 1 1/2 in. diameter, involving skin and chest wall.	10 × 1.5 mc. seeds	Very rapid disappearance of tumour. Well after 11 months.
49	71	2 years	One year ago amputation of left breast for carcinoma. Early recurrence in scar. Now three hard nodules and pain and swelling in arm.	7 × 1.5 mc. into nodules	Nodules disappeared. Not traced.
50	59	4 years	Huge ulcerating carcinoma of left breast fixed to skin and muscles. Nipple destroyed, glands in axilla, secondary nodules in skin.	50 × 2 mc.	Rapid absorption of tumour, which was in 4 months replaced by scar. After 6 months recurrence in axillary glands. 20 × 2 mc. Silver seeds inserted. Glands disappeared. After 10 months swelling and paraesthesia in hand. No local recurrence in breast or axilla.
51	81	5 years	Ulcerating carcinoma in axillary quadrant of right breast, fixed to muscle.	50 × 2 mc.	In 3 months surface healed and growth replaced by fibrous mass. Well after 10 months.
52	56	10 months	Large ulcerated tumour in axillary quadrant of right breast. Fixed to deep tissues. Quite inoperable. Patient very ill.	50 × 2 mc.	Six weeks later whole tumour sloughed out; small granulating cavity left. Local success complete, but after 4 months secondary tumour appeared in frontal bone. Died after 5 months with very extensive secondaries. No local recurrence.
53	70	12 months	Large nodular tumour in axillary quadrant involving skin. Secondary glands.	50 × 2 mc.	Gradual shrinkage of tumour. Ulceration of involved skin. Well after 8 months.

OESOPHAGUS.

No.	Age.	Duration.	Character of Growth.	Dosage.	Result.
54	53	6 months	Carcinomatous stricture 12 in. from teeth.	6 × 1.5 mc.; dilated	Very marked improvement. Swallowed well for 8 months. 10 months—oesophagoscopy showed a dense stricture 1½ in. long, the walls of which were apparently formed of scirrhous carcinoma. Dilated up to 12 mm.; tube inserted. In the lumen of this tube were packed six needles containing in all 24 mg. of radium. They were left in for 4 days and then removed, the tube being left in place. Marked improvement. Lived 14 months.
55	61	4 months	Large growth 10 in. from teeth.	8 × 1.5 mc.	No improvement. 2 months, oesophagoscopy showed hard growth extending into pharynx. 8 × 1.5 seeds. Later, gastrostomy. Lived 7 months.
56	53	4 months	Carcinoma 15 in. from teeth.	8 × 1.5 mc.	Marked improvement. Swallowed well for 5 months. Recurrence at 6 months. Gastrostomy. Lived 14 months.
57	54	4 months	Carcinoma 10 in. from teeth.	7 × 1.5 mc. Tube	Marked improvement. Recurrence at 5 months. Oesophagoscopy. Infiltrating growth 2 in. above level of tube. (Post-mortem, perforation of aorta by growth.) Lived 5 months.
58	76	6 months	Carcinoma 10 in. from teeth.	8 × 1.5 mc.	No improvement. Not traced.
59	72	4 months	Carcinoma 10 in. from teeth. Condition of patient desperate.	8 × 1.5 mc.; dilated	Very marked improvement. Swallowing almost normal. At 6 months radiogram showed definite obstruction at level of hilum, but still swallowing well. Lived 9 months.
60	53	10 weeks	Obstruction above cardia, also obstruction 10 in. from teeth.	6 × 2 mc.	Marked improvement. Two months later developed pyloric obstruction. Lived 2 months.
61	49	5 weeks	Ring carcinoma 12 in. from teeth.	8 × 1.5 mc.; dilated	Very marked improvement. After 7 months cerebral embolus. Lived 7 months.
62	59	5 weeks	Large growth in anterior wall.	15 × 3 mc.; dilated	Marked improvement. Lived 10 months.
63	69	2 months	Carcinoma 2½ in. above cardia.	11 × 2 mc.; dilated	Improvement. Lived 2 months.
64	51	9 months	Growth encircling oesophagus 12 in. from teeth.	9 × 2 mc.	Marked improvement. Living after 5 months.
65	58	7 months	Fungating carcinoma 12 in. from teeth.	10 × 2 mc.; dilated	Improvement. Living after 4 months.
66	62	12 months	Large tumour in anterior wall.	10 × 2 mc.	No improvement. Not traced.
67	60	6 months	Large fixed ulcer in anterior wall. Dilatation impossible.	12 × 2 mc.	Very marked improvement. Well after 4 months.
68	61	5½ months	Round disc-like growth on posterior wall 12 in. from teeth, below this encircles wall. Dilatation impossible.	6 × 2 mc.	No improvement. Not traced.
69	49	4 months	Large growth completely obstructing lumen.	12 × 2 mc.	Improvement. Not traced.
70	55	4½ months	Fungating irregular nodular growth extending across oesophagus 13 in. from teeth.	12 × 2 mc.	Marked improvement, but intubation required later.
71	71	6 months	Large fungating growth 8 in. from teeth.	12 × 2 mc.	Marked improvement. Well after 3 months.
72	70	4 months	Carcinomatous stricture 8 in. from teeth, another much narrower just below.	12 × 2 mc.; dilated	No improvement.
73	56	6 months	Carcinomatous stricture 10 in. from teeth. Nodular growth extending for about 2 in.	10 × 2 mc.	Improvement. Gastrostomy later. Lived 4 months.
74	60	4 months	Tumour 17 in. from teeth bulging into oesophagus from left side. Condition of patient desperate.	8 × 1.5 mc.	Very marked improvement. 6 weeks later swallowing normal. X-ray, apparently normal oesophagus. Swallowing normal for 9 months. Then recurrence of dysphagia. Oesophagoscopy. Secondary nodules 6 in. above site of original growth. 10 × 2 seeds. Immediate improvement. (Haemorrhage.) Lived 11 months.
75	60	6 months	Fungating carcinoma at middle of oesophagus.	8 × 1.5 mc.	Marked improvement. Lived 3 months.
76	53	18 months	Fungating carcinoma 12 in. from teeth.	10 × 2 mc.	No improvement. Lived 2½ months.
77	42	8 months	Nodular carcinoma encircling oesophagus, 18 in. from teeth.	12 × 2 mc.	Marked improvement. Well after 8 months.
78	77	3 months	Carcinomatous stricture 12 in. from teeth.	12 × 2 mc.	Improvement. Lived 4 months.
79	56	4 months	Nodular carcinoma 12 in. from teeth.	12 × 2 mc.	Remarkable improvement. Swallowing normal for 8 months. Recurrence of obstruction after 8 months. Localized fungating carcinoma at same site. Radon again inserted.

VARIOUS.

No.	Age and Sex.	Duration.	Characters of Growth.	Dosage.	Result.
80	M. 60	1 year	Indurated nodular carcinoma of lesser curve of stomach extending on to posterior wall.	18 mg. radium for 6 days	Improved at first. Died after 6 weeks from peritonitis. Post mortem, tumour had disappeared and was replaced by a large chronic ulcer involving liver and pancreas.
81	F. 72	5 weeks	Nodular growth involving both lobes of thyroid, attached to skin and compressing oesophagus.	20 × 2 mc.	10 days complete disappearance of growth and of pressure symptoms. No local recurrence. Died 7 months later from secondary deposits in liver.
82	F. 58	1 month	Spontaneous fracture. Large tumour replacing neck of right femur. Sections: columnar carcinoma of intestinal type.	8 × 1.5 mc.	Size of tumour rapidly diminished, bone united. 5 months later, reappearance of tumour. 50 × 2 radon seeds. Tumour diminished in size and pain reduced. One year later leg soundly united. No local recurrence, but secondaries in spine.
83	M. 68	9 months	Large mass of carcinoma in right anterior triangle of neck extending deep to jaw. Gross sepsis.	30 × 2 mc.	Very temporary improvement. Essentially a hopeless case.
84	M. 62	1 year	Large tumour in upper part of anterior triangle of neck. (L.)	31 mg. radium for 5 days	Swelling reduced in size and pain entirely disappeared. Four months later recurrence of swelling and pain.
85	F. 45	4 months	Hard ulcerated mass on posterior surface of rectum, 3 in. diameter; absolutely fixed to sacrum.	30 × 2 mc.	Rapid diminution in size of tumour, which was replaced by a firm fibrous nodule. 11 months later, small local recurrence. 14 × 2 mc. Well after 16 months.

The cases show that, as a rule, carcinoma of the breast readily responds to radium, both in the primary tumour and in secondary deposits. In inoperable cases brilliant local results may be expected, but as in these cases the ultimate outlook depends on the existence of secondary deposits, local disappearance must not be interpreted as cure. In operable cases we feel that the results so far obtained justify the use of radium by the method we have indicated. In these cases, however, it is of the utmost importance that they should be kept under the closest observation, so that any recurrence may receive immediate attention. The treatment of carcinoma of the breast by radium must at present be regarded as in the experimental stage, although personally we regard the experiment as a very hopeful one.

The Oesophagus.—Carcinoma of the oesophagus is at the present time, and perhaps essentially, an incurable condition, and one can only aim at enabling the patient to swallow. The 26 cases here reported show beyond question that in a large proportion of cases this can be achieved by means of radium, giving relief for periods up to fourteen months. In 15 of these cases the relief was such that the patient could swallow soft solids with ease, and in 4 he returned to an almost normal condition; in 5 other cases there was definite improvement. There is thus no doubt that carcinoma of the oesophagus responds readily to radium introduced by this technique. We may have been unduly cautious in dosage, but those who are familiar with the direct examination of these cases will realize the risks involved. We can happily claim that no untoward event has followed on the operation in any instance, so that in skilled hands the method would appear to be reasonably safe.

Various Sites.—These were all experiments in otherwise hopeless cases. In 3, however, there was very striking improvement and relief over a long period. In many ways Cases 81 and 82 showed the most remarkable results in the whole series, although followed later by secondary deposits. In the case of carcinoma of the rectum the tumour has entirely disappeared, and the patient is in perfect health after sixteen months.

THROMBO-ANGIITIS OBLITERANS IN NON-HEBREW SUBJECTS, AND REPORT OF A CASE OF CHRONIC ULCUS CRURIS IN A YOUNG MAN.

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A CONSIDERABLE proportion of cases of thrombo-angiitis obliterans have been reported during recent years as occurring in Great Britain and Ireland, in English, or at least non-Hebrew, families.* The following men were recently almost simultaneously in-patients at the German Hospital, and their symptoms present certain special points of interest. The first two are certain cases, the third one is altogether doubtful.

CASE I.

An Englishman (no Hebrew ancestry), aged 22 years, was admitted on July 24th, 1929, on account of cyanotic discoloration of the region of the left great toe, and pain and symptoms typical of thrombo-angiitis obliterans dating from January, 1928. In other respects the patient appeared healthy, and his Wassermann reaction was negative. From the age of 16 he had been accustomed to smoke cigarettes up to twenty daily.

On September 7th, 1929, a modification of periarthral sympathectomy was performed on the left thigh by Mr. Wright during Mr. Rast's absence. The operation was followed by an immediate rise in the superficial temperature of the affected limb and by diminution of pain, but the improvement was not lasting, nor was the result of diathermy really satisfactory. Although slight "mummification" developed at the tip of the left great toe, the condition is now rather better than worse, and amputation has not yet been resorted to. The clinical picture is the typical one seen by us in Hebrew cases, but the patient's age is younger

than that of most Hebrew sufferers. Though the local condition in this case is very bad, it was almost as bad for a long while in one of the earliest of Dr. Weber's Jewish cases of the kind—a man who is still living and has all his limbs.*

CASE II.

An English assistant in a drug factory, without any Hebrew or foreign ancestry, and aged 38, was admitted on June 1st, 1929, with a large chronic deep ulcer, like a tabetic "perforating" or pressure ulcer, about the size of a penny, at the back of the right heel. This had started as a mere crack in the thick skin in February, 1928, and had gradually enlarged since then; so far as the patient himself knew there had been no traumatic or other cause for its commencement. He compared the pain in his right heel and right calf with that of a toothache. For about six months before the appearance of the ulcer there had been pains in the calf of the right leg on walking; these were of the usual intermittent claudication type, as in typical Hebrew cases of thrombo-angiitis obliterans. The patient had been a great smoker in the army during the war. Before the commencement of the ulcer there had likewise been attacks of pallor and numbness in the toes of the right foot, but otherwise the patient had enjoyed good health.

No pulsation was felt in either arteria dorsalis pedis. Apart from the thrombo-angiitis obliterans we found no abnormal symptoms by examination of the thoracic and abdominal viscera, the nervous system, the eyes, and the blood and urine. The brachial blood pressure was 135/75 mm. Hg. The Wassermann reaction was negative. The knee-jerks were rather active. Warm weather somewhat lessened the pain. On July 9th, 1929, Dr. A. P. Cawadias examined the patient's limbs with Pachon's oscilometer, and found the oscilometric index as follows:

		Right side	Left side
Calf of leg	...	0	1½
Thigh	...	6	6
Upper arm	...	5½	5½

Both legs therefore showed arterial ischaemia.

After treatment by insulin and other methods—including periarthral sympathectomy on August 30th—had been tried in vain, Mr. Rast resorted to amputation of the right leg on September 14th; owing to gangrene in the stump a second amputation had to be performed on September 21st through the middle of the thigh. The patient left the hospital on October 18th in good condition, though he still had a little pain "in the amputated limb." Since then he is reported to have been doing well. On macroscopic and microscopic examination of the parts from both amputations the arteria tibialis anterior seemed normal, but the arteria tibialis postica appeared to be rather small, and was blocked by a canalized thrombus. The popliteal artery (removed at the second amputation) was blocked by more recent, partly organized, thrombus.

In this case the deep ulcer at the heel was an unusual early symptom in thrombo-angiitis obliterans. In the hospital at the same time with this patient was a somewhat older man, aged 50, complaining of a chronic callous ulcer under the left great toe, but his blood serum gave a strongly positive Wassermann reaction, and antisyphilitic treatment led to an excellent result. It is interesting that in the older man the pulsation in the arteria dorsalis pedis on both sides was excellent, and by Pachon's oscilometer Dr. A. P. Cawadias found the "oscilometric index" at the right calf to be 4, against 5 at the left calf, suggesting that the chronic ulcer in the left foot had increased the blood supply on the left side and had made the "oscilometric index" somewhat greater in the left than the right leg.

CASE III.

An Englishman, aged 25 years (without any Hebrew or foreign ancestry), was admitted on May 8th, 1928, on account of a large indolent chronic ulcer on the left leg, with much pigmentation in the neighbourhood; on the other leg he had similar pigmentation and scars of previous ulcers. He said he had never had any decided varicose veins, and the leg ulcers had first developed after pneumonia about the winter 1925-26. He was of slender build and rather pale, but otherwise apparently healthy. He mentioned that he had been accustomed to smoke about twelve cigarettes daily since the age of 16. There was nothing special in the family history, except that his father had suffered from chronic ulcers on both legs for thirty years before his death at the age of 66. Examination of the thoracic and abdominal viscera, nervous system, eyes, urine, and blood revealed nothing abnormal, and the Wassermann reaction was negative. A periarthral sympathectomy in the left thigh in February, 1927 (at another hospital), had done no good.

After prolonged rest in bed, and the failure of a variety of methods of treatment, Mr. Rast, at the patient's urgent request,

* See, for instance, Telford and Stopford, *British Medical Journal*, 1924, ii, p. 1035; Sir W. I. de Courcy Wheeler, *ibid.*, 1927, i, p. 225; Marnoch and MacRae, *Journ. Path. and Bact.*, 1927, vol. 30, p. 39; R. O. Girdwood, *ibid.*, 1927, vol. 30, p. 643; Girdwood, *ibid.*, 1928, vol. 31, p. 549.

* F. Parkes Weber, *Lancet*, 1908, i, p. 152; 1925, ii, p. 21.