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Treatment of carcinoma of the prostate with estrogens and orchiectomy

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THE TREATMENT OF CARCINOMA OF THE PROSTATE WITH ESTROGENS AND ORCHIECTOMY

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INTRODUCTION

Any doctor who has a serious regard for the highest ideals of his profession is anxious to consider any available means to alleviate suffering and to make life more worthwhile for his fellow man. Treatment of carcinoma of the prostate is most important for consideration because of the high incidence and the increasing frequency of the disease.[1] It is a disease of longevity, and this is an age of ever increasing life expectancy. Years ago, when life expectancy of man was less than fifty years, carcinoma of the prostate was infrequently encountered. Records of the Metropolitan Life Insurance Company show that man's life expectancy has risen from 46.6 years in 1911 to 63.4 in 1941, and that with this increase in life expectancy has come a concurrent increase in the number of prostatic carcinoma victims. Statistics state that the incidence of prostatic carcinoma as a cause of death increased from 0.8 per 100,000 in 1917 to 3.7 per 100,000 in 1928. Pathological study of serial sections of the prostate, taken at random from autopsies of men over fifty years of age, revealed small carcinomatous degeneration to be present in 18 to 21% of the cases. Carcinoma of the prostate affects possibly 5% of all men who reach the age of 60 years.[2;3]

The purpose of this paper is to call attention to a comparatively new treatment of cancer of the prostate. This treatment makes possible the immediate relief of symptoms as soon as there are signs of retention, and the treatment is accomplished without major surgery. It consists of estrogen therapy and castration used individually or in combination with each other.

Because the success of the treatment depends upon the early diagnosis of the carcinoma, it is the further purpose of this paper to emphasize that it is important for every man past fifty years of age to have a routine rectal examination of the prostate annually.

Early carcinoma of the prostate is rarely seen by the clinician. Most writers agree that the carcinomatous growth is still confined to the prostate in less than 5% of the cases which they examine. In 1938 Browne[4] stated that three-fourths of his patients had metastasis when he first examined them, and half of his patients had metastases a year after the symptoms first appeared. Barringer[5] found only 4.5% of 352 cases in which carcinoma of the prostate appeared to be localized.

There are many reasons for the late discovery of the disease. The average prostatic carcinoma develops slowly, and it causes no symptoms until it interferes with urination or until it produces pain either by local

extension or by metastasis. The urinary obstruction develops late because three-fourths of the cases arise in the posterior lamella at a relatively great distance from the urethra. About 8% of the prostatic cancers develop within the spheroids of benign hypertrophy, which hides them from the examining finger. Most elderly men regard a certain amount of urinary difficulty as an inevitable accompaniment of advancing years, and they delay medical consultation until severe retention or pain appears. Many physicians are not thoroughly aware of the serious significance of isolated hard nodules in the prostate.[6]

ANATOMY

The prostate is a firm body which lies immediately below the internal urethral orfice and around the commencement of the urethra. It is partly glandular and partly muscular. It is situated in the pelvic cavity, below the lower part of the symphysis pubis, above the superior fascia of the urogenital diaphragm. It is in front of the rectum through which it may be destinctly felt, especially when the prostate is enlarged. The prostate is about the size of a chestnut and somewhat conical in shape; it is made up of a base, an apex, and an anterior, a posterior, and two lateral surfaces.

The prostate is immediately enveloped by a thin firm fibrous capsule which is distinct from that derived from the fascia endopelvina, and which is separated from it by a plexus of veins. This capsule is firmly adherent to the prostate, being composed of the same tissues, and it is structurally continuous with the stroma of the gland. The substance of the prostate is a pale reddish-gray color, very dense, and not easily torn. It consists of glandular substance and muscular tissue.

The muscular tissue constitutes the proper stroma of the prostate. There is a small amount of connective tissue, which form thin trabeculae between the muscular

fibers. The vessels and nerves of the gland ramify in these trabeculae. The muscular tissue is arranged as follows: Immediately beneath the fibrous capsule is a dense layer, which forms an investing layer of circular fibers. These fibers are continuous above with the internal layer of the muscular coat of the bladder, and they blend below with the fibers surrounding the membraneous portion of the urethra. Between these two layers, strong bands of muscular tissue decussate freely and form meshes in which the glandular structure of the organ is imbedded. In that part of the gland which is situated in front of the urethra, the muscular tissue is especially dense, and there is little or no gland tissue present; in that part which is behind the urethra, the muscular tissue presents a wide-meshed structure, which is densest at the base of the gland near the bladder, and which becomes looser and more sponge-like toward the apex of the organ.

The glandular substance is composed of numerous follicular pouches, whose lining frequently shows papillary elevations. The follicles open into elongated canals, which join to form from twelve to twenty small excretory ducts. These ducts are connected together by areolar tissue; they are supported by prolongations from

the fibrous capsule and muscular stroma, and they are enclosed in a delicate plexus. The epithelium which lines the canals and the terminal vesicles is of the columnar variety. The prostatic ducts open into the floor of the prostatic portion of the urethra, and they are lined by two layers of epithelium. The inner layer consists of columnar epithelium and the outer layer consists of small cubical cells. Small colloid masses, which are called amyloid bodies, are often found in the gland tubes.[7]

The high plane of efficiency in the treatment of the prostatic patient did not just happen. It is the result of a definite plan of preoperative study and preparation, and it was developed step by step during the past twenty to twenty-five years.

The specific observation which eventually led to the modern therapy of carcinoma of the prostate was first made several centuries ago. It was probably discovered by accident, that the removal of the testes was followed by certain distinctive physical changes. As early as the seventeenth century castration was used to cause a permanent artificial heightening of the voice. Castration in animals produced a tendency to become more obese and less active. Castration of male chickens caused atrophy of the comb and wattles so characteristic

of the rooster. Pre-pubertal castration caused an individual to have little or no sexual drive.

With the development of scientific inquiry in the eighteenth and nineteenth centuries, efforts were made to study more in detail the effects of castration. One observed effect, present in all animal species, was atrophy of the prostate. It was found that after removal of the testes, the prostate decreased progressively in size, until no more than a slight thickening and induration about the urethra could be palpated by rectum. Later microscopic study revealed a decrease in the size of the acina and a change of the normal columnar cell to a cuboidal or flat type.[8]

From 1880 until 1890, castration to produce atrophy of the prostate was used therapeutically for nodular hyperplasia, but castration was not widely used until about 1930, when sex hormones were discovered.

In 1893, White found that the castration of dogs was followed invariably and promptly by atrophy of the prostate. The glandular elements atrophied first, and then the muscular elements. There was coincidental reduction in both the bulk and the weight of this organ.[9] Two years later, the same writer reported generally favorable clinical results, when he castrated a group of 111 patients for prostatic enlargement.

Huggins[10] did some of the first experimental work in castration. In his ingenious animal experiments, he and his co-workers isolated canine prostates from their bladders to study the normal excretion of prostatic fluid. The administration of androgens was found to stimulate prostatic activity and to increase the flow of prostatic fluid; the administration of estrogens promptly put an end to the flow of this substance. The androgens caused hyperplasia of the epithelial cells of the prostate and in some cases caused metaplasia, which was so pronounced that the appearance of the gland simulated cancer. Estrogen therapy caused these glands promptly to become normal. Huggins also showed that prostatic secretion stopped, and metaplasia of the epithelial cells regressed, after surgical
After much animal experimentation, Huggins began experimental human castration for advanced metastatic cancer of the prostate.

After the publication of Huggin's results, many other reports were published. Randall published a report on five cases of prostatic carcinoma which were treated by bilateral castration. The cases were studied incompletely, primary x-ray studies were not done, and the diagnosis of one case is questionable. All of the cases had transurethral resection in addition to orchiectomy. His clinical results were unsatisfactory, and the method was soon discarded.[11]

Young is generally regarded as the first man to remove the testicles for the retardation of the development of prostatic cancer.[11]

PHYSIOLOGY

The interrelationship of the testes, the prostate, and the pituitary gland has long been recognized. These glands are bound closely together by a mutual interdependence. Changes in the physiology of one cause changes in the physiology of the others, and these changes are evidenced by physiologic and anatomic variations in the individual. Admittedly, experimental data give considerable conflicting evidence on the hormonal relationships of these glands. However it generally recognized that hypophysectomy causes prostatic atrophy and that the injection of the normal male with the anterior pituitary lobe hormone, antuitrin S, causes prostatic enlargement. The administration of testosterone will prevent this atrophy after hypophysectomy.[12]

The gonodal hormones normally regulate the pituitary gland, and their removal causes the pituitary to become overactive. There is a theory that the male gonadal secretion contains two hormones. One, which is

called "inhibin", holds the pituitary in check, therefore it prevents the over-stimulation of the prostate. The second, which is called androgen and which is the true sex hormone, maintains the prostate nd may cause prostatic hyper plasia. Consequently, it is reasonable to assume that dysfunction of either of these hormones may cause prostatic enlargement. Large doses of testosterone will not prevent the over-action of the pituitary gland. Therefore, the therapeutical administration of testosterone for prostatic hypertrophy is theoretically unsound. This mutual dependence and interrelationship of these three glands still needs experimental investigation.[13]

Krichesky[14] recently used intra-ocular prostatic implants to show the relationship between the prostate and the testes. He obtained the same result with his implants by castration that he obtained with the injection of testosterone. In prostatectomized castrated animals, the injection of testosterone causes rapid and continued growth of the implant. In prostatectomized animals with testes, the injection causes only a slight temporary rise and then a continual decrease in the size of the prostatic implant. This action on the prostatic implant suggests that the testes secrete a hormone which inhibits

the action of the androgen on the prostate. It is not known whether this action is direct or indirect through the hypophysis. Krichesky's experimental results support Lower's theory of inhibin.

The relation of age to male hormonal secretion has been investigated by many. Womack and Koch[15], among others, have shown that no male hormonal secretion is found in the urine of boys under ten years of age. There is the greatest amount of hormonal secretion in the urine between the ages of twenty and forty. Between forty and sixty there is just half as much as in the preceeding group, and after sixty years there is very little.

Huggins and Stevens[16] have also shown that prostatic epithelium is under the control of the testes. If this control actually occurs, the injection of male hormone in prostatic hypertrophy or carcinoma of the prostate is contraindicated.

In the common adenomatous type of prostatic cancer, the cells are fully differentiated, which led Huggins to suspect that they would be affected similarly to the normal adult cell by hormonal imbalance.

The administeration of an androgen stimulates the growth of prostatic cancer while estrogens retard it. The elimination of gonadal androgens by castration like-

wise has a retarding influence on the growth of the majority of prostatic cancers. However, there is nothing to justify the belief that cancer of the prostate may be permanently arrested by such measures.[11]

It is important to note that theoretically stilbesterol acts in four ways. It acts through the hypophysis. It acts directly on the elaboration of androgenic substances by the gonads. It acts by changes in the androgen-estrogen balance. It acts directly on cell proliferation or cell metabolism.[17]

THE ACID AND ALKALINE PHOSPHATASES

Phosphatases are enzymes which in vitro catalyze the splitting off of phosphoric acid from phosphoric esters. Biologically, there are two phosphatases now recognized. They are acid phosphatase and alkaline phosphatase. The former has a pH of approximately 5.0, while the latter reacts best at a pH of 8.5 to 9.5.

The use of acid phosphatase is important in the iagnosis and treatment of metastatic carcinoma of the prostate, because the percentage of acid phosphatase

present in the prostate is in direct relation to the extent of the metastasis.

Investigation of the relation of the phosphatases to the prostate is a relatively new scientific study. In the 1920's it was noted that the urine contained a relatively large amount of an enzyme capable of hydrolyzing organic phosphates at a pH of about 5. This enzyme was called acid phosphatase. Little further investigation was needed to demonstrate that the source of the phosphatase was largely prostatic secretion.

In 1933, Dumochowski[18], Kutscher and Wolbergs[19], the Gutmans[20], and other workers began to investigate the sources of acid phosphatase in urine. They discovered that acid phosphatase is a constituent of many kinds of body tissues. However, it is present in far greater concentrations in the adult prostate gland and prostatic fluid than in any other part of the body. Acid phosphatase constitutes a prostatic component of the ejaculate, and it is excreted by way of the prostatic fluid.[21]

In 1938 the Gutmans[20] established the fact that little acid phosphatase could be found in the prostates of infants, but that the substance increased with puberty and was present in the normal adult prostate,

the hyperplastic gland, and the cancerous prostate. Gomori later demonstrated through his microphosphatase tests that acid phosphatase was present only in the adult epithelial cells of the gland.

The presence of acid phosphatase is significant because most carcinomatous prostate tissue contains large amounts of acid phosphatase, whereas highly malignant tumors, being made up of functionally immature cells, contain but little acid phosphatase. When metastasis of a prostatic carcinoma occurs, presumably the acid phosphatase is allowed to escape into the blood and lymph. This escape of acid phosphatase results in the elevation of the blood serum level. The acid phosphatase is measured in units per 100 c.c. of serum, three to five units being regarded as the range of normal by scientific investigators. Elevated levels may fail to appear because of insufficient invasion, lack of differentiation of the tumor, or treatments preceding the examination.[18,19,20,21]

When Paget's disease and other bones lesions have been ruled out, an acid phosphatase of 0.8--1 unit, especially when the alkaline phosphatase is normal, warrants a suspicion that the patient has metastasizing carcinoma of the prostate.[22]

An acid phosphatase of 1.2 units or more may be considered pathogonomic of carcinoma with bony metastasis, especially if the alkaline phosphatase also is elevated.[21]

On the other hand, a normal acid phosphatase is no assurance that metastases are not present, in the undifferentiated types of carcinoma.[22] It was stated previously that acid phosphatase is present in MOST carcinomatous prostatic tissue.

Serum alkaline phosphatase is less specific than acid phosphatase in its prostatic origin. It is found in a wide variety of normal tissues. It is elaborated at sites of osteoblastic activity, particularly at sites of bony metastasis where new bone is being formed. Therefore, if one employs the level of this substance as a measure of osteoblastic metastatic lesions, Paget's disease and other lesions characterized by osteosclerosis must be excluded.

It is a justified conclusion that the elevation of the serum acid phosphatase level signifies prostatic cell activity communicable to the blood stream. This elevation indicates extracapsular prostatic tissue and presumably carcinoma. Likewise, elevation of the serum alkaline phosphatase accompanies the change in

the metastatic bone lesions from osteolytic lesions to osteoblastic lesions, and the elevation indicates sclerosis and regression, which are a result of a defensive reaction of bone to the tumor.[18, 19, 20, 21]

The phosphatases are valuable not only diagnostically, but they are also valuable prognostically in the clinical follow-up period, because they serve as a guide to additional endocrine therapy.[22]

AN ANALYSIS OF CASES TREATED WITH ESTROGENS AND ORCHIECTOMY

Three basic procedures to lower or block the androgens are available today. They are relative inactivation of the testes by radiant energy, removal of the source of testicular androgen by castration, and neutralization of the androgen by administering estrogen.

Although a few urologists still favor irradiation, most urologists use castration, or therapy with estrogens, or both of the latter methods. Diethylstilbesterol and the propionate ester have been the most widely employed estrogens.

In 1893 White[9] pointed out that prostatic atrophy follows castration. At that time oophorectomy was the accepted treatment for myoma of the uterus, and White applied this principle to analogous conditions of the prostate. He claimed that 87% of his patients with

prostatic enlargement were improved by castration.

Randall[23] states that in 1933 he became interested in reports from foreign clinics of the benefits to be derived from bilateral oopherectomy in mammary cancer. It was these reports which stimulated him to do orchidectomy on his small group of cases.

Randall says, "We can deduce from this small group of cases now seven, eight, and nine years since orchidectomy was done in the hope that it would affect the course of prostatic carcinoma. Against this, let us put (secondly) that in three patients it has apparently played a part--how specifically I cannot say--that ameliorated pain, fatigue, lassitude, increased appetite, and weight, and life became again worth while. Thirdly, how much of the symptomatic improvement should be accredited to transurethral resection? In other words, was the resection partly or entirely possible for the alleviation of urinary retention and nocturnal frequency? Fourthly, in the one patient who is still alive, six and a half years since castration--though with xray proof of metastasis--several accessory therapeutic measures became necessary and were applied, such as spinal absolute alcohol injections for pain, roentgen therapy to the prostate, stilbesterol injections, et cetera; he is reported comfortable. Fifthly, each case was one of

advanced carcinosis, and metastasis were probably existent at the time of castration. Should we limit the procedure to those in whom we feel sure that metastasis are not present? Should all have stilbesterol routinely as a preoperative measure? Our greatest present need is to follow all cases by some biochemical test and by xray studies, in the hope of finding a means to evaluate clinical improvement."[23]

Huggins[24] treated 45 consecutive patients with advanced prostatic carcinoma. In all of these patients, the primary therapy was bilateral orchiectomy, and eight of the patients died with metastasis to the bone. In four of these patients cancer was the primary cause of death; in five, castration caused no clinical improvement; in nine, there was temporary improvement; and in thirty-one, there was inhibition of the disease of at least thirty months duration. In some cases metastasis to the bone apparently disappeared. All of the deaths from carcinomatosis and all of the patients with little or no improvement after orchiectomy showed undifferentiated carcinomatous cells, while the most satisfactory cases showed histologic evidences of adenocarcinoma. When the testes were much lighter than the usual weight of twenty grams, the prognosis was poor. In five cases a great decrease in the size of the primary neoplasm in the

prostate was observed while the metastasis were advancing. Estrogen was not found useful as a supplement after orchiectomy. Irradiation of the testes produced atrophy of the terminal epithelium but it did not produce atrophy of the interstitial cells of the testes, and it was found to be inadequate as a therapeutic agent in human prostatic cancer.

Horsley[25] has done thirteen bilateral orchiectomies in the treatment of carcinoma of the prostate. Two patients who entered the hospital in a semimorbund condition did not show any improvement and they died within thirty days. Very definite improvement was noted in the remaining eleven cases. Particularly noticeable was the relief of difficult and frequent urination, and the relief of referred pain. Six of the patients had metastasis to the spine and pelvic bones. A check up xray study made three months after orchiectomy on one of these patients showed no noticeable improvement and no increase in the metastatic lesions.

H. S., male, ages 62, with a two year history of symptoms suggesting increasing bladder obstruction, had a sudden complete urinary retention in April, 1940.

April 15, 1940. The patient having successfully sustained operative treatment, was discharged from the hospital. The pathological report on the sections removed

was "Carcinoma, showing fairly extensive infiltration."

July, 1941. The patient, since operation, had been examined periodically, and was now given stilbesterol, the average daily dose being mgm. 5.

September, 1942. Since the institution of therapy he has taken about 1,000 mgm. of stilbesterol at intervals to date. During this time he has shown the most remarkable improvement in his general and ability to work. His outlook on life has become more cheerful, and any symptoms of a distressing nature have completely disappeared.

September 26, 1942. Resection of prostatic tissue for histological study was performed. These sections, in comparison with those removed previously, exhibited remarkable and interesting changes. Carcinomatous cells were present, but they were scattered and in such small numbers that they could actually be counted. ost of these cells appeared swollen and distorted. The areas in general showed practically no glandular elements, but they presented a loosely packed field of muscle fibers and connective tissue.[26]

Alyea[27] treated a series of 110 patients who were suffering from carcinoma of the prostate. He treated them by orchiectomy and stilbesterol therapy, and he obtained the following results: 105 patients were over

six months postoperative. Of these 105, 25% were dead in two years postoperative.

In a closed series of 40 cases, all between two to three years since operation, 32% were dead in two years.

In the same series of 23 having metastasis, 32% were dead in one year, and 41% were dead in two years.

In 36 patients with metastatic pain at the time of operation, 41% had return of pain, and the pain occurred within the first postoperative year.

Obstruction returned after primary regression in only three out of eighty-three cases over one year postoperative.

In a group of 26 patients with no signs or symptoms of metastasis at the time of operation, none showed any metastasis one year postoperative.

After this survey, Alyea suggests orchiectomy plus small postoperative doses of stilbesterol as routine therapy.

Herman and Greene[28] present a brief analysis of 47 advanced cases of carcinoma of the prostate, many of which have had stilbesterol before orchiectomy and a few of which have had stilbesterol after orchiectomy. Twenty-six of the series had metastasis. There was bone involvement in twenty-five, and there was lung involvement in the other case. Three of the cases have shown

partial recalcification of the involved areas. all of those having pain attributable were promptly relieved but the relief was not always permanent. In twelve of the cases, orchiectomy alone served to relieve either irritative or obstructive bladder symptoms, but the relief was of in some instances. It was necessary to apply trans-urethral resection or permanent suprapubic cystostomy for relief of obstruction in thirty-three patients. Five of the patients in this series had been subjected to prostatectomy for supposed benign hypertrophy from six months to seven years prior to the orchiectomy. Microscopic examination of the specimens removed at original operation failed to reveal carcinoma. As a result of orchiectomy patients gained in weight, showed an increase in appetite, showed a decrease in the acid phosphatase level, and, most of important of all, were relieved of the pain due to metastasis.

The patients in this series were operated upon within a period of twenty-seven months; all were in advanced stages of the disease. The results seem to justify the opinion that orchiectomy is well worth while as a means of palliation in advanced prostatic carcinoma.

Nesbit and Cummings[29] of Ann Arbor, Michigan, noted

the following clinical response to orchiectomy:

PAIN--relief of which occurs in from twenty seventy-two hours in most instances in which relief is obtained.

WEIGHT--eighteen patients complained of significant weight loss on admission to the hospital. Thirteen of these regained their weight losses, however, thirty-eight additional patients had appreciable gains in weight following orchiectomy, some gaining as much as fifty to sixty pounds. There are undoubtedly many factors which contribute to these post castration increases in weight.

URINARY OBSTRUCTION--fourteen patients on whom orchiectomy was performed and on whom no operation for relief of prostatic obstruction was complained of difficulty in voiding, or complete retention of urine. Five of these patients were placed on suprapubic drainage at the t ime of orchiectomy, and all of them were eventually able to urinate satisfactorily so that the cystostomy tubes were removed. At the time of orchiectomy nine patients complained of significant difficulty on urination and all had experienced more normal urination subsequent to castration.

TRANSVERSE MYELITIS--two patients were admitted to

the hospital complaining of severe metastatic pain and complete transverse myelitis below the mid dorsal level. Both had complete relief of pain and complete return of neuromuscular function following orchiectomy, and both subsequently had a recurrence of symptoms and died.

It is evident that hormone therapy increases life expectancy of patients with prostatic cancer by causing suppression of carcinogenic activity for temporary but varying periods of time, and that rary control of the neoplasm is accompanied clinically by a period of relief from symptoms resulting from the malignant disease.

It would seem logical to conclude that the maximum benefit to the patient may be derived by delaying hormone treatment until indicated by the onset of symptoms arising from advanced or metastatic lesions. Only in this manner can the longest period of palliative relief be assured.

Duncan[30] reports three advanced cases of carcinoma of the prostate. Improvement by therapy with large doses of oestradiol benzoate and diethylstilbesterol was marked and sustained. Duncan says, "My feeling is that the former works better than diethylstilbesterol, but is much more costly".

Willelts, Chute, and Gens[31] clinically found ~~that~~

when stilbesterol alone was used, the results were the same as castration and stilbesterol were used, although the beneficial effects last only as long as administeration of the drug was continued.

Smith and MacLean[32] of Montreal, Canada, have had experience with fifteen patients who have been castrated for carcinoma of the prostate. Their results confirm Huggin's major premise that the patients general health is remarkably improved, but so far they have been unable to demonstrate any great roentgenological change in the metastatic lesions.

It is not claimed that surgical castration is a cure for carcinoma of the prostate. Howeverin the majority of cases, it relieves pain, and it gives the patient a new lease on life. In some cases there is a regression in the primary growth.

Dr. Carleton B. Pierce, Radiologist in-chief of the Royal Victoria Hospital, has recently reviewed the roentgenograms of the series done in some other centers. He says, "The possible palliation to be afforded by orchiectomy in carcinoma of the prostate presents a hopeful move in the therapy of this neoplasm. The response, so far as our experience goes, and in the material which I have seen from other centers, is not uniform, either clinically or in the xray changes.

There would appear to be group of patients in which no major effect is induced in the metastic lesions, at least radiologically. This, however, should not be taken as a major contraindication, but rather as a lead for further investigation as to cause."

When patients with carcinoma of the prostate admitted to the Royal Victoria Hospital, a surgical castration is done, if it is possible. If improvement is not maintained, stilbesterol therapy is then instituted. The dose of stilbesterol given is 5 mgm. per day orally for two weeks, then 5 mgm. twice per week thereafter.[32]

Munger[33] in 1941 reported the results in fifty-six cases of carcinoma of the prostate. Of eighteen survivors, ten were from a group of forty-five who had transurethral resection and deep x-ray therapy, while eight were from a group of eleven patients who had this same therapy plus x-ray irradiation of the testes. He noted the marked difference in the rate of survival in these two groups, and he stated that the rectal examination in the latter group of patients showed minimal evidence of carcinoma of the prostate. The longest follow-up period has been seven years.

Chute[31] and his colleagues observed the reduction of the action of androgens in the body, by surgical

castration, or by biochemical neutralization through the administeration of the synthetic estrogen stilbesterol, or by a combination of the two. In 77% of the cases, they used a combination of the two methods, and twenty-six out of twenty-seven cases of carcinoma of the prostate were benefited.

Beneficial effects in these cases included rapid relief from the pain of any metastasis present, great improvement in appetite, and general health with gain in weight, and reduction in the size and induration of the prostate with improvement in ability to in most cases.

The injection of 10 mgm. of stilbesterol a day for five to ten days augmented the beneficial effects of castration markedly and rapidly. Similar injections of stilbesterol without castration gave equally marked and rapid effects, but these disappeared when its administration was discontinued, whereas the effects of castration, while slower to appear, were permanent. If stilbesterol alone is used, patients have to be carried indefinitely on a small oral maintenance dose, one to two or three mgm. per day.[31]

The authors of this reference felt that the quickest and most satisfactory results in this series were obtained by castration followed by the injection

of ten mg. of stilbesterol a day for five to ten days. In thirteen patients who were suffering from moderate or marked inability to urinate and were treated in this way, the size of the obstruction was so reduced in nine cases that they could void freely, did not have much residual urine, and escaped having to undergo an operation for the relief of prostatic obstruction. The authors recommend this latter type of therapy.

No serious harmful effects were noted from the oral ingestion of two to three mg. of stilbesterol a day over a period of nine months. Unpleasant side-effects of stilbesterol therapy were loss of libido and power of erection, tenderness and hypertrophy of the nipples and breasts, atrophy of the testes, anorexia, and occasionally nausea.

After castration, libido and power of erection usually disappeared, but there were no other harmful effects. However, bony metastasis did not disappear after castration. X-rays taken over a period of more than six months showed them apparently progressing as usual.

If the acid phosphatase level was elevated, stilbesterol therapy or castration caused it to fall rapidly towards normal. This fall usually was accompanied by

a rise in the alkaline phosphatase level.

Estimations of the seventeen ketosteroids were made in eighteen cases before and after castration, and from this, the authors have gained the impression that the level of seventeen ketosteroids does not give information of value as to the progress of the disease in cases of carcinoma of the prostate.[31]

Bergman[34] says that hope and encouragement can be given to the patient with carcinoma of the prostate. Pain has been relieved in nearly 90% of cases by utilization of hormonal factors in its therapy.

Thirty-one cases treated by castration and stilbesterol therapy showed improvement in appetite and gain in weight. Actual regression in the size of gland has been noted after several months treatment.

Rupel[35] of Indianapolis, Indiana, surveyed twenty-six cases in which he treated them by testicular excision, and he noted relief of pain, increase in weight and appetite, regression of the tumor, etc., after the treatment. He says that orchiectomy is the method of treatment for carcinoma of the prostate.

Creevy[36] presented sixty cases of carcinoma of the prostate, and his experiences have led him to agree with Huggins and his followers. Creevy feels that it seems permissable to recommend that estrogens be tried

in every case of prostatic cancer not confined to the gland itself and that if they fail, castration be performed. This operation is, of course, to be avoided except in the presence of absolutely unmistakable cancer.

Bumpus[37,38] and his colleagues say that the result of orchiectomy in twenty-five cases of carcinoma of the prostate confirm the impression that temporary relief accrues to almost all patients. Forty per cent of their patients who have been observed for a year or more following orchiectomy have had recurrence of symptoms. It is to be anticipated that they will eventually relapse.

We have not yet learned how to regulate our use of orchiectomy and estrogens. They probably should be delayed until symptoms of an advanced malignant condition are manifest, then be used separately and in succession rather than in conjunction.

Emmett and Greene[39] state that the indication for bilateral orchiectomy is carcinoma of the prostate with metastasis. Bilateral orchiectomy is especially efficacious when the metastatic growths have given rise to symptoms within one year.

Alyea[27] reports eighty-three cases, all one to three years postoperative. There are fifty-eight who

had an orchiectomy plus a transurethral resection. None of these have required a second operation.

In general it may be said, that of patients with urethral obstruction caused growth of the tumor in the prostate will be relieved by orchiectomy. Return of obstructive symptoms is observed in only an occasional case. This is, as one might expect, from the peculiar phenomen noted by Gilbert[40], that when the tumor progresses, it is usually reactivated in its metastasis rather than in its primary growth.

Robert Moore[41] observed clinically from his treatment of many cases of carcinoma of the prostate that within a few days the patient is greatly relieved. The pain of bony metastases is no longer disturbing, the appetite improves, and there is at least some sense of well-being, reaching a maximum benefit in from two to eight weeks. The weight increases, and as much as fifty pounds is gained in from six to nine months. If edema has been present, it disappears.

The prostate decreases progressively in size and becomes somewhat softer. The patient, who was unable to void, can again empty his bladder. Any sexual drive which was present is lost and some symptoms of

the climacterium may become evident, especially hot flashes, however, control of them is usually accomplished by the administeration of one mgm. of stilbesterol daily.

In patients with estrogens, the side effects are apparent but not disturbing. A few complain of nausea, anorexia, tenderness of the breasts and atrophy of the testes.

EFFECTS NOTED ON LABORATORY TESTS:

There was a precipitous fall in the acid phosphatase livel in the blood to a nearly normal level. The alkaline phosphatase usually increases for some weeks and then falls to the pre treatment level or lower.

If an anemia were present, a slow restoration to normal is seen in two to five months after beginning therapy.

The effect of the urinary excretion of hormones depends on the procedure used. With castration, the urinary estrogens fall to 50% of normal, the urinary 17-ketosteroids increase to values as much as 100% above normal, and the gonadotropin increases slightly. With estrogens, the urinary 17-ketosteroids decrease.

EFFECTS OBSERVED ROENTGENOGRAPHICALLY:

In most patients there is little observable change in the bony metastasis. In fact, there is a slow progressive growth. However, in a few patients, the metastatic

deposits gradually decrease in size and, as far as be demonstrated in the roengenogram, disappear. involution of metastasis in the lymph nodes has been observed.[41]

EFFECTS OBSERVED ANATOMICALLY:

No only is there clinical improvement, but the structure of the neoplastic cells is altered. In patients treated with diethylstilbesterol, Schenken, Burns, and Kahle[42] described the process of as follows: "The first stage of regression shows a decrease in the size of the nuclei and condensation of the nuclear chromatin. Nucleoli are no longer visible and mitosis are absent. The cytoplasmic vacuoles are located predominantly at the base of the cells. The nuclei in the second stage are pyknotic. The cytoplasm is practically clear and the cell membranes have ruptured resulting in the coalescence of the vacuoles. With the rupture of all the cell membranes, the pyknotic nuclei and cell membrane fragments are clustered in the acinar space. The end state is represented by the clear acinar spaces containing only r emnants of pyknotic nuclei."

EFFECTS OBSERVED ON THE ACID PHOSPHATASE IEVEL AND ALKALINE PHOSPHATASE LEVEL:•

Trafton and Perkin[43] noted that castration in every case was followed by a pronounced fall in the serum acid

phosphatase level within twenty-four to forty-eight hours. There was often a transient secondary rise small degree, followed by gradual decline until an equilibrium was reached after about two months. After an interval of one to three years, the majority of cases again showed an elevation of varying amounts. This secondary rise correlated fairly well with clinical evidence of recurrence of carcinoma and seemed to be only slightly reduced by treatment with stilbesterol.

Alkaline phosphatase values were found to be elevated in diseases of the liver and in various types of bony activity of the osteoblastic type. Since metastasis from prostatic carcinoma are predominantly osteoblastic in type, an associated elevation of the alkaline phosphatase level is the rule, but this rise is only roughly parallel to the acid phosphatase level, and it is an inadequate indicator of the total amount of metastasis and of the clinical course. It is not elevated in those cases in which metastasis are confined to the soft tissues, and in rare instances, in which the metastasis are osteolytic in nature, it is not proportionately elevated.

A study of fifty cases of carcinoma of the prostate showed an elevated serum acid phosphatase in twenty-four cases (48%). In twenty-two cases the serum alkaline phosphatase was elevated, and in seventeen cases both

phosphatases were elevated. However, it was in the group of twenty-one cases with bony metastasis that the acid phosphatase elevation was most closely correlated. 81% showed an initial elevation, the highest being a value of thirty-four units.

The acid phosphatase determinations appeared to be considerably more applicable to the adenocarcinoma group than to the undifferentiated simplex type. Histologically, there were twenty cases of adenocarcinoma, and ten cases of carcinoma simplex, and in twenty cases of undiagnosed carcinoma. In nine cases of adenocarcinoma out of twenty the acid phosphatase was definitely elevated whereas, in two cases of carcinoma simplex out of the ten it was elevated. These results are in keeping with the concept that the more slowly growing types of adenocarcinoma have more nearly normal secretory capacity.[43]

Fergusson[44] noted that when patients with metastasizing prostatic carcinoma were treated with estrogens there was a fall in their serum acid phosphatase--an enzyme produced in large amounts by adult prostatic epithelium.

The usual therapy employed has been to start with moderately large doses of stilbesterol, five mgm. twice or thrice daily by mouth, and to diminish this if possible

later in conjunction with a declining acid phosphatase level, or if certain complications supervene, a maintenance dose of one to two mgm. twice a day often suffices. In a case which reacts well the response is rapid; within a few days the phosphatase value declines and the symptoms improve.

He found that the prostate usually seems to become smaller and softer. Frequency of micturition diminishes and with in a few days of starting estrogen therapy a patient will often say he is passing water better than he has for years. Discontinuance of estrogen is likely to be followed by a return of symptoms. One patient more or less bedridden has been able to get about fairly normally, and several, previously prevented by pain, are now able to dig in their gardens. The relief of edema in advanced cases is also striking. One of the best examples is a man who was employed by a herbalist. The man came in with edema up to the waist and a recommendation for cystostomy was made. The edema subsided and operation was avoided, but later he reverted to his occupation and gave up treatment. He was readmitted moribund three months later. In other series regression of metastasis in the lungs and spinal cord has been reported.

Fergusson[44] noted that the side effects are fortunately few. The commonest in his experience is tender enlargement

of the breasts, but this sign gives no indication of the prostatic reaction. Other therapeutic complications are dizziness and occasional headaches, skin irriatation, decline of seminal activity, and inability to ejaculate. There is some evidence to suggest that the administeration of stilbesterol causes cerebral hemorrhage, because hemorrhage is commoner in patients receiving stilbesterol than one would expect at this age. One of Fergusson's patients and three of Nesbit's (1942) died from this cause.

In subscribing to the value of estrogen therapy in many of these cases, it is Fergusson's opinion that a combination of estrogen therapy with endoscopic resection, when needed, will probably do much to prolong life and ameliorate the patients pain.

Graves and Cross[45] present a report of cases in which they show that when bilateral orchiectomy is followed up with stilbesterol therapy, the lymph node metastasis diminish.

Charles B. Huggins,[46] in a series of forty-seven men with advanced prostatic cancer, found that twenty-four had an elevation of acid and alkaline phosphatases, and that twenty-three had a normal level of the enzyme. By very frequent observation of the serum phosphatases of men with far-advanced prostatic cancer who had an

elevation of the serum phosphatases, it was found that decreasing the amount or the activity of the androgens by castration or administering estrogen (stilbesterol one mgm. daily) caused a decrease of serum acid phosphatase values, whereas androgen administeration of testosterone propionate, twenty-five mgm. daily, caused exacerbation of serum phosphatase values and of the disease.

The beneficial results of decreasing the androgens were not limited to the serum phosphatase. Forty-six men with advanced and metastatic cancer were treated by castration since October, 1939. When the cancer was discovered early, total perineal prostatectomy was done.

According to Huggins, certain benefits usually follow orchiectomy. Among the earliest benefits are increased appetite and relief of pain. These effects are often seen within several days following castration. The result of these effects is a gain in weight and a return of the anemia towards normal. Frequently, there is a decrease of the primary tumor, so that the hard, nodular, craggy prostate becomes smooth and soft and decreases markedly in size. On roentgenographic examination changes in the bony metastases are often found. Usually the metastatic lesions undergo increased calcification within several months after orchiectomy. This increased density is often followed by a stabilization in growth

or by a disappearance of the metastases to xray examination. Other objective evidences of improvement which occurred in this series have been, in two cases, disappearance of paralysis due to compression from metastasis in the central nervous system; and in two other cases, disappearance of enlarged lymph nodes on the side of metastases.

Huggins[46] noted certain undesireable orchiectomy. These were abolition of the adult sexual capacity and the onset of hot flashes similar to menopausal changes in women. The symptoms can be mitigated by estrogen administeration. Huggins believes that all in all, the benefits which occur following orchiectomy far outweigh the undesireable effects.

Smith[47] reported a series of cases in which he had found that relief from local symptoms of prostatic carcinoma from metastasis in soft tissues or in bone were afforded by castration, administeration of estrogens, or a combination of the two methods of therapy. The results that he obtained were as follows: There was symptomatic improvement, a reduction of the acid phosphatase content of the blood, and a regression of metastasis as shown by xray evidence. To date there is reason to question the really curative value of these types of therapy, but palliation is of value even though it may

not do more than prolong life and comfort for several months.

It is probable that the use of estrogenic materials for this purpose is safe. Accordingly, the council has adopted the following paragraph for insertion in the New and Nonofficial Remedies Section, "Ovaries".

'"Estrogenic materials have been reported to act together with or as a substitute for castration in the palliation of the local discomforts from prostatic cancer and its metastasis. The action is apparently not curative but may persist for a number of months."'[47]

Huggins and Hodges[48] report that after the relatively insignificant operation of castration, patients with advanced prostatic cancers improved in general, their primary tumors became smaller, and metastasis regressed.

Heckel and Kretschmer[49] say that it is difficult to explain how the histologic changes that occurred in the prostate gland could be due to anything except the administration of diethylstilbesterol, because the patients had no other form of therapy. His clinical improvement and the fact that the prostatic cancer, as determined by numerous rectal examinations, gradually became softer while the patient was under treatment.

Rathburn[50] believes that orchiectomy will never permanently cure any case of carcinoma of the prostate,

but that it is a valuable addition to our armamentarium in the handling of these cases, especially when combined with other methods, and particularly when combined with the local application of radium.

Bowler and Pedley[51] report the early results castration in twenty-two cases of carcinoma of the prostate seen during 1942. Until recently transurethral resection for the relief of obstruction and radiation for the relief of pain have contributed considerable temporary alleviation to these patients. The position of the advocates of radical perineal prostatectomy as the only possilbe direct attack on carcinoma of the prostate is surgically sound, but it fails to meet the general problems for many reasons. First, the disease originates most frequently in the posterior lamella, thereby giving rise to urinary symptoms relatively late in the carcinomatous development. Second, the carcinoma is slow growing, and it is well advanced by the time that the typical patient of prostatic age, feels an undue degree of urinary difficulty and decides to obtain medical advice. The most enthusiastic supporters of radical perineal prostatectomy agree that the percentage of cases to which it can be applied, is not over 5%. These 5% are those patients in which a malignant lesion is still confined within the prostatic capsule when the patient is first seen. At least 95%

of prostatic carcinomae must therefore be treated by other methods. The importance of the lesion is brought out by the fact that the number of men living into the prostatic age doubled in the United States between 1911 and 1935 according to Creevy.[52]

Bowler and Pedley agree with Huggins and his associates, and they obtained the same clinical results.[51]

Barringer[53] believes that the following suggestions as to treatment of prostatic carcinoma are justified: Orchiectomy and stilbesterol medication should be the treatment in all cases of prostatic carcinoma. This therapy should be preceeded by transurethral resection, if urinary retention is a dominant factor. Transurethral resection is unnecessary to establish the diagnosis. Aspiration biopsy should be sufficient for this. If the prostatic carcinoma is small, confined to the prostate and peri-prostatic region, radiation of the prostate or operation of total prostatectomy should be considered.

Sullivan, Gutman, and Gutman[54] have noted the effects of castration on serum acid and alkaline phosphatase levels in patients with metastasizing prostatic carcinoma. The writers observed the effect of castration in thirty-three patients with prostatic carcinoma. Thirty-one of the cases in this series had increased preoperative serum

acid phosphatase levels, ranging from 520 to 4.2 units percent. Castration, in every instance except one case, was followed by an early precipitous fall in serum acid phosphatase, often demonstrable after twenty-four hours. On the second postoperative day the mean decline in acid phosphatase was 55% of the preoperative level. On the fourth postoperative day the mean fall was 64% of the initial value; by this time, in fact usually within forty-eight hours, it was definitely ascertainable whether or not a satisfactory chemical response to castration would be obtained. The mean decline in serum acid phosphatase was 70% after one week and 73% after two weeks. At about the third week, occasionally in the second or fourth weeks, the postoperative downward trend was temporarily arrested in many patients, and a slight transient secondary rise in serum acid phosphatase was evident; the mean fall was 66% of the preoperative value three weeks after operation. Thereafter, particularly in patients who were very satisfactorily clinically, the acid phosphatase usually showed a prolonged decline until after two or three months equilibrium was reached. The equilibrium level which was finally approached varied in different patients. It was usually five units percent or less when the preoperative values did not exceed twenty or thirty units

percent. In patients with very high preoperative serum acid phosphatase values however, the final equilibrium level was apt to be somewhat higher. The prognostic significance of such persistent postoperative elevations in serum acid phosphatase is not yet clear.

These workers also noted the effect of castration on the serum alkaline phosphatase levels and the serum acid phosphatase levels of patients with prostatic carcinoma and bony metastases. The serum alkaline phosphatase level seemed to be less consistently affected in magnitude and direction by castration. The first four days or week following castration constitute a latent period in which erratic fluctuations below or above the initial value occur. In patients with pronounced preoperative elevations, the trend at first is often downward. About the second or third week, an increased alkaline phosphatase level develops, not infrequently to more than twice the preoperative level. Occasionally this increase is marked within the first preoperative week, with little or no latent period. It does not become evident sometimes until the fourth week, and sometimes not at all. A prolonged period of gradual decline then ensues for many months after castration until equilibrium is reached at serum alkaline phosphatase levels; these levels are usually nearer normal than the level

prevailing before operation.[54]

Donahue[55] reports nineteen cases of carcinoma of the prostate which he treated with stilbesterol. He administered forty intragluteal injections of five mgm. each, making a total of 200 mgm., and then he gave a maintenance dose of ong mgm. each night on retiring. In seven patients who had grade II adenocarcinoma and who were given the above treatment, three were cured, one showed marked improvement, and three showed some improvement. It is important to note that there were no failures. In five patients who had Grade III adenocarcinoma, one showed marked improvement and four showed improvement. In two patients who had grade IV adenocarcinoma, there was one failure and one clinical cure. In other words, in this series there was only one failure, an individual who reacted unfavorably to the stilbesterol and who received a total of only thirty mgm.

Herger and Sauer[56] report here ninty-four cases which they treated with stilbesterol and castration. They obtained the same results as Huggins and his followers. Since 50% of these patients received stilbesterol medication exclusively and responded with regression or softening of the prostate, they conclude that estrogen administration without castration should have its place in selected cases of prostatic cancer. In their opinion

an indication for such treatment is present in the following cases: (1) in patients with operable of the prostate who refuse radical operation; (2) in patients with moderately advanced lesions who have little or no symptoms; (3) in patients in whom there is comparatively low grade, malignant, well differentiated adenocarcinoma, and in whom progression of the lesion is slow; (this group includes patients who may live for many years without adequate treatment, although the diagnosis of cancer has been proved by biopsy); (4) in patients who refuse castration, or in patients on whom orchiectomy is contraindicated.

He states that castration should be recommended in prostatic carcinoma patients in whom metastases are demonstrable and in patients with a type of lesion which usually has a tendency to rapid progression. In addition, castration should be carried out in patients who do not respond favorably to stilbesterol administeration.[56]

Dean, Woodard, and Twombly,[57] Scott and Benjamin,[58] Kahle, Schenken, and Burns,[59] Ordnoff,[60] Huggins[61], and many other such men have reported cases of carcinoma of the prostate treated with orchiectomy and estrogens, and they have all come to the same conclusion in general: Orchiectomy, or estrogen therapy, or a combination of the two should be adapted to the needs of each patient in

order that his carcinomatous symptoms may be ameliorated, and his sense of well being restored as much as possible.

SIDE EFFECTS CAUSED BY DIETHYLSTILBESTEROL [62, 63]

BREAST CHANGES--The breast became grossly enlarged and often painful. The tissue removed from the breast before therapy showed scarce amount of interstitial tissue, an occassional duct, and a few small blood vessels. The epithelial cells were mostly in a single layer. No definite acini were seen.

While the patient was treated, periodic sections which showed a progressive proliferation of duct epithelium were taken; cells of ducts became elongated and budding was present. There was edema of all the tissues, and there was an increase in connective tissue and in vascularity. The duct cells often multiplied to such an extent to occlude its lumen. A deposition of fat was present in some sections. No changes were present in the acini, and there was no evidence of secretion.[62,63]

EDEMA--The edema which often occurs during treatment of carcinoma of the prostate is a troublesome side-effect. Very often edema of the lower extremeties occurs first, and it can be either unilateral or bilateral. It also can occur in the scrotum or penis. When edema occurs, the patient often lowers the dose or ceases taking the

estrogen. The edema is due to a decreased renal excretion of sodium and chloride which keep water in the tissues and reduce the volume of urine. The reduction of urine volume causes dependent edema.[64]

SIDE EFFECTS NOTED IN THE TESTES--The testes secrete an androgenic hormone. Many medical authorities have the theory that this androgenic material is produced by the interstitial cells; however, this theory has never been proved. Estrogen is thought to neutralize the androgen substance. This in turn reduces the stimulation to the prostatic carcinoma. A normal testes before treatment has semininiferous tubules which have a thin fibrous basement membrane. The many tubules are filled with spermatozoa, and spermatogenesis is complete. After treatment with diethylstilbesterol, the basement membrane can become thickened with fibrous tissue. Often a rapid and advanced degree of atrophy of the testes takes place. At times vascularity, edema, and fibrous tissue increase in the interstitial tissue and in the seminiferous tubules. Arrest of spermatogenesis is usually complete.[62,63]

Matthews[65] did a very interesting study on the effect of stilbesterol on the spermatogenesis of male rats. He treated seventeen male rats for fifty-eight days with one mgm. of stilbesterol three times weekly for each rat.

Then the rats were semi-castrated. Sections of the removed testicles were made, and they showed an absence of spermatogenesis. All the rats were found sterile at the completion of stilbesterol administeration. These rats were placed with two test females to determine the interval necessary to attain a functional testicle and the return of spermatogenesis. The remaining testicle was found to recover sufficiently to affect successful impregnation or a functional level in thirteen of the seventeen male rats in an average of 47.5 days after stilbesterol was discontinued.

If the testes became small and soft or became atrophic, perhaps very little regeneration of interstitial cells took place, therefore theoretically, a small dosage of estrogen is needed to neutralize the androgen secretion. Whereas, if the testicle remains large and of a good substance, then one can suspect that a regression of the tubular cells is taking place, while the interstitial cells are increasing and are showing edema. Such an increase of interstitial cells then could be secreting no more androgen, and more and more estrogen would be necessary to neutralize the androgen they elaborate. This can be considered as a theoretical working basis.[62, 63]

Burrows[66] found that there is an acquired resistance to estrone in male mice. A mouse, after prolonged

dosage with estrogen, ceased to react in the usual way. The testicle of such a mouse consisted mostly of large interstitial cells and contained an unstained substance resembling lipoid.

SUMMARY

A. Serum acid phosphatase is important as an indicator of the presence of carcinoma of the prostate. The serum acid phosphatase is found most extensively in adult prostatic epithelium and in cells of carcinoma of the prostate. The serum acid phosphatase level is elevated in metastatic carcinoma of the prostate. It rises with prostatic epithelial activation, and it falls with prostatic epithelium inactivation.

B. The results of castration are:
   1. Prostatic atrophy in the normal male, an atrophy which may be prevented by testosterone injections.
   2. Possible atrophy of the prostatic hyperplasia.
   3. Atrophy of the prostatic epithelium, which is under the control of the testes.
   4. Fall in the serum acid phosphatase level.

C. The results of neutralization of the androgens by estrogens are:

1. Prostatic atrophy.
2. Possible atrophy of the prostatic hyperplasia.
3. Atrophy of the adult prostatic epithelium of prostatic carcinoma.
4. Fall in the serum acid phosphatase level.

D. An imbalance of the estrogens and androgens may cause prostatic enlargement. Thus, an injection of Antuitrin S causes prostatic enlargement, if the testes are present.

CONCLUSION

Cancer of the prostate is insiduous in its onset, and it is frequently inoperable before it is diagnosed. It is the attempt of this paper to emphasize the importance of carcinoma of the prostate to every man over fifty years of age. Orchiectomy, estrogen therapy, or a combination of the two methods offers the most satisfactory treatment for carcinoma of the prostate today. Because success of the treatment depends upon early diagnosis of the disease, annual examinations are necessary after fifty years of age to make possible an early diagnosis. The treatment is a worthwhile ameliorate even in advanced stages of the disease.

There are disadvantages in this treatment, which

deserve consideration. It advances neither permanent relief nor complete cure as yet. It causes loss of libido and power of erection. It may have injurious side effects.

These disadvantages are of comparative unimportance, when one considers the advantages of the treatment. It offers temporary relief of pain. It causes an increased appetite and sense of well being. It defers death.

The study of the endocrine effects on prostatic carcinoma is a relatively new and unexplored field. Perhaps in it lies the cure for carcinoma of the prostate, perhaps not. The destiny of medicine has been fulfilled, when human life is sustained and benefited through the efforts of science. If a medical technique makes life one degree more livable, it is of value until it has been replaced by a better method.

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