vidual case. In hypochondria they play little or no rôle, the symptoms being almost altogether autogenous. In conclusion, it should be emphasized that the neuroses are physical, biologic and neuropathic in origin, and that psychogenic factors, when they play a rôle, do so merely in the surface manifestations.

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RADIUM IN THE TREATMENT OF CARCINOMA OF THE BLADDER AND PROSTATE

REVIEW OF ONE YEAR'S WORK *

B. S. BARRINGER, M.D.

NEW YORK

FOREWORD BY DR. KEYES

The results achieved by Dr. Barringer in the control of malignant disease of the prostate and bladder by the application of radium (unconfirmed though they be by the lapse of a number of years) are nevertheless striking and offer a prospect of amelioration and a possibility of cure for early and circumscribed neoplasms such as has not before been claimed for any physical agency.

In view of the skepticism which will naturally be aroused by these claims, I feel the obligation of intruding my concurrence.

The condition of Prostatic Cases 1, 3, 9 and 10 has been observed by me, both before and after treatment by radium. The condition of Prostatic Cases 5, 8 and 12 I have noted only after treatment. These observations, though few, are sufficient to justify Dr. Barringer's claim to have checked the growth of prostatic carcinoma in apparently incipient cases for periods varying from a few months to a year. Whether this check has amounted in any of these cases to a total destruction of the carcinoma within or about the prostate, or whether there has simply been a temporary regression, cannot be known at the present time. We know only that the major lumps have been absorbed, and that in many instances the remaining irregularities in the prostate are such that they cannot be distinguished from scars. Moreover, the improvement in the condition of these patients, as evinced by the relief of pain and the increase in weight, is truly remarkable.

I have also observed a regression in three cases of bladder carcinoma, all of which had been vainly treated by fulguration, two of which (Cases 6 and 16) were at the time of treatment flat and sloughy in type, and all of which had been diagnosed as carcinoma by pathologic examination of pieces removed by the cystoscopic forceps, after the last fulguration.

E. L. KEYES, JR., M.D.

RESULTS OF RADIUM TREATMENT

The least that can be said of the result herewith published of radium treatment of carcinoma of the prostate is that radium has produced a marked relief of the symptoms and diminution in the growth, if not a total disappearance of it in certain cases, and this in cases in which the carcinoma had exceeded the limits of the prostate gland—a condition in which it is recognized that surgery is impotent.

The superiority of radium in the treatment of carcinoma of the bladder is not so clear because of the cures that have been alleged from surgical treatment of this condition in its various stages. But with radium we have obtained local cures of flat, sloughy carcinomas of the bladder which, according to the surgical theories of today, would have required resection

of the bladder for their removal. Unless these cases promptly recur (which they have not done up to the present) we are therefore in a position to state that we have with the placing of a tube of radium in the bladder for a few hours achieved as much as the surgeon does by a capital operation.

YEAR'S WORK IN CARCINOMA OF THE PROSTATE

1. Radium treatment has caused with surprising regularity the reduction or disappearance of carcinomatous nodules of the prostate. Striking results have been obtained both in early and in advanced cases (Cases 1, 3, 5, 8, 9, 10 and 12). The early cases, those in which the carcinoma is fairly well confined to the prostate and in which there is little or no perivesicular infiltration, all show a shrinkage of the carcinoma.

2. The reduction which occurs in carcinomatous lobes is, as far as has been observed, permanent. One case has been followed ten months; two for six months, and more recent cases but one or two months after the reduction.

3. The symptoms in those cases in which the carcinoma has been reduced generally show striking improvement (Cases 1, 3, 8, 9, 10 and 12). This symptomatic improvement is evidenced in increase in weight and strength, decrease in frequency of urination, and return of or improvement in erections. One patient of 74 years, on whom a suprapubic exploration showed carcinoma of the prostate, and who was treated but once with radium, gained 8 pounds, and reported five months later that he was then "doing a full day's work on steam boilers." He narrated on questioning that a full day's work was from 5 a. m. to 11 p. m. Another (Case 1) who had had no erections for one and one half years, had a permanent return of this function. This patient, who had been invalidated, gained from 16 to 18 pounds, started in mild work "shoveling snow and lifting ash cans," and now is doing a full day's work in a machine shop, one year after his first treatment.

4. I have not departed from the technic used in my first case one year ago. Different strengths of radium have been used, but the application is the same. The radium is placed in the end of a needle extending from the tip from 1 to 1½ inches along the shaft. These needles¹ are from 4 to 6 inches long, and are inserted through the perineum into the prostate or further into the perivesicular sheath. Anesthetization of the perineum and the prostate with 0.5 per cent. novocain and epinephrin makes the insertion of these needles practically painless. Little or no pain is felt during the sojourn of the needle (about twelve hours), and the patient can either urinate or be catheterized. This means at most but twenty-four hours in the hospital.

The radium so used is practically unscreened, but *the maximum effect of the radium takes place directly in the center of the carcinomatous nodule.*

The patient usually has pain in the prostate and urinary frequency, beginning about three days after irradiation, and lasting a number of days. In some of the cases in which I have used large doses the reaction has been severe and has lasted several weeks. I believe that lesser doses are about as effective and not so painful. Nearly all of my patients have been irradiated only once in two or three months and no second treatment is given until the effect of the first is entirely over.

1. I am now having gold needles made. These will form a better screen than the steel needles.

* From the service of the Memorial Hospital.
* Read before the Genito-Urinary Section, New York Academy of Medicine, Nov. 15, 1916.
* Owing to lack of space, this article is abbreviated in THE JOURNAL by omission of a number of case reports. These will be included in the reprints, a copy of which will be sent by the author on request.

5. The primary effect of the radium may be to increase the amount of the residual urine. The ultimate effect of the radium application on residual urine is probably nil, the amount neither increasing nor decreasing. Hence those patients who have chronic retention of urine require either the catheter or operation in addition to irradiation. It would seem wiser not to operate until the carcinomatous prostate had at least been given one dose of radium.

6. No sloughs have resulted from the radium needles.

7. Radium apparently has a selective action on carcinoma. I conclude this from descriptions by Dr. James Ewing of carcinomas examined after radium treatment, and from my own experience.

I have used radium on a hypertrophied prostate with absolutely no effect, neither burning nor shrinkage occurring; yet the same amount of radium would markedly reduce a carcinomatous lobe. I have had a similar experience in a case of chronic contractive fibrosis of the corpora cavernosa, barring the fact that the radium caused a superficial burn of the penis.

8. The pathologic examination of a prostate removed five months after irradiation is of interest (Case 5). The prostate was removed because of retention of urine. Only one treatment was given this patient because he was old and very feeble. The prostate had been considerably reduced in size following the radium treatment. At operation the prostate shelled out like a nonmalignant adenoma. Dr. Ewing's report is as follows:

Material consists of several lobulated opaque portions of prostate making a mass as large as a hen's egg. Much of this has the honeycomb appearance of chronic prostatitis. But some areas are very firm and solid. Two such areas, size of bean, were sectioned. The main tissue of the gland shows lesions of chronic prostatitis with dilated glands and feeble epithelial proliferation. The solid areas show fibers of muscle tissue separated by rows of small epithelial cells with hyperchromatic nuclei. The appearance is that of diffuse carcinoma in a state of fibrosis. One area of adenocarcinoma is found in the center of a fibrosed area. There is no necrosis.

In view of the history the diagnosis may be made of carcinoma, diffuse and adeno, arising on prostatitis, and undergoing atrophy and fibrosis from radium.

9. As far as I have observed, clinically all of the cases treated are of about the same degree of malignancy. There is a class of cases of prostatic carcinoma, however, of marked malignancy. In these the primary focus in the prostate is often overlooked, and the patient comes to be treated for his secondary focus. There have been two such cases at the Memorial Hospital in both of which there was a large carcinoma of the neck, and it was only by routine examination in one case and necropsy in the other that the primary focus in the prostate was found. Such cases are apparently very malignant, and it is a question if we would ever get them early enough for any treatment to count.

10. Very large carcinomas accompanied by cachexia and loss of weight on the part of the patient are beyond radium and any other treatment.

11. The first year's work has not revealed what, if any, cases have been cured. Time alone will answer that question. To carry my work further, therefore, with the hope of really curing some cases, I am attacking the paths of metastasis, the perivesicular lymphatics with longer needles which are inserted through the perineum and prostate high up along both seminal vesicles.

SUMMARY OF PROSTATIC CASES

Seventeen cases of prostatic carcinoma have been treated. The seventeen cases may be roughly divided as follows:

Advanced Cases.—Eight of the cases (2, 4, 7, 8, 9, 10, 11 and 13) were hopeless; in two of these (Cases 8 and 9) the carcinoma had invaded the bladder. Two patients have died (Cases 2 and 4). Two (Cases 7 and 11) are going down hill. One has been lost track of; seven months after a single treatment, however, I heard that he was up and working. Three (Cases 8, 9 and 10) are improved. In two of these the diagnosis was confirmed by microscopic examination (Dr. Ewing). In the first, the prostatic carcinoma has almost disappeared and the carcinomatous lump which projected into the bladder has about gone. The second patient has gained about 14 pounds in weight, goes from four to six hours without urinating, has good erections, and his carcinoma, with the exception of a small lump remaining in the right vesicle, has disappeared. The third patient looks well, urinates less frequently at night, and has no residual urine, as against from 2 to 3 ounces before the radium treatment.

Early Cases.—Nine of the seventeen cases (Cases 1, 3, 5, 6, 12, 14, 15, 16 and 17) were, roughly speaking, fairly early. This does not mean that they were suitable for operation. As a matter of fact, because of the initial success of radium treatment I now take the stand that no patients with prostatic carcinoma should be operated on. The diagnosis of carcinoma was confirmed by microscopic examination in four of these nine cases. Five of the nine have been too recently treated to report in detail. The remaining four (Cases 1, 3, 5 and 12) have much improved as far as the prostate goes, and three have improved symptomatically. One has gained 16 pounds, and has no night frequency, as against from three to four times, and works a full day, as against no work. One gets up at night not at all as against from three to four times, and has had no catheterization since the radium treatment (eight months ago); whereas before treatment he had one or more attacks of acute retention. One has gained 5 or 6 pounds, and has come back to a full day's work (from 5 a. m. to 11 p. m.) on steam boilers. The fourth patient did not improve symptomatically because of his urinary retention. This patient's prostate was removed five months after irradiation, and he is now recovering from his operation.

BLADDER CARCINOMA

My statistics in bladder carcinoma, viewed from different points of view, are both good and bad—bad because five of sixteen patients treated have died² and three are rapidly getting worse. The fact that in the first year I have treated nearly every patient sent to me, and that thirteen of the sixteen cases were advanced carcinoma, explains these statistics.

I consider the results good because four cases of carcinoma of the bladder (three advanced, one early, Cases 2, 6, 10 and 16), three confirmed microscopically as carcinoma (Dr. Ewing), have been cystoscopically proved cured, one for ten and one half months, one for five months, and two recently.

These few cases have so impressed me that I believe the cure³ by radium of carcinoma of the bladder

2. Two as a result of transplantation of the ureters because of intolerable pain.

3. Cure as far as the bladder is concerned; it is too early to speak of permanent cure.

depends on two conditions: first, to get cases early enough, and, second, actually to apply the radium to the carcinoma.

Application of Radium in Bladder Carcinoma.—The technic of the application of the radium has been outlined in my preliminary report.⁴ A capsule of screened radium (0.6 mm. of silver and 1 mm. of rubber) from 100 to 200 mc. is placed in the bladder through the sheath of the cystoscope and allowed to remain there from six to ten hours. As 90 per cent. of bladder tumors are on the bladder base, the radium so inserted is in close contact with the tumor. If the carcinoma is on the vault or lateral walls, the patient lies on his abdomen or on one or the other side. After the treatment the radium is removed through the urethra by a linen thread attached to the tube.

In my year's work I have seen no reason to depart from this technic. The initial pain experienced is only that of the cystoscopy. The after-burn varies from none at all to more or less severe pain beginning a few days after treatment and lasting from one day to several weeks.

In extensive carcinoma involving the bladder, sphincter irradiation may greatly increase both the pain and the urinary frequency. It is to be used in these cases with caution.

CASE REPORTS OF PROSTATIC CARCINOMA⁵

CASE 1.—J. C. D., aged 59, complained chiefly of loss of flesh and strength, and night urinary frequency, from three to four times for four months. He had had pain in the right thigh for five years. Prostatic examination (with Dr. Keyes) revealed a large, hard, fixed, irregular prostate, each lobe of which was about as large as an English walnut; the left lobe was more prominent than the right, and there was little extension toward the seminal vesicles. Radium treatment was given, Oct. 20, 1915, 50 mc. for six hours in each lobe.

November 17, the patient reported that he had considerable burning after the treatment, and that he had a number of erections since (erections had been lost for one and one-half years). The prostate felt the same.

Jan. 14, 1916, the patient had gained about 10 pounds; he felt fine; erections had diminished. Examination of the prostate (with Dr. Keyes) revealed marked shrinking of the carcinoma. Dr. Keyes said that it was more the slight irregularity of the prostate than anything else that suggested carcinoma. I gave the patient 60 mc. of radium for four hours in both lobes.

January 31, he had gained about 6 pounds more, making 16 in all. He had had no pain from the radium, and rose once at night to urinate.

February 18, he did not get up at all at night to urinate, and had gained 2 pounds in weight. There was slight induration at the base of the prostate, and the right lobe was treated for eight and one-half hours with 38 mc. of radium.

April 4, treatment with 75 mc. was given the right lobe for four hours, and then the left lobe for four hours.

November 7, he had been working in the machine shop for six months, and had lost a couple of pounds. He had had some burn after the radium, which had caused an increase in night urination (from three to four times). In the center of the left lobe there was a small, fairly hard lump, and a slight, hard ridge in the right lobe. The patient's condition was fine.

CASE 9.—M. H., aged 65, had a sloughy, pedunculated carcinoma removed from the neck of the bladder by Dr. Keyes. This grew from the prostate, no removal of which was attempted. The pathologic examination (by Dr. Ewing) was thus reported: "The section is from a mass of tumor tissue 1.5 cm. in diameter. It shows a solid carcinoma composed of small and large groups of compact tumor cells, with very little

stroma. The cells are of medium size, polyhedral, with hyperchromatic nuclei. The vessels are scanty. There is no necrosis. It is impossible to state from the section whether there is any infiltration of the bladder wall. In structure the tumor is a fully developed carcinoma."

June 6, the right lobe of the prostate, which had a hard ridge, was treated with 93 mc. of radium.

July 5, there was slight burning after the radium; the lump in the prostate was the same.

September 12, the patient did not have to rise at night. He went from four to six hours without urinating. He had gained 15 pounds. The lump in the right lobe was about gone. Drs. Keyes and Jeck saw it as infiltrations running up into the right vesicle. This is to be treated with radium.

CASE 12.—F. S., aged 74, was operated on at Mount Sinai Hospital, and carcinoma of the prostate was found. When I first saw him he had a night frequency of three times, and the right lobe of the prostate was small, hard and irregular.

June 29, this lobe was treated with a radium needle of 86 mc. for four and a half hours.

October 29, the patient still urinated from three to four times at night; he had a good appetite, had no pain, and worked from 5 a. m. to 11 p. m. on steam boilers. He reported having had but little burn from the radium. The prostate was flat and somewhat irregular with some induration beyond the prostate across the bladder base. No carcinoma was palpable in the prostate. (Examination was made with Dr. Keyes.)

CASE REPORTS OF BLADDER CARCINOMA⁶

CASE 2.—C. A. G., woman, aged 69, complained chiefly of urinary frequency for the past year, at night three or four times, during the day every three or four hours, and pain following urination. She had been passing bloody urine for the past four months. A number of months before I saw her, cystoscopic examination had been made, with a diagnosis of inoperable carcinoma. Cystoscopy revealed a large red carcinoma with necrotic patches on the left side of the bladder obscuring the left ureteral orifice. The tumor was probably as large as a half dollar. The specimen removed was thus described (by Dr. Ewing): "The section is of a small mass of tumor tissue 2 mm. in diameter. It shows the structure of a small alveolar carcinoma, much inflamed, with dilated blood vessels. The cells are cleared, irregular in size, with large hyperchromatic nuclei, and arranged in small groups. The stroma is scanty."

Jan. 19, 1916, 100 mc. of screened radium were placed in the bladder and allowed to remain for eight hours.

February 4, she reported that she had had some frequency and severe bladder pain for two days; then everything was normal. Cystoscopy (performed with Drs. Keyes and Jeck) revealed that the tumor had gone, the area was covered with normal mucous membrane, and the ureter was visible.

July 6, she had gained from 4 to 5 pounds, and had a slight cystitis due to a cystocele, but there was no tumor.

December 19, she had a stellate white scar over the place occupied by the tumor. No tumor was visible.

CASE 6.—C. T., man, aged 59, eight months before being seen had occasional painless hematuria. Cystoscopy revealed papilloma near the left ureter. This was burned with the high frequency current four times in about six months, but had always recurred. Dr. Keyes saw it in January, 1916, when it was an ulcerated area with carcinomatous looking lumps. A piece removed was thus described (by Dr. Ewing): "The section is from a mass of tumor tissue 5 mm. in diameter. It presents a small alveolar and diffuse carcinomatous structure. The cells are extremely atypical, and some are of very large size, with very hyperchromatic nuclei. The outer portions are hydropic, the central areas show fibrosis, and here the tumor cells run in narrow rows or small groups."

Feb. 11, 1916, 214 mc. of screened radium were inserted for seven hours.

May 2, cystoscopy revealed normal mucous membrane over the space occupied by the carcinoma. The patient had had seven or eight erections since treatment, while he had been practically impotent for ten years before.

4. Barringer, B. S.: *The Treatment by Radium of Carcinoma of the Prostate and Bladder*, *THE JOURNAL A. M. A.*, Nov. 11, 1916, p. 1442.
5. Treated from October, 1915, to October, 1916.

6. Treated from October, 1915, to October, 1916.

In July, he had gained 10 pounds. Cystoscopy (by Dr. Ballenger) was negative.

November 8, Dr. Ballenger reported that he "had passed no more blood. Cystoscopy about a month ago showed only a reddened place where the growth was. There has been a rather persistent cystitis."

CASE 16.—J. A. H., man, aged 62, had had two attacks of total hematuria, one month and eight days before he was seen. There were no night frequency and no loss of weight. Dr. Keyes saw by cystoscopy a red, lobulated, rather flat carcinoma above the right ureter; he burned it with the high frequency current and advised radium. The patient went to another physician, who fulgurated the tumor and decided against both operation and radium. About three months later he returned when (on examination with Dr. Keyes) a flat carcinoma, sloughy in part, two or three times the original size, was revealed, extending from the bladder neck to a point 2 cm. above the right ureter. It had raised, thick, indurated edges. A specimen removed revealed carcinoma (Dr. Ewing). Two tubes of screened radium (one 90 and one 89 mc.) were left in the bladder six hours.

Two months later the patient returned, when redness of the right side of the bladder was seen and a small ulcer back of the ureter (well away from where the tumor was) probably due to radium burn. *No other lesion was seen.*

SUMMARY

Three out of eight patients with advanced carcinoma of the prostate have been markedly improved. In three out of four early cases the patients have been relieved of their symptoms, and the growth has so far shrunk as hardly to be appreciable by the finger. Moreover, four patients with bladder carcinoma appear to be cured by the use of radium. Of course I use the word "cured" in a restricted sense, but radium has done for these patients what no other agent short of operation could possibly have done, while for the prostatic patients it has done much more than operation could have done.

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THE ABSORPTION OF APOMORPHIN AND MORPHIN THROUGH THE CONJUNCTIVA *

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While surgeons, gynecologists, and even authorities on internal medicine have on frequent occasions looked with little faith on the efficiency of drug medication, an attitude of drug nihilism cannot be imputed to the ophthalmologist. Indeed, some of the most important pharmacologic contributions have been in the field of ophthalmology, and some of the most strikingly beneficial therapeutic effects have been produced in the treatment of eye conditions. We need but mention the employment of atropin, cocain, physostigmin, epinephrin and many other mydriatics, miotics, astringents, analgesics and antiseptics.

When we consider the highly developed blood and lymph supply of the eye and its appendages, especially the patent tear ducts, it is surprising that so few cases of drug absorption and intoxication through them are on record. So few are the cases found in the literature that many physicians deny the possibility of such absorption through the conjunctiva and the lacrimal apparatus, and attribute the poisoning in such cases to the careless administration of the drugs and to their absorption through the mouth of the patient.

A careful examination of the literature, however, will soon establish the authenticity of such poison cases. Thus, for instance, systemic poisoning by cocain through absorption from the eyes has been not infrequently observed. An interesting summary of such cases has been published by Falk.¹ That author collected reports of twenty cases of such poisoning. In one of them, a boy, aged 14 years, was severely poisoned by the instillation of 1 drop of 1 per cent. solution of cocain. In another case, a man, aged 40, suffered a collapse and respiratory failure after the instillation of 2 drops of a 4 per cent. solution.

Systemic symptoms from instillation of atropin into the conjunctival sac are even more frequent than those from cocain, and have been reported by Feddersen,² Lewin,³ von Jaksch,⁴ Blyth,⁵ Kunkel⁶ and other toxicologists as well as by many ophthalmologists.

In connection with pharmacologic investigations on opium alkaloids, which I have been conducting for some time past, an interesting observation was made which strikingly establishes the fact that certain drugs can be quickly absorbed through the conjunctiva.

If a few milligrams of apomorphin hydrochlorid are sprinkled into the eye of a dog and the animal is held still for a minute or two in order to allow the drug to dissolve, emesis follows in from two to five minutes.

The same phenomenon is produced by the instillation of a few drops of a 1 or 2 per cent. solution of apomorphin hydrochlorid. I have been able to produce a state of vomiting by the instillation or dusting of apomorphin into the conjunctiva, in every case in which it was tried. In all the experiments, care was taken to eliminate any possibility of the animal's absorbing the drug by licking. Furthermore, the experiments were repeated also on animals under anesthesia, and in a moribund state after prolonged operations; even in those cases retching movements followed the administration of apomorphin through the eye.

As vomiting is produced in dogs almost as easily with morphin as with apomorphin, experiments were also made with instillations of morphin solutions and insufflations of morphin powder into the conjunctival sac; here again emesis followed, although after a somewhat longer interval (five or more minutes).

It may be well to call attention to the fact that in the experiments described above, which were made on normal dogs, no cruelty was practiced, as I have quantitatively shown, in my work with Johnson and Bollinger,⁷ that the opium alkaloids have a slightly analgesic, local effect on mucous membranes.

I have had no experience with local applications of apomorphin or morphin on human subjects, nor do I recommend such practice. The foregoing experiments, however, should serve to emphasize the possibility and importance of drug absorption through the conjunctiva, and to render the ophthalmologists more cautious in the employment of toxic alkaloids.

Further experiments now in progress seem to indicate that the absorption of the foregoing drugs takes place through the blood and lymph channels, and not altogether through the nasal duct. The full data will appear in due time in the *Journal of Pharmacology and Experimental Therapeutics*.

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1. Falk: *Therap. Monatsh.*, 1890, 4, 511.

2. Feddersen: *Diss.*, Berlin, 1884.

3. Lewin: *Nebenwirkungen der Arzneimittel*, 1910.

4. Von Jaksch: *Die Vergiftungen*, 1910, p. 471.

5. Blyth: *Poisons*, 1906, pp. 358, 385.

6. Kunkel: *Handbuch der Toxicologie*, 1901, p. 706.

7. Macht, Johnson and Bollinger: *Jour. Pharmacol. and Exper. Therap.*, 1916, 8, 451.

* From the Pharmacological Laboratory, Johns Hopkins University.