

WHAT MAKES THE PROSTATE GROW

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It is a great privilege and pleasure to be here at the meeting of the Western Section, and first I wish to thank those responsible for my invitation. Having familiarized myself with the list of distinguished men who have preceded me as Robert V. Day lecturers, I approach my assignment with considerable apprehension and humility.

My age prevented me from knowing Dr. Robert Verne Day, chemist, surgeon, urologist, professor and past president of the Western Section, whose untimely death occurred on April 30, 1939. Yet from what I can deduce from his biography and writings, I am sure that association with him would have been most pleasurable and profitable to me, particularly profitable in ideas concerning the mechanisms of action of the male sex hormones.

You of the Western Section will recall that the last article he wrote for the *Journal of Urology* and which appeared therein in the February 1939 issue was entitled "Male Sex Hormone Therapy."¹ In spite of the expenditure of large sums of money and the time and effort of many, few truths have been added to what he wrote then. In spite of leads which were inviting and results which were encouraging he wisely recognized that, "Hormone therapy is in no sense to be considered a substitute for surgical relief in major prostatic obstructions, [and] in true hypertrophy, it is a mistake to resort to any type of surgical relief until the so-called false capsule is well formed, that is to say, until it is ripe, so to speak, just as we remark in speaking of cataract. The reason for this, when a premature enucleation is performed, is that a ragged prostatic bed is left, and prolonged or permanent post-operative urinary irritation [or recurrence] ensues. If, on the other hand, transurethral resection is performed, the residual prostate is eventually almost sure to undergo marked hypertrophy and necessitate further surgical relief. The so-called prophylactic resection is a misnomer, is evidence of bad surgical judgment and approximates the supreme error." We would do well to recall these principles today.

His optimism was illustrated by the following: "Indeed it is risky to venture an opinion as to what will be the true field of male sex hormone therapy until the collective experience of clinicians and research scientists (over a period of perhaps 10 to 25 years) has filled many now empty gaps in our knowledge. Nevertheless, the present status of our knowledge warrants a prediction that its therapeutic potentialities are enormous in both men and women."

My subject is, "What Makes the Prostate Grow." To be consistent with the facts, the listing of the title should have included a question mark at the end.

The Robert V. Day Lecture read at annual meeting, Western Section, American Urological Association, Pasadena, Calif. May 20, 1952. Read in part at 1952 annual meeting of Mid-Atlantic Section, American Urological Association and at the 1952 annual meeting of American Association of Genito-Urinary Surgeons.

¹ Day, R. V.: *J. Urol.*, **41**: 210, 1939.

and others feel it reasonable from the normally present prostate and the sphincter muscles, Shattock was of the opinion displaced beyond their normal position. The bladder gave rise to the failure to explain the occurrence as reported by both

bladder is extremely dismal. All cases occurring in the period of survival being reported in adults with the tumor concurred and seventeen months later. The latter case revealed an unrelated cause.

Other than by distant blood, early radical surgery offers no improvement in technic of cystectomy. That earlier diagnosis will be made. Where the tumor occurs, wide segmental resection

of the bladder is reported. This is briefly discussed. The procedure is recommended.

W. B. Saunders Co., 1951.
1943.

1928.

, **61**: 525, 1949.

171, 1907.

356, 1933.

: 167, 1930.

, **109**: 624, 1939.

36: 150, 1936.

Understanding fully that we don't know precisely what makes the prostate grow, I shall endeavor to outline what might be considered the present status of the problem and, if time permits, indulge in a little biological extrapolation.

Most of the work which I shall report from our laboratory is principally the result of the efforts of our resident staff, my function being largely that of providing a modern mammalian laboratory in which to work. Most of the work has been done in animals, and almost all of it concerns the effects of endocrine manipulation on prostatic size, histology and function. All has been done with the thought that in order to understand abnormal prostatic growth in man we must first understand normal growth.

During the normal course of events placental male mammals are born with prostate glands. During the last trimester, and for a short time after birth, distinct histological changes can be observed which include squamous metaplasia and focal hyperplasia of fully differentiated epithelium. These changes occur at a time when changes also occur in the breast, uterus and vagina of females, and it has been suggested that these changes are due to the action of gonadal hormones, derived either from the mother or from the fetal gonads under the stimulus of maternal gonadotrophic hormones.

Shortly after birth retrogressive changes occur, and it is not until the testes begin to elaborate their hormones that we again note changes in the size, histology and function of the prostate gland.

Barring the occurrence of acute, subacute and chronic inflammation or the development of prostatic stones, few changes are usually observed during the next two score years and ten. Thereafter, nodular hyperplasia develops in most glands and carcinoma in many. To this author, with the evidence at hand, the best working hypothesis is that both benign hyperplasia and cancer of the prostate result from a disturbance of the ratio and quantity of androgens and estrogens in these older men.

Let us first examine the evidence for endocrine regulation of normal prostatic growth.

THE EFFECT OF CASTRATION

For centuries it has been known that castration, both in animals and man results in profound changes in male accessories. That genius and tireless experimenter, John Hunter,² seems to have been one of the first to succinctly describe the effects of castration on prostatic size and functional capacity. Describing his observations in the bull, he wrote: "The prostate gland, Cowper's glands and the glands along the urethra are in the perfect male large and pulpy, secreting a considerable quantity of slimy mucus which is salt to the taste; while in the castrate animal these are small, flabby, tough and ligamentous and have little secretion."

This observation has been confirmed repeatedly in man and in many species of animals. Two examples follow:

Slide 1 [based on data from table 1³] shows the prostatic weight response in young adult rats 5 weeks after castration. Referring to group A, we see that in

² Hunter, John: In collected works, edited by J. F. Palmer, London, 4: 31, 1786.

³ Grayhack, J. T. and Scott, W. W.: *Endocrinology*, 48: 453, 1951.

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300 gm. control rats, intact and fed normally, the prostate gland weighs some 600 mg. Five weeks after castration, rats of the same age, strain and weight and fed with the same food, group B, have prostates which weigh less than 50 mg. A profound atrophy has occurred, and histologically this atrophy includes both fibromuscular and epithelial elements.

Slide 2 [fig. 1⁴] prefaces slide 3 and shows a diagram of a prostatic fistula in the dog which permits a study of prostatic secretion, a function of the prostate. In slide 3 [fig. 4⁴] we see that castration virtually abolishes prostatic secretion even under parasympathetic stimulation. Histological studies of such castrate-fistula preparations show atrophy of all elements.

Let us ask ourselves the obvious question: What have we eliminated from the body when we have removed the testes? The answer is less obvious.

TESTICULAR HORMONES

Somewhat over 100 years ago Berthold,⁵ on the basis of transplantation experiments in the cock, presented evidence that the testes exert decided effects on the organism through the blood stream independent of established nervous pathways. Since then, tremendous energy has been expended on determining the nature of the hormones elaborated by the testis, the cells responsible for their production and the physiological actions of the hormones produced.

Both crystalline androgens and estrogens have been extracted chemically from testicular tissue. This, however, does not necessarily mean that both are made in the testis nor in the form in which they were isolated. Several schools of thought exist currently with regard to the particular testicular cells responsible. Thus, one school presents evidence to support their belief that the interstitial cells of Leydig make both androgens and estrogens;⁶ a second, that androgens are made by these same cells but estrogens are made by tubular cells, most likely the Sertoli cells;⁷ a third, that whereas androgen is most likely made by Leydig cells, estrogen is formed outside the testis; a fourth, that the second hormone of the testis, although like estrogen, being water-soluble is not identical with it, and most likely is formed by the tubules.⁸ This substance has been named "inhibin."

Several years ago our laboratory investigated certain aspects of this particular problem, and briefly the results were as follows: 1) Sertoli cell tumors in dogs produce estrogen, and 2) the lipid content of the Leydig cell and Sertoli cell changes with age.

First about the dog: Dr. Willard E. Goodwin,⁷ formerly not only my right hand but my left, observed that certain testicular tumors in male dogs were associated with sudden and marked feminizing changes. These dogs developed breasts, abdominal pigmentation and became sexually attractive to other male dogs. Their prostates were large and on section showed marked squamous metaplasia. The breasts on section showed marked cystic hyperplasia similar to that

⁴ Huggins, C., Masina, M. H., Eichelberger, L. and Wharton, J. D.: *J. Exp. Med.*, 70: 543, 1939.

⁵ Berthold, A. A.: *Arch. f. Anat., Physiol. u. wissensch. Med.*, 1849, p. 42.

⁶ Maddock, W. O. and Nelson, W. O.: *J. Clin. Endocrinol.*, 11: 769, 1951.

⁷ Berthrong, M., Goodwin, W. E. and Scott, W. W.: *J. Clin. Endocrinol.*, 9: 579, 1949.

⁸ McCullagh, D. R. and Walsh, E. L.: *Endocrinol.*, 19: 466, 1935.

found in dogs experimentally given estrogen. Their urinary estrogens were high, and analysis of the tumors themselves showed increased estrogen content. On section these tumors were composed almost entirely of Sertoli cells, all sudanophilic. This caused us to wonder, as had others before us, if the Sertoli cell normally produced estrogen.

One year later my former associate, Dr. Kenneth M. Lynch, Jr.,⁹ taking a similar tack, began to study the lipid distribution in the cells of the human testis at all ages. He found that only two types of testicular cell accepted the fat stain, oil-red-O; the Leydig cell and the Sertoli cell. Independently the two of us graded the amount of fat present in these cells in 168 testes from humans ranging in age from 2 months premature to 84 years. The results of these estimations revealed that from puberty to old age Leydig cell lipid falls off and Sertoli cell lipid increases. In an independent study by Sargent and McDonald,¹⁰ the curve which they obtained when they plotted the number of Leydig cells per seminiferous tubule against age compared nicely with ours for Leydig cell lipid and age.

Of particular interest to us was the observation that no variation from the normal pattern was observed in either benign prostatic hyperplasia or cancer.

On the basis of this work, and the work in the dog, it is tempting to assign estrogen production to the Sertoli cells, and to postulate that, with age, estrogen production exceeds androgen production. However, the evidence is not conclusive. Furthermore, solution of the problem by present histologic techniques does not appear possible, for histochemists are not yet in a position to identify or localize the steroids of the testis.

Unfortunately then, the nature of the internal secretions of the testis remains in doubt and probably will until the steroid chemist turns his attention from the analysis of dead tissue to the analysis of testicular effluent blood. Until such a time as the nature of testicular hormones is determined, it is inaccurate to assign the effects of castration to only androgen withdrawal, as is commonly done.

THE PHARMACOLOGIC ACTION OF ANDROGENS AND ESTROGENS

This author has chosen to use the term pharmacologic rather than physiologic because, to date, rates of secretion of androgens or estrogens have not been defined. Initially, I wish to emphasize that the pharmacologic, physiologic or pathologic actions of androgens and estrogens depend on a multiplicity of conditions which include among many the size of the dose administered, whether administered singly or in combination and whether to an intact animal or castrate, the condition of the liver and the organism as a whole and the state of nutrition. Furthermore, when we are talking of their effects on the prostate gland, we must describe them in terms of whether it is an effect on the size of the gland, its function and the histologic elements effected, whether fibromuscular or epithelial.

Androgen administration. Slide 4 [based on data from table 1³] shows that in the young adult rat the prostate weighs approximately 600 mg. (A). Five weeks

⁹ Lynch, K. M. Jr. and Scott, W. W.: *J. Urol.*, **64**: 767, 1950.

¹⁰ Sargent, J. W. and McDonald, J. R.: *Proc. Staff Meet., Mayo Clin.*, **23**: 249, 1948.

ary estrogens were high, reduced estrogen content. On Sertoli cells, all sudanophilic if the Sertoli cell normally

M. Lynch, Jr.,⁹ taking a few cells of the human testis which had accepted the fat stain, found only the two of us graded from humans ranging in age. These estimations revealed that Sertoli cell lipid increased with age, the curve which indicates the number of Sertoli cells per seminiferous tubule and age.

That no variation from the normal hyperplasia or cancer. It is tempting to assign the age that, with age, estrogen therapy. The evidence is not consistent. Histologic techniques are in a position to identify

changes of the testis remains. He turns his attention from the abundant blood. Until such a time, it is inaccurate to assign an age, as is commonly done.

ESTROGENS AND ESTROGENS

Physiologic rather than physiologic or estrogens have not been pharmacologic, physiologic or endocrine administered, whether intracutaneous to an intact animal or a castrate as a whole and the state of their effects on the prostate. It is an effect on the size of the prostate effected, whether fibro-

From table 1³ shows that in the castrate weighing 600 mg. (A). Five weeks

1950. *Mayo Clin.*, **23**: 249, 1948.

after castration it weighs approximately 50 mg. (B). If the castrate is given 0.4 mg. of testosterone propionate every other day for 2 weeks, the prostate may weigh 1100 mg. (D). Histologically one observes a uniform development of all the true prostate tissue in these androgen-treated castrates with no recognizable abnormal changes.

Slide 5 [fig. 5¹¹] shows that in the immature dog, prepared according to the Huggins' technique previously illustrated, no secretion occurs. If one administers 25 mg. of testosterone propionate to the immature dog, within 1 week the prostate begins to secrete in response to pilocarpine and the gland increases in size. In the mature castrate [slide 6—fig. 6¹¹] secretion is maintained as long as testosterone is given, in this case in pellet form. Other examples of androgen stimulation of prostatic growth could be given.

Estrogen administration. Great confusion arises as to the effect of estrogen on prostatic growth, and as stressed earlier, much of this confusion revolves around the size of the dose given and the particular portion of the prostate to which reference is made. As early as 1933, Lacassagne,¹² administering estrogen to mice for periods as long as 5 months, observed considerable growth of the dorsal prostatic lobes, leading to retention of urine and hydronephrosis. These initial observations were confirmed by many, including de Jongh,¹³ Burrows and Kennaway,¹⁴ David and his co-workers¹⁵ and Korenchevsky and Dennison.¹⁶ Subsequently, Burrows¹⁷ showed that this growth was not limited to the dorsal lobes but extended to all the lobes of the prostate, effecting changes primarily in the fibromuscular components and to a lesser extent in the epithelial elements. It is interesting to note that Moore and Price¹⁸ did not observe these striking changes presumably because of too low dosage and too brief periods of injection.

On the contrary, certain doses of either naturally occurring or synthetic estrogens will shrink the prostate glands of a mature rat and will cause cessation of prostatic secretion in the Huggins' fistula dog. Whether this action is a direct antagonistic one to testicular androgen or acts indirectly through the pituitary is as yet unsettled. Huggins believes it is a direct one and slide 20 [chart 3¹⁹] shows one of his experiments which he uses to support his view. Although castrate, these dogs' pituitary glands are intact, and as I shall endeavor to point out later, probably were producing prolactin.

In this connection it will be recalled that Kirchesky and Benjamin²⁰ observed that estrogen administration after castration in the prostatectomized rabbit almost restored the precastration size of intraocular prostatic transplants.

Lastly, with regard to estrogen effects, we have been unable to counteract

¹¹ Huggins, C.: Harvey Lectures, series 42, pp. 148-193, 1946-1947.

¹² Lacassagne, A.: C. R. Soc. Biol., **113**: 590, 1933.

¹³ deJongh, S. E.: Acta Brev. Neerl., **3**: 112, 1933.

¹⁴ Burrows, H. and Kennaway, N. M.: Am. J. Cancer, **20**: 48, 1934.

¹⁵ David, K., Freud, J. and de Jongh, S. E.: Biochem. J., **28**: 1360, 1934.

¹⁶ Korenchevsky, V. and Dennison, M.: Biochem. J., **28**: 1474, 1934.

¹⁷ Burrows, H.: J. Path. Bact., **41**: 423, 1935.

¹⁸ Moore, C. R. and Price, D.: Am. J. Anat., **50**: 13, 1932.

¹⁹ Huggins, C. and Clark, P. J.: J. Exp. Med., **72**: 747, 1940.

²⁰ Kirchesky, B. and Benjamin, J. A.: J. Urol., **58**: 114, 1947.

prostatic weight gain in castrate rats maintained on constant doses of testosterone propionate with doses of either estradiol or stilbestrol, large, small or in between.²¹ Much more work is necessary.

EXTRAGONADAL SOURCES OF ANDROGEN AND ESTROGENS

I should now like to leave this phase of the subject and turn to a brief consideration of extragonadal sources of androgen and estrogens. This subject looms large today in connection with the rationale for bilateral adrenalectomy in the treatment of relapse after castration-estrogen therapy for disseminated prostatic cancer.

Both androgens and estrogens have been extracted from the adrenal gland, presumably the cortex. But, as in the case of the testis, this does not necessarily mean that both are made in the cortex nor in the form in which they can be isolated.

Reasons for believing that the normal adrenal cortex makes androgen and estrogen stem in part from observations on patients with either masculinizing or feminizing tumors. Yet, I beg that this is an abnormal situation and one in which there is distinct cellular alteration. In the mouse, Price²² has suggested that the X-zone has an andromimetic function, and many people have accepted this. Yet, experiments by Jones²³ indicate that the X-zone does not secrete an androgen, since in hypophysectomized, castrated mice whose X-zones are maintained in a histologically normal state with gonadotrophin, the prostate and seminal vesicles are atrophied to the same extent as those of untreated, hypophysectomized, castrated mice.

Recently in a comparative study of the effect of castration on the spontaneous running activity of wild and domestic rats, Dr. Curt Richter²⁴ observed that whereas the adrenals of the wild rat showed considerable hyperplasia after castration and spontaneous running activity was little altered, the seminal vesicles and prostates of these animals remained atrophic. This would suggest that the hypertrophied adrenals made a cortisone-like substance but not a secondary sex gland stimulating androgen.

Time does not permit further discussion of this important phase of the problem and certainly it remains unsettled. However, no less of an authority than Dr. George Sayers of the University of Utah²⁵ concludes a recent discussion of the subject by stating that adrenal cortical androgens are not likely to have an important role in man, since a compensatory increase in androgen secretion by the adrenal cortex, if it does occur, is not of sufficient magnitude to prevent the development of deficiency symptoms following castration of the human male.

In leaving this phase, if you are not already thoroughly confused, you perhaps will be, as I was, when I saw the following sections: Slides 21 and 22 (fig. 1) are sections from the enlarged, obstructing prostate of a male, age 60, castrated at

²¹ Grayhack, J. T., Kearns, J. W., Bunce, P. L. and Scott, W. W.: Unpublished data.

²² Price, D.: *Am. J. Anat.*, 60: 79, 1936.

²³ Jones, I. C.: *Endocrinol.*, 45: 514, 1949.

²⁴ Richter, C. P. and Uhlenhuth, E. H.: Unpublished data.

²⁵ Sayers, G.: *Physiol. Rev.*, 30: 241, 1950.

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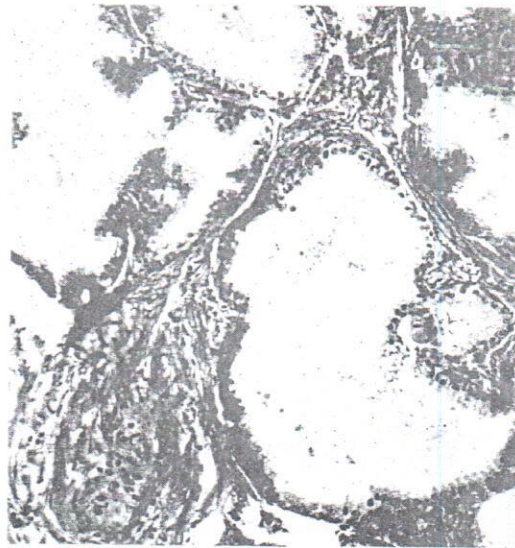
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A



B

FIG. 1. Sections from prostate gland of a man, aged 60 years, whose testes were removed at age of 28 years because of tuberculous epididymitis and orchitis. A shows typical benign prostatic hyperplasia; B shows classic squamous metaplasia. Both sections $\times 150$.

age 28. One shows typical hyperplasia and one classic squamous metaplasia. If these are androgenic and estrogenic effects, respectively, as some believe, action must have either occurred prior to castration some 32 years before, developed after as a result of hormones formed extragonadally, or hormones had nothing to do with it.

Studies in many animals indicate that profound changes occur in the pituitary gland after castration. So-called castration cells appear in the anterior lobe, and urinary gonadotrophins, thought to arise in the pituitary, increase markedly. These changes can largely be prevented by the administration of either androgen or estrogen. On a weight basis more of the former is required.

THE HYPOPHYSIS AND PROSTATIC GROWTH

For years it has been known that the hypophysis, or pituitary gland, exerts a regulatory effect on the testes and on the prostate gland. Heretofore, growth stimulation of the prostate by the pituitary was considered to be entirely dependent upon intact testes, i.e., a pituitary principle known as interstitial-cell-stimulating-hormone (ICSH) stimulates the interstitial cells (Leydig cells) to produce androgen which in turn stimulates prostatic growth. In part this must be true for pituitary gonadotrophins will partially restore the prostate which has undergone atrophy following hypophysectomy. Androgen will also (slide 10 [based on data from table 3³]), but recently Dr. Grayhack and I have observed that the prostates of hypophysectomized castrate rats are less responsive to testosterone propionate than those of non-hypophysectomized castrates. Comparing groups H and D in this slide one can see that the prostate glands of those castrate rats whose pituitaries were intact (D) responded much more to an identical dose of androgen than did those castrate rats who were also hypophysectomized (H). Until recently we had no explanation for this. This explanation, if it truly is one, is the result of a combination of an accidental observation, a hunch and experimental application. It may interest you. Approximately one year ago Sonnenberg and co-workers²⁶ were studying the distribution of radioactive prolactin in the female rat. Prolactin, you will recall, is the pituitary lactogenic hormone. Strangely enough, they observed concentration of this material in the ovary *not* the breast. A few male rats were studied and again strangely enough this material was concentrated in the prostate *not* the testis. Learning of this, we had a hunch that prolactin would increase the responsiveness of hypophysectomized castrate rats to testosterone. Experimentally, Doctors Grayhack, Kearns, Bunce and your speaker²¹ have found this to be true.

In prolactin then we have another prostate stimulating hormone, and of added interest is the previous observation of others that estrogen inhibits either the release of prolactin from the pituitary or its action after release.

In the time that remains, I should like to skim over the results of the work in our laboratory which deals with efforts to induce inhibition of prostatic growth by chemical means other than by the administration of estrogens which has been discussed in part previously. These efforts have included attempts to interfere with sex hormones from the time of injection or ingestion, during their course through the circulation, especially the liver, to the time when they reach the particular end organ such as the prostate gland. They have included a study of most hormones thought to be concerned with prostatic growth whether these

²⁶ Sonnenberg, M., Money, W. L., Keston, A. S., Fitzgerald, P. and Godwin, J. T.: *J. Clin. Endocrinol.*, 11: 747, 1951.

changes occur in the pituitary near in the anterior lobe, and pituitary, increase markedly. Administration of either androgen is required.

GROWTH

is, or pituitary gland, exerts the gland. Heretofore, growth considered to be entirely due to cells known as interstitial-cell-stitial cells (Leydig cells) to prostatic growth. In part this must be to restore the prostate which has been removed. Androgen will also (slide 10) Grayhack and I have observed that castrate rats are less responsive to androgen than intact rats. At the prostate glands of those castrate rats responded much more to androgen than intact rats who were also hypophysectomized for this. This explanation, based on an accidental observation, interest you. Approximately one-third of the distribution of radioactivity will recall, is the pituitary gland. In castrate rats observed concentration of this androgen in the prostate *not* the testis. Androgen would increase the responsiveness to testosterone. Experimentally, Doctors have found this to be true. Androgen stimulating hormone, and of course that estrogen inhibits either action after release.

Over the results of the work in the inhibition of prostatic growth by the administration of estrogens which have been included attempts to interfere with the secretion of androgen, or ingestion, during their development, to the time when they reach maturity. They have included a study of prostatic growth whether these

Fitzgerald, P. and Godwin, J. T.

hormones are derived from the pituitary, the testes, the adrenals or the thyroid. The prostate gland itself has been studied from the standpoint of whether or not it is an endocrine gland.

THE SITE OF INJECTION AND THE ROLE OF THE LIVER

Since Zondek²⁷ in 1934 first demonstrated that the liver inactivates estrogens, numerous investigators have studied the role of the liver in sex hormone metabolism. These studies are of practical importance when one considers that orally administered hormones are first presented to the liver, a situation which does not obtain when parenteral routes of administration are used. The following experiments performed largely by our present assistant resident, Dr. John T. Grayhack,³ have a direct bearing on this problem. In this work, Dr. Grayhack used the technique devised by the Biskinds²⁸ which needs a word of explanation. By measuring the differential growth response of secondary sex glands, such as the uterus or prostate, in female or male animals in whom the gonads have been removed, to either subcutaneous or splenic implants of estrogen or androgen, one can determine the effect of the liver on hormonal action.

Under conditions of normal feeding, implanting pellets of estrogen into the spleen fails to reverse uterine atrophy induced by oöphorectomy, whereas under identical conditions, implanting estrogen pellets subcutaneously, will. The recent work of Kirgis and Rothchild²⁹ in the human is consistent with these observations in animals. They report that: "Seven ovariectomized women with mesenteric estradiol implants showed little cornification, and a high incidence of menopausal symptoms up to four months postoperatively, while four similar women, with rectus estradiol implants, showed a high level of vaginal cornification and no menopausal symptoms up to seven months postoperatively.

In the animal, under conditions of experimental cirrhosis, liver damage secondary to carbon tetrachloride feeding or during inanition, particularly protein deficiency, the liver fails to inactivate estrogen implants in the spleen.

Our work indicates that androgens are dealt with by the liver in a different fashion. For example: severe liver damage by carbon tetrachloride (slide 11 [fig. 1³]), to the point where it is estimated that at least 50 per cent of the liver parenchyma was severely damaged, failed to permit sufficient androgen to pass through the liver and cause prostatic growth in the castrate rat (slide 12 [based on data from table 1³]). In group A, with intact testes and fed a stock diet, the total prostate weight averaged 550 mg. In group B, with intact testes and fed the same stock diet *but* who were injected with carbon tetrachloride, the prostates weighed somewhat less, averaging 390 mg. Group C represents castrate rats fed stock diet. Their average prostate weights were 58 mg. Group D represents castrate rats fed stock diet and injected with carbon tetrachloride. Their average prostate weights were in the same range, 66 mg. Animals in groups E and G had pellets of testosterone implanted in their spleens. Both groups were castrate and fed stock diet. Group G differs from group E in that in G liver

²⁷ Zondek, B.: *Skandinavisches Arch für Physiologie*, 70: 132, 1934.

²⁸ Biskind, M. S. and Biskind, G. R.: *Endocrinol.*, 32: 97, 1943.

²⁹ Kirgis, H. and Rothchild, I.: *Endocrinol.*, 50: 269, 1952.

damage was caused by carbon tetrachloride. In spite of this, sufficient androgen did not get through the liver to cause prostatic growth. That the prostate was responsive to androgen is illustrated by groups F and H. Here testosterone was implanted subcutaneously, and in spite of severe liver damage secondary to carbon tetrachloride injections, the prostate of the castrate rat grew rapidly in response to androgen, H. (Compare G and H in concluding this phase.)

The results of a similar study involving complete starvation are substantially the same and again show that the liver continues to inactivate androgen under conditions of stress. We can conclude this phase with the statement that it seems that even under severe stress the liver is a "physiological filter" for testosterone propionate and probably for other androgens but not for estrogens. A hint that this may hold for man is suggested by the observations in World War II that male prisoners, when starved and for a short time after feeding, developed gynecomastia.

As yet no clinical use has been found which embraces these observations, and yet in time one may be. Last year, two members of our resident staff, Doctors Grayhack and Harris,³⁰ explored the possibilities of creating an adrenal shunt in the dog in an effort to cause the liver to inactivate adrenal androgens. In so doing their thought was that such a procedure in man might be of importance in the treatment of the invariable relapse following castration-estrogen therapy for disseminated prostatic cancer. Using the technique illustrated in slide 13 [fig. 1³⁰] they succeeded in causing left adrenal blood to first traverse the liver (fig. 2). If an excretory urogram revealed left kidney function, the right adrenal gland could be removed and the animal would live. At present the feasibility of such a procedure in humans with advanced prostatic cancer is being investigated.

Time does not permit a detailed consideration of the effect of dietary alterations on the prostate-stimulating action of parenterally administered androgen. However, at this time work in our laboratory suggests that a specific dietary substance, probably a protein, is necessary for maximal action of testosterone. We are presently engaged in studies designed to tell us the nature of this protein in an effort to eliminate it from the diet, or if possible, to find chemical means of interfering with its action.

Before concluding this phase of the subject, I wish to state a specific example of how the absence of a specific dietary substance can interfere with the action of a sex hormone, and how certain chemical substances can bring about this action independent of dietary restriction of this specific dietary substance.

For the last 5 years it has been known that the vitamin, folic acid, is necessary for the action of estrogenic hormones.³¹ This has been determined by experiments in which folic acid has been eliminated from the diet. Three years ago, Dr. Herbert Brendler,³² working in our laboratory, found that a chemical substance, bearing the trade name Aminopterin, and also known as an anti-folic acid compound, or an antivitamin, could effectively inhibit the action of estrogen on the

³⁰ Grayhack, J. T. and Harris, A. P.: Method for establishing portal drainage of adrenal venous blood in dogs, with metabolic studies included. In press, *J. Urol.*

³¹ Hertz, R.: *Endocrinology*, **37**: 1, 1945.

³² Brendler, H.: *Science*, **110**: 119, 1949.

rat prostate even though the diet was adequate in folic acid. Slide 14 [table 1³] illustrates his experiments in part. Referring only to experiment one, we observe that alpha-estradiol will shrink the prostate gland of the intact adult rat when given alone, but the same dose in combination with Aminopterin will not. Further experiments of his proved that this action was not due to any androgenic action of Aminopterin but to its interference with folic acid. Unfortunately,

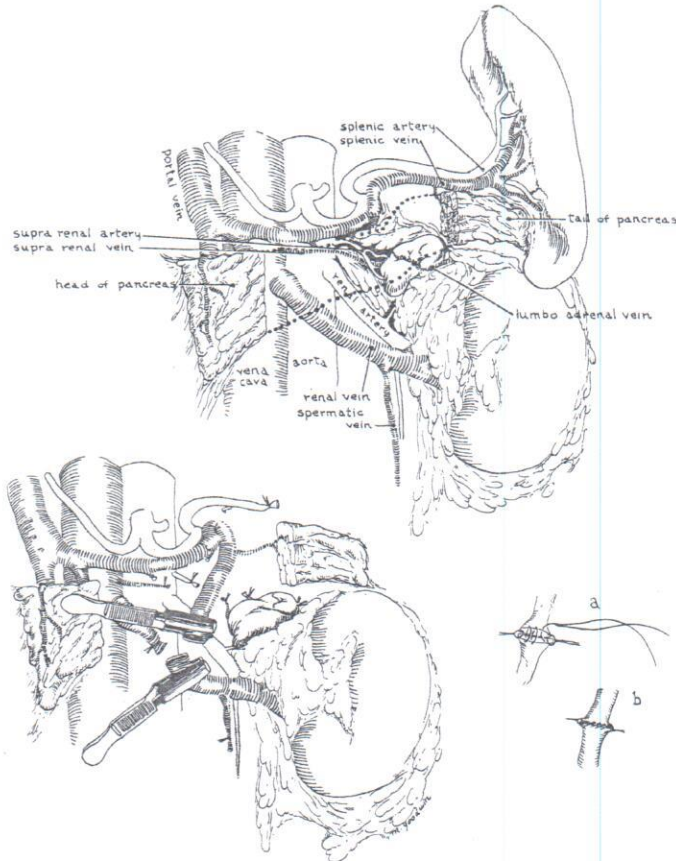


FIG. 2. Illustrating technique of Grayhack and Harris³⁰ for establishing portal drainage of venous blood from left adrenal gland of dog. Right adrenal is removed at second operation.

to date no specific vitamin has been found necessary for androgen action, thus preventing the development of an antivitamin to it. The search continues.

I shall conclude my remarks on chemical inhibitors with a few words on the search for inhibitors of pituitary action. As indicated earlier, the action of the pituitary gland on prostate growth is mediated through the testes. In recent years numerous substances have been suggested as pituitary inhibitors, notably parahydroxypropiophenone, suggested by the French,³³ and an extract of the

³³ Perrault, M.: *Presse méd.*, 58: 1010, 1950.

weed, *Lithospermum ruderales*, suggested by Dr. Marian Drasher³⁴ of Indiana University. Both have been without effect when tested on rats in our laboratory, neither causing any decrease in testicular or prostatic size or observable function. Work on the latter compound continues, primarily because of the rather authentic reports that the Western American Indians formerly brewed a tea of the weed which when taken by mouth was said to have contraceptive properties. Dosage was expressed in P-P units (papoose-preventing).

In what little time remains, I should like to relate briefly how knowledge gained in the laboratory has helped us in the clinical care of the patient with disseminated prostatic cancer.

It is now over 12 years since Dr. Charles Huggins and Dr. C. V. Hodges,³⁵ the latter now of your Section, demonstrated the profound beneficial effects of castration and/or estrogen therapy in the treatment of this disease. Doctor Huggins will tell you that this work was largely the result of study of hormonal action in the fistula dog.

Encouraged with the results, but dissatisfied with eventual relapse, Huggins and his associates continued to investigate the problem. Again, on the basis of animal studies suggesting that the adrenal produced androgen and thus leading us to believe that adrenal androgen was responsible for relapse, together we attempted to maintain life after bilateral adrenalectomy in the prostatic cancer victim relapsing after castration and estrogen therapy. We were only partially successful.³⁶ Now with cortisone we can with ease, and it has been the experience of our now separate groups that over half receive distinct benefit from this procedure.

Recently, we in our laboratory have pushed the mechanism back one step further, observing profound atrophy of a prostatic cancer, as well as considerable general improvement, in a single patient in whom hypophysectomy was done.³⁷ The fact that this patient's testes and adrenals were surgically intact prior to hypophysectomy indicated to us, in the light of observations in animals, that this action was mediated at least through the testes and possibly the adrenal.

In concluding I hasten to admit that this has been a long and rambling discourse, devoid of synthesis, and yet the facts prevent the telling of a simple story of what makes the prostate grow. Apropos are the words of Hermann von Helmholtz, renowned physicist, physiologist and physician, in his masterful lecture "Dan Denken in der Medicin,"³⁸:

"To one who has to contend with the hostile forces of fact, indifference and romance disappear; that which he knows and can do, is exposed to severe tests; he can only use the hard and clear light of facts, and must give up the notion of lulling himself in agreeable illusions."

³⁴ Drasher, M. L. and Zohl, P. A.: *Exper. Biol. & Med.*, **63**: 66, 1946.

³⁵ Huggins, C. and Hodges, C. V.: *Cancer Res.*, **1**: 293, 1941.

³⁶ Huggins, C. and Scott, W. W.: *Ann. Surg.*, **122**: 1031, 1945.

³⁷ Grayhack, J. T., deKlerk, J. N. and Scott, W. W.: Unpublished data.

³⁸ von Helmholtz, H.: *Bull. Inst. Hist. of Med.*, **6**: 117, 1938.