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Basis for castration therapy in advanced prostatic carcinoma

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THE BASIS FOR CASTRATION THERAPY IN ADVANCED PROSTATIC CARCINOMA

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INTRODUCTION

The physician is in general granted by his fellowmen the highest of esteem and admiration. This respect is merited by the physician, and his existence justified, only by the measure of service he is able to render to his fellowmen in the promotion of their health and happiness, in the relief of their suffering, and in the prolongation of their period of life. This is true in all the physician's relations, but if possible is accentuated in his care of the aging.

Prostatic carcinoma has added more than its equal share to the miseries of human kind and to the burden of the physician. Through the years it has presented a perplexing and unsolved problem. The gravity of the situation was well expressed by Dr. Louis M. Orr, Jr. (1) in a discussion of the problems of prostatic carcinoma with the American Urologic Association in 1941:

> "....a majority of the medical profession, and many among us, have come to look upon this condition, whether it is early or late, with a definite sense of futility. An examination of the results obtained up to the present time from all types of therapy is sufficient to justify that pessimism."

In 1941, largely through the efforts of Huggins and his associates, a new method of treatment of carcinoma of the prostate gland, endocrine therapy either by orchiectomy or estrogen administration, was introduced to the medical profession, and has been practiced widely since. As five years is a customary period for an initial appraisal of the results of treatment of cancer, and

this time has elapsed since the introduction of endocrine therapy of prostatic carcinoma, it would be well to review the special problems of cancer of the prostate, the basis for endocrine therapy and the best method of administration, and to compare the results obtained with those of other methods of management of the malady.

Not only has prostatic carcinoma withstood the onslought of those who have attempted its control, it is a disease of increasing incidence. Duff (2) quotes the Metropolitan Life Insurance Company statistics which show prostatic cancer to cause 0.8 deaths per 100,000 population in 1917 and 3.7 per 100,000 in 1928, and Ewell (3) quotes 1930 census reports as 4.5 deaths per 100,000 population caused by prostatic carcinoma. Stirling (4) states that the disease affects 15% of men alive over the age of 50 years, of whom it is the cause of death in 5%. Graves and Militzer (5) report it to be present in 15 to 20% of all obstructive prostatic lesions, and to comprise 1.7% of general hospital admissions over a 6.5 year survey. Young (6) estimates its presence in 14% of all males past 44 years, and states it is 300% more frequent in occurrence than any other internal cancer in the male. Microscopic study of serial sections of prostates removed from non-selected, consecutive cases of men over 50 years of age who came to post mortem examinations has shown carcinoma to be present in from 14 to 46% (7) (8) (9).

As is true of all carcinoma, little is known as to the specific

etiology of prostatic carcinoma. However, in common with carcinoma in general, it is a disease of the aging process. Cowdry (10) states that in age group of 50 to 69 one-eighth of all male deaths are due to cancer of some type. He further gives the information for the accompanying diagram (Figure 1).

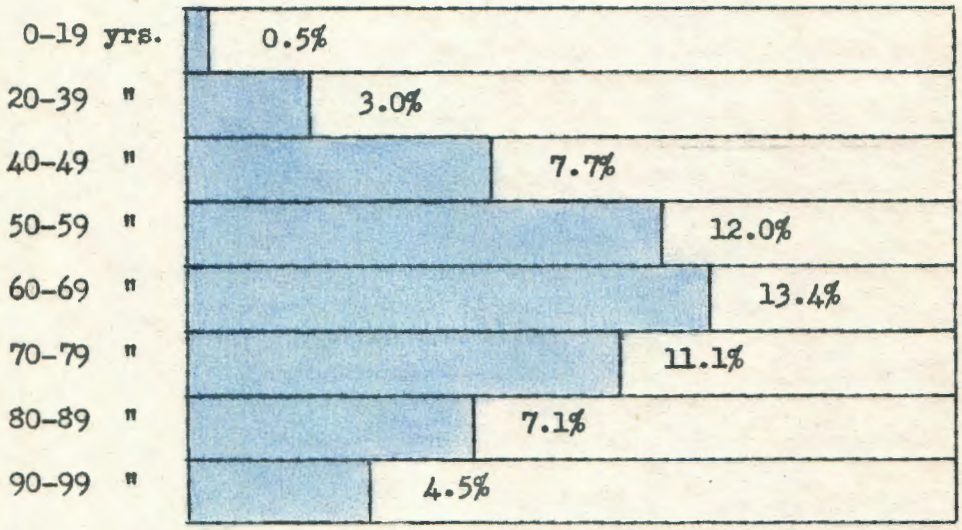

Fig. 1. Per cent of total white male deaths caused by all types of cancer in relation to age groups.

Moore (8), Thompson (11), Colston (12), Strohm (13), and Palomo (14) in their case studies have listed the percentages of the total diagnosed cases of prostatic carcinoma in relation to the various age groups. Their data combined and averaged yields a graph (Figure 2, page 4) strikingly similar in general age distribution incidence to Figure 1 for all types of cancer, both figures accentuating the relationship of age and the incidence of specific and general carcinoma.

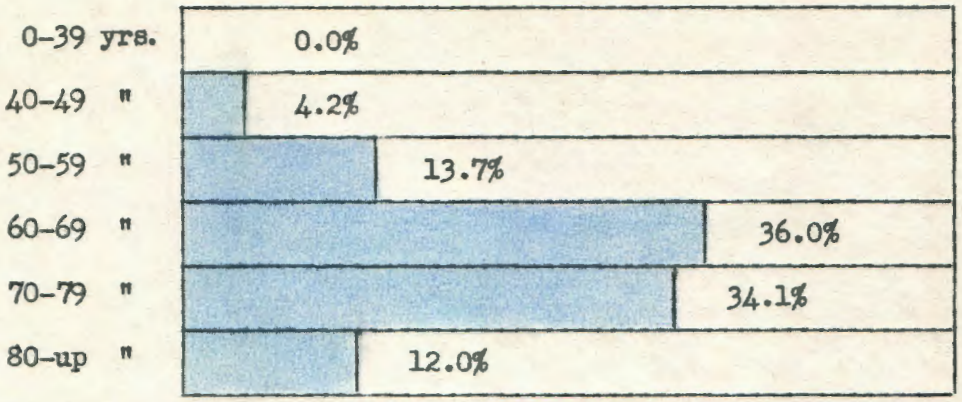

Fig. 2. Per cent of total diagnosed cases of prostatic cancer in relation to age groups.

The average age of the patient at the time of discovery of the cancer of the prostate has been listed from 65 to 70.2 years (3) (4) with 50% of the total incidence between 65 and 74 years (5) and 75% between 50 and 75 years of age (3).

When the age group incidence of prostatic carcinoma is considered, a study of population statistics reveals the main factor in the increasing numbers of those afflicted with the disease. The mean length of life from early fragmentary records are given in 1755 as 34.5 years, by 1850 it was 40 years, in 1900 was 50 years, and by 1930 was approximately 60 years. Metropolitan Life Insurance Company statistics list the mean length of life in 1941 as 63.4 years. A definitely decreased birth rate, estimated at 30 per 1,000 in 1900, 25 per 1,000 in 1915, and 16 per 1,000 in 1941, has further accentuated a swing to an elderly population (15).

As complied from U.S. Census reports (16) (17), the vast effects of these influences on the age distribution of the population are

reflected in Figure 3.

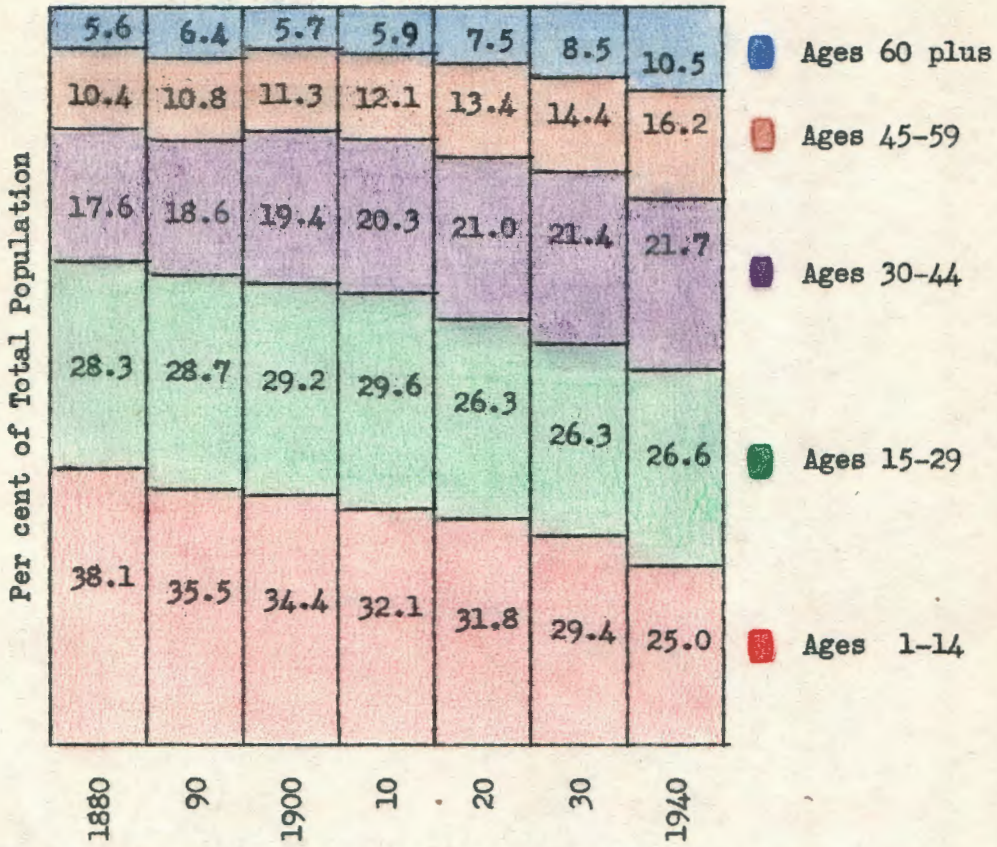

Fig. 3. Age of the population of the United States 1880 to 1940: Percentage distribution by age groups.

Further, it has been estimated (10) that by 1980 the age group over 45 will comprise 40.3% of the total United States population, while that over 65 will be 14.4%. Creevy (18) has stated the number of men over 65 has doubled between 1911 and 1935, and from estimates it appears that the number in this age group will triple the 1911 figure by 1980.

These figures have been presented here specifically in their

relation to the incidence of prostatic carcinoma. However, they also carry far-reaching medical, politico-social, and economic implications with which the physician should be well cognizant.

Another of the truly real problems of prostatic carcinoma is the fact that the only absolute cure is surgical removal of all malignant tissue, and case studies in general have shown that to the present time only 5% or less of the diagnosed cases are discovered before the process has spread beyond the localized area amendable to surgery (11) (13) (19) (20) (21) (22). As further evidence as to how late the diagnosis is usually made, metastatic lesions are reported present in from 24% to 75% of the cases at the time of first discovery of the prostatic carcinoma (14) (20) (23) (24) (25) (26) (27), and Bumpus (20) reports metastatic pain as the first symptom in 16%. Stirling (4) reports 19 months as the average duration of symptoms before the patient presents himself for medical care.

There are numerous factors to explain the usual late diagnosis of prostatic carcinoma:

1. As with cancer in general, prostatic carcinoma has no primary symptoms, but rather the symptoms are of its complications, largely urinary function disturbance and pain from local or metastatic spread.
2. Approximately 75% of the cancer arise in the posterior lamella of the gland distant from the urethra so that

obstruction is usually a late symptom (8) (14) (18).

3. Many elderly men expect a certain amount of urinary difficulty as "natural" and therefore decline attention, while 65% of the first complaints of prostatic cancer patients are frequency and difficulty (20).
4. Approximately 20% to 30% of "benign hypertrophied" prostates when sectioned and examined show carcinomatous areas present, demonstrating that cancer sites may be hidden from physical examination by spheroids of hypertrophic tissue (14) (29) (30).
5. NOT ENOUGH RECTAL EXAMINATIONS ARE DONE. All authors are emphatic in this point, and make a plea that an adequate rectal be made a routine part of the examination of every patient if prostatic cancer is to be discovered while early enough to be treated adequately.
6. Some evidence has been presented (7) (9) indicating that possibly in a large percentage of the cases by the time the cancer becomes evident by physical examination it likely has progressed beyond curable limits (See pages 10 and 11).

PROSTATIC ANATOMY

The prostate develops from multiple outgrowths of urethral epithelium, above and below the entrance of the definitive ejaculatory ducts, that branch into the surrounding mesenchyme, which in turn differentiates into connective tissue and smooth muscle fibers. Thus the normal adult prostate develops into a fibromusculoglandular mass approximately 2 cm. by 3 cm. by 4 cm., weighing 15 to 40 grams, lying between the two sphincters surrounding the urethra from which it arises. Its apex is directed downward to rest upon the superior fascia of the urogenital diaphragm, and its base is directed upward and applied to the inferior surface of the bladder, the greater part of this surface being continuous with the bladder wall. The posterior surface of the gland approximates the rectum, the prostatic sheath and Denonvillier's fascia being interposed, and is exposed for digital examination through the rectum as are usually the lateral borders of the gland lying against the medial borders of the anal levators.

The glands and ducts of the prostate are embedded in the extensive framework of fibromuscular tissue, the forty-odd ducts opening onto the lateral and posterior walls of the urethra. The substance of the gland is penetrated by the ejaculatory ducts which open on the verumontanum midway in the prostatic urethra posteriorly.

Classically the prostate is described as being composed of five separate lobes, with corresponding sets of glands and ducts

arising from different portions of the urethra. However, by careful study LeDuc (31), by India ink injection of individual ducts and demonstrating the distribution of each unit later after the gland was made transparent, has shown lateral and medial portions only, no separate anterior or posterior lobes.

The prostate, like the thyroid, has an intrinsic capsule and an extrinsic sheath. The capsule consists of parallel layers of fibromuscular tissue continuous with the stroma of the organ. The sheath is formed anteriorly and laterally by connective tissue derived from the pelvic fascia, and posteriorly by the avascular rectovesical fascia which acts as an efficient barrier to the spread of prostatic malignancy to the rectum until it has overgrown the superior limits of the fascia.

The veins of the prostate form a plexus around the sides and base of the gland, anteriorly draining the dorsal vein of the penis, and draining into the hypogastric vein. The innervation is derived from the pelvic plexus, the nerves being heavily supplied with perineural lymphatics which are important in the metastatic spread of prostatic cancer.

The normal adult prostate glands are composed of tall columnar cells with indefinite luminal cell borders and basal, round or oval, moderately chromic nuclei. The acini of the glands are invested with a narrow band of collagenous connective tissue. This zone follows all the irregularities of the alveoli, and is devoid of

capillaries. In the senile gland the cells atrophy, become cuboidal, have distinct walls and more deeply chromic nuclei nearly one half the size of the cell.

In malignant anaplasia of the earliest degree there is a beginning loss of the limiting zone, and the acini are arranged without regard to the regular whorles of smooth muscle, connective tissue, and elastic membranes of the gland. The acini become smaller and show no papillae, the cells becoming low columnar or cuboidal with definite cell walls and relative dense, deeply acidophilic cytoplasm. The nuclei are large in relation to the cell size, and are variable in their staining and morphology. Even in advanced carcinoma the epithelium often retains orientation and forms acini, this being true even in many of the metastatic lesions.

Mention has been made (page 2) of the 14% to 46% incidence of carcinoma in non-selected prostates taken from post mortem examinations. Moore (8) found the carcinomatous areas most often surrounded by spheres of atrophic cells, and concluded the cancers to have arisen from stimulated, autonomous growth of atrophic epithelial cells. Rich (7) found 65.8% of the carcinoma he studied undiagnosed clinically because of their small size, but, even though too minute to be diagnosed, that the carcinoma had invaded the capsules and the perineural lymph spaces in and around the glands, suggesting that when the malignancy could be discovered

by physical examination it very often had advanced beyond surgical cure. Baron and Angrist (9) have also expressed the opinion, based on similar studies, that physical examination methods cannot locate prostatic carcinoma in time for resection. Graves, Warren, and Harris (32) have further emphasized the importance of the perineural lymphatics in the metastatic spread of malignancy from the prostate to the pelvis and the lumbar spine. Moore (8), however, considers extracapsular spread of prostatic carcinoma to be a late manifestation of the disease, and Henline (33) reports seven cases of prostatic cancer which were diagnosed by digital examination, surgically removed, and were examined microscopically with a confirmed diagnoses, yet without spread outside the capsule or along the perineural lymphatic sheaths.

PROSTATIC PHYSIOLOGY

Huggins (34) describes the normal adult prostate as a non-endocrine gland, and states the only proven function of its external secretion is to increase the volume of the ejaculate and dilute the sperm. It is an accessary in function along with the seminal vesicles and the bulbourethral glands of Cowper. The normal resting gland at infrequent intervals secretes small amounts of fluid, 0.5 to 2.0 ml. per day, discharged through the urethra in the urine. The prostatic secretion is composed of approximately 93% water, and contains small amounts of sodium, potassium, and calcium salts, protein and non-protein nitrogen, glucose, ascorbic and citric acids, cholesterol and other lipoids, and contains 250 to 1725 King units of acid phosphatase. During sexual stimulation and ejaculation prostatic secretion is largely under the control of parasympathetic stimulation, with a greatly augumented quantity of secretion. However, prostatic secretion is primarily a function of androgenic activity (See pages 21-23) and only secondarily of nervous or chemical stimulation.

One of the most characteristic features of adult prostatic epithelium is the presence of an acid phosphatase in rather large amounts. Gomari (35) estimates 500 to 2000 units of acid phosphatase per gram prostatic tissue, the acid phosphatase being apparently elaborated by the epithelium.

The phosphatases are dephosphorylating enzymes which catalyze the splitting off of phosphoric acid from certain organic phosphate esters. They are most significant in the general body economy, as many of the physiologically important substances (hexose and triose phosphates, phospholipids, nucleotides, creative phosphate, cocarboxylase and others) are organic phosphate esters, and dephosphorylation is an important step in their metabolism in such diverse activity as bone formation, glycolysis, glucose absorption from the small intestine and resorption from the proximal convoluted tubules. The phosphatases are broadly classified as "acid" or "alkaline" depending upon which side of neutrality they show their greatest enzymatic activity. They are distributed widely through plant and animal tissues, but the function of the acid phosphatase in the external secretion of the prostate is unknown as yet.

Huggins and Hodges (36) credit the German authors Gosser and Husler with the discovery of phosphatase. Robinson (37) in 1923 reported alkaline phosphatase especially high in activity in growing bone and cartilage. Kay (38) in 1928 found alkaline phosphatase increased in the serum of many bone diseases including carcinomatous metastases. Davies (39) in 1934 discovered in the spleens of swine and cattle an acid phosphatase in addition to the alkaline phosphatase already known. Two German authors, Kutscher and Walberts, as quoted Huggins and Hodges (36), in 1935 found what they considered an identical acid phosphatase in adult human and monkey prostates

(which later has been proven to be distinct and specific for the prostate) in larger amounts than any phosphatase in any other tissue. Gutman, Sproul, and Gutman (40) in 1936 confirmed these findings, and further reported that carcinomatous prostate cells retained the ability to elaborate acid phosphatase at the primary site of growth and even at distant metastatic growth areas. Gutman and Gutman (41) studied the enzyme activity of the prostatic epithelium in relation to age, and concluded that the ability to elaborate acid phosphatase was characteristic of adult epithelium since only minute amounts of the enzyme were found in the glands of infants or children, whereas there was a sharp rise at puberty and high values were found in the prostates of adults. This suggested carcinomatous prostatic tissue was of the "adult" type in that it still elaborated the enzyme characteristic of the adult gland.

Inasmuch as the metastatic growths of malignant prostatic tissue are no longer located where external secretion is possible and yet are fully capable of phosphatase elaboration, it was suspected that these growths would become "pseudo-endocrine" glands with an internal secretion, and should be evident by increased amounts of the enzyme in the blood stream, in amounts depending upon the activity of the metastatic growths. Gutman and Gutman (42) in 1938 first reported the presence of an acid phosphatase, indistinguishable from that of the prostate, in the serum of patients with metastatic prostatic carcinoma. Barringer and Woodard (43) reported

similar findings the same year. The diagnostic value of this test in metastatic carcinoma of the prostate was emphasized by Robinson, Gutman, and Gutman (44) and in numerous other studies (14) (23) (26) (36) (37) (45) (46) (47) (48).

The validity and specificity of the serum acid phosphatase test for metastatic prostatic carcinoma was well established by Sullivan, Gutman, and Gutman (49) in the study of a large series of cases including 30 normals for controls, 285 cases of prostatic disease, and 570 cases of various non-prostatic disease. Their results showed the normal limit of serum acid phosphatase to be 3 units by their method of determination, and that 85% of the patients with demonstrable or suggestive roentgenologic evidence of metastatic prostatic carcinoma showed elevated levels, while 15% were in the normal range. If 3 to 5 units were set as a suggestive range and above 5 units as a diagnostic range, 73% of the above group fell in the diagnostic serum levels and 12% in the suggestive range. In those cases of prostatic cancer in which metastases were not demonstrable, 89% had normal serum acid phosphatase levels, and 100% of the non-cancerous prostatic disease had normal levels. Further, only 2.5% of the cases of non-prostatic pathology studied had levels near the diagnostic level for metastatic prostatic carcinoma, and nearly all of these were caused by advanced bone tumors, Paget's bone disease, or hyperthyroidism that were usually easily diagnosed clinically.

These findings have been substantiated by many other workers, including Huggins and Hodges (36), Barringer and Woodard (48), and Alyea and Henderson (47). Thus, a serum phosphatase level in the diagnostic range without clinical evidence of the previously mentioned diseases is proof of metastatic carcinoma of the prostate, but a negative test does not rule out the possibility of metastatic lesions. These studies of the Gutmans and their associates first suggested that serum acid phosphatase levels taken in series over a period of time might be of value as an objective method for following the activity of prostatic carcinoma and its metastatic lesions.

The alkaline phosphatase increase in the serum of patients with metastatic prostatic lesions has been shown by Woodard and his associates (50 (51) to be a non-specific defensive bone response, and it is seen in many other conditions where osteoblastic activity is pronounced.

The prostate, pituitary, and adrenal glands are closely interrelated in their physiology, and are bound together by mutual interdependence. In the experimental development of their relationships there has been, as in all experimental work, numerous conflicting articles. However, it has been known for more than one hundred years that the testes bear some relation to the activity of the prostate gland, as D'Etoille and Civiale, quoted by Herger and Sauer (23), in 1836 and 1837 mentioned the complete disappearance,

to physical examination, of the prostates in men who had bilateral orchiectomy for hernia. Hunter (52) in 1840 described the degeneration of the prostate and other accessory glands, and the decrease in their secretions, in bulls that had been castrated. Krichesky, Benjamin, Belt, and Schwartz (53) cite Berthold as observing in 1849 that testicular grafts would prevent castration changes from occurring in male foul. Similar findings were reported by others during the nineteenth century, and in 1893 White (54), following a systematic study of the effects of castration upon the prostates of dogs, reported that when orchiectomy was done there followed a marked decrease in the gland, first glandular then fibromuscular. McGee (55) and McGee, Juhn, and Domm (56) in 1927 and 1928 reported that a lipoid fraction of bull testis caused the development of secondary sex characteristics in capons. McCullagh (57) in 1932, and McCullagh and Walsh (58) in 1935 published reports of their studies showing that fat solvent extracts of testes caused regeneration of prostatic tissue that had previously undergone castration atrophy. They named this fraction "androitin".

Scientific interest in the control of the primary and secondary sex glands led to the study of the nature and metabolism of the testicular substances. Andosterone was isolated from male urine in 1931 and synthesized from cholesterol in 1935. Also in 1935 a crystalline steroid, testosterone, the purified male sex hormone, was isolated from the male testis, and likewise it was synthesized

from cholesterol. Testosterone was shown to be most active in its ester forms, and andosterone in the urine was demonstrated as the end product of the testosterone ester metabolism.

The relationship of the testes in their activity of androgen production and the activity of the gonadotropic substances of the anterior pituitary has been demonstrated by many. Womack and Koch (59) found no male sex hormone in the urine of boys under ten years of age, with a gradual rise after ten years and a sharp increase at the clinical onset of puberty. Simultaneously with this increase of androgenic activity, the prostate develops from its infantile state to its adult form, and, as Gutman and Gutman (41) have shown, attains the ability to elaborate acid phosphatase. The absolute relation between androgenic activity and the ability of the prostatic epithelium to produce acid phosphatase has been conclusively demonstrated by Gutman and Gutman (60) by injecting immature monkeys, who have no phosphatase in the glandular epithelium, with testosterone and obtaining high levels of the phosphatase within 14 days. Walsh, Cuyer, and McCullagh (61) reported that when adult rats were hypophysectomized there followed atrophy of the testes and prostate, but that the prostate could be maintained histologically by injection of the male sex hormone isolated from urine.

The testes produce another hormonal substance beside the androgenic substance, and it acts as a counter-balance to the

androgenic stimulation of the prostate. It is thought that this substance exerts its influence probably thru an inhibition of the pituitary activity, and possibly as a direct inhibition at the prostatic epithelium. Lower, Engle, and McCullagh (62) isolated an aqueous extract of the testes, "inhibin", capable of producing prostatic atrophy when injected into normal rats. McCullagh (57) demonstrated that in the castrated animal there developed an hypophyseal and adrenal hypertrophy and hyperfunction. The castration effect resulting in pituitary hyperfunction was further substantiated by Martins and Rocha (63) who produced prostatic hypertrophy by injecting a normal animal with the pituitary hormone from the hypertrophic hypophysis of a castrated animal. This experiment was verified by McCullagh and Walsh (58). The natural deduction being that with the loss of the germinal epithelium of the testes, the probable source of inhibin, the pituitary was released from its testicular inhibition and became overactive. The adrenal hyperplasia supposedly arose through the resulting overstimulation from the hyperactive pituitary. Burrill and Greene (64) and Howard (65) found that the adrenals in immature rats and mice produce an andromimetic hormone, as castration in these animals does not result in prostatic atrophy until adrenalectomy has been done. On the basis of this type of experimental evidence, and of studies of the 17-ketosteroid content of urine after castration, the possibility of the adrenals as being a site of post-castration

androgen elaboration has been frequently proposed. However, most authors agree that the quantitative estimation of 17-ketosteroids in the urine is not a true index of the androgenic hormones of the individual.

The urine of man contains both androgenic male and estrogenic female sex hormones, and it has been postulated that the control of the prostate is mediated through an estrogen-androgen balance, with prostatic pathology resulting in a disturbance in this equilibrium. Krichesky et al (53) have shown that prostatic implants into the anterior chambers of the eye of a completely prostatectomized male rabbit show marked atrophy following castration but can be maintained, and show growth, for at least three months by testosterone injection. Krichesky and Benjamin (66) have shown in similar experiments that estrogens up to 200 i.u. per kilogram injected into a non-castrated rabbit causes marked atrophy of the prostatic tissue due to glandular involution, the reaction being reversible if the estrogen is stopped. If estrogen in equal doses is injected into a rabbit in which castration atrophy has taken place in the intraoccular prostatic tissue, marked hypertrophy of the implant may take place by thickening of fiberous and muscular tissues and metaplasia of the epithelium. Increased activity of the epithelium of the tubules of the prostate in castrated rats following estrogen administration has been reported, and estrogen administration to monkeys has produced an increase in fibromuscular

stroma and epithelial hyperplasia in the uterus masculinus. Funk, Harrow and Lejwa (67) have reported less androgenic (cocks comb-growing) activity in urine of elderly men than young adults. Dingemanse and Laqueur (68) stated the ratio of estrogens to comb-growing substances is higher in the normal male than those with prostatism in the same age groups, and on the other hand, Moore, Miller, and McLellan (69) state the urinary output of androgens is lower in old men than young men, and that the decrease is greater in men with prostatic hypertrophy. In brief, as these representative views express, the matter is far from decided. It is of interest to note that Deming (70) states he can find no instance of prostatic carcinoma developing in a patient who has been castrated early in life, and thus he considers testicular androgen as probably a main carcinogenic factor.

Huggins, Masina, Eichenberger, and Wharton (71) and Huggins and Clark (72) carried out extensive animal experimentation in which dog prostates were isolated and the excretion of prostatic fluid was studied along with the histologic reaction of the glands under many physiologic conditions and in response to androgen and estrogen administration and to castration. As a result of their exhaustive studies the loose ends of previous experimental knowledge was nicely integrated. They demonstrated that testosterone administration to an immature dog brought an increase in secretion and transformed the gland to an adult state; that with adult epithelium

estrogens caused a ceasation of secretion and atrophy of the glandular tissues; that with surgical castration secretion decreased within 24 hours and ceased in 7 to 23 days, and that there was marked atrophy of adult prostatic epithelium following castration but that the gland could be restored with testosterone. Huggins and Stevens (73) applied these principles to benign hypertrophied prostates in the human and following castration with biopsies taken approximately three months later found a much atrophied gland with flat or cuboidal epithelial cells, less papillary infolding, and a decrease in size of lumina of acini.

Thus, with the following points as background, hormonal therapy was applied to carcinoma of the prostate by Huggins and his associates:

1. Normal adult prostatic epithelium is characterized by the elaboration of acid phosphatase.
2. Normal adult prostatic epithelial activity is under androgenic control.
   a. Castration removes the androgen and epithelial atrophy results.
   b. Estrogens counteract the androgens and epithelial atrophy results.
3. Nearly all (if not all) carcinoma of the prostate is physiologically of the adult epithelial type in that it retains the ability to elaborate acid phosphatase both at its primary and metastatic sites.

4. Therefore, if removal of androgenic stimulation inactivates adult type prostatic epithelium and prostatic carcinoma is an adult epithelium, removal of androgenic stimulation by castration or estrogens should bring about a ceasation of the activity of the carcinomatous tissue.

5. Serum acid phosphatase levels in series should be an objective method of following the disease.

The hormonal physiology as it applies to the treatment of carcinoma of the prostate is shown diagramatically in Figure 4, as adapted from Alyea and Henderson (47).

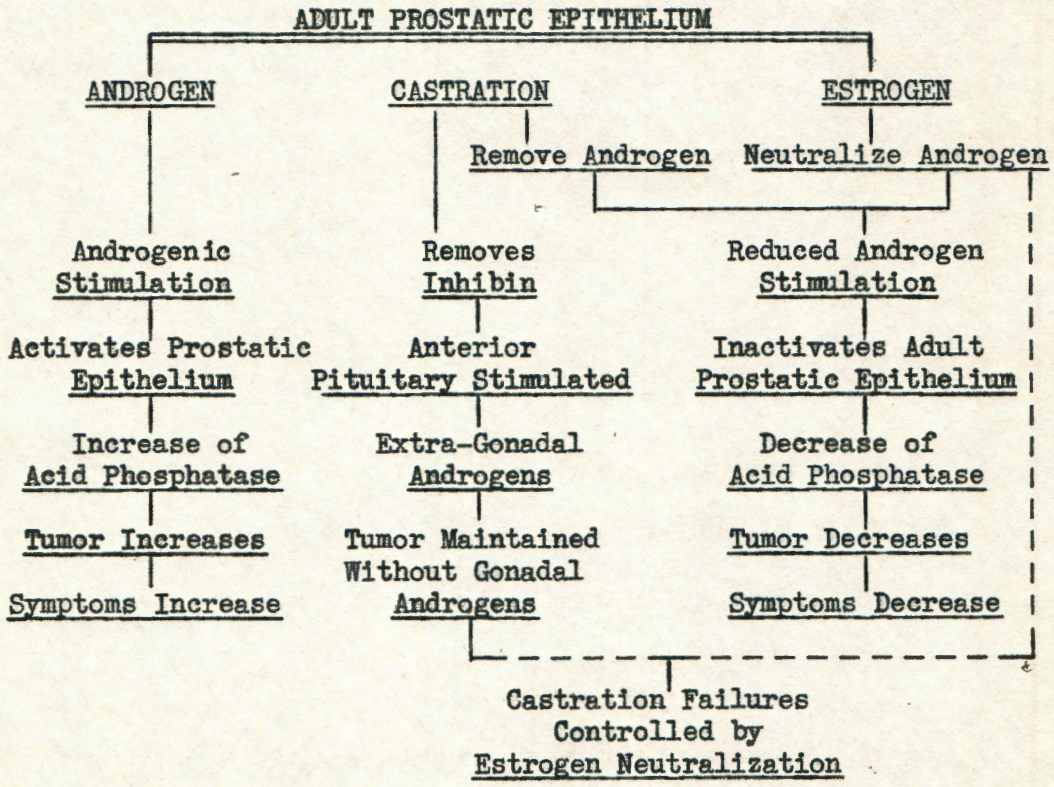

Fig. 4. The Hormonal Relationships in Endocrine Therapy of Prostatic Carcinoma.

THE HISTORY OF HUMAN CASTRATION

The beginnings of castration were probably from the domestication, and consequently gelding, of animals. Cattle, sheep, pigs, and goats were associated with the Neolithic peoples of Asia Minor by at least 4000 B.C. It is assumed that at some time during the course of the process of domestication, the discovery was made that gelding increased the stature, strength, and docility of some animals and enhanced the palatability of their flesh, Spencer (74).

The mists of antiquity obscure the point at which gelding of humans was begun, nor can it be said with any certainty what were the first reasons for castration in men. The earliest mention of castration in recorded history seems to be found in the Babylonian Code of Hommurabi (about 2000 B.C.) which prescribed castration as a punishment for sexual crimes. Likewise, in Egypt adultry was punishable by emasculation beginning in the Twentieth Dynasty (1200-1085 B.C.), as it was in China a few centuries later. The Egyptians, beginning about 1200 B.C., made somewhat of a practice of using eunuchs as royal servants. Around 1250 B.C. eunuchism emerged as an institution in the Israelite domain, and Mosaic law specifically forbid eunuchs entering the priesthood or even entering the congregation (Deuteronomy, Chapter 23, Verse 1).

Eunuchism was prominent among the priests of the god Attis, in the anchient kingdom of Phrygian in Asia Minor where they were used pederastic priests associated with prostitute priestesses of

the goddess Cybele, the "Earth Mother". Likewise, in Syria a similar institution existed, the male prostitutes here being associated with the worship of Adonis, and the female with the worship of Ischtar.

The Valesians, a Gnostic sect of the third and fourth centuries, carried the practice of eunuchism to an extreme, comporting themselves in a manner similar to the earlier priests of Phrygia. The Church Council of Nicaea, in 325 A.D., forbade the priesthood to eunuchs in an attempt to stamp out the idea. However, it still remained, and in Constantinople some eunuchs even became Patriarchs of the Church.

The use of eunuchs as keepers of harems probably dates back to the time of Confucius (500 B.C.), but it was the slave traders of the seventh and eighth centuries who did a thriving business in selling of eunuchs, and the Moslems from Spain to Afghanistan and India who were wealthy enough to support a bevy of wives or concumbines entrusted their supervision and chastity to eunuchs.

Remondino (75) refers to the description of the early traveler, Bisson, who in Mecca saw the Chief Eunuch of the Grand Sherif on his way to Stamboul for trial.

> "He was heavily chained and well guarded. It appears that the eunuch had been only partially castrated, and that the operation had been performed during infancy; his testicles had not fully descended so that in the operation the sac was simply obliterated, which gave him the appearance of an eunuch. In this condition he seemed to have kept perfect control of himself and his passions until made Chief Eunuch of the Sherif, who possessed a well-assorted harem of choice Circassian, Georgian, and European beauties.

"The negligee worn at the bath and the seductive influence of the Koranic seventh heaven was too much for the warm Soudanese blood of the Chief; his forays were not suspected until a blond Circassian houri presented her lord and master with a suspiciously mulatto-looking son and heir. A consultation of the Koran failed to explain this discrepancy and suspicion pointed to the Chief Eunuch who was accordingly watched; it was found that he had not only corrupted the fair Circassian but every inmate of the harem as well. The harem was promptly sacked and drowned, and the false eunuch shipped to the Sultan for sentence, the Sherif having the right to sentence and drown the harem, but having no such rights over such a high personage as the Chief Eunuch."

Even until rather recently small boys were castrated to keep them as sopranos in some choirs in Italy, and they sang in some of the Church choirs despite the open disapproval of a number of Popes. The custom finally was terminated by Leo XIII.

It has been only within the last fifty-odd years that castration has been applied to the human in an attempt to obtain relief from prostatic pathology. White (76) and Cabot (77) in 1895 and 1896 summarized the use of castration in the therapy of benign prostatic hypertrophy, and there appeared articles by numerous authors for a few years following this on castration as a treatment for prostatic hypertrophy. Little was done subsequently with castration as a therapy for prostatic pathology until the study of the relationships of the sex hormones relighted interest in the subject.

Young (78) in Cabot's Urology text in 1936 reported casterating two patients with prostatic carcinoma (with negative results), and is generally considered to have been the first to apply castration to carcinoma of the prostate. Strohm (79) in 1938 reported that

placental blood was a great boon to men suffering from prostatic malignancy. Counsler (80) in 1936 stated that the metastatic pain of prostatic carcinoma subsided after sterilizing dosage of X-ray to the testes, but gave no supportive evidence for the statement. Huggins and his associates, Huggins and Hodges (36), Huggins, Stevens, and Hodges (81), and Huggins, Scott, and Hodges (82), first published the results of their studies of the effects of castration on metastatic prostatic carcinoma over a period of 20 months in a series of three articles in 1941. Nearly simultaneously Munger (83), who had been working entirely separately from Huggins, published his report indicating that those who received testicular irradiation in addition to regular treatment seemed to have a slightly better prognosis. Subsequently a deluge of articles were published proclaiming the possibility that hormonal therapy could be the answer to the problem of prostatic carcinoma. Randall (84) published the first "damper" article on the subject when he released his results on five cases of prostatic carcinoma which had been castrated by him in the period 1933-1935, and which he had observed since that time. He considered their response as unsatisfactory and that his discouraging observations "should be recorded before a wave of enthusiasm, and castration, passes over this country".

CLINICAL STUDIES IN CASTRATION THERAPY FOR PROSTATIC CARCINOMA

The response of patients with prostatic carcinoma to castration can be divided into three general temporal groups; the immediate postoperative response, the intermediate response, and the delayed or long-term response. The long-term response is the main interest of this paper, and the reactions in the first two groups will be largely in the form of a summary.

The favorable immediate response to hormonal therapy in patients with advanced prostatic carcinoma is characterized by:

1. Relief from metastatic pain. This is usually spectacular often taking place within 12 to 48 hours, but occasionally requiring 7 to 14 days, and can be expected in 50% to 100% of those suffering from pain. In many cases patients who have been bed-ridden and taking large doses of opiates are able to become ambulatory, even to the point of resuming gainful occupation, and necessity of any medication for the relief of pain is abolished (4) (21) (23) (27) (29) (49) (85) (86) (87).
2. Improvement in the general clinical condition of the patient. There usually is within the first few days after the start of hormonal therapy a marked increase in appetite, a rise in energy, a relighted interest in living, psychic improvement, and a general sense of well being. There also is the

start of a gain in weight, red blood cells, and hemoglobin. This is seen in 60% to 80% of the patients (14) (21) (29) (45) (49) (81) (89) (90).

3. A rapid fall toward normal of the serum acid phosphatase. Sullivan, Gutman and Gutman (49) first performed serial serum phosphatase levels on patients with metastatic prostatic carcinoma. In 30 out of 31 in their series, there was a percipitious fall following castration, often within 24 hours, of the acid phosphatase level. Their series showed by the second postoperative day the mean decline was to 55% of the preoperative level, by the end of the first week a decline of 70%, the second week 73%. During the third week in most there was a small transitory rise. Subsequently there was a slow decline to stability at near normal levels in two or three months in those patients who were clinically responding favorably. The alkaline phosphatase on the other hand displayed a latent period of several postoperative days, then in the second or third weeks showed an abrupt rise, followed by a slow decline toward more nearly normal levels than preoperative. Huggins et al (81) (82) demonstrated similar results and showed that estrogens produced like results while being administered whereas androgens produced a marked rise in the acid phosphatase levels that had previously fallen;

the presumption followed that the serum acid phosphatase level was an accurate indicator of varying activity in the metastatic carcinomatous tissue. Barringer (48) demonstrated that those patients whose acid phosphatase levels did not fall also often failed to progress well clinically under hormonal therapy.

These various authors have found in general that from 50% to 80% of the patients with metastatic cancer of the prostate demonstrate a favorable immediate response to hormonal therapy. Why the others do not respond is not known. At one time it was suspected that the more malignant and highly anaplastic cancers were less physiologically mature cells, and hence would not respond to the lack of androgen stimulation. However, Herger and Sauer (23), Herman and Greene (46), Emmett and Greene (27), and Graves and Cross (90) have demonstrated that the anaplastic cell types respond as well, or better, to hormonal treatment than do the less anaplastic tumors.

The intermediate response in patients clinically progressing staisfactorily consists of a progression of the gain in weight, red blood cells, hemoglobin, and vitality, a gradually declining acid phosphatase, and also various phenomena associated with the regression of malignant tissue both at its primary and metastatic points.

Regression of the prostate starts in some cases soon after

therapy is instituted, and Huggins, Stevens, and Hodges (81) in their original article described the prostates becoming soft, small, and barely palpable, or not palpable, usually within 12 weeks. Sullivan, Gutman, and Gutman (49) reported similar findings, and in one of their patients who preoperatively had a prostate the size of a grapefruit with rectal erosion and melena, the melena stopped abruptly following orchiectomy and the prostate was of normal size in three months. The clinical evidence of regression of the malignant prostate is shown with the relief of urinary symptoms. Emmett and Greene (27) found 71% of those who had obstructive lesions before the institution of therapy were relieved. Herger and Sauer (23) reported regression in the size and consistency of the gland with relief of obstruction in only about 40% of their patients. Alyea and Henderson (86) and McCrea (91) have reported satisfactory results by using a retention catheter for two to four weeks after the start of therapy, at which time the catheters could be removed and urinary difficulty did not return.

At the metastatic sites partial or complete healing is often observed, most authors having described increased calcification occurring around the boney sites in from two to six months, in some cases the lesions disappearing entirely. Several cases, Huggins et al (82), Nesbit and Cummings (92), and Clark and Viets (93), of metastases causing spinal cord tumors with severe neurologic symptoms, including a complete transverse myelitis, have been reported

as returning to normal following endocrine therapy. Several instances of resolution of secondary malignancy in the lung are recorded, and numerous cases where lymph node involvement has disappeared, even when the tumor was of the highly anaplastic type, Graves and Cross (90).

The cytological change in the malignant prostatic tissue has been studied, and Schenken, Burns and Kahle (94) have described tissues biopsied from 25 to 67 days after endocrine therapy was started. In the first stage of regression there is a decrease in the size of the nuclei and a condensation of the nuclear chromatin, while nucleoli are no longer visible and mitoses are absent. The cytoplasmic vacuoles are located predominately at the base of the cells. The nuclei in the second stage are pycnotic, and the cytoplasm is practically clear. The cell membranes are ruptured resulting in the coalescence of the vacuoles. With the rupture of all cell membranes, pycnotic nuclei and cell membrane fragments are clustered in the acinar spaces. The end stage is represented by the clear acinar space containing only remnants of pycnotic nuclei.

Early response of metastatic carcinoma to hormonal therapy had been fruitful almost beyond the realm of belief, but it is with the delayed respone that castration looses its panaceal aspects for prostatic carcinoma, much as Randall(84) had forewarned when enthusiasm was waxing at its highest. The delayed response is delayed failure; the relapse of the patient who previously had

shown a satisfactory clinical course. The exacerbations are characterized by development of typical signs and symptoms of metastatic prostatic cancer.

Increased growth of metastatic lesions, either old or new, are common and often times develop even with marked regression at the primary tumor site, Alyea and Henderson (86). Emmett and Greene (27) castrated 52 patients with prostatic carcinoma who had no signs of metastases, and within 30 months 35% of them had demonstrable secondary malignancies. Alyea (95) in a similar study on 24 patients was able to find no signs of metastases when the group was from one to three years postoperative.

The primary lesion which so typically undergoes regression in the early stage very often again enlarges and brings back urinary difficulty. Herger and Sauer (23) report that in 12 months one-fifth of those originally regressed will show recurrence and by 30 months the firgure is raised to 56%.

Weight loss and anemia occur as they do in the natural course of the disease, and recurrent pain is regarded as a serious symptom, many times being associated with a terminal rapid downhill course ending soon in death. Herger and Sauer (23) showed 13% recurrence of pain in 12 months, but others have recorded higher rates than this; Alyea and Henderson (86) 41%, and Emmett and Greene (27) 50% in 12 months time.

Concerning delayed failure in general, Higgins (21) records

58.5% exacerbations in 8 to 11 months, Nesbit and Cummings (92) 47.5% in 21 months, Herger and Sauer (23) approximately 76% failure in 25 to 30 months, Bumpus and Massey (96) 40% failure in those followed a year or more. More and more evidence is at hand making it doubtful that any case of prostatic carcinoma has been cured by endocrine treatment and that in all probability, if death from other causes does not intervene, each case sooner or later would terminate in delayed failure. If this be true, the therapy is relegated to the rank of a temporary palliative measure.

As with those cases of prostatic cancer which fail to show a primary response to endocrine therapy, little is known as to the physiology that eventually leads to the androgen independent malignancy and a delayed failure response. Even the serum acid phosphatase often fails as an objective sign of metastatic activity of malignant prostatic tissue in the course of the disease after endocrine therapy has started, and it has been considered the best by many including Huggins (88) and Sullivan, Gutman and Gutman (49), who demonstrated than an increasing acid phosphatase level in several patients anticipates demonstrable metastases by as much as several months. However, Herger and Sauer (23) McCrea (91) and others have shown that, following the initial decline of the acid phosphatase following the institution of therapy, the metastatic disease may flourish even to the terminal stages without any re-elevation of the phosphatase level. Kearns (97) has studied blood

sedimentation rate deviation, and has described its occurrence in 100% of the cases of metastatic prostatic carcinoma and is an excellent method of following the disease. Higgins (21) is of the same opinion.

A constant disagreement has appeared in the literature ever since endocrine therapy was initiated as to how it was best administered, by castration or by estrogen medication. Huggins, Scott, and Hodges (82) favored castration, even as they introduced estrogen therapy, on the grounds that metaplasia and hyperplasia of squamous cell epithelium had been produced with estrogens and in several instances the estrogens had been proven carcinogenic in animals. Huggins (88) has maintained the opinion that castration is the preferred method, postutating that the estrogen-androgen neutralization is complex and its efficiency can never be judged completely while minute amounts of androgens maintain the activity of the malignant tissue. He also has obtained better clinical results with castration as the primary means of therapy, using estrogens only for those cases which show immediate failure of satisfactory response in the serum acid phosphatase. Alyea and Henderson (86) likewise use castration on the basis of absolute removal of androgens rather than an uncertain neutralization with estrogens. They also report a more marked clinical and objective relief than with estrogens. Herger and Sauer (23), in comparing results of their series where castration alone or with preoperative and/or post-

operative estrogens was used as therapy, found no better results when estrogens were used than with castration alone, and that the main factor as to how long the patient remained in remission was the presence or absence of metastases rather than the type of hormonal therapy he received. Once in postcastrative relapse they found stilbesterol did little for the patient, whereas in a few cases castration relieved the patient temporarily when in relapse under estrogen therapy.

Diametric to these views are those of the group exemplified by Higgins (21) (who considers castration of greater value than estrogens only in those cases where fast relief from pain is desired) who maintains castration does not depress all androgenic activity in that following orchiectomy the anterior pituitary becomes hyperactive, due to loss of testicular inhibition, in its secretion of gonadotropins and the adrenal elaborates extra-gonadal androgens; the net result being that castration has defeated its own purpose. They maintain, on the other hand, that estrogens in adequate dosage neutralize the effects of all androgen, and further they depress the gonadotropic activity of the pituitary. Dean (98) found, while treating alternate cases in a series with castration and estrogens, that he obtained better clinical results, more involution of the primary growth, fewer relapses, and that estrogens benefited the castration failures and relapses. Kearns (97) has expressed the belief that all the clinical benefits of castration are obtainable

by estrogen therapy, and this view is shared by Moore, Wattenberg, and Rose (99), and Deming (70). It has been considered that the increased 17-ketosteroid excretion found in the urine of many post-castrates was evidence in favor of the estrogen neutralization method of androgen control, but the work of Scott and Vermeulen (100), Chute, Willets, and Gens (45) and others has indicated that there is little or no relation between 17-ketosteroid excretion and androgen activity and the clinical course of the patient.

Theoretically, those who have used combined castration and estrogen neutralization have the benefit of the odds, since they are removing the main source of the androgens and are depressing anterior pituitary activity with estrogens while simultaneously neutralizing any extra-gonadal androgens that might be formed. Chute, Willets, and Gens (45), McCrea (91), Mathe' and Ardila (101), and Crane and Rosenbloom (102) have reported better results with combined hormonal therapy than by either method alone.

When it was found that so great a percentage of those who had earlier shown satisfactory response soon relapsed, and that in many cases metastases developed extensively in patients who previous to the start of hormonal therapy had shown no evidence of metastases, the question arose as to when was the proper time in the course of the disease to institute endocrine treatment for the advanced case of prostatic carcinoma if it is to be of the most benefit to the patient. In considering that hormonal therapy does not prevent the occurrence

of metastases, continued relief from pain is not the rule over a length of time, and that the patient even with demonstrable metastases may be for a long period of time free of pain without any treatment, many of the authors are in favor of delaying endocrine treatment until the onset of the symptoms of an advanced fast growing local lesion or of advanced metastatic lesions. Nesbit and Cummings (92), Nathanson (103), Stirling (4), Herger and Sauer (23), Bumpus (96), Higgins (21), Emmett and Greene (27) are all in accord with this trend, as is Bugbee (104), who has expressed this opinion in plain but forceful words:

> "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."

The antithesis of this is found in the opinion of those who consider that, in those cases where it is certain the malignancy has spread beyond the prostatic capsule and is beyond surgical cure, time is lost in determining the final outcome of the disease by not initiating hormonal therapy as soon as the diagnosis has been made. Huggins, as quoted by Meads (105), and Deming (70) are just as emphatically in favor of early treatment as Bugbee (104) and others are in commendation of delayed initial treatment.

Meads (105), in an attempt to find the general reaction to this problem, sent questionnaires to leading urologists and in a total of 78 responses he found 23 in favor of early institution of hormonal therapy, 47 recommending delay of therapy at least till

metastases were demonstrable by X-ray, one that was in doubt as to the value of the therapy, and seven who were opposed to it entirely.

The side reactions following castration are usually few and mild. Edema of the legs is noticed in some, while numerous cases develop vasomotor "hot flashes", which are controlled by small doses of stilbesterol for a few days. Sexual desire and erection are usually lost, and in a very occasional instance the breasts become somewhat tender and slightly enlarged. Estrogen administration produces essentially the same changes with a loss of sexual activity and often an atrophy in the penis and testes. Leg edema is noticed as in castration, but the breast symptoms are much more marked as a rule, occasionally with the nipples quite sore and the breasts showing considerable hypertrophy. Gastrointestinal upsets and nervous instability are seen at times.

The final evaluation of castration and estrogenic therapy for advanced carcinoma of the prostate can be made only by comparison of the results obtained by these methods over a long period of time with those of the other known treatments. Only in the classic study of Bumbus (20)has an extensive series of cases been followed without treatment from the time of diagnosis till death to determine the natural history of the disease, and hence has been the standard with which methods of therapy have been compared for twenty years. He found that of those patients who had metastases at the time of

diagnosis, 66.6% were dead in nine months, and 58% of those without metastases had died in 12 months. Only four cases of the series (less than one per cent) lived more than 36 months, and two lived more than ten years. Nesbit (106) has carried a series of 781 controls with his group of cases being studied by hormonal therapy and has had, relative to Bumpus' figures, a lower mortality in his controls for the four year period the survey has thus far covered. The comparison of these two sets of controls with the results obtained by hormone therapy in groups that have passed, or approached, the five year mark, along with some non-endocrine therapy results, is given in Figure 5, page 41.

Further comparisons of results of hormonal therapy with those of other methods can be made with Caulk and Boon-Itt (109) who reported 10% of those treated with the cautery-punch operation and irradiation lived beyond the live year mark, Barringer (110) who found 5.7% controlled over five years after external irradiation and implantation of radium needles, and Prince and Vest (111) who treated a series of patients in a total of 13 different ways and 7% survived five years or more.

With regard to shorter term results, Nesbit (106) has shown that following castration one year 26.6% of those with preoperative metastases were fatalities, and that between 30 and 36 months were required to match the 66.6% fatalities that Bumpus' (20) controls with metastases showed in six months. Similarly, with the patients

in the two series who were free of metastases at diagnosis, Nesbit's had a 48 month duration of life before equaling the 58% mortality Bumpus' showed in 12 months. Data that closely corresponds to this

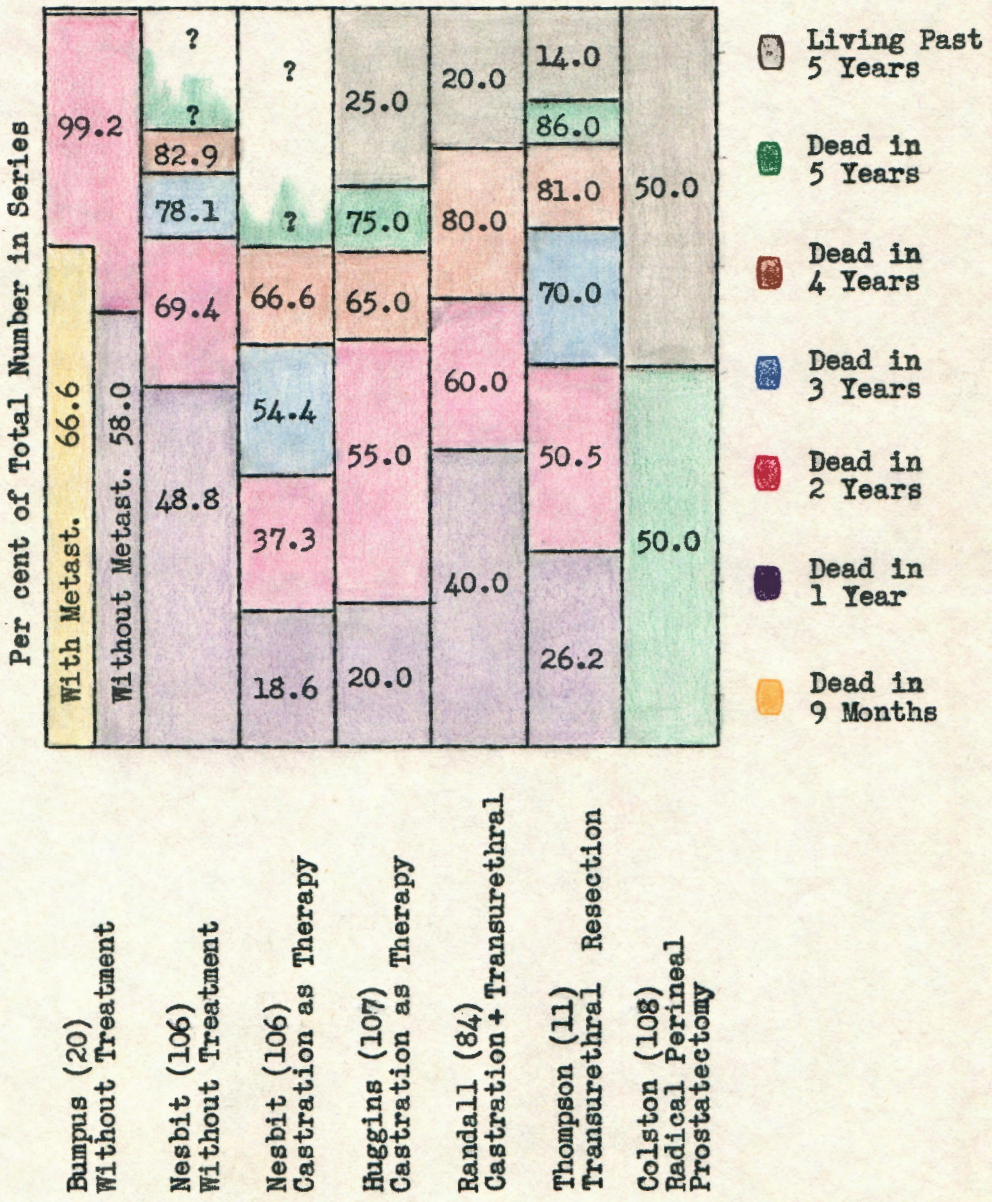

Fig. 5. Mortality Studies in Prostatic Cancer Therapy.

is available in most of the many reports of hormonal therapy carried on over two to three years time, Alyea (95), Emmett and Greene (27), Herger and Sauer (23), Higgins (21), Bumpus, Massey, and Nation (96), Stirling (4), McCrea (91), and many others.

Thus, it has been well established that for a shorter or longer period, hormonal therapy produces a marked lowering of mortality, as well as morbidity, in advanced cases of prostatic carcinoma. Many more cases need to be studied over long periods of time before the final evaluation of the process can be made, but the series of Huggins (107) and Nesbit (106) tend to indicate that the beneficial results in numerous cases may be extended over a number of years, possibly to the point of being 50% as efficient as radical perineal prostatectomy is for early carcinoma of the prostate, as Colston's (108) figures show only a 50% five year "cure" for this procedure. To date hormonal therapy has offered more to the unforturnate afflicted with the disease than any other method.

COMMENT

Prostatic carcinoma has presented to the patient and the physician one of the most trying and perplexing of problems in morbidity and mortality.

It is a disease that in the last fifty years has shown a startling increase in incidence, this probably relative to an absolute rise in the number of living males in the prostatic cancer age group.

Prostatic carcinoma has been a disease that in 95% of the cases has gone undiagnosed until it has passed the bounds of surgery, the only known cure. The prostate in every male over 40 years of age should as routinely be palpated for the earliest evidence of malignancy as are the breasts in the female.

The resemblence physiologically of carcinomatous prostatic epithelium to normal adult prostatic epithelium, whose activity had been demonstrated to be relative to the amount of testicular androgenic stimulation, in its ability to elaborate acid phosphatase led to the application of androgen-deficiency therapy, either by castration or estrogenic neutralization, in cases of prostatic carcinoma which had progressed beyond the possibility of surgical cure.

Metastatic carcinomatous prostatic tissue becomes a "pseudo-endocrine" gland in its secretion of acid phosphatase, and increased blood levels of this enzyme are helpful in the diagnosis of the

disease and in watching the progress of the individual patient under hormonal therapy. In some cases the blood sedimentation rate may be additionally helpful in following the patient's course.

Hormonal therapy for advanced prostatic carcinoma can be expected to bring remissions from the ravages of the disease in approximately four-fifths of those cases in which it is instituted, the period of remission varying from a short to a protracted time. It is suspected that if death from another cause does not intervene, all cases of remission, even those showing protracted beneficial results, will sooner or later die in an exacerbation of the malignant process. However, morbidity and mortality from advanced prostatic cancer has been lowered, or delayed, for many at least for a period of two or three years, and for some longer than this.

As to whether castration or estrogen administration will prove to be the more beneficial to the patient, it is a question that can not be answered to date, and will require much more work before any well-founded opinions can be formed. The same is true of the controversy as to whether it is more advantageous in rendering a service to the patient to institute therapy early or late in the course of a case of advanced carcinoma of the prostate. On strictly theoretical grounds, castration plus estrogen administration should be the best treatment, and early better than late.

The final efficacy of hormonal therapy of advanced prostatic carcinoma will be determined only after a study of many more cases over a long period of time.

The greatest significance of hormonal therapy may lie not in the results obtained in treating advanced prostatic carcinoma, but rather in the fact that it has been a pointer toward a manner in which malignancy in general will some day be controlled by an upheaval in the metabolic mosaic of the malignant cell.

CONCLUSION

It is the physician's desire to restore each of his ailing fellowmen to complete health, but in the instance where this is impossible, the physician carries a deep obligation to that fellowman to do everything humanly possible to relieve his suffering and prolong his life. Castration therapy for advanced prostatic carcinoma certainly fulfils this obligation, for while it can never be considered a cure, it is the straw to which drowning men, both the patient and the physician, clutch as one of the last, best, and only hopes. It is a straw that for many patients expands into a raft which affords them a repreive, sometimes brief and sometimes protracted, from the dark ugly pools of agony and debilitation which are the very essence of prostatic carcinomatosis. It is but one straw among the many that truly justify the existance of the physician.

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