

CONCLUSION

1. Beta radiation proved beneficial to many patients, because even slight improvement lessened their dependency and enhanced their usefulness.

2. Beta radiation offers another method in the treatment of corneal scars and certain lid lesions, especially if applied early and in conjunction with other therapy. We believe that gamma radiation of the most dense scars can be used in conjunction with beta radiation treatment.

3. Cost, lack of availability, and persistency of the scar detract from the value of beta radiation.

REFERENCES

1. Moore, J. E.: Personal communication to author, (A.D.R.).
2. Gifford, S. R.: Personal communication to author, (A.D.R.).

TREATMENT OF CARCINOMA OF THE PROSTATE

CHARLES C. HIGGINS, M.D.

With the introduction of estrogen therapy and orchiectomy as supplemental measures in the treatment of cancer of the prostate, new concepts were made available for combating this disease.

Sufficient time has now elapsed to warrant evaluation of the various types of treatment. Opinions of other surgeons and a personal experience with 100 cases forms the basis for such an evaluation.

In 1941 Huggins demonstrated the effect of certain hormones upon carcinoma of the prostate.¹ With the advent of this knowledge a new era in the treatment of this disease has been entered.

Various treatments have been recommended: orchiectomy, administration of estrogen substances, and irradiation of the testes. Interesting observations have been made regarding such treatment. Alleviation of pain, pronounced regression of the primary neoplasm, and disappearance of metastasis have occurred in many patients. Some, however, do not respond to treatment satisfactorily; relief of symptoms is transitory, and in a few little benefit is obtained.

Randall in 1942 reported a series of 5 cases in which castration had been performed for carcinoma of the prostate in 1934.² Transurethral

CARCINOMA OF THE PROSTATE

resection was employed to relieve the obstructive symptoms. He stated that the clinical course following surgical castration was similar to that following a transurethral resection alone. This first suggested that the beneficial effects obtained by hormonal therapy would not exert a permanent effect.

A review of the cases of prostatic carcinoma occurring in two successive years is presented to evaluate the various types of treatment employed at the present time, their indications, and the end results.

In considering the role of radical perineal prostatectomy certain features warrant elucidation. Carcinoma of the prostate in 75 per cent of cases arises in the posterior lobe. It invades the remainder of the gland slowly; extension through the capsule is impeded by the two layers of Denonvilliers' fascia, which is devoid of lymphatics. During this time the disease is confined to the gland, although later the seminal vesicles are invaded or dissemination through the perineural lymphatics occurs. While the disease is confined to the prostate gland, radical perineal prostatectomy should be followed by a cure.

It has been my experience, however, that, due to the absence of symptoms, patients rarely present themselves for examination until the carcinoma has extended beyond the confines of the gland. The periprostatic tissue has been invaded as evidenced by fixation of the gland, or the lesion has extended beyond the base of the seminal vesicles, or has involved the membranous urethra. If radical operation is to be recommended, early recognition of the lesion is essential. Therefore, in patients in whom the lesion is still confined to the gland, metastases are not demonstrable, and phosphatase studies suggest the absence of metastasis, I believe a radical perineal prostatectomy should be recommended. Only one patient in the group was in this category. He lived for two years after operation when metastasis resulted in death.

HORMONAL TREATMENT

Three methods of approach are available in hormonal treatment of carcinoma of the prostate: (1) administration of estrogenic hormones, (2) surgical castration, and (3) irradiation of the testes. Surgeons, among them Kearns and Dean, prefer the administration of estrogens. Kearns states,³ "Simple estrogen therapy will gain in favor because all the attainable benefits of castration minus some of the undesirable side effects are obtainable by the judicious use of the true hormone estradiol given to each individual by the most effective route."

Dean also has indicated a preference for the use of stilbestrol:⁴ "When they first began to treat cancer of the prostate by modification

of the endocrines, alternate patients were treated by castration and by the administration of stilbestrol. After observing the results, 1 mg. of stilbestrol daily by mouth at bedtime has remained the primary treatment of choice."

I have arrived at similar conclusions after comparing the results secured by orchiectomy and estrogenic treatment and recommend stilbestrol 1 to 3 mg. by mouth daily.

By selecting cases occurring in two successive years, I hope to demonstrate the progressive decrease in the choice of orchiectomy in the treatment of carcinoma of the prostate and its replacement by estrogenic therapy. From Nov. 1, 1942, to Nov. 1, 1943, I treated 52 patients with carcinoma of the prostate. A bilateral orchiectomy was performed on 25 patients and estrogen therapy was the treatment employed for the remainder. From Nov. 1, 1943, to Nov. 1, 1944, of 49 patients with carcinoma of the prostate treated, 17 were subjected to bilateral orchiectomy. During 1945, however, the administration of estrogens practically replaced surgical castration as the treatment of choice.

In those patients treated by orchiectomy all androgenic activity of the body does not cease. Other androgenic activity is present after bilateral orchiectomy as indicated by excretion of androgens in the urine and presence of androgens in the adrenal cortex. Estrogen therapy, on the other hand, depresses the anterior pituitary gland and may depress the andromimetic function of the adrenal glands.

In 44 per cent of patients a decrease in the size of the primary neoplasm occurred following the administration of estrogens. The gland became softer in consistency and in a few instances it would have been difficult at a later date to arrive at a diagnosis of carcinoma of the prostate by rectal examination. Other surgeons still prefer bilateral orchiectomy for the relief of patients with carcinoma of the prostate. Scott,⁵ for example, in 1945 reported 82 consecutive patients in various stages of development of the disease, all of whom were treated by orchiectomy. Emmett believes that,⁶ "The indication for bilateral orchiectomy is carcinoma of the prostate with metastasis." He states further that his present practice is to advise orchiectomy primarily for patients suffering metastases for the relief of metastatic symptoms. In 61 per cent of the cases from Nov. 1942, to Nov., 1944, treated by orchiectomy a regression of the neoplasm occurred, with a softer consistency of the gland, and less fixation.

As stated previously administration of estrogens has practically replaced surgical castration during the past year. The only patients being subjected to bilateral orchiectomy are those bed-ridden from intolerable

pain and in whom I believed a more rapid response to treatment could be secured by castration.

IRRADIATION OF THE TESTES

Munger has advised irradiation of the testes to replace surgical castration.⁷ In his hands this treatment compares favorably with the results secured by bilateral orchiectomy. This procedure has not been employed in any of the patients in this series.

The study of the acid and alkaline phosphatases is of considerable value in the diagnosis of metastases before bilateral orchiectomy or the administration of estrogens. It will be observed that following bilateral orchiectomy the acid phosphatase quickly approximates normal levels. In patients in whom metastasis to the bony skeleton had occurred it was observed that following castration there was an initial elevation of the alkaline phosphatase in 58 per cent of the cases. However, this was followed later by a decrease in the alkaline phosphatase. On the other hand, when estrogen therapy was employed there was a more gradual decrease in the acid phosphatase to normal limits. If metastasis were present the initial rise in the alkaline phosphatase was not so constant. If an elevation of the alkaline phosphatase occurred the later fall was more gradual.

According to Kearns,³ deviation of the blood sedimentation rate occurs in 100 per cent of the patients and is an excellent procedure to follow the clinical progress of the patient. Remarkable improvement in the sedimentation almost invariably follows the institution of endocrine therapy. While I have not adopted estimation of the sedimentation rate as a routine procedure, but have relied on the acid and the alkaline phosphatase determinations, in a few cases in which such studies have been made I believe Kearns' opinion to be justified.

GENERAL CONSIDERATIONS

Castration or the administration of estrogens in a small group of patients treated by either method showed little response to treatment. The course of the disease is not arrested and death ensues. The second and largest group shows a definite and satisfactory response with pronounced improvement following either castration or the administration of estrogens. Following castration the pain due to metastatic involvement of bones disappears quite promptly in twelve to thirty-six hours, while from administration of estrogens similar relief occurs in seven to ten days. A patient who has been confined to bed with pain becomes active. Not only the pain disappears, but appetite and the general condition

also are noticeably improved. The patient gains in weight, probably due more to the eunuch state than to improvement in the general physical condition. In spite of this improvement it has been disappointing to find that after a period of eight to eleven months a relapse occurred in 58.5 per cent of the patients.

In the third group treated by orchiectomy or estrogen therapy a patient may continue in excellent health, free from symptoms for an indefinite period of time. Such a favorable course may occur in patients who have had no treatment at all. A patient, not included in this series, was diagnosed clinically several years ago as having carcinoma of the prostate. There was complete absence of symptoms and no treatment was instituted. He has been followed for fifteen years and has continued to be free of symptoms. Unfortunately this diagnosis was not confirmed by biopsy.

Another group of patients with carcinoma of the prostate requires relief of obstructive symptoms. Between Nov. 1, 1942, and Nov. 1, 1943, among 52 patients treated for carcinoma of the prostate, I performed a transurethral resection of the prostate on 17 to relieve obstructive symptoms. In the following year, 21 among the 49 patients were similarly relieved.

In the series reviewed there has not been a single instance of the complete disappearance of a metastatic lesion in the bones or the lungs following either castration or the administration of estrogens. It is true that in many instances roentgenograms led me to infer a definite improvement has occurred, but biopsy studies were not available to substantiate the impression.

Dean does not depend entirely upon the roentgenograms and states,⁴ "We have experienced difficulty in recognizing x-ray evidence of changes in the bony metastasis during and after treatment." He relies on phosphatase studies to indicate the status of the bone lesions.

In reviewing the results obtained in treatment of carcinoma of the prostate either by castration or estrogen therapy it is essential to compare these results with a similar group of patients in whom such therapy was not employed.

Bumpus,⁸ in a review of 1000 cases of carcinoma of the prostate, reported that 485 patients who received no treatment from the onset of symptoms lived for an average of thirty-one months. Among these untreated patients 66.7 per cent had untreated metastasis at the time of diagnosis, and died within nine months.

As previously mentioned 58.5 per cent in this series had a recurrence of symptoms nine to eleven months after orchiectomy or estrogen therapy. The disease continued to progress in spite of all therapeutic pro-

cedures. It has been my experience that the administration of estrogens helps but little when the patient has had a recurrence after castration. There appears to be no significant difference between the results of estrogen therapy and those of orchiectomy. In our series of cases of carcinoma of the prostate treated by orchiectomy or estrogens 38 per cent died within twelve to fourteen months.

32.6 per cent of patients treated by orchiectomy succumbed within twenty-four to thirty-two months; dead or delayed failures in same period of time 56.4 per cent; 62 per cent succumbed in a like period of time when treated with estrogens, and 68.9 per cent are dead or delayed failures. All were clinically free of metastasis at the time treatment was instituted. When metastasis was present at the time of treatment, 71 per cent died in a similar period of time.

An important question now arises: If orchiectomy or estrogen therapy is to be employed for carcinoma of the prostate, and the relief of symptoms is only temporary, should it be recommended as soon as the diagnosis is established or held in reserve until urgently required? Treatment at the later time may be expected to afford relief from pressure, from local invasion of the growth or of a metastasis. Another variation occurs between the orchiectomy group and the stilbestrol group in that in the latter group several patients discontinued stilbestrol medication. In many advanced cases stilbestrol was also used as a palliative procedure.

Bugbee believes,⁹ "If orchiectomy is carried out early in the disease, the relief it affords at a later period when it is most needed, is denied the patient." Nesbit and Cummings likewise comment¹⁰ that "the maximum benefit to the patients may be derived by delaying endocrine treatment until indicated by advanced or metastatic lesions."

In view of available statistics demonstrating the temporary relief afforded by castration or estrogen therapy, the question arises whether in the majority of cases endocrine therapy should be reserved for later relief of pain associated with this disease.

SUMMARY

1. Orchiectomy or estrogen therapy is not a cure for carcinoma of the prostate.
2. Estrogenic therapy or orchiectomy have about the same value in treatment.
3. Obstructive symptoms may be relieved by transurethral resection of the obstructing gland.

4. Radical perineal prostatectomy should be recommended when it is technically possible and when the disease is contained wholly within the gland.

5. Because of the temporary relief it affords it may be wiser to reserve the employment of endocrine therapy until the disease is well advanced.

6. Acid and alkaline phosphatase studies are a valuable aid in the diagnosis of prostatic cancer before and after operation.

REFERENCES

1. Huggins, C., Stevens, R. E., Jr., and Hodges, C. V.: Studies on prostatic cancer; effects of castration on advanced carcinoma of prostate gland. *Arch. Surg.* **43**:209-223 (Aug.) 1941.
2. Randall, A.: Eight-year results of castration for cancer of prostate. *J. Urol.* **48**:706-709 (Dec.) 1942.
3. Kearns, W. M.: Treatment of carcinoma of prostate with estrogens. *Wisconsin M. J.* **41**:575-581 (July) 1942.
4. Dean, A. L.: Discussion. *Bull. New York Acad. Med.* **21**:326-329 (June) 1945.
5. Scott, W. W., and Benjamin, J. A.: Role of bilateral orchiectomy in the treatment of carcinoma of prostate gland; report of 82 cases, *New York Acad. Med.* **21**:307-332 (June) 1945.
6. Emmett, J. L., and Greene, I. F.: Bilateral orchiectomy for carcinoma of prostate gland; clinical experience. *J.A.M.A.* **127**:63-67 (Jan. 13) 1945.
7. Munger, A. D.: Treatment of carcinoma of prostate by irradiation. *Radiology* **45**:31-39 (July) 1945.
8. Bumpus, H. C., Jr., Massey, B. D., and Nation, E. F.: Experience with orchiectomy for carcinoma of prostate. *J.A.M.A.* **127**:67-68 (Jan. 13) 1945.
9. Bugbee, H. G.: Discussion. *Bull. of New York Acad. Med.* **21**:320-323 (July) 1945.
10. Nesbit, R. M., and Cummins, R. H.: Prostatic carcinoma treated by orchiectomy; secondary report based on 75 cases observed for at least 21 months following operation. *J.A.M.A.* **124**:80-81 (Jan. 8) 1944.



CLEVELAND CLINIC BUILDINGS

Fronting on East Ninety-third Street

- a. Seven stories to be added to the Clinic in 1946
- b. Research Division
- c. Additional building for 35 hospital beds in rear of this entrance
- d. Cleveland Clinic Hospital
- e. Hospital addition for 120 patients