

# EFFECT OF ORCHIECTOMY AND IRRADIATION ON CANCER OF THE PROSTATE\*

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THE RELATIONSHIP OF FUNCTION of certain endocrine glands to prostatic carcinoma was first demonstrated by Huggins and Hodges<sup>6</sup> who showed that this cancer is frequently inhibited by eliminating the testicular androgens by bilateral orchietomy or by neutralization of androgenic activity by estrogen administration; conversely, cancer of the prostate is activated by injection of androgens. Subsequently, the favorable action of estrogens in prostatic cancer was confirmed by Herbst<sup>3</sup> who reported that estradiol and diethylstilbestrol—the estrogens used by Huggins and Hodges—are substances which “seem to relieve pain due to local prostatic malignant tissue and bony metastatic carcinoma.” Huggins, Stevens, and Hodges<sup>8</sup> showed that prostatic carcinoma is an abnormal growth of cells resembling adult prostatic epithelium rather than tissue of a more primitive nature. These cancers responded to modifications of the androgenic hormonal status like adult prostatic epithelium such as the cystic hyperplasia of the prostate of senile dogs which increases and decreases in size and function corresponding to changes in the androgenic activity as was shown by Huggins and Clark.<sup>5</sup>

In line with the work cited is the observation of Munger<sup>9</sup> who treated 11 patients with prostatic cancer by transurethral resection of the prostate, irradiation of the prostatic area (several mapped-out areas were treated until usually each had received 2,000 roentgen units) and irradiation of each testicle (500 r.). Munger stated: “A study of several cases treated by testicular irradiation with resection seems to indicate that slightly better results were obtained than in those cases treated by resection and roentgenotherapy exclusive of the testicular application.”

It is the purpose of the present paper to survey the course and the results of treatment by surgical excision of the testes alone, and evidence is presented that irradiation of the testes in two cases did not eliminate the interstitial issue of the testes.

**MATERIAL.**—In most instances after opening the tunica vaginalis, the testis was dissected away from the epididymis, followed by closure of the tunica and skin in layers, without drainage. This achieves cosmetic and psychological effects in that two masses of tissue remain in the scrotum.

During the last 30 months, 45 patients with advanced prostatic carcinoma accompanied by local infiltration or metastases have been treated in this clinic

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by orchiectomy; 32 of these men had metastases demonstrable on roentgenologic examination of the bones; 21 patients were operated upon more than one year ago, and 15 men in this group had osseous metastases. Roentgenotherapy was employed in no case in this clinic.

### RESULTS OF ORCHIECTOMY FOR PROSTATIC CANCER

In the entire series of 45 patients subjected to orchiectomy, there have been eight deaths, all in men with extensive metastases to bone (Table I).

FIG. 1.

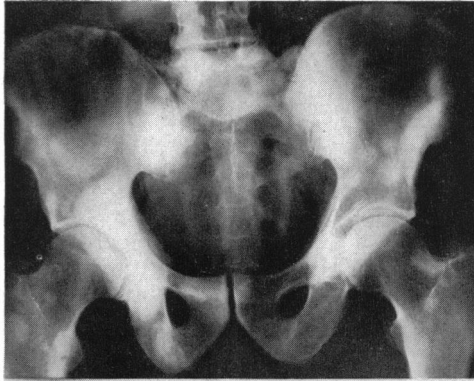


FIG. 2.

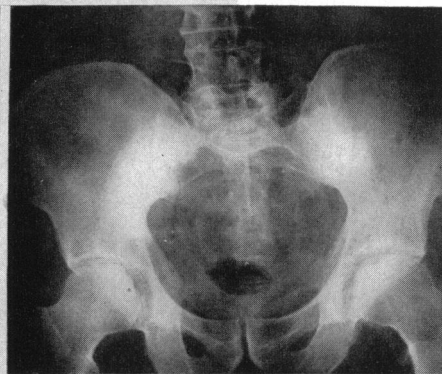


FIG. 3.

FIG. 1.—(Hospital No. 62292) Adenocarcinoma of prostate with extensive metastases to pelvis; pre-operative roentgenogram.

FIG. 2.—(Hospital No. 62292) The same patient as in Figure 1, 201 days after orchiectomy.

FIG. 3.—(Hospital No. 62292) The same patient as in Figures 1 and 2, 467 days after orchiectomy, showing complete disappearance of the radiographic evidence of metastases.

In four of these men, carcinomatosis was the principal cause of death, while in the others it was of secondary importance. From a clinical standpoint, 31 men have had a sustained improvement lasting as long as 30 months; nine men have had a temporary improvement followed by recurrence of symptoms; and in five men there was no improvement following castration.

In 11 men of the group of 21 patients operated upon 12–30 months ago, there has been significant improvement; these patients are free from symp-

TABLE I  
MORTALITY FOLLOWING ORCHIECTOMY FOR PROSTATIC CANCER

45 Patients Treated in 30 Months

Initials	Hospital Unit No.	Age, Years	Weight of Testes		Histologic Nature of Neoplasm	Time Since Orchiectomy, Days	Apparent Cause of Death
			Gm.	Gm.			
(1)... F. F.	274090	70	18	18	Adenocarcinoma	4	Pulmonary embolism
(2)... J. W. G.	26645	67	10	10.3	...	9	Pulmonary embolism
(3)... C. R.	49318	74	18	20.6	Undifferentiated carcinoma	10	Pneumonia. Pyogenic arthritis of knee
(4)... O. A.	252777	75	12.7	18.1	Adenocarcinoma	53	Cerebral apoplexy
(5)... S. R.	241797	72	0.7	10.2	Undifferentiated carcinoma	193	Lobar pneumonia. Carcinomatosis
(6)... G. P.	246583	73	9.0	8.2	Undifferentiated carcinoma	234	Carcinomatosis
(7)... P. M.	256818	56	13.4	17.0	Undifferentiated carcinoma	332	Carcinomatosis
(8)... M. M.	247587	57	8.6	7.8	...	500	Carcinomatosis

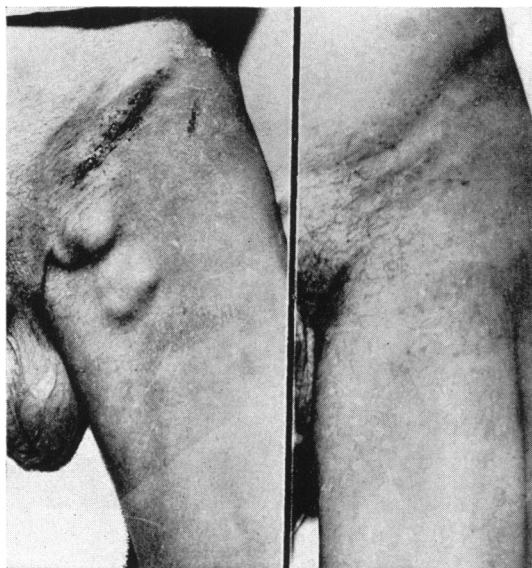


FIG. 4.—M. C. (a patient of Dr. W. S. Grant). Metastatic adenocarcinoma of the prostate in inguinal nodes on the left; the same region 107 days after orchiectomy is shown on the right

toms, acid and alkaline phosphatase values of serum are in or near the normal range, there has been complete or partial resolution of roentgenographic evidence of osseous metastases, and a great decrease in size and in the stony consistency of the primary neoplasm on rectal examination. In four patients, extensive osseous metastases have completely disappeared, as determined roentgenographically (Figs. 1, 2 and 3).

Thus, it is clear that there are many failures in the treatment of prostatic cancer by orchiectomy.

THE "FAILURE CASES" FOLLOWING ORCHIECTOMY FOR PROSTATIC CANCER

The following observations were made in those patients in whom orchiectomy did not produce marked resolution of the neoplasm or in whom clinical improvement was not long sustained.

(1) *The Histologic Nature of the Tumor.*—Sections of the prostate gland were studied in 16 patients and it was found that a correlation could be made

with the clinical course following orchiectomy. Cytologically, the tumors were classified into two groups: (a) Adenocarcinoma where the tumor formed acini (Fig. 5). All of these tumors were in Grades II or III. (b) Undifferentiated carcinoma where tubular structure was not fabricated but the tumor presented solid masses of malignant cells (Fig. 7). The clinical course following orchiectomy could be related easily to the cellular pattern. Without exception the tumor was undifferentiated in all of those patients who died from carcinoma, while it was adenocarcinoma in those patients whose course was satisfactory (Figs. 4-6). Classification of the tumors into adenocarcinoma and undifferentiated carcinoma, therefore, seems to have meaning although the types interdigitate. Both undifferentiated carcinoma and adenocarcinoma contained large amounts of acid phosphatase and are regarded as

FIG. 5.

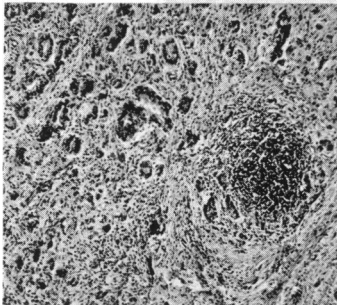
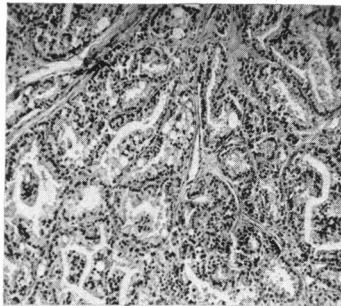


FIG. 6.

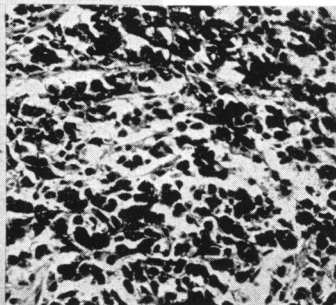


FIG. 7.

FIG. 5.—M. C. Metastatic prostatic adenocarcinoma, Grade II, in inguinal lymph node, before orchiectomy.

FIG. 6.—M. C. An inguinal lymph node 107 days following bilateral orchiectomy. There has been a marked decrease in the size of the acini which contain little or no secretion, and an increase of connective tissue stroma. There are areas of connective tissue scarring containing slits occupied by pyknotic and fused cellular nuclei.

FIG. 7.—Undifferentiated carcinoma of the prostate, stained by the method of Gomori for acid phosphatase.

cancers of adult prostatic epithelium, since the formation of large amounts of acid phosphatase in the prostate is a secondary sex characteristic of a chemical nature. For purposes of prognosis, it is impossible to distinguish between them by studying the serum phosphatases since both may cause elevation of acid phosphatase when they have metastasized.

(2) *The Size of the Testis.*—Three of the patients who died of carcinoma had testes which, considered singly, weighed 8–10 Gm. at operation. The smallness of the testis is due to a decrease of germinal epithelium, although sheets of Leydig cells remain. The presence of testes, markedly lighter than the normal weight of about 20 Gm., is a bad prognostic sign. Atrophy of germinal epithelium with real or apparent hypertrophy of the interstitial cells is not confined to prostatic cancer. Sand and Okkels<sup>10</sup> observed grave destruction of tubular epithelium in 24 instances in 72 cases of men dying from accidental causes or sterilized by law.

(3) *Decrease of the Primary Neoplasm when the Metastases are Producing a Fatal Carcinomatosis.*—It was observed in certain of the failure cases that the primary tumor greatly decreased in size while the metastases were advancing to produce serious illness, such as spinal cord compression (two cases) or even fatal carcinomatosis. This strange phenomenon, in which the hard, and more or less enlarged, prostate gland—at times greatly enlarged—underwent a decrease in size and hardness so that the prostate was completely soft and very small, was observed five times in the presence of the advancing neoplastic process elsewhere in the body. It appears that in certain patients the site of prostatic cancer in bone marrow or lymph nodes as metastasis is more favorable than the original prostatic location; it is possible that adjacent macrophages may facilitate separation of essential foodstuffs, such as androgens, from the body fluids for the improved nutrition of the cancerous metastases.

In other patients in the failure group, slight or no decrease in size of the primary neoplasm occurred, and here the prognosis is bad. Therefore, in advanced prostatic cancer when the primary tumor has undergone marked atrophy, one cannot say merely from atrophy of the primary tumor, as determined by local examination, that the course of the disease is favorable.

(4) *Supplemented Estrogen Administration in Postcastration Failure.*—It was shown by Huggins and Clark<sup>5</sup> that in dogs estrogen administration in adequate dosage masks the stimulating effect on the prostate of injected androgens; it was further demonstrated in this laboratory<sup>6,7</sup> that estrogen has a beneficial effect at times in prostatic cancer. Accordingly diethylstilbestrol, 1–3 mg. daily by mouth, was administered to ten patients with advanced prostatic cancer, who had an unsatisfactory response to castration. In one patient, there was a slight reduction of serum acid phosphatase but not to the normal range.<sup>7</sup> In nine patients, the disease was not perceptibly influenced. It seems that estrogen is able to neutralize to some extent the physiologic properties of the testis androgens, such as testosterone, but not to neutralize the effect of the adrenal androgens. It is believed that estrogen does not usefully supplement orchiectomy in prostatic cancer.

(5) *Hot Flashes: A Favorable Prognostic Sign.*—The presence of severe hot flashes was seen in all of the cases favorably influenced by orchiectomy, but also in certain of the unfavorable cases. These vasomotor incidents are not believed to be of therapeutic importance but are taken as a sign of androgen-

estrogen deficiency and are usually of favorable prognostic importance. There is no contraindication to their suppression with small doses of estrogen as described by Huggins, Stevens, and Hodges.<sup>8</sup>

**THE EFFECT OF IRRADIATION OF THE TESTES IN ADVANCED PROSTATIC CANCER**

Data were obtained on two patients in whom roentgenotherapy was applied both to the pelvis and testes. The clinical course following irradiation was similar in each.

**CASE REPORTS**

**Case 1.**—Hospital No. 269674: F. M., age 47, complained of perineal pain radiating into the right leg, and rectal examination disclosed a large indurated cancer of the prostate, which on biopsy was found to be an adenocarcinoma, Grade II. Four months after the onset of symptoms irradiation was applied to the pelvis over 55 days, according to the following formula: 800 KV; 10 Ma.; Filtration, 1 Mm. Pb; 1.56 Mm. Sn; 2.62 Mm. Cu; 3 Mm. Al; portals 15×20 cm.; tube distance 70 cm.; F.S.D. 250 roentgen units; duration of each treatment 7.5 minutes; ten treatments each to anterior and posterior right hip region and ten treatments each to anterior and posterior pelvis. There was symptomatic relief for two months when symptoms recurred and a second series of treatments were given through a 20×30 cm. portal; eight treatments to anterior and seven to posterior pelvis; the testes were not screened during the second course of treatments. Relief of symptoms occurred for about six weeks.

Eighty-seven days following the completion of therapy the original symptoms had returned and the patient used canes for walking. On rectal examination, the prostate was nodular, greatly enlarged and of stony consistency; a roentgenogram showed osteoplastic metastases in the right side of the pelvis. Orchiectomy was then performed; the testes weighed 15.7 and 16.3 Gm.

**Case 2.**—H. J. (ref. by Dr. C. C. Moore, Pittsburgh), age 63, complained of pain in the lower back and in the right leg; clinical and biopsy examinations of the prostate gland revealed carcinoma, and there was roentgenographic evidence of metastases in the spine. Roentgenotherapy was administered as follows: In a seven-day period, he received a total dosage of 1,600 roentgen units to each of four portals cross-firing the prostate gland given at the rate of 200 r. to each of two anterior portals daily with fields 16×19 cm. in size (200 K.V. constant potential; 0.5 Mm. Cu, 2 Mm. Al. Filtration added). The testes were protected in the usual way with lead rubber but undoubtedly received "back-scattering" of radiation in this series. A second irradiation was given six months later, without lead rubber protection, and the patient received 1,000 roentgen units measured in air, to each of four portals using a field 18×21 cm. in size with the application of 100–200 r. daily without screening of the testes. The patient failed to improve from this regimen and the prostate gland remained hard and nodular, so that bilateral orchiectomy was performed three months later. The operation was followed by a relief of symptoms and decrease in the size and consistency of the prostate gland.

The testes in each case presented similar cytologic characteristics, namely, profound atrophy of the germinal epithelium with preservation of Sertoli cells and apparent or real hyperplasia of the Leydig cells (Fig. 8).

The histologic appearance of the testis following irradiation in man corresponds to data obtained in experimental animals. Bourg<sup>1</sup> in the immature rat found that 1,000 roentgen units destroyed the seminiferous epithelium, but left interstitial cells intact. Heald, Beard, and Lyons<sup>2</sup> found in rats that an irradiation dosage of 1,152–4,608 roentgen units left the Leydig cells in a functional condition. Hu and Frazier<sup>4</sup> subjected rabbits to a series of ex-

posures to roentgen ray, aggregating 2,268 roentgen units (4.4 erythema skin doses) over a period of 15 days and produced complete atrophy of the germinal epithelium without interference with the secretory functions of the testes.

It is thus apparent that roentgen ray irradiation, in the amounts stated, is ineffective in destroying the secretory function of the testes and is inadequate as a therapeutic agent in prostatic cancer in man.

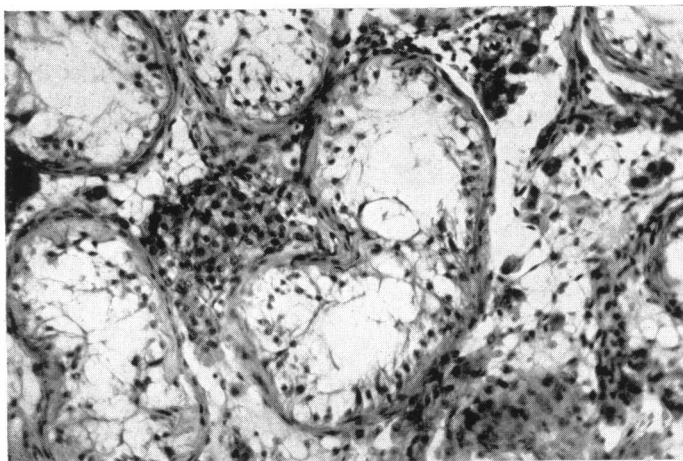


FIG. 8.—F. M. (Hospital No. 269679). Histologic appearance of the testis 87 days following completion of extensive irradiation with roentgen ray. The dosage is described in the text. Note tubular atrophy with preservation of interstitial cells.

#### SUMMARY AND CONCLUSIONS

In a series of 45 consecutive patients with advanced prostatic cancer, in whom the primary treatment was bilateral orchiectomy, there were eight deaths, all in men with metastasis to bones; in four of these, carcinomatosis was the principal cause of death. In five men, castration caused no clinical improvement; in nine patients there was temporary improvement, and in 31 cases a sustained inhibition of the disease occurred, lasting at least as long as 30 months.

The tumors were classified according to their cytologic appearance into two groups: adenocarcinoma and undifferentiated carcinoma. All of the deaths from carcinomatosis and the patients with no or slight improvement after orchiectomy had undifferentiated carcinoma, while in the more satisfactory cases the cytologic appearance was adenocarcinoma. The findings of testes much lighter than the usual weight of 20 Gm. signified a poor prognosis.

A phenomenon of interest, in which a great decrease occurred in the size of the primary neoplasm, while the metastases were advancing, was observed five times in this series.

Estrogen administration was not found to be a useful supplement in the failure cases after orchiectomy.

Roentgen irradiation of the testes in the doses stated, produced atrophy of

the germinal epithelium, but not of the interstitial cells of the testis, and is inadequate as a therapeutic agent in human prostatic cancer.

DISCUSSION.—DR. EVARTS A. GRAHAM (St. Louis, Mo.): I rise only because Doctor Phemister asked me to stick my neck out. I do not know anything about the prostate, of course, but I do want to say that I am delighted to have this work presented here. I have been hearing about it. I think it is the sort of presentation that the American Surgical Association needs more of.

The apology which I made, in getting to my feet, about the fact that I knew nothing about the prostate was meant to emphasize another point about this Association. The Association, up until a few years ago, was degenerating, may I say, into an organization which had only so-called general surgeons in it. I do not know whether you can degenerate into a general surgeon or not. At about that time it was felt desirable that the membership of the Association be leavened somewhat by adding to it some of those men who had gone off into specialties of various kinds. Now some of us who went off into thoracic surgery already had our membership in this Association, so nothing could be done about us. But an attempt was made to add new life to the Association by adding such people as Doctor Huggins, and I think the fact that that was done has been amply justified by his splendid presentation to-day.

I think this has another very important bearing, and that is, to my mind, it represents an approach to the subject, to the problem of cancer which is of interest, of course, to so-called general surgeons the same as to anyone else. We are particularly fortunate in having a paper of this sort, dealing with the subject of cancer in a broad aspect like this.

There are one or two specific points to which I would like to refer. Doctor Huggins did not have time to go into the historic aspects of this question, but castration for cancer of the prostate is a very old idea. If I am not mistaken, I think Bland-Sutton advocated it in the eighties, but it was given up, and it has been taken up since then by others and dropped after one or two experiences.

It was partly on the basis of the early results obtained in cancer of the prostate after orchietomy that the effort was made to treat cancer of the breast by removal of the ovaries, and the same sort of thing has happened again, namely, that after a little experience it has been dropped. But there have been sufficiently interesting results accumulated to make this approach at least one of great interest to the study of certain types of cancer.

Of course, Doctor Huggins has carried the procedure very much farther by applying new knowledge, new fundamental knowledge about cancer of the prostate and about the acid and alkaline phosphates to the rationality of the idea of orchietomy. But all in all, from every possible point of view from which one regards this work, one can only commend it to the highest degree.

DR. ALFRED BLALOCK (Baltimore, Md.): As a member of the Program Committee, I would like to express our appreciation for this paper and comment on one or two things Doctor Graham has said.

In the first place, Doctor Huggins was a general surgeon, who later developed a particular interest in genito-urinary surgery. But the main thing I want to say is this, that he demonstrates in this work, I think, the value of a prepared mind. Doctor Graham made the comment that the testicles were removed in a few instances many years ago for this lesion, but Doctor Huggins came across this because of the fundamental nature of his work in other fields. Many of you know of the notable contributions he has made to the study of bone. It was because of that information that he was able to grasp the significance of these findings on acid phosphates and to apply them to the treatment of this disease.

Having visited in Doctor Phemister's clinic, and having seen Doctor Huggins' cases, I can tell those of you who have not seen them that I am sure you will be perfectly amazed.

As Doctor Graham has said, if a real contribution is made in cancer in any one field, such as Doctor Huggins has made, at least, it raises our hopes of being able to find out something about cancer in other parts of the body.



I think that we as an Association should be very happy in having this excellent work presented here.

DR. WILLIAM JASON MIXTER (Boston, Mass.): I simply wish to say that we have had one such case at the Massachusetts General Hospital that I know of, treated in this way, a case of carcinoma of the prostate with metastasis to the spine, and with very severe pain, that I operated upon for cord compression. Roentgenotherapy did not work very well, and orchietomy seems to have done a very good piece of work.

DR. CHARLES HUGGINS (closing): I am highly flattered, and very much embarrassed, by the kind remarks of Doctor Graham and Doctor Blalock. I would like to make just a few comments on the matter of the history of orchietomy for carcinoma of the prostate. I believe the only person who, knowingly, operated to remove the testes for carcinoma of the prostate was Dr. Hugh Young, who did this in two patients, with negative results. It is unfortunate that his cases apparently were not of that type which responds well.

The wave of operations that has been mentioned for removal of the testes for prostatic conditions, I believe, has been confined otherwise to benign prostatic hypertrophy.

With regard to the breast, I am on very uncertain grounds, because I think it is extremely unwise to carry over data from one cancer to another cancer. We do know that in the case of the breast this structure is affected by two hormones, one estrogen, from the ovary, the other, prolactin from the pituitary. If it is a prolactin tumor, then ovariectomy would obviously be a suitable procedure. I think we have fallen into one error lately, and that is to treat patients who are still menstruating, with cancer of the breast, by roentgenotherapy of the ovaries. Certainly, it is impossible to eliminate the interstitial cells of the breast by roentgenotherapy of the ovaries, and I think it is extremely likely that the bad results that are obtained in the breast cancer, at the present time, by attempting to modify the endocrine state, are due to the use of roentgen ray. I strongly feel that surgical ovariectomy should be performed in patients with advanced cancer of the breast, with metastasis, who are in the menstrual age rather than irradiation.

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