

# THE PRESENT STATUS OF CASTRATION FOR CARCINOMA OF THE PROSTATE

C. C. HIGGINS, M. D. and C. L. GOSSE, M. D.

The treatment of carcinoma of the prostate has long been considered a major problem in the practice of urology. Resection of the gland by one technic or another, x-ray therapy, or both have been the chief methods of treatment. However, the condition has been so far advanced when the patient has presented himself that the outlook has been pessimistic. Now and then hope has been offered by some new therapeutic measure, but the proof of time and experience usually has been lacking.

Today castration as a new method of treatment seems to promise gratifying results. This procedure may be compared with oophorectomy for carcinoma of the breast in that both are on a hormonal basis. However, from early conservative reports castration for prostatic carcinoma seems to have a definitely more favorable outlook.

It has been shown that when androgenic hormones are reduced sufficiently, prostatic epithelium undergoes atrophy. Conversely, the injection of adrogens stimulates the growth of prostatic epithelium, and the injection of estrogens retards its growth. Furthermore, eunuchs who are without a primary source of androgens do not develop prostatic hypertrophy.

Carcinoma of the prostate results from overgrowth and invasion of adult epithelial cells. Concrete evidence of this has been shown by phosphatase estimations. Gutman and Gutman<sup>1,2</sup> and Kutscher and Wolbergs<sup>3</sup> made extensive studies of the subject. The former examined prostate glands at various ages for acid phosphatase. They observed low values in children, a slight increase through puberty, and high values in adults. The phosphatase values for carcinoma of the prostate were similar to those for the adult gland. Huggins et al,<sup>4,5,6</sup> confirmed this work by staining methods and found that the enzyme phosphatase of normal adult and hypertrophied prostates compared in quantity with that of carcinomatous glands. From this they concluded that the prostatic carcinomas examined consisted of adult rather than of more primitive neoplastic epithelium. Further evidence has been found in the levels of urinary keto-steroids. Slatterthwaite, Hill, and Packard<sup>7</sup> showed that the mean level of excretion of 17 keto-steroids in ten cases of benign prostatic hypertrophy did not vary significantly from that in carcinoma of the prostate.

The determination of the serum phosphatase is a valuable aid in the diagnosis of metastatic bone lesions from carcinoma of the prostate. It also helps to evaluate the effects of therapy and may be significant in determining the patient's prognosis.

The enzyme phosphatase has been found in body tissues and fluids in varying amounts. It has the ability to liberate phosphate ions from a solution containing esters of phosphoric acid. Two methods of determination are the King-Armstrong and the Bodansky. Both express the phosphatase activity in units. The pH of the medium determines the amount of phosphatase activity. The optimum pH for acid phosphatase is 4.9, whereas that for alkaline phosphatase is 8.6. One acid phosphatase unit (K-A) is defined as "that degree of phosphatase activity which at pH 4.9 and 37 degrees C. will liberate 1 mg. of phenol from the specific buffer—monophenylphosphate substrate solution—in one hour. The number of units is determined to express the amount of phosphatase activity in 100 cc. of blood serum."<sup>5</sup>

The acid phosphatase level is undoubtedly more significant in cases of carcinoma of the prostate, and whenever it has been increased appreciably, metastasis has invariably been present.<sup>8</sup> However, metastasis has also been present when the acid phosphatase levels have been normal. Thus there are false negative but no false positive reactions. The normal level is from 0 to 4 K-A units, although 4-6 units is considered high normal under certain circumstances.

The alkaline phosphatase level may be considered as a diagnostic adjunct to acid phosphatase in borderline cases. The normal is from 0 to 6 units. Herger and Sauer<sup>8</sup> warn that in the interpretation of 4-6 units of acid phosphatase activity the utmost caution should be exercised when the alkaline phosphatase is under the average normal of 6 units or elevated above 12 units, and that frequent determinations should be made. Alkaline phosphatase estimations are also of value in the differential diagnosis of bone metastasis from carcinoma of the prostate and Paget's disease of the bone.<sup>10</sup> In the latter the acid phosphatase level is usually normal, whereas the alkaline phosphatase is increased. High alkaline phosphatase readings are also obtained in active rickets, generalized osteoporosis, hyperthyroidism, and biliary obstruction. In these conditions acid phosphatase levels are usually normal.

Castration for carcinoma of the prostate has been performed by Huggins et al,<sup>5</sup> and their series of 21 cases has been reported in detail. Nine cases showed osteoplastic metastasis, six showed osteolytic, and the remaining six cases presented no evidence of metastasis. The average age of the patients was 69, the youngest being 54, and the oldest 84 years of age.

In the last 14 cases serum phosphatase levels were recorded before and after orchidectomy. Phosphatase levels associated with the various metastatic bone lesions were within the following limits:

Phosphatase Levels in K-A Units		
Nature of Metastasis	Acid Phosphatase	Alkaline Phosphatase
Osteoplastic	22 — 75 units	22— 78 units
Osteolytic	1.5— 37 units	6— 24 units
None	1 —4.5 units	6—9.75 units

Castration was performed under local anesthesia in most cases. Transurethral resection of the prostate was performed in seven instances, and suprapubic prostatectomy in one case. Roentgen therapy was not used in any of the patients. Pathologically, the testis revealed nothing of significance.

Three patients in this series died within a few months of cardiac disease or pneumonia. Another patient died in 234 days without any pronounced relief of symptoms or other improvement. The remaining patients maintained gains in weight of 3 to 18 kg. within two to 18 months. The trend of the erythrocyte count was upward. Pain which had been prominent in patients with metastasis showed either a recession or complete remission within two to eight weeks after castration. Of the seven patients previously confined to bed, six became ambulatory. One patient with involvement of the cauda equina showed resolution of the lesion. Sexual desire and penile erections were absent, but no mental changes were noted. Hot flashes similar to those experienced by women after the menopause were evident in six cases, but were relieved by the use of stilbestrol in small doses.

By rectal palpation the prostate gland was found to be diminished in size in the majority of cases to the extent of being just preceptible or actually impalpable within 12 weeks. This decrease in size was maintained throughout the periods of observation, the longest of which was 18 months. Roentgenograms taken following operation showed increased osteosclerosis within three to six months. Whether or not this phenomenon signifies remission is still a matter of conjecture. High acid phosphatase levels before castration usually became or approached normal following operation. When the normal was not attained, it was believed that there may have been an increased extratesticular output of androgens.

Satterthwaite, Hill, and Packard<sup>7</sup> have reported a series of ten cases of extensive carcinoma of the prostate in which castration was performed. These workers made a study of the excretion of the 17 keto-steroids in the urine both preoperatively and postoperatively as well as

phosphatase levels and found a general reduction in the output of the 17 keto-steroids, varying from 12 to 60 per cent of the preoperative level.

Their results seem to be almost as promising as those of Huggins et al.<sup>5</sup> Two patients had "complete relief from pain, increase in appetite, gain in strength, a marked decrease in obstructive symptoms, and a drop in the basic phosphatase to normal levels." These two cases which showed the most improvement had a drop in the 17 keto-steroid output; in one case from 2.3 to 0.9 and in the other from 12.6 to 6.7 mg. in 24 hours. One patient who showed virtually no improvement had a reduction of from 3.9 to only 3.4 mg. in 24 hours. In the other seven cases clinical improvement apparently coincided with the reduction in the urinary output of the 17 keto-steroids. These workers suggest the advisability of estrogen therapy as an adjunct in cases in which sufficient reduction of 17 keto-steroids is not obtained.

Simple bilateral orchidectomy can hardly be considered a major operation. However, it requires at least two or three days' bed rest and is associated with a certain amount of discomfort following the procedure. Consequently, irradiation to the testicles as a substitute for orchidectomy is worthy of consideration. Only a small amount of irradiation is necessary to destroy the spermatogenic cells of the testicle. However, the interstitial cells which are responsible for the androgen supply are comparatively radioresistant. Munger<sup>9</sup>, however, has shown clinically that supervoltage irradiation of the testicle has produced diminution of the symptoms and physical findings and comparatively has increased longevity. His measurements were purely qualitative, and little quantitative laboratory or other data were recorded. He reported 76 cases of carcinoma of the prostate in patients admitted to his service in a five year period ending December 1938. At the time of the report (May 1941) 51 patients were dead, seven were unaccounted for, and 18 were alive. Of the 76 patients 12 had prostatic resection alone; 45 had resection and irradiation to the prostatic area; and 11 had resection, irradiation, and an additional 500 r supervoltage therapy to the testicles.

The results were rather significant. Of the 12 patients which had resection alone, all died. Of the 45 who had resection and irradiation, only ten were alive. Of the 11 who had resection, irradiation, and adjunct x-ray therapy, eight were still alive. Furthermore, this latter group had improved symptomatically, and the prostatic bed by rectal examination was found to be "smooth, resilient, and free of nodules." The longest period of survival was seven years and the shortest three years.

A comparison of the results from irradiation of the testicles with the results from orchidectomy is difficult to establish. The scientific data are not quantitatively available from the cases in which irradiation

of the testicles was performed. The keto-steroid and phosphatase levels were not recorded. Therefore, a common basis for accurate judgment obviously is lacking. Consequently, more detailed studies must be made before drawing any definite conclusion.

No one can deny castration a scientific parentage, nor that, according to early reports, the procedure is warranted, especially since there is much to gain and little to lose. Even if only the intense pain from bony metastasis has been alleviated and the patients allowed to die in comparative comfort, something has been accomplished. The scientific material at hand is by no means sufficient to warrant its adoption without reservation as to the end results. In the presence of obstruction transurethral resection also may be advisable.

The Cleveland Clinic has followed the procedure of advising orchidectomy for carcinoma of the prostate, or orchidectomy and transurethral resection for nearly a year. The results have been variable, but on the whole have been successful enough to justify the procedure.

*Results:* Our series consisted of 16 cases. The average age of the patients was 69 years. In 12 of the 16 cases there was no evidence of metastases, while four showed an osteoplastic type of lesion chiefly of the pelvis and spine which was observed on x-ray examination. In cases without metastases the blood counts for the most part were normal; those with metastases showed varying degrees of anemia. The acid phosphatase ranged in the nonmetastatic cases from 1.0 to 2.6 units and in cases with metastases from 5.6 to 80 units.

Nine of the 16 cases had transurethral resections of the prostate as well as orchidectomy. In seven cases there was no biopsy of the prostate. The nine cases in which biopsy was obtained at the time of transurethral resection showed four adenocarcinomas, three undifferentiated carcinomas, one medullary duct type of carcinoma, and one papillary carcinoma. It was noted that bony metastasis was present only in those cases which showed adenocarcinomatous growths.

In five instances only a few weeks had elapsed since operation, or no follow-up data were obtained. Seven cases showed definite improvement in relief from symptoms. One showed a gain in weight but developed slight incontinence for some unexplained reason (transurethral resection was not performed); and three showed an increase in appetite and a gain in weight, diminution in the size of the gland by rectal examination, diminution in the obstructive symptoms, and lessening or complete remission of pain. Furthermore, these patients felt improved generally.

In four cases subsequent laboratory estimations were made, and in these the acid phosphatase, which originally had been normal, showed a decrease varying from 0.1 unit to 1.8 units over periods ranging up to five

months. In two cases subsequent alkaline phosphatase estimations were made, both of which had showed normal readings. In one case the change was from 2.5 units on the day of operation to 2.8 units four months later. In the other case the reading was 1.9 units at operation and 1.7 units six weeks later. In two cases 17 keto-steroid estimations were made preoperatively and postoperatively. Before operation the first case showed an output of 3.3 mg. per 24 hours; 8.8 mg. the day following operation; and 5.6 mg. six weeks later. The second case showed an output of 7 mg. per 24 hours before operation and 4.3 mg. two days after operation. In another case the 17 keto-steroid estimation one month following operation was 4.6 mg. per 24 hours. Two months postoperatively it was 7.5 mg.

Only when there had been definite anemia was the trend of the erythrocyte count decidedly upward. Hot flashes occurred in three cases, but there were no mental changes. Penile erections and sexual desire were absent in the majority of cases postoperatively.

#### CASE REPORT

The following case report is illustrative.

The patient was admitted on June 19, 1941 with complaints of frequency, urgency, dysuria, dribbling, and nocturia as many as fifteen times. There was considerable pain in the lumbar region, pelvis, and thighs. These symptoms had been of approximately six months' duration. During this time he had lost 25 pounds in weight. There was no history of hematuria.

Upon rectal examination the prostate gland revealed grade IV enlargement, was hard, nodular, and fixed, and there was marked extension to both vesicles. The residual urine was 285 cc. The blood count upon admission showed 4,980,000 red blood cells, 91 per cent hemoglobin, and 5,500 white blood cells. The urine and blood chemistry studies were essentially normal. Estimation of alkaline phosphatase was 2.5 units per 100 cc. serum; acid phosphatase 1.8 units per 100 cc. serum. There was no evidence of bony metastasis by x-ray.

On June 27, 1941, under low spinal anesthesia, a bilateral orchidectomy was performed. The patient was discharged from the hospital on the tenth postoperative day after an uneventful convalescence.

Subsequent acid phosphatase estimations were as follows:

6/28/41	2.1	8/19/41	3.0
6/30/41	1.9	10/31/41	1.1
7/1/41	1.9		

Alkaline phosphatase estimations were:

6/28/41	2.7	7/2/41	2.6
6/30/41	2.7	8/19/41	3.0
7/1/41	2.6	10/31/41	2.8

17 keto-steroid estimations were:

6/30/41	11.3 mg. per 24 hour specimen
11/4/41	13.0 mg. per 24 hour specimen

Follow-up examination on February 23, 1942 showed the patient to be generally improved in appearance. His symptoms had entirely disappeared; pain was absent; there was marked improvement in the caliber of the urinary stream; and no residual urine was noted. He had gained 50 pounds in weight since the operation. The gland

had diminished in size to almost normal; there were no palpable nodules; and the consistency of the gland had changed from stony hardness to a more normal one. However, the extension to the vesicles seemed to be just as prominent if not more so. Sexual desire was absent, and penile erections were impossible. However, there were no mental changes. The patient had been having hot flashes once daily which lasted for about five minutes and were associated with flushing and perspiration.

#### SUMMARY

Orchidectomy appears to be a valuable adjunct in the treatment of carcinoma of the prostate.

Individualization of the patient is essential, as in some cases transurethral resection is also required to relieve the immediate obstruction. However, not until a large number of cases have been so treated, and detailed laboratory and clinical data compiled over a longer period of time, will we be able to evaluate scientifically the results of this procedure.

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