RADIUM

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A MONTHLY JOURNAL DEVOTED TO THE CHEMISTRY
PHYSICS AND THERAPEUTICS OF RADIUM
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Edited and Published by Charles H. Viol, Ph. D., and William H. Cameron, M. D., with the assistance of collaborators working in the fields of Radiochemistry, Radioactivity and Radiumtherapy.

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VOL. V. MAY, 1915 No. 2

THE WORK CARRIED OUT AT THE RADIUM INSTITUTE, LONDON, IN 1914.†

BY A. E. HAYWARD PINCH, F.R.C.S.,

MEDICAL SUPERINTENDENT.

This report deals with the cases which presented themselves at the Radium Institute from January 1st, 1914, to December 31st, 1914, inclusive. The cases treated were in no instance selected. The only cases refused have been those in which the patients were practically moribund, or in which the disease was of a kind for which radium therapy was manifestly unsuitable. No examples of malignant disease—rodent ulcer alone excepted—have been treated other than those in which operation had been declared to be unjustifiable, or in which operation had been absolutely declined by the patient.

The term "apparent cure," used in relation to cases of malignant disease, must be interpreted as representing a condition in which all trace of the original lesion or lesions has disappeared, in which there is no sign of any recurrence, and in which the patient is, so far as can be determined by a thorough and careful examination, free from any indication or symptom of the disease.

Cases have been classed under the heading "improved" only when the result of treatment has been to produce a definite and marked degree of benefit, either in the direction of retardation of the progress of the disease, diminution in the size of a growth, healing of ulceration and arrest of hæmorrhage and discharge, or of relief to such subjective symptoms as itching, tenderness, pain, dyspnoea, and dysphagia.

The character of this report is in many respects similar to that of the reports previously published in 1913 and 1914.*

†British Medical Journal, Feb. 27, 1915, p. 367. An abridged form of the report.

*British Medical Journal, 1913, p. 149; and 1914, p. 1107. Copies of the full text of this report can be obtained by medical men on application to the Medical Superintendent at 16, Riding House Street, London, W. The second Report was quoted almost in its entirety in Radium, vol. 3, p. 49, 1914.

SUMMARY OF CASES:

Examined, but not treated	95	231
Recently treated, and results not yet noted	136	
Received prophylactic irradiation only	16	16
Apparently cured	50	397
Cured	19	
Improved	328	
Not improved	158	
Abandoned treatment	11	197
Dead	28	
	841	841

APPARATUS.

Radium may be used in the treatment of disease either in the form of radium salts or radium emanation, the therapeutic effects being identical.

(*a*) *Radium salts* are contained in—

1. Flat varnished applicators, rectangular, square and circular, their superficial area ranging from 0.7 sq. cm. to 28 sq. cm. Consideration must be paid to the concentration of the radium salt per unit area, as well as to the purity of the salt. The unit of concentration adopted consists of a centigram of radium bromide spread over a square centimetre. Applicators containing radium salts to this extent of concentration are said to be "full strength" applicators; similarly, "half" and "quarter" strength applicators contain respectively 0.5 and 0.25 cg. of radium bromide to each sq. cm. Radium bromide* has been accepted as the unit of measure for describing the content of radium applicators, but as it is readily soluble it is most unsuitable for fixing to applicators by means of varnish, or for filling tubes. It is therefore always converted into sulphate. The smallest applicator contains 7 mg., the largest 150 mg.

2. Capillary glass tubes, filled with radium sulphate, closely packed so as to prevent any movement of the salt. Their length varies from 2 to 4 cm. and their diameter 0.2 to 0.3 cm. The amount of radium sulphate contained is the equivalent of 25, 30, 50, 60, or 100 mg. of radium bromide.

(*b*) *Radium emanation.* This may be collected in glass tubes or metal containers, and used with appropriate screens, as the radium salts themselves, or dissolved in distilled water or a weak saline solution, and administered by drinking or injection.

Emanation applicators are often of the greatest value in the treatment of malignant growths, as in them it is possible to concentrate the activity per unit area to a very high degree. For example, the 100 mg. tubes of radium sulphate used in the Institute measure 4 cm. in length by 0.2 cm. in diameter. It is quite easy to make an emanation tube of equal activity measuring only 0.6 cm. in length by 0.13 cm. in diameter. Such a tube can be enclosed in an iridium pointed platinum needle with walls of 0.3 mm. in thickness, thus forming a very small but extremely powerful apparatus for the treatment of nodules in tongue, palate, breast, or other organs. Radium emanation falls to half-strength in 3.85 days, losing 16 per cent. of its initial activity during the first twenty-four hours.

The duration of an exposure rarely exceeds twenty-four hours, and if it be decided to give a treatment for that time with a radium emanation

*Radium element is the standard in America. To express radium bromide in terms of radium element, multiply by 0.536. Thus 100 milligrams of radium bromide contain 53.6 mgm. radium element. Ed.

applicator of, say, 100 mg. strength, the apparatus leaves the laboratory with an initial activity of 109 to 110 mg. At the end of twenty-four hours its activity will have fallen to 92 to 93 mg., so that its mean activity throughout that period will have been approximately that of 100 mg.

Screens.

The screens employed as filters for the various rays are:

(*a*) *Aluminium.*—0.01, 0.02, 0.04, 0.08 mm. thick. These are principally used with short exposures in the treatment of capillary naevi, pruritus, neuro-dermatitis, and superficial skin lesions.

(*b*) *Silver.*—0.5 and 1 mm. thick. These are most useful as screens for the glass tubes of radium when introduced into tumors, and also in the treatment of keloid and vicious cicatrices.

(*c*) *Lead.*—0.1, 0.2, 0.4, 0.5, 1, 1.5, and 2 mm. thick. Screens less than 0.5 mm. in thickness are valuable in the treatment of flat superficial epitheliomata, leucoplakia, fibromata, and granulomata.

(*d*) *Platinum.*—0.3 and 0.5 mm. thick, chiefly employed as screens for small powerful emanation tubes.

Radium salts, when in equilibrium with the emanation produced from them, give out three kinds of ray:

The alpha ray is particulate. The particles lose their velocity, and therefore their activity, in a few centimetres of air, and will be completely absorbed by a very thin screen of aluminium (about 0.01 mm.). As the layer of varnish in most applicators is more dense than this amount of aluminium, it follows that the alpha rays are completely stopped by it, but the coats of varnish gradually become permeable, due partly to minute cracks, which spread throughout the layers, and partly to the absorption of emanation by the varnish, so that in course of time an applicator emits alpha rays.

The beta rays, far more penetrating than the alpha rays, consist of negatively charged bodies projected with velocities of the same order as the velocity of light. Their velocity varies considerably, and are distinguished by the terms "soft beta" and "hard beta." A considerable variety of screens is used, according to the nature of the radiation required.

The gamma rays are extremely penetrating, and are somewhat analogous to the very penetrating Roentgen rays. With the screens used at the Institute none of the gamma rays are absorbed.

Secondary Rays.—The use of thick screens of heavy metal is accompanied by the production of secondary rays, capable of causing considerable surface irritation. They may be absorbed by the use of many layers of black paper or thick rubber tubing.

Duration of Applications (Exposures).

Very short exposures of one to ten minutes, according to the age of the patient and the character of the lesion, are principally used in the treatment of superficial skin troubles. The apparatus is applied without any screen beyond that afforded by a covering of thin rubber sheeting.

Short exposures of fifteen minutes to one hour are most frequently resorted to when treating warts, senile keratoma, some forms of naevi, shallow ulcers, lupus erythematosus, etc. The screening in these exposures rarely exceeds 0.02 mm. of aluminium.

Moderately long exposures of one to twelve hours are adopted when it is desired to obtain the destructive action of the rays, and used in cases of rodent ulcer, rapidly growing epithelioma, lupus vulgaris, etc. Exposures of three hours' duration and upwards are usually spaced over a period of two or three days, and no screening or a screening of 0.1 mm.

lead employed.

Prolonged exposures of twenty to one hundred hours are used in the treatment of deep-seated malignant growths, in cancer of the rectum, uterus, breast, etc. Lead screens are always employed, usually of 2 mm. thickness. Exposures are given in periods of six to twelve hours, with an interval of at least twelve hours between successive exposures.

Screens and Appliances.—A varnished applicator is always covered with a thin layer of rubber sheeting to protect it from contact with any excretions or moisture, and avoiding the necessity of repeatedly cleaning the apparatus.

Method of Application.—The lesion is gently cleaned and dried, and all crusts or flakes of secretion removed. The healthy skin and tissues surrounding the lesion protected by a layer of lead-rubber sheeting, an aperture being cut in it the exact size and shape of the lesion. For external lesions the apparatus is best fixed in position with some non-irritant adhesive rubber plaster. To retain tubes in the vagina or uterus a tampon or gauze packing is generally necessary. In the rectum, bladder, oesophagus, nasal and buccal cavities, the apparatus is attached to a handle of pliable silver wire, which can be bent and fastened to the gluteal fold, cheek, or ear by adhesive plaster.

THE REACTION.

All tissues when treated with radium respond in some manner, but the nature and extent of this response vary very greatly, and depend upon:

1. *The apparatus, screening, and dosage employed.*
2. *The nature of the tissue treated.*
3. *The condition of the tissue treated.* If x-rays, ionization, CO_2 snow, etc., have been previously used in the attempts to bring about a cure, the reaction in such cases is frequently atypical, and repair is exceedingly slow.
4. *The extent of the area treated.* The reaction from an applicator of half strength applied over an area of 4 sq. cm. is often not more intense in degree than that obtained with an applicator of quarter strength over a surface area of 16 sq. cm.
5. *Personal idiosyncrasy.* This is often productive of puzzling results. Factors to be considered are age, sex, and temperament, susceptibility to actinic rays generally—for example, persons who suffer much from freckling or solar eczema—hyperidrosis, exalted vasomotor sensibility, etc.

Nature of Reaction.—The reaction usually appears between the seventh and fifteenth days, and four degrees may be clearly distinguished: (1) Simple erythema. (2) Erythema followed by desquamation. (3) Vesication with superficial ulceration. (4) Deep ulceration, sometimes accompanied by the production of an eschar.

Cases of capillary naevi have been seen in which, instead of the reaction appearing on about the seventh or eighth day, it has been evident three days after the exposure. In others a period of four weeks has elapsed before any effort has been perceptible, though in all of these cases the applicators employed, the screening, and the times of exposure have been identical. A very marked condition of lethargy is frequently noted in patients receiving prolonged exposures with large quantities of heavily screened radium. It generally makes its appearance about the fourth day of the treatment, and passes off within a few days of the cessation of the exposures.

CARCINOMATA.

Squamous Celled (*Epitheliomata*).—Surgical measures are always to be preferred to radium treatment in those cases where a complete and wide excision of the growth is practicable; but if operation be impossible or the patient refuses to submit to it, radium will often prove of great service, and in some instances, if glabrous surfaces only be affected, will bring about an apparent cure. Heavy dosage must be resorted to, however, and the resultant reaction carefully observed, as an irradiation of insufficient intensity may act as a powerful stimulus to the lesion.

Epitheliomata of the face, trunk, or extremities, if flat and superficial and accompanied by little or no ulceration, give satisfactory results when treated with quarter or half strength apparatus, screened with 0.1 mm. of lead, the exposures varying from six to twelve hours' duration, spread over a period of three or four days. The retrogression of the growth is quickly brought about and little or no scarring results.

Ulcerating epitheliomata, without much subjacent infiltration, require treatment with quarter or half strength apparatus applied unscreened for a total exposure of two to six or eight hours, spread over a period of four or five days, and repeated after an interval of six weeks, if necessary. A destructive reaction follows, but the result is usually quite good, and there is but little cicatricial contraction.

Ulcerated epitheliomata with great infiltration require prolonged treatment with heavily screened apparatus emitting only hard beta and gamma—the so-called "ultra-penetrating"—rays. Exposures of thirty to sixty hours given during one week and repeated in five or six weeks' time are best, but if the growth shows signs of rapid extension the borders should be given a vigorous treatment with unscreened apparatus.

Epitheliomata of the buccal, lingual, and pharyngeal mucous membranes usually prove both refractory and disappointing in their response to radium, but a new method of treatment has been devised, which in instances of cancer of the tongue has given somewhat encouraging results; it consists in the burying within the carcinomatous nodule of a very small but intensely powerful radium emanation tube possessing an initial activity equivalent to that of 80 to 100 mg. of radium bromide, enveloped in a screen of 1 mm. of silver or 0.3 mm. of platinum, and giving an exposure of twenty-four hours duration. A fairly severe reaction follows, and in some cases the nodule ceases to grow and becomes replaced by dense fibrous tissue.

Unfortunately, however, the treatment appears to have but little effect in arresting the dissemination of the disease, which sooner or later affects the neighbouring lymphatic glands or recurs close to the original lesion. The rate of growth of the infected glands can often be retarded by the prolonged and persistent use of the "ultra-penetrating" rays. If the dose given be a large one the glands sometimes break down and discharge a milky-white fluid through a small sinus, and it is remarkable that ulceration of glands thus treated rarely occurs.

Considerable difficulty is experienced in giving satisfactory exposures within the oral cavity, as patients are often unable to tolerate the presence of applicators in their mouth for the necessary length of time, and should the reaction be at all pronounced the congestion of the tissues occasions great discomfort. There is the further danger that a severe reaction may act as a stimulus to the original growth, increase its size, and hasten metastasis.

Some cases of epithelioma of the oesophagus have been under treatment, but unfortunately the majority of these have been in so advanced

a stage as to preclude all hope of success. In those instances, however, in which complete occlusion had not occurred—and it was possible to introduce radium actually into the lumen of the growth—distinct, though temporary, benefit has resulted; and that this effect is not merely mechanical, due to the dilatation of the stricture by the apparatus, is evidenced by the fact that the improvement in the power of swallowing has persisted for six or even nine months after the termination of the treatment.

Carcinoma of the Uterus.—Uterine cancer continues to yield most gratifying results, and the effects of radium treatment in operable cases are far in advance of those obtained by any other known medical or surgical methods. The local manifestations of the disease are benefited in the most striking fashion, and the complete disappearance of fungating growth, arrest of hæmorrhage and discharge, healing of ulceration and relief from pain are phenomena of frequent occurence. In favorable cases, moreover, the treatment appears to exert a distinctly retarding influence on the dissemination of deposits, and thus to arrest the progress of the disease. It is not possible, however, to speak of "cure" even in these latter instances.

The routine treatment consists of thirty hours' exposure—five days, six hours a day—to a 100 mg. tube screened with 2 mm. of lead and 3 mm. of rubber applied per vaginam, supplemented by a plate of 70 to 100 mg. activity screened in similar fashion and applied over the pubes. In this way a powerful and effective cross-fire irradiation of the affected parts is obtained.

Small isolated nodules in the vaginal walls, recurrent after hysterectomy and inoperable, respond very well to treatment with large doses heavily screened, and not infrequently cease to grow, contract, and become replaced by fibrous tissue.

Great care must be exercised in the treatment of recurrences which make their appearance within six months of the performance of a Wertheim's operation. The functions of the trophic nerves of the pelvis seem often to be impaired seriously by the extensive and elaborate dissection which is associated with this method of hysterectomy, and for this reason the amount of radium used should be small, not exceeding 50 mg., the screening not less than 1.5 mg. of lead, and the total exposure not longer than twenty-four hours spread over four or five days. Unless these precautions be observed a severe and extensive destructive reaction may follow the application of radium. In all cases in which radium has been applied within the vagina, the patient should be instructed to douche freely night and morning for at least six weeks after the termination of the treatment, as unless this be done an adhesive vaginitis not infrequently occurs. In some extremely susceptible subjects a transient proctitis has been noted to follow upon intravaginal treatment.

The number of cases of carcinoma of the uterus treated to a conclusion was 27; of these, 1 was apparently cured, 17 improved, 7 not improved, and 2 died. Detailed reports are given of 4 cases. In one of these, inoperable when first seen by a surgeon, the patient, aged 34, two years after beginning radium treatment, was very greatly improved, fibrosis having apparently arrested the disease. In 2 cases of recurrence after abdominal hysterectomy very good results were obtained.

Carcinoma of Bladder.—Six cases of this disease have been treated, and in two instances the results have been most gratifying. The hæmaturia, cystitis, and all subjective symptoms have disappeared, and cystoscopic examination has shown that the size of the growth has been greatly

lessened, and any ulcerated surface has become covered with healthy epithelium.

The treatment has consisted of the introduction of a 50 mg. tube of radium bromide in a "window" screen of 1 mm. of silver and 1 mm. of lead inserted per urethram, and maintained by means of a pliable silver wire in such a position that the window side of the apparatus is in actual contact with the growth. If the lesion be on the base of the bladder, a second tube screened with 2 mm. of lead is placed in the vagina in female, or in the rectum in male patients; but if on the interior bladder wall, a flat applicator, similarly screened, is fixed over the pubic region. The usual length of exposure is ten hours intravesically in five daily applications of two hours each, and thirty hours with the vaginal, rectal, or pubic applicators, spaced over the same days.

Carcinoma of the Breast.—The number of patients with this disease applying for treatment far exceeds that of any other malignant condition. The policy of declining to treat operable cases is still rigidly adhered to—unless the patients have absolutely refused to submit to operation, and radium is used as a last resource.

The progress of inoperable, slow-growing cases of the atrophic type is usually much retarded by the use of radium, especially when the metastases are confined to the skin, axillary, and supraclavicular lymphatics and do not affect the lungs or abdominal viscera.

Very small isolated cutaneous nodules on the chest wall, if few in number, may be effectively treated by unscreened exposures of one or one and a half hour's duration with a half-strength radium plate. If very numerous and closely set, prolonged exposures of thirty to forty hours' duration to heavily screened rays are preferable, and this method of treatment should also be resorted to for the primary growth, infected glands, or ulcerated surfaces if such exist.

Superficial ulcerations unaccompanied by much subjacent induration are peculiarly susceptible to the action of radium, and complete healing of these lesions is frequently observed. Isolated recurrent nodules—inoperable by reason of their attachment to the sternum, clavicle, ribs, or rib cartilages—are best treated by burying a small powerful emanation tube, screened with 1 mm. of silver in them, for a period of twenty-four hours.

Little or no effect appears to be exerted in the prevention of metastatic deposits, though the treatment does not, at any rate, hasten their dissemination. Some cases in which pleurisy or ascites, dependent upon carcinomatous invasion of the pleura or peritoneum, has been present have shown remarkable improvement, and the application of powerful apparatus screened with 2 mm. of lead over the affected pleura or peritoneum, after a preliminary paracentesis, has effectually prevented the further formation of effusion.

A few patients have been under treatment at intervals of three or four months since the opening of the Institute in August, 1911, and it has been observed that a stage in their treatment is reached sooner or later at which the response to radium fails, and the benefit derived becomes negligible.

In rapidly growing carcinoma of the medullary type radium can do very little except relieve pain, even though enormous doses be employed.

The number of cases of cancer of the breast was 67; of these 1 was apparently cured, 40 were improved, 17 not improved, 1 abandoned treatment, and 8 died. Nine cases are related at length. In one of these

the right breast had been removed and the axilla cleared on March 31st, 1911. In July, 1913, she began to suffer from pain in the upper part of the abdomen, and the surgeon she consulted diagnosed inoperable recurrence in the omentum. Ascites subsequently developed and required paracentesis. When seen on February 16th, 1914, ill-defined nodules could be felt immediately under the abdominal wall in the epigastric and left hypochondriac regions. She was treated from February 23rd to 27th inclusive, having six hours' exposure each day with flat applicators containing 350 mg. of radium, screened with 2 mm. lead over the epigastric and left hypochondriac regions. The pain diminished, and when seen on May 4th the ascitic fluid accumulated more slowly. The treatment was repeated, and on July 27th great improvement was apparent. The treatment was then repeated on five days. On October 16th, when last examined, the improvement was maintained, abdominal pain had ceased, she had gained altogether 21 lb. since May, and had a good colour.

In another case of local recurrence an emanation tube with initial activity 45 mg. screened with 1 mm. silver was buried in the nodule for twenty-four hours. When seen on April 6th no trace of the nodule remained, and the patient subsequently kept perfectly well.

Another case, in which two and a half years after *Halsted's* operation there was thickening of the anterior wall of the axilla and induration in the left supraclavicular fossa, was treated with 250 mg. radium, screened with 2 mm. lead, and disposed so as to secure cross irradiation from February 16th to 20th inclusive, six hours on each day; on April 2nd her surgeon stated that the induration had disappeared, and she has since been perfectly well. In another case, two years after excision a large, hard tumor occupied the left mammary region and presented an ulcerating area, the patient improved rapidly under radium treatment, and the ulcer healed. After five treatments during a year scarcely any induration could be felt, and a sixth was given. Since then there has been no further evidence of the disease, and the patient is in good health.

Carcinoma of Rectum.—The adoption of radium therapy in inoperable cases of this disease is usually justified by the results obtained, though the amount of benefit is rarely so marked or so great as in carcinoma of the uterus.

The disease displays much variation in its response to radium, and numerous factors have to be considered in prognosis. Speaking generally, the soft annular and vascular type of growth is much more favourably affected than the flat, hard, non-annular plaque with much subjacent induration. In the treatment of this latter class of growth the action of the gamma rays (which it is impossible to prevent) on the healthy rectal mucous membrane opposite the plaque produces a proctitis which, though generally transient, sometimes proves both persistent and severe, and adds greatly to the patient's discomfort. In the treatment of the former type, if the radium tube be of proper dimensions and introduced accurately within the lumen of the growth, little or no healthy mucous membrane is affected by the gamma rays, and no proctitis occurs.

Growths situate in the upper half of the rectum appear to be more amenable to treatment than those in the lower, though this may be due to the fact that tenesmus is always more constant and severe when the growth is near the sphincters.

The performance of colostomy before radium treatment is often advisable, as the constant passage of faeces over a surface that is reacting to radium frequently causes much pain. Idiosyncrasy is sometimes responsible for curious results. Some patients are extremely susceptible to

the action of radium, and proctitis appears quickly, is very severe, and persists for a long time. With others the reaction takes six or eight weeks to develop, proceeds exceedingly slowly, and does not disappear for two or three months.

The routine method of treatment consists of a thirty hours' exposure —six hours on each of five consecutive days—with a tube containing 100 mg. of radium screened with 2 mm. of lead and 3 mm. of rubber, and applied in actual contact with the growth. This is frequently supplemented by a flat plate containing 80 mg. of radium screened in the same way, and applied over the sacrum at the level of the tumor.

In two or three instances growths treated in this manner which were considered inoperable before radium was resorted to have been so much diminished that their removal has been successfully accomplished. In some other cases where the disease is of the annular type, the carcinomatous material shrinks, and is replaced by fibrous tissue forming a stricture which may need frequent and regular dilatation.

The treatment of 29 cases of carcinoma of the rectum was completed during the year; of these, 22 were improved and 7 not improved. Two cases are reported at length, in both of which the improvement brought about rendered it possible to perform an operation.

Carcinoma of Prostate.—The number of cases of this condition which have been treated up to the present is not very large, but benefit has been noted in all of them. Hæmaturia, when existent, has been either diminished or abolished, pain has been greatly lessened, and the size of the growth decreased. Various methods of treatment have had to be adopted according to the nature of the case. When catheterization can be well tolerated, a 50 mg. tube of radium in a "window" screen of 1 mm. of silver and 1 mm. of lead is introduced per urethram, and maintained in actual contact with the growth for a period of two hours a day on five successive days, and its action is supplemented by another tube of 100 mg. in a screen of 2 mm. of lead, introduced into the rectum for six hours a day on five successive days.

When catheterization is not practicable or advisable, the action of the rectal tube is reinforced by a powerful flat applicator screened with 2 mm. of lead, and placed either on the perineum or over the pubes.

Two cases of carcinoma of the prostate were treated during the year, with improvement in both. In one case, reported at length, three treatments were given at intervals of three months. When first seen in April a large, very hard, firmly fixed mass was projecting into the rectum. In October the mass was reduced to one third of its former size, and was much softer. At the end of the year he had regained his normal weight.

Rodent Ulcer.

Of all forms of malignant disease this is the one which is most amenable to radium treatment.

For the purpose of prognosis it appears justifiable to divide rodent ulcers into two definite clinical types:

1. The hypertrophic nodular type, with slight superficial ulceration of a scaly character. This class responds extremely well to radium, and yields most satisfactory results.
2. The excavating type, with undermined and overhanging edges and a gelatinous base. This not infrequently proves very intractable and repair is most difficult to effect.

Increasing experience in the treatment of this condition has strongly confirmed the opinion expressed in a previous report, that the best results

were obtained by exposures of one and a half to three hours' duration to full strength applicators unscreened. Although the reaction following upon this procedure is in some cases severe, and accompanied by a transient oedema of the surrounding tissues, the scars are invariably smooth, supple and inconspicuous, and the tendency to recurrence is exceedingly slight.

When the size or position of the ulcer precludes the adoption of this method of treatment, prolonged exposures of six, twelve, eighteen or more hours, with half-strength applicators screened with 1-10 mm. of lead, often prove most effective, and repair is obtained without any very marked local reaction.

Some cases of rodent ulcer which are of very long standing and have been subjected to many and various treatments, show greatly thickened and heaped-up edges, with much circumjacent induration extending for a considerable distance into the tissues. These edges often respond in a most satisfactory fashion to treatment with emanation tubes of 20 to 30 mg. activity in small screens of 0.3 mm. platinum, the tubes being buried in the thickened tissue and exposures of from twelve to eighteen hours being given.

When a mucous membrane is affected rodent ulcer proves much more refractory, though exception should perhaps be made in regard to the palpebral mucosa, as small rodent ulcers in this situation often respond well to exposures of strong unscreened apparatus of fifteen to twenty minutes' duration given consecutively for three days.

If the rodent ulcer has attacked bone or cartilage, great care must be exercised not to give too heavy an exposure, or a very acute, painful and prolonged inflammation may be produced.

Many of those ulcers which have received treatment extending over a period of many years with x-rays, zinc ionization, CO_2, etc., respond badly to radium treatment, and it is unwise to attempt to make any pronouncement as to the probable result. Quite frequently the previously treated tissues break down to an extent which far exceeds the existing ulceration, and repair is very slow and imperfect. Several of the cases of rodent ulcer which applied for treatment at the Radium Institute during the past year were of this character, and the already existing destruction of tissue was so great that no hope of satisfactory repair could be entertained.

The number of cases of rodent ulcer treated to a conclusion was 65; of these, 41 were apparently cured, 22 improved, and 2 not improved. Four cases are reported at length—one of the nose, one of the scalp, one of the cheek, and one of the temple; in all the treatment was highly successful.

Sarcomata.

Speaking in general terms these growths, if taken in their early stages and before dissemination has occurred, do very well under radium treatment. The burying within the growth of tubes of radium salts or radium emanation should be resorted to whenever practicable, and the action of these tubes may be much helped by the external application of radium plates heavily screened.

The screening of the tubes should not exceed 1 mm. of silver, as the employment of thick lead or platinum screens is often followed by necrotic changes in the cells in their immediate neighbourhood, and a sinus forms and remains open for a very long time.

It is essential to give as vigorous a treatment as possible, as the great vascularity of these growths, and their rapid and wide dissemination

by the blood stream, are factors which militate very strongly against the chances of success. The best results are obtained in sarcomata of the tonsil and post-nasal space, and the effect in many such cases is amazing, the growths completely disappearing within six weeks of the treatment.

Lympho sarcomata (2 cases) also give excellent results.

Of 22 cases of sarcoma treated to a conclusion, 3 (1 spindle celled and 2 round celled) were apparently cured, 10 were improved, 3 not improved, 2 abandoned treatment, and 4 died. Five cases are reported at length; in one of these, mediastinal tumor, after some temporary improvement, the patient died suddenly of heart failure.

Lymphadenoma.

The most striking feature in the treatment of this disease with radium is the extreme rapidity with which the size of the affected glands is diminished, the effect being often clearly perceptible to the patients themselves within a week of the first exposure.

To obtain this result, the employment of numerous large and powerful applicators, heavily screened, is necessary, and this heavy dosage is almost always followed by severe systemic disturbance, with high temperature and general malaise. After the reaction has subsided, considerable improvement is generally apparent, though in the majority of cases recrudescence occurs. The time at which this takes place, however, varies within very wide limits, and instances have been noted in which the disease has remained quiescent for more than a year.

The best results are obtained when the condition is confined to the lymphatic glands—the spleen not being affected.

The 4 cases of lymphadenoma were all improved; 2 are reported at length.

Adenoma of Thyroid.

A few cases of this condition have been treated during the past twelve months, the patients being unwilling to submit to operation. In all some benefit resulted, and in two the improvement was very marked, the swelling shrinking to less than half-size.

The treatment has been the same in all instances, powerful flat applicators screened with 2 mm. or 1.5 mm. of lead being applied to the surface of the growth in such a manner as to procure an effective "cross-fire" irradiation. A series of exposures on five successive days, amounting in all to thirty hours, has been given, repeated, if necessary, at intervals of six weeks or two months.

Four cases were treated; all improved; one is reported in detail.

Fibroid Disease of the Uterus.

Radium exerts a most beneficial action upon the distressing symptoms of menorrhagia and metrorrhagia, which are the almost invariable concomitants of this condition, and occasionally produces considerable diminution in the size of the uterus. As the cervical canal is rarely sufficiently patulous to admit a screened radium tube without previous dilatation, and patients are often averse from this, the treatment may be carried out by the introduction of a tube containing 100 mg. of radium, screened with 2 mm. of lead, into the posterior fornix, and the application of a plate of from 80 to 100 mg. similarly screened over the fundus uteri.

The total exposure should be between thirty and sixty hours, spread over from five to ten days, and the series should be repeated after six or eight weeks. The first effect noted is the checking of the metrorrhagia, and this is followed by a progressive decrease of the menorrhagia until

the flow becomes normal, or sometimes ceases altogether. If any leucorrhoea exist, this, too, is much diminished in amount, and not infrequently completely disappears.

Four cases were treated to a conclusion; all improved; two are reported in detail.

Naevi.

Flat Superficial Naevi, Capillary Naevi, "Port Wine Stains."—Before expressing an opinion as to the possibility of radium treatment effecting an improvement in any particular instance, it is advisable to subject the lesion to diascopy. If blanching is readily effected by gentle pressure, the result of the treatment will probably be satisfactory; but if it be found impossible to produce blanching except by great pressure, it is unlikely that radium can do much for the condition. The factor of personal idiosyncrasy is always a prominent one, and it is exceedingly difficult to lay down any rules as to the strength and duration of exposures.

Infinite patience is necessary in the treatment of superficial naevi, and the utmost caution must be observed. The effect of each exposure should be most carefully studied, as too frequent treatments or excessive dosage may result in the production of troublesome telangiectases. It is best to use quarter or half strength applicators screened with 1-100 mm. of aluminium, and to start with short exposures of from fifteen to twenty minutes' duration, gradually increasing the length of the same until a satisfactory reaction has been obtained. So soon as the lesion has assumed a salmon-pink color, the screening should be altered to 1-10 or 2-10 mm. of lead, and the length of exposure increased to one, one and a half, or two hours.

The best results can be looked for when the naevus is quite superficial, and shows no tendency to infiltration. If much infiltration exist, the treatment will have to be much more vigorous, and a destructive reaction of slight degree produced. A smooth, supple, and white scar will be left.

The number of cases treated to a conclusion was 15; of these 1 was cured and 11 improved. Reports of 3 are given.

Cavernous Naevi.—These do excellently under radium, especially when of such shape that "cross-fire" radiation is possible. Half-strength applicators screened with 1-10 mm. of lead should be employed, and the exposure should be from one to three hours' duration, spread over three successive days. Little or no surface reaction is produced by this method of treatment, and the naevus shrinks gradually and steadily. If, on palpation, the presence of a pulsating vessel is appreciable, the case is not likely to prove completely successful unless the vessel first be ligated.

The number of cases was 14, of which 1 was cured and 10 improved; 2 are reported at length.

Warts and Papillomata.

Warts and papillomata yield readily to exposures, with half-strength apparatus unscreened, of from thirty minutes to two hours' duration, according to the size and thickness of the lesion. The reaction is but slight, and the resultant scar scarcely noticeable.

Tuberculosis.

Tuberculosis of Glands.—In cases in which surgical measures have been declined for cosmetic reasons radium often proves of considerable value, either when used alone or as an adjunct to vaccine treatment.

Heavily screened exposures of twenty or more hours' duration should be resorted to and an effort made to secure "cross-fire" irradiation where practicable. If the glands are caseating, radium treatment is of very little use.

Lupus Vulgaris.—As a routine treatment for this disease Finsen light is greatly to be preferred to radium, but where it fails to effect a cure or improvement radium sometimes proves of great use. Unscreened exposures of one or two hours' duration must be given and a destructive reaction produced. The resultant scar is usually firm, smooth, supple, and inconspicuous.

Spring Catarrh.

In this condition the employment of radium is strongly to be advocated, as it will sometimes cure the most intractable cases. Personal idiosyncrasy is, however, a very important consideration, and it is essential to proceed with great caution, giving short unscreened exposures at intervals of a fortnight, and carefully noting the reaction. If the dosage be accurately adjusted, the granulations on the orbital conjunctiva gradually disappear, there is no marked inflammation and no resultant scarring of the mucous membrane. A special form of applicator should be used which can readily be introduced into the conjunctival fornices. It should be of full strength, and the first exposure should not exceed fifteen minutes' duration. No screening is employed. If the effect be not satisfactory, the length of the exposure may be increased to twenty, twenty-five, or thirty minutes until the desired result is obtained.

Two cases were treated during the year; one improved, the other did not.

Skin Diseases.

Keloid.—This condition continues to give most excellent results when treated with radium; and a great improvement, if not complete cure, can be safely predicted when the condition is of recent origin and occurs in young subjects. In tender and painful keloids the anaesthetic effect of radium is generally very marked, and appears early in the treatment. Half-strength applicators screened with 1 mm. of silver are almost always employed, and an exposure of from eighteen to thirty hours spread over from three to five days, according to the size and thickness of the lesion, is given. This brings about a gradual absorption of the keloid unaccompanied by any surface irritation. If, however, time be of importance, or the keloid prove refractory, screening of ½ mm. of silver or 1-10 mm. of lead may be employed, though the reaction is likely to be definite and accompanied by vesication.

Lupus Erythematosus.—In early cases of this disease which have not been subjected to much other treatment, one or two exposures not exceeding an hour in duration with a half-strength apparatus unscreened or screened with 1-100 mm. of aluminium may suffice to bring about the disappearance of the lesion. Care should be taken to ensure that the applicator employed is sufficiently large to reach well beyond the borders of the patch treated.

Lichenification of Skin.—Patches of lichenification almost invariably yield to one treatment of ten minutes' duration with a half-strength applicator unscreened, or screened with 1-100 mm. of aluminium. The attendant intolerable itching is often markedly alleviated within sixty hours of the exposure. Some very obstinate cases, which had hitherto defied all the usual methods of treatment, have responded most favorably to this procedure, the lesions have disappeared, and have not recurred.

Pruritus.—The analgesic effect of radium is often of the greatest use

in this disease, and short unscreened exposures frequently produce a degree of relief which is unattainable by any other measures. This is especially noticeable if the pruritus occur in association with a definite lesion such as leucoplakia or hyperkeratosis. No definite rules can be laid down for treatment, as the local conditions vary so greatly, but the screening and exposures must be adjusted in relation to the character of the lesion. If the dosage be carefully considered, and the treatment repeated at fortnightly intervals until the skin is restored to its normal condition, complete and permanent cure may result. If, however, the condition be a neurosis, the prognosis is not so hopeful, and the benefit derived, if any, is not likely to be of very long duration.

Angio-Neurotic Oedema.

Three patients suffering from this condition have received treatment during the past year. In one instance a cure has apparently been effected; in the other two considerable benefit has been obtained.

Three cases were treated; one was cured; the two others improved, but are still under treatment. All three are reported in detail.

Arthritis Deformans.

The daily administration of 250 c.cm. of radium emanation solution of a strength of not less than 1 millicurie per litre to patients suffering from this obstinate, painful, and crippling disease is sometimes attended by very remarkable results. It is difficult to predict with certainty the degree of improvement likely to occur in any particular instance, but the cases which appear to derive most benefit are those in which the disease is of relatively short duration, and the changes are periarticular in type and multi-articular in distribution. The age of the patient also exerts some influence, those under 40 responding more quickly to the action of the emanation. Cases with a definite gouty history sometimes experience an acute exacerbation of all their symptoms within the first week or ten days of their treatment, but this disturbance is quite transient, and is usually followed by a distinct change for the better.

Little or no improvement can be looked for in instances where cartilaginous or osseous changes are predominant, and the radium emanation solution is powerless to bring about the absorption of osteophytic growths or the loosening of bony ankylosis.

When limitation of movement is due to periarticular fibrous thickening, considerable increase of mobility often follows on the taking of the radium water and enables patients to perform actions, such as feeding themselves, brushing their hair, shaving, etc., which they may have been powerless to do for some months or even years.

Other favorable effects of the treatment are that the muscular and articular pains are lessened or disappear, the grating of the joints on movements is not so marked, the muscles regain much of their lost tone, and the patient's general health is much improved. This is especially noticeable when the patients are suffering from anaemia, the haemoglobin index being rapidly increased. The treatment must, however, be persisted in for quite a long time, and at least six weeks are likely to elapse before any change is noted.

With the majority of patients the emanation solution produces a definite diuresis, and with a few it acts as a slight laxative, though free purgation has never been observed.

Much research work has yet to be undertaken to enable an accurate opinion to be formed of the manner in which radium emanation solution produces these results, as its action appears to be a multiple and highly complex one, but the reinforcing of the body ferments, the increase of

tissue oxidation, and the dissolving of uric acid are probably factors which contribute to its success.

Under this head 168 cases are shown; of these, 91 were improved, leaving 77 not improved. Ten cases are reported in detail; of these, one is described as fibrous ankylosis of the elbow in a woman aged 50, and another as chronic rheumatism in a woman aged 42.

Prophylactic Irradiation.

Since the opening of the Radium Institute in August, 1911, numerous patients who have undergone operation for malignant disease have received post-operative prophylactic irradiation. It would be exceedingly difficult, if not impossible, to make any statement as to the precise value of radium treatment in preventing or minimizing the danger of recurrence, but as the majority of these patients had suffered from extensive, severe, and rapidly progressive malignant disease, and the operators had expressed grave doubts as to the probability of their remaining free from the disease for more than a few months, the relatively slight proportion of recurrences so far recorded (19 per cent.) does much to justify the routine adoption of post-operative irradiation. It should prove of especial service in those cases of malignant growth in which it has been found impossible to operate well beyond the appreciable area of the disease.

The Chemico-Physical Laboratory.

Mr. W. L. S. *Alton*, F. I. C., Director, reports that the work of the laboratory during the past year shows in all its branches a marked increase over preceding years. The staff of the laboratory have been almost entirely occupied in making emanation and radium applicators, and in estimating the activity of various specimens of radium submitted to them for testing.

Emanation Applicators.—The records show that flat applicators have not been much in demand, and the tendency has been to use smaller and smaller emanation tubes for treatment of cases. The total number of applicators of all kinds made during the period was 547, as compared with 241 in 1913 and 44 in 1912.

The combined activity of this large number of applicators was equal to that of over 42 grams of radium bromide, giving an average strength for each of about 80 mg. of radium bromide. A considerable quantity of the above emanation was sent to medical men and hospitals for the treatment of necessitous patients.

Radio-active Water.—More than 6,630 litres of this water has been sent out to patients during the year. This compares very favorably with previous years, 3,600 litres being dispatched in 1913, and 400 litres in 1912. The output has been restricted to 100 bottles a day and the activity correspondingly increased to between 1.5 and 2 millicuries per litre. Water of this strength appears to have a more beneficial effect on the patient than that with activity of 1 millicurie; 600 milligrams of radium bromide have been set aside to evolve emanation exclusively for the purpose of making this water.

Radium Applicators and Measurements.—The stock of radium applicators for use in the Institute has been increased during the year by nine pieces of apparatus of various strengths and sizes. Some plates which had been in use a long time were remade.

THE ELIMINATION OF SOLUBLE RADIUM SALTS TAKEN INTRAVENOUSLY AND PER OS.†

HARVEY A. SEIL, PH. D., CHARLES H. VIOL, PH. D. AND M. A. GORDON, B. CH.

The elimination of soluble radium salts after subcutaneous injection of the salt into dogs was studied in two cases by *Brill* and *Zehner**, and the data in tables I. and II. represent their results:—

TABLE I.

18.4 micrograms radium element as chloride injected subcutaneously into a dog weighing 9 kg.

Day	Radium (element) content of Feces micrograms	Urine micrograms	Per cent. of the injected radium. Feces	Urine
1	None	0.046	....	0.02
2	3.34	?	18.2	?
3	0.21	0.0001	1.2	0.001
4	?	0.00007	?	0.0004
5	0.0378	?	0.2	?
6 & 7	0.0001	0.00005	0.001	0.0003
11	0.0001	0.0007	0.008	0.004

TABLE II.

47 micrograms radium element as chloride injected subcutaneously into a dog weighing 8.5 kg

Day	Radium (element) content of Feces micrograms	Urine micrograms	Per cent. of total radium injected Feces	Urine
1	0.97	?	2.1	?
2	0.53	0.27	....	0.5
3	0.38	0.031	0.9	0.07
4	0.34	0.040	0.9	0.09
5 & 6	0.029	0.0002	0.06	0.004

From this data *Brill* and *Zehner* conclude that the excretion of subcutaneously injected soluble radium salts takes place mainly with the feces, and only in a slight measure in the urine. During the first four days after injection 4 to 19% of the injected radium is excreted, and after that the rate of excretion is very slow. The results of *Brill* and *Zehner* are approximate, since the figures are not very concordant.

A great many experiments have been carried out on the effects of intravenous injections of soluble radium salts, and on the effects of radium solution per os, and it therefore was important for comparative purposes to know the relative rates of excretion of the radium when using either of these methods. The intravenous solution usually consists of 50 micrograms (0.05 mgm.) of radium element in the form of radium chloride dissolved in 2 c.c. of normal physiological salt solution. The solutions used for administration per os, consist of a solution of radium chloride in two ounces of distilled water, each bottle of the solution containing two micrograms (0.002 mgm.) of radium element.

†New York Medical Journal, May 1st, 1915.
*Berl. klin.Wochenschr. No. 27, 1912.

A study of the effects of radium on the metabolic processes in normal man is being made by one of us,* and the study of the elimination of intravenously injected radium was made on the subject of this metabolic study. A normal man of about 23 years, who had been on a diet, was given 100 micrograms of radium (element) by injection into the cephalic vein, on December 11th, 1914. Table III. shows the elimination of radium in the feces and urine.

TABLE III.

Day	Micrograms radium element in Feces	Urine	Combined	Micrograms radium remaining	Per cent. rate of elimination of radium.
1	Injection 100 micrograms radium element.				
2	17.9	1.75	19.65	80.35	19.65
3	16.6	0.22	16.82	63.53	20.9
4	7.12	0.065	7.185	56.34	11.3
5	1.6	0.040	1.640	54.70	2.9
6	1.6	....	1.6	53.10	2.9
7	0.98	....	0.98	52.12	1.8
8	0.58	....	0.58	51.54	1.1
9	0.44	....	0.44	51.10	0.85
10	0.42	....	0.42	50.68	0.82

The radium determinations were made by the radium emanation method using aliquot parts of the feces and urine. Cold concentrated nitric acid was added to the feces samples, and after the first violent reaction was over, the sample was heated with more nitric acid. Sulfuric acid was then added, and the clear solution heated until free from nitric acid. The urine samples were similarly treated to secure a clear solution in strong sulfuric acid. The samples were diluted with pure sulfuric acid and aliquot portions of the sulfuric acid solution served for the radium analyses.

This method of preparing the samples is superior to incineration since there is no loss of radium salt by volatilization.

From the data in table III. it is clear that at first there is a rapid elimination of the radium, mainly in the feces. The absolute amounts of radium eliminated from day to day will depend somewhat on the quantities of feces and urine excreted. Since the radium salts are not volatile, the only other manner in which they might be eliminated is in the skin secretions. The radium eliminated in the urine is so much less than that in the feces that it is not unreasonable to expect that the amount eliminated through the skin would be very small. This point is being examiner and will be reported on later.† Radium is an element closely related chemically to barium and the other metals of the alkaline earths, strontium and calcium. From chemical considerations it would be expected that the radium held in the body, would be found wherever other alkaline earth elements are found. The bones should there-

*The results of this study will be reported later, S.

†The following experiment on the elimination of radium through the skin was carried out by Dr. L. W. Ketron, of the Johns Hopkins Hospital, Baltimore, Md., and we wish to acknowledge our indebtedness to him for the kindness in permitting use to give the result here. The details of this experiment, as well as the results obtained in some work on radium injections, which Doctor Ketron is carrying out in the Dermatological Department of the Johns Hopkins Hospital, will be published later. A normal young man who was in the hospital for the teratment of a few furuncles as given 100 micrograms of radium (element) by intravenous injection, April 1st, 1915, at 3:00 P. M. At 5:00 P. M., on the same day he was subjected to a very severe sweating, 280 c. c. of the perspiration being obtained. This upon analysis was found to contain only 0.025 micrograms of radium. This result is in accord with the results of Bellingham-Smith (Quarterly Medical Journal, vol. v, No. 18, page 249) who found no radium eliminated through the skin after subcutaneous injections of radium in mice. It also confirms the views expressed in regard to the "fixing" of radium in the body tissues and the falling off in the daily rate of elimination of radium.

fore contain the largest amounts of the radium, and analysis in many cases shows that that the bones* do have the highest concentration of radium of any of the tissues. Following the bones, in the order of concentration of radium, come the liver, lungs, blood vessels and spleen. The explanation of the rapid fall in the daily rate of excretion of the radium from 20% of the radium present during the first two days to less than one per cent. of the radium present at the tenth day (cf. last column in table III.) lies in the gradual absorption of the radium in the various tissues. When injected into the blood stream the quantity of radium (0.1 mgm. radium element equalling 0.13 mgm. of radium chloride or 0.14 mgm. radium sulfate) is so small that it would hardly give a visible precipitate in the form of sulfate. As a result the radium is carried in solution or suspension in the blood until it either becomes absorbed by the various tissues in proportion to their alkaline earth salt content and to the accessibility of the blood to the organ, or is eliminated.

To check the results in Table III., a similar intravenous injection of 100 micrograms of radium was made in the same man, Feb. 3, 1915. By this date the radium eliminated as a result of the first injection on December 11th, 1914, was assumed to be negligible, and the analytical results as given in Table IV. show this to be the case.

TABLE IV.

Day	Micrograms radium element in Feces	Urine	Combined	Micrograms radium remaining	Per cent. rate of elimination of radium.
1	100 micrograms radium element injected.				
2	18.4	1.4	19.8	80.2	19.8
3	12.58	0.16	12.74	67.4	15.9
4	3.34	0.065	3.40	64.0	5.0
5	1.68	....	1.68	62.3	2.6
6	0.54	....	0.54	61.8)	
7	1.67	....	1.67	60.1)	Av. 1.8*
8	0.45	....	0.45	59.7	0.75
10	0.30	....	0.30	ca. 59.0	ca. 0.5
12	0.20	....	0.20	ca. 58.5	ca. 0.34
21	0.14	....	0.14	ca. 57.0	ca. 0.25

These results are in good accord with the data in Table III.

To determine the rate of elimination of radium taken per mouth, one of us (S.) ingested a solution containing 50 micrograms of radium element. Through a blunder on the part of a janitor, the feces samples for the first two days were interchanged and the sample for the second day was thrown out before the exact weight was determined. The data in Table V. therefore are in part only approximate and are recorded simply for a comparison with the data obtained in a similar experiment, made later, the results of which are given in Table VI.

*Results for two days averaged, because total weight of feces on 6th day was only 25 gm., and weight of feces on 7th day was abnormally high.

*Cameron and Viol. "Radium," vol. 4, p. 66, 1915. Plesch and Karczag. Verh. d. kongr. f. inn. Med. 1912, and Muench. med. Wochenschr. 1912. cf. also Caan and Ramsauer. Muench. med. Wochenschr. No. 27, 1910; ibid No. 21, 1911; Brill, Kriser and Zehner, Strahlentherapie, vol. 1, p. 347 (1912). Lazarus Barlow, Arch. Middlesex Hosp., 1913, p. 92; Dominici, Petit and Jaboin. Comptes Rendus, vol. 120, p. 726, 1910.

TABLE V.

Elimination of Radium. 50 micrograms of radium element taken by mouth. March 2, 1915.

Day	Micrograms radium in Feces	Urine	Combined	Micrograms radium remaining	Per cent. rate of elimination of radium.
1	Radium taken at mid-night.				
2	7.6	0.124	7.72	32.38	15.4
3	ca. 16.0	0.015	ca. 16.0	ca. 16.28	ca. 50.0
4	2.9	....	2.9	ca. 13.38	ca. 18.
5	0.38	....	0.38	ca. 13.0	ca. 3.

TABLE VI.

Elimination of Radium. 50 micrograms radium element taken by mouth. March 9, 1915.

Day	Micrograms radium in Feces	Urine	Combined	Micrograms radium remaining	Per cent. rate of elimination of radium.
1	Radium taken about mid-night.				
2	17.9	0.102	18.0	32.0	36.0
3	12.2	0.013	12.2	19.8	38.1
4	2.19	....	2.19	17.61	11.0
5 & 6	0.626	....	0.626	16.98	3.5

Radium taken into the body is continually disintegrating with the formation of the gaseous radioactive substance, radium emanation. This gas is carried by the blood to the lungs, where the emanation passes out of the blood by diffusion, and is lost from the body in breathing. The amount of emanation in the exhaled air was measured after the first experiment on radium taken by mouth, the data in Table VII. being a record of the results.

TABLE VII.

Concentration of radium emanation in the exhaled air, after taking 50 micrograms of radium (element) by mouth. March 2, 1915.

Day	Hour	Radium emanation per liter of air in milli-microcuries.	in mache units.
March 3	10:40 A. M.	0.588	1.59
3	4:50 P. M.	0.551	1.49
4	10:30 A. M.	0.182	0.49
5	2:50 P. M.	0.070	0.19

CONCLUSIONS: Taken by mouth a much greater part of a soluble radium salt is eliminated during the first three or four days, but after that, the rate of elimination is sensibly the same as when the radium is introduced by intravenous injection.

The main part of the radium is eliminated in the feces. When the radium is taken by mouth, a smaller proportion of the excreted radium is found in the urine than when the radium is injected intravenously. From 25 to 35% of the radium taken by mouth remains in the body four or five days after ingestion. From 55 to 65% of the radium injected intravenously remains in the body four or five days after the injection. From this time on the elimination proceeds at about the same rate in each case. By the 10th day after taking the radium the daily rate of excretion is less than one per cent. This results in an exceedingly slow elimination of the last of the radium, the process going on for months. The first rapid elimination takes place before the radium has been "fixed" in the tissues. After that has taken place the excretion is much slower, and even the amount of emanation which is given off, is less. It is a well

known fact that a solution of radium salt can be completely de-emanated by passing a current of air through the solution. Even the dry radium chloride and bromide (soluble salts) give up quite large proportions of their included radium emanation. Insoluble radium sulfate, even when finely divided, holds the emanation very strongly, so that less than 5% of the emanation escapes from the salt.

From the above results, a rational method for maintaining a certain amount of radium in the system can be suggested. If for example, it is desired that about 50 micrograms of radium be maintained in the body—an intravenous injection of about 100 micrograms is made, and after 10 days, it will suffice to take 2 micrograms of radium by mouth, every few days, in order to make up for the radium being lost. Radium solutions taken by mouth repeatedly will have a cumulative effect. However, the elimination of radium taken by mouth is about twice as rapid as when the radium is injected intravenously. Therefore, there will be required about twice as much radium to produce a given result, when the radium is taken by mouth. This is in accord with the clinical findings of many workers, who have obtained results more rapidly with smaller total quantities of radium injected intravenously than with larger total quantities of radium taken by mouth.

RADIUM IN CANCER OF THE BLADDER*

Applied by Means of a Cystocope. Report of Case.

BY WINFIELD AYRES, M. D.,
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Reports coming from various men in this and other countries seem to have demonstrated the fact that radium has benefited, and possibly cured many cases of cancer. Cases that seem to have been beyond any form of help other than by constant use of morphine, have been wonderfully benefited, in that pain and other annoyances have been relieved and the rapid progress has been checked. Nearly every one, whether skeptic or enthusiast, agrees that in nonsurgical cases radium is worthy of a trial. At present also there is a growing tendency to combine operation with radium treatment. The reason for reporting this case is twofold; first, because of the great benefit from treatment; and, second, the unusual method of its administration.

Radium rays are more easily screened, more easily applied, and, when properly handled less dangerous to the patient than Röntgen rays. Especially is this the case in neoplasm of the bladder, where radium may be brought in direct contact with the tumor, an impossibility with the Röntgen rays. Against radium is the enormous cost of sufficient quantity to be effective.

It is the general opinion that too small a dose of radium will increase cell proliferation and a consequent more rapid growth of the tumor, but a proper dose causes disintegration of cellular structure. Reports that radium, instead of improving cancerous conditions, increases the rapidity of growth of the tumor, probably concern cases which have received entirely too little radiation. A slow growing tumor requires less radiation than one of rapid growth. In cancer of slow growth a small quantity of radium over a very long period, or applied repeatedly for short periods, is sometimes of decided benefit, but as a rule the

*Reprinted from the New York Medical Journal for February 20, 1915.

quantity should correspond to the size of the tumor.

The most brilliant results so far obtained from the use of radium have been in epitheliomata of the superficial tissues. Cancer of the bladder wall simulates this structurally to such an extent that one would be led to hope a like brilliant result might be obtained here, or at least better than could be expected in cancer of the prostate.

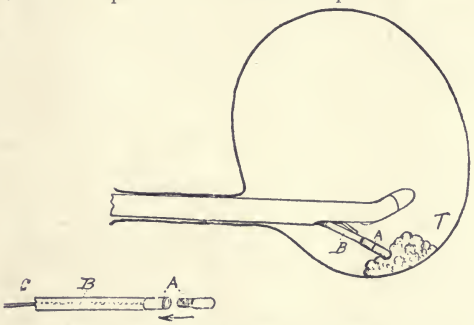

Fig.—Reprinted from a paper in the New York Medical Journal for July 18, 1914; shows the method of application of the capsule to a neoplasm.

As this case was an inoperable one, some means had to be devised for direct application of the screened capsule of radium. The instrument was described in the NEW YORK MEDICAL JOURNAL for July 18, 1914. Gold was selected for screening, because an extremely thin layer of this metal is sufficient to shut off the alpha and primary beta rays. Because of the difficulty of use and the nature of the tumor, a capsule of ten mgm. of radium was first employed, but this proving insufficient, the amount was doubled and again doubled. The use of the larger quantities was made possible by discovery of a cystoscope of unusually large capacity, and the second doubling was accomplished by using a higher concentration of radium.

It was necessary to use anesthetics, and the method which proved most satisfactory was to allow two ounces of a one per cent. solution of alypin to remain in the bladder for one half hour, and a one per cent. solution of cocaine in the urethra for ten minutes before the cystoscope was introduced. An irrigation tank was filled with a one per cent. solution of alypin and this was used to refill the bladder when necessary. In this way the patient was fairly comfortable, and only on very few occasions did treatment have to be curtailed on account of spasms of the bladder. During one treatment the patient fell asleep, but often there was a great tendency to spasm and the bladder contents had frequently to be changed. For this reason a second tank was always ready, filled with a solution of boric acid for use in the last few minutes in case the alypin solution should become exhausted.

Novocaine was tried with utter failure. Cocaine was used with partial success three times, but its action on the bladder wall from repeated and prolonged use was so bad that rest from instrumentation was made necessary for one week.

Treatment by this method requires a careful observation of asepsis, a very gentle hand, a steady nerve, infinite patience, care of the bladder on the off days, and hearty co-operation of the patient. Cystoscopy three times a week of a few minutes duration, is quite a tax on the resistance of the bladder and urethra, but when each sitting is prolonged for one

hour, the danger of infection is still greater.

The question might arise as to why the cystoscope is necessary. Passage of a flexible container for the radium would certainly be easier on patient and physician, but there would be no certainty that the capsule would ever come in direct contact with the neoplasm. It certainly would come in contact with the normal bladder wall, and there would be no way of screening it from healthy tissue. But with the cystoscope the radium may be held in direct contact with the tumor all the time and the healthy bladder wall is kept from it by fluid—a poor screen, but the farther away from tissue, the less effect has radium on it. Therefore the writer believes the best results will be obtained by applications under direct vision.

CASE. Mr. S., aged seventy-two years, planter by occupation, was referred to me, May 4, 1914, by Doctor *Alvarez*. During November, 1913, he had noticed bubbles of air passing in his urine, and he was compelled to urinate every two hours. In December, he noticed in addition that his urine was tinged with blood. These symptoms persisted without change, until February when he found the amount of blood in his urine to be markedly increased. In March he had quite a severe hemorrhage and consulted a doctor in Havana. Cystoscopy was done, but the cause of the hemorrhage was not discovered. The patient had had three attacks of severe hematuria. The only thing which at all controlled the escape of blood was a decoction of Desmonium supinatum, a remedy much used in Cuba by the natives for control of internal hemorrhage.

On examination, Mr. S.'s urine was seen to be quite red and cloudy. The sediment was composed principally of blood, but there was a little pus and very many bacteria, that most numerous being a long, Gram positive bacillus occurring for the most part in chains. This was found to be a gas forming bacillus of unknown classification and will be reported in another paper. Nothing was found microscopically to indicate malignancy. The finger in the rectum disclosed nothing pathological and neither did palpation of his kidneys. The return wash from his bladder was typically that of tumor, and the cystoscope revealed the growth. It was sessile, approximately an inch in all diameters, and projected from the lower left wall of his bladder, back of his left ureteral orifice. It was so situated that the left ureter crossed behind and about bisected it. It was apparently a solid mass with no projecting papillomatous offshoots. To the eye it was a typical cancer. A small section was sent to Doctor *Sondern,* who corroborated the diagnosis.

On account of the patient's age, the presence of three per cent. of sugar in his urine, and a blood pressure of 196 to 120, an operation for removal of the tumor with the necessary transplantation of his left ureter in all probability would have proved fatal. Even opening his bladder and placing radium in contact with the neoplasm for a number of hours seemed contraindicated in this case. It was therefore decided to use radium through the cystoscope. While the instrument divised and the special form capsule of radium was being prepared, an attempt was made to check the hemorrhage and get rid of some of the tumor by sparking. Four sparkings were given with very little effect on either hemorrhage or the size of the growth.

Ten mgm. of radium, screened by 0.5 mm. gold was the largest amount which would pass through my *Buerger* operating cystoscope This was applied for the first time on June 22d and thereafter three times a week until August 24th. The first application was for thirty

minutes, but on the third a full hour was given; in all 265 mgm. hours. The tumor began to disappear, the blood to cease, and large pieces of necrotic tissue to appear in the urine in about two weeks. But from August 12th, no improvement was noticed.

A new cystoscope had to be purchased and this was of so much greater capacity it was found that twenty mgm. could be used through it. This was used for the first time on August 31st and thereafter twice a week until October 19th. Each application with a few exceptions was for one hour—seventeen treatments yielding 320 mgm. hours. Under the stronger radiations the remains of the tumor began rapidly to disappear and large masses of necrotic tissue to reappear in the urine.

On October 19th, there was left only a sloughing area about an inch in diameter, the edges of which were slightly raised above the normal bladder wall.

On October 31st, cystoscopic examination showed the same sloughing area, but the necrotic tissue had dropped off the edges and their appearance was decidedly unsatisfactory. Cancerous tissue was unquestionably still present. Again on November 3d, the growth appeared to be taking on a new lease of life and further treatment with stronger radiation was deemed necessary.

Twenty mgm. were applied for one hour on November 4th and 9th. Beginning on November 21st half hour applications of forty mgm. were made three times a week until December 11th. A gold screen of 0.5 mm. thickness was used. On November 30th, Doctor *Bissell* being present in consultation, no evidence of cancerous tissue could be discovered. At the last treatment, December 11th, the bladder wall was seen to be markedly irritated by the action of the secondary beta rays, and on account of spasms of the bladder only twenty-seven minutes could be endured. The condition of the bladder wall was unquestionably due to slight burning by radium and not infection, as there was no increase of pus in his urine.

Cystoscopic examination, December 18th, showed a sloughing area about one half by three fourths of an inch in diameter. The edges of this slough were even with the bladder wall and no sign of malignancy was discernible. His bladder was very irritable, but no distinct burn was discovered. His urine contained less pus than at any time since he first came under observation.

It was exceedingly interesting to watch the progress of the case. During the earlier sessions application of radium would, in about ten minutes, cause a blanching of the surface of the tumor, and in a very short time thereafter shreds of whitened tissue would form on the surface and drop off into the bladder fluid. After twenty mgm. had been applied a few times the tumor presented only a sloughing, raised area, and blanching action of the radium could no longer be observed, but more necrotic tissue was thrown off at each sitting. Often during treatment large pieces would become detached, and from two weeks of the first treatment more or less would pass off with each urination until December 7th. From that date no large masses were observed. Blood began to lessen in quantity during the second week, but appeared at times up to December 11th. In the writer's opinion a fair proportion of this was due to instrumentation—holding a solid metal against a vascular or ulcerated surface during spasms of the bladder, but sometimes during the earlier periods of treatment considerable blood would follow the passage of a particularly large piece of tissue.

The fact that no large pieces were seen during the last eleven days

of observation, would indicate that the substance of the tumor had been destroyed and only bladder wall left at the site of the tumor, corroborating the cystoscopic findings.

Mr. S. has returned to his home in Cuba, but will again come under observation after the cold weather. If at that time any evidence of malignant growth is discovered, further applications of radium will be employed.

Mr. S. was given 265 mgm. hours from a ten mgm. capsule of radium; 360 mgm. hours from a twenty mgm. capsule; and 180 mgm. hours from a forty mgm. capsule; in all 795 mgm. hours. Probably fewer mgm. hours would have been sufficient to accomplish the same result had forty mgm. been used from the first, but because this was the first time radium had been used in this manner, the method followed was probably the best.

A gold screen of only 0.5 mm. thickness is not sufficient to shut off all the primary beta rays from a forty mgm. capsule of radium, but one mm. prevents practically all these rays from passing. As the 0.5 mm. screen was used, it might be deemed probable that the slight burning of the bladder was caused by the primary beta rays, but another patient under treatment at the same time was given half hour applications three times a week with a one mm. gold screen, and his bladder reacted in exactly the same manner. Evidently the secondary beta rays caused the burns in both cases. A screen which will shut off both primary and secondary beta rays has been devised for use with the cystoscope, and will be tried as soon as it is delivered. It is evident that forty mgm. cannot be applied for a half hour three times a week with only a one mm. gold screen.

Care of the urethra and bladder during the course of such a treatment is of vital importance. After the cystoscope has been removed, the urethra and bladder are washed without a catheter, with a non-irritating antiseptic and then two drams of oil are injected into the bladder. On the days when radium is not used the patient must also report for urethral and bladder irrigation with the soothing antiseptic. During any period of rest from treatment, an occasional wash of silver nitrate is of decided benefit. Hexamethylenamine is of a certain amount of value, but a combination of belladonna and benzoate of sodium is better, especially when treatment is being pushed to the limit of endurance.

Radium in this case has been a decided success. I do not maintain that a cure has been accomplished, but the tumor has been destroyed more thoroughly than it could have been by any means except operation. The action of radium rays on cancerous tissue continues for quite some time after applications have been discontinued, and it is possible that there will be only a slight return, which may be kept under control by further use of radium and quite probably prevent any serious urinary complication so annoying in cancer of this tract.

This case seems to prove that in inoperable cancer of the bladder wall, we have in radium an agent which will cause at least temporary disappearance of cancer growth much better than any known remedy.

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