MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

2/13/69

BENIGN PROSTATIC HYPERTROPHY

Case. GR 08 35 38 Klinefelter's Syndrome with Benign Prostatic Hypertrophy.

This 41 year old man has known Klinefelter's syndrome, e.g. marked bilateral gynecomastia, small testes (< 2.5 cm), a female type chromatin pattern on buccal smear, and 47 chromosomes with an XXY karyotype. In addition, he has either an inadequate or a sociopathic personality, is an alcoholic, and has been addicted to antacids ever since he had a peptic ulcer in 1951. In 1966 he was seen at Methodist Hospital because of acute urinary retention (residual volume of 1700 ml) which was diagnosed as secondary to benign prostatic hypertrophy. An operation was recommended and refused. He was subsequently seen at St. Paul's in early 1968 with uremia, hyperkalemia, anemia, back pain, edema, and alkalosis. He had 1100 cc residual urine and an enlarged prostate to palpation, and a voiding cystourethrogram revealed trabeculation of the bladder, a diffusely enlarged prostate gland, and concentric narrowing of the prostatic urethra. He was subsequently transferred to Parkland where a transurethral prostatectomy was performed on 4/18/68 (20 grams of tissue being removed). This tissue on histological examination showed nodular hyperplasia typical of benign prostatic hypertrophy; in one section there was a small focus of adenocarcinoma. On review by the tumor board, no further extirpation was recommended.

Following the surgery he has undergone an extensive endocrinological work-up by the Department of Obstetrics and Gynecology:

1. Blood

testosterone	0.45 µg%
androstenedione	0.13 µg%
dihydrotestosterone	0.017 µg%
dihydroisoandrosterone	0.138 µg%

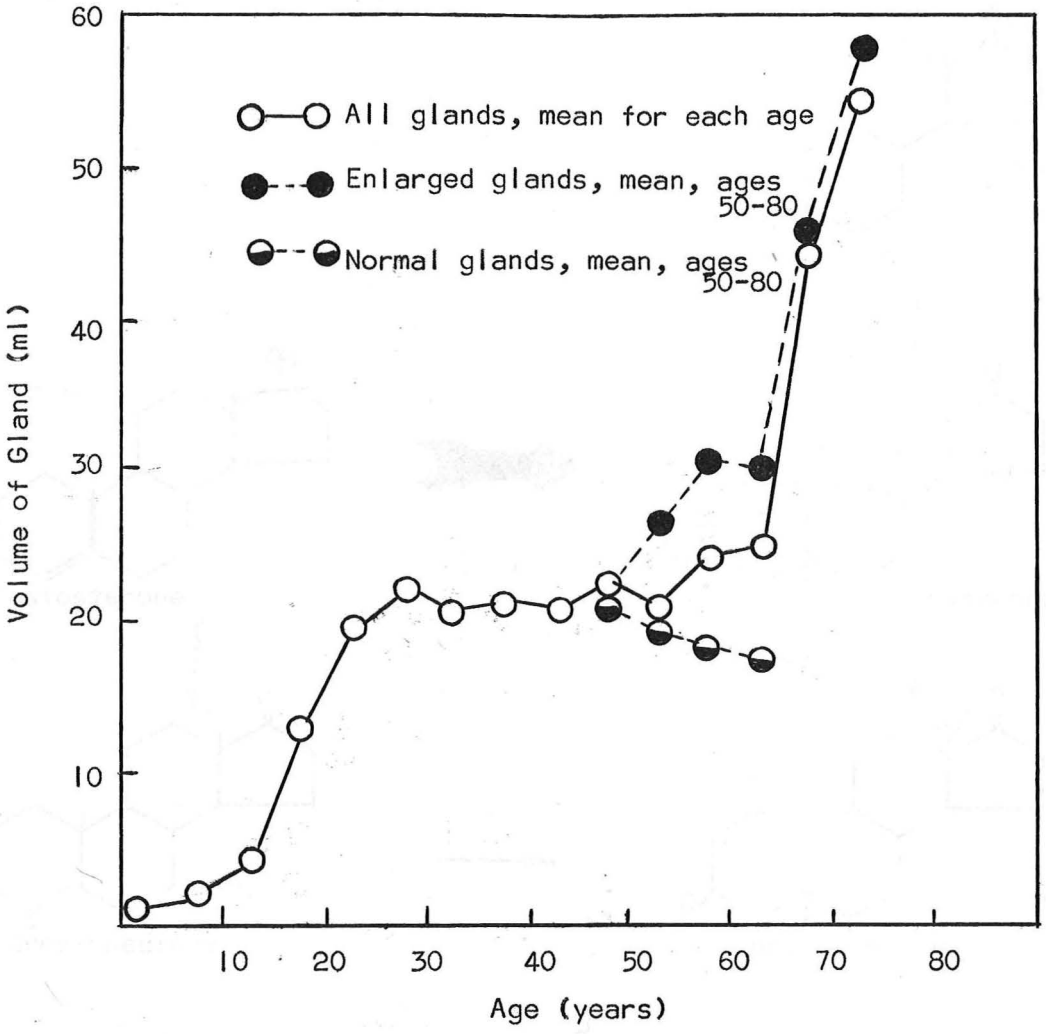
2. Urine

FSH between 16-50 mouse units per 24 hours

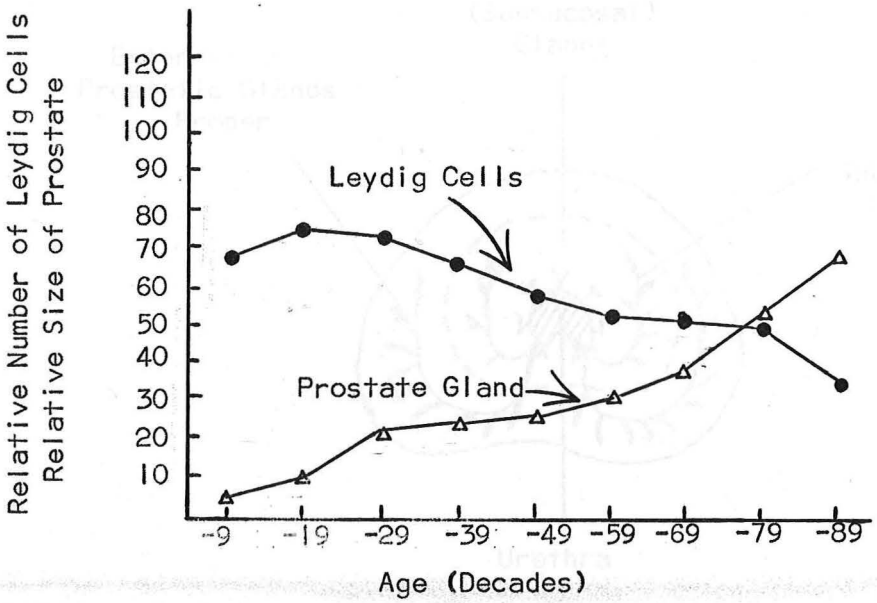
17 ketosteroids	2.7 mg/24 hours
17 hydroxycorticoids	7.6 mg/24 hours

He has had two more hospitalizations since that time as the result of metabolic alkalosis secondary to bicarbonate ingestion and chronic renal failure with azotemia and anemia; the etiology of the renal failure is unclear and may be due to the milk alkali syndrome.

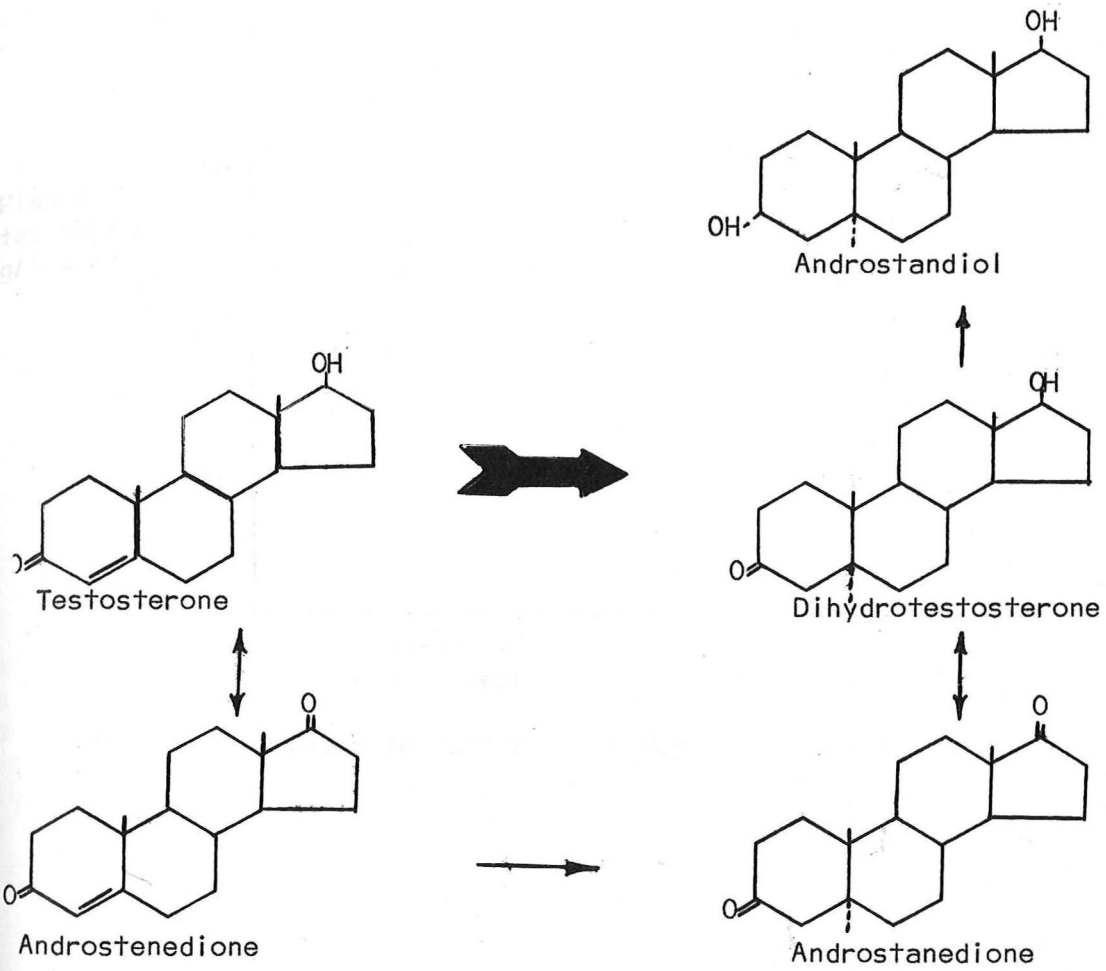
Change in Mean Volume of Prostate with Age. (Swyer, Ref. 10)



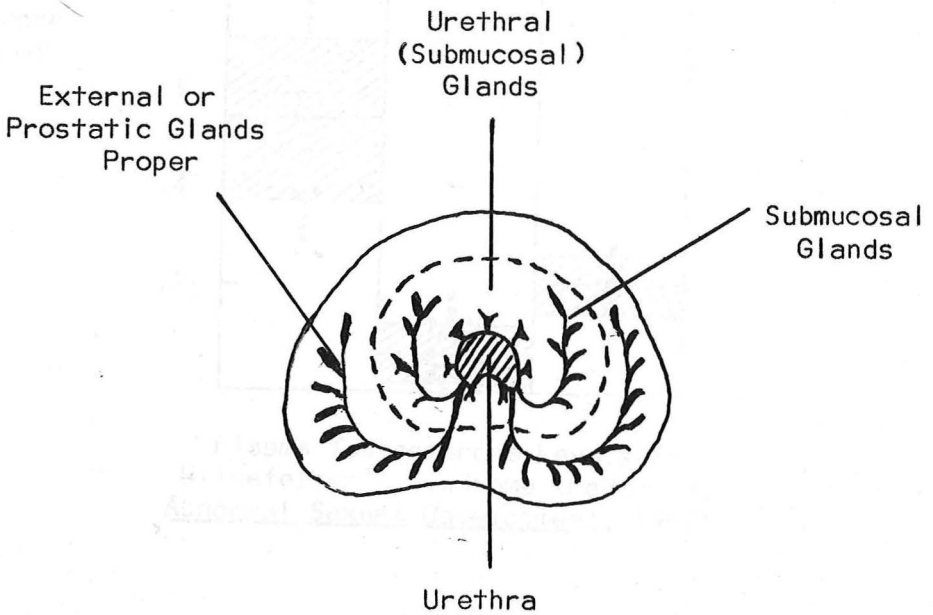
A Comparison Between Mean Number of Leydig Cells and Mean Size of the Prostate for Each Decade (Ref. 29)

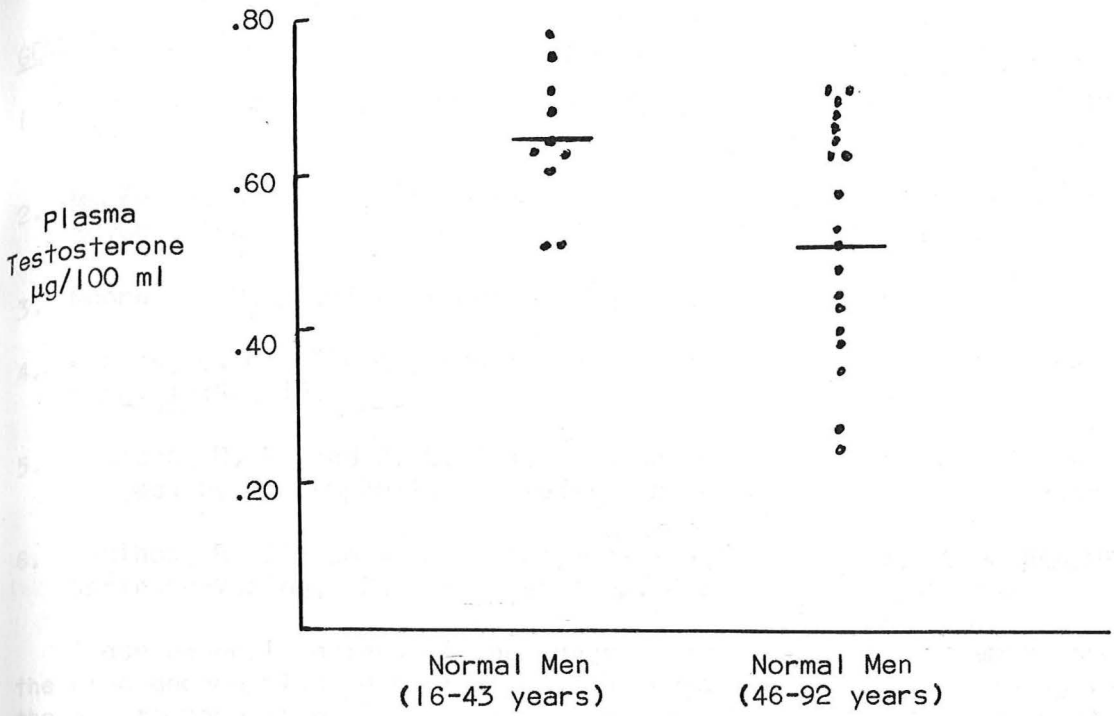


Principal Pathways of Testosterone Metabolism in Prostate

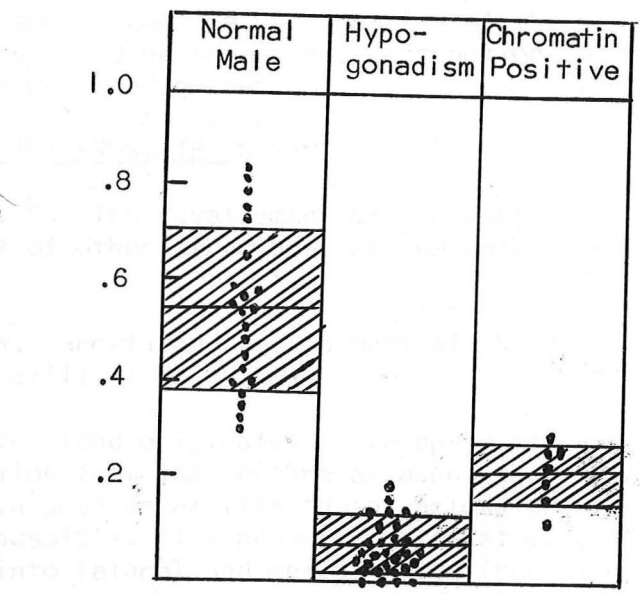


Distribution of the Normal Prostate Glands (Transverse Section)(Ref. 4)





Plasma Testosterone in Normal Men (Ref. 31)



Plasma Testosterone Levels in Klinefelter's Syndrome (Federman, Abnormal Sexual Development, 1967)

GENERAL REVIEWS

1. Deaver, J. B. Enlargement of the Prostate. Philadelphia. P. Blakiston's Son & Co., 1905.

2. Moore, R. A. Benign hypertrophy of the prostate. A morphological study. J. Urology 50:680, 1943.

3. Moore, R. H. Benign hypertrophy and carcinoma of the prostate. Surgery 16:152, 1944.

4. Franks, L. M. Benign nodular hyperplasia of the prostate: a review. Ann. Royal Coll. Surg. 14:92, 1954.

5. Thomson, R. V. and J. E. Ash. Benign hyperplasia of the prostate gland. Urology, Vol. II, ed. by M. Campbell. Philadelphia: W. B. Saunders. Co., 1954, p. 1095.

6. Ubelhor, R. Die sog. prostatahypertrophie, ch. in Encyclopedia of Urology. Berlin: Springer-Verlag, 1962, vol. VIII, p. 233.

These general reviews of the subject are in uniform agreement about the high incidence, the wide geographical distribution, the relative infrequency among the Asiatic races, and the age factors in benign prostatic hypertrophy. They also describe the early history of the problem (most attributing the first meaningful description to Morgagni), and the development of various surgical approaches to the problem. The early theories as to etiology including tumor, infection, sexual excess, arteriosclerosis, nutritional imbalance are described and discarded.

7. Chapman, I., N. Lapi, and W. Fethiere. Prostatic enlargement and lower urinary tract obstruction. Geriatrics 19:231, 1964.

This paper emphasizes the universality of the disease, clearly demonstrating that the pathogenic picture and urinary tract obstruction can occur in the absence of enlargement of the gland as measured at autopsy.

DEVELOPMENT OF THE PROSTATE IN MAN

8. Lowsley, O. S. The development of the human prostate gland with reference to the development of other structures at the neck of the urinary bladder. Am. J. Anat. 13: 299, 1912.

9. Scott, W. W. Growth and development of the human prostate gland. Nat. Canc. Inst. Monograph 12:111, 1963.

The prostate gland originates as independent groups of tubules which begin to grow in every direction from the urethra at about the twelfth week. From the last months of gestation and in post natal life these various groups of glands fuse, and no division into lobes is possible. The prevalent view at present is that the meaningful regional separation is into lateral and medial lobes (see also Ref. 4). On cross section of the normal gland three general regions can be delineated - external, submucosal, and mucosal areas.

10. Swyer, G. J. M. Postnatal growth changes in human prostate. J. Anat. (Lond.) 78: 130, 1944.

As the result of the analysis of 192 prostate glands at autopsy Swyer has been able to construct the growth curve for the prostate of man. It weighs about 1.4 grams at birth, increases to about 4.2 grams prior to puberty, then grows to about 21 grams by the age of 21. There is no change thereafter until about 55 years of age when a second growth spurt begins, reaching a mean of about 55 grams by age 70.

PATHOGENESIS OF BENIGN PROSTATIC HYPERTROPHY

11. Deming, C. L. and J. S. Wolf. The anatomic origin of benign prostatic enlargement. J. Urol. 42:566, 1939.

This paper clearly demonstrated that benign prostatic hypertrophy begins in the periurethral area as a fibromuscular mass into which duct epithelium forming glands invade. The glandular tissue grows much more rapidly so that in time the mass may appear wholly glandular.

12. Semple, J. E. Surgical capsule of benign enlargement of prostate: its development and action. Brit. Med. J. 1:1640, 1963.

As the mass in the periurethral area enlarges it may so compress the remainder of the gland as to cause a surgical "capsule" to develop.

13. Clarke, B. G. and R. Latorraia. Pathology of the prostatic median bar. AMA Arch. Pathol. 61:37, 1956.

A variety of other lesions may occur including varying degrees of involvement of smooth muscle, particularly in selective enlargement of the median lobe. The other histological lesions are much less frequent.

HISTOLOGICAL FEATURES OF BENIGN PROSTATIC HYPERTROPHY

14. Niemi, M., M. Harkanen, and T. K. I. Larmi. Enzymic histochemistry of human prostate. Arch. Path. 75:528, 1963.

15. Kirchheim, D., F. Gyorkey, D. Brandes, and W. W. Scott. Histochemistry of normal, hyperplastic, and neoplastic human prostate gland. Invest. Urology 1:403, 1964.

16. Mao, P., K. Nakao, R. Bora, and J. Geller. Human benign prostatic hyperplasia. Arch. Path. 79:270, 1965.

17. Mao, P., K. Nakao, and A. Angnist. Acid phosphatase and 5'-nucleotidase activities of human nodular prostatic hyperplasia as revealed by electron microscopy. Lab. Invest. 15:422, 1966.

In regard to ordinary histology, the histochemistry of the tissue, and analysis by electron microscopy there is nothing distinctive about the pattern of benign prostatic hypertrophy except for an increase in size which includes both stromal and glandular elements.

18. Huggins, C. and R. A. Stevens. The effect of castration on benign hypertrophy of the prostate in man. J. Urology 43:705, 1940.

19. Huggins, C. The etiology of benign prostatic hypertrophy. Bull. N. Y. Aca. Med. 23:696, 1947.
(Also see Ref. 2-4)

However, it is clear that the total number of tall columnar cells is decreased in relation to the size of the gland.

20. Huggins, C. and P. J. Clark. Quantitative studies of prostatic secretion. II. Effect of castration and of estrogen injection on normal and on hyperplastic prostate glands of dogs. J. Exp. Med. 72:747, 1940.

21. Moore, R. A., M. L. Miller, and A. McLellon. The chemical composition of prostatic secretion in relation to benign hypertrophy of the prostate. J. Urol. 46:132, 1941.

As a result, the prostatic secretion, while qualitatively normal in benign prostatic hypertrophy of dog and man, is strikingly reduced in volume. This relationship has led Huggins to make a functional definition of benign prostatic hypertrophy as prostatic enlargement under circumstances in which prostatic secretion is diminished.

ENDOCRINOLOGICAL CONTROL OF PROSTATIC DEVELOPMENT AND FUNCTION

22. Farrell, J. I. Studies on the secretion of the prostate gland. Trans. Am. Assn. of Genito-Urinary Surgeons 24:221, 1931.

23. Huggins, C. The physiology of the prostate gland. Physiol. Rev. 25:281, 1945.

24. Huggins, H. The prostatic secretion. Harvey Lectures, 1946-47, p. 148.

25. Huggins, C. Physiology of the prostate and seminal vesicles. Urology, Vol I, ed. by M. Campbell. Philadelphia: W. B. Saunders Co., 1954, p. 111.

26. Price, D. and H. G. Williams-Ashman. The accessory reproductive glands of mammals. Ch. in Sex and Internal Secretions, ed. by W. C. Young. Williams and Wilkins, Baltimore, 1961, p. 366.

27. McDonald, D. F. The prostate gland. Ch. in Encyclopedia of Urology, Berlin: Springer-Verlag, Vol. II, p. 601, 1962.

Not only is both the growth and secretion of the normal prostate under the almost exclusive control of testicular androgen, but it is also clear that benign prostatic hypertrophy never occurs in individuals who have been castrated prepubertally. However, experimental benign prostatic hypertrophy has never been produced by the administration of testosterone to experimental animals, possibly because a critical time factor is involved.

Also see Ref. 18 and 1-4.

And, while castration was a popular means of treating benign prostatic hypertrophy in the late nineteenth century, there is no definitive evidence at present that it does anything more than arrest further progression of the disorder in most patients, possibly because of the degree of fibrosis in many glands.

28. Lesser, M. A., S. N. Vose, and G. M. Dixey. Effect of testosterone propionate on the prostate gland of patients over 45. J. Clin. Endocrinol. 15:297, 1955.

Furthermore, the administration of large doses of testosterone may paradoxically have a slight beneficial effect; it clearly does not enhance the frequency of BPH even when given for 1-4 years.

29. Teem, M. V. B. The relation of the interstitial cells of the testis to prostatic hypertrophy. J. Urol. 34:692, 1935.

30. Vernet, S. G. Prostate-gonad correlations. J. Urol. Paris 68:391, 1962.

There is rather impressive indirect evidence that the burst of growth at about age 50-55 correlates with a decrease in testicular function, at least as measured by the interstitial cells of the testis.

31. Coppage, W. S., Jr. and A. E. Cooner. Testosterone in human plasma. NEJM 273:902, 1965.

There is, in addition, this one report of the measurement of testosterone blood levels as a function of age. Blood T decreased from a mean value of 0.65 µg/100 ml in patients age 16-45 to 0.50 µg/100 ml in men over the age of 45, suggesting that BPH does in fact evolve in the background of a decreasing testicular function.

32. Miller, H. C. and D. F. McDonald. Klinefelter's syndrome and benign prostate hypertrophy. JAMA 186:215, 1963.

BPH also occurs in individuals who are somewhat underandrogenized, although the exact frequency is difficult to estimate.

33. Zuckerman, S. The endocrine control of the prostate. Proc. Roy. Soc. Med. 29: 1557, 1936.

The occurrence of BPH in the presence of an apparently diminishing testicular function led several early investigators to the thesis that the hypertrophy is due to continued production of estrogen. And while estrogen in pharmacological doses does cause a variety of histological changes in the prostate (in particular a squamous metaplasia of the periurethral area), no picture suggesting BPH has ever been produced convincingly with estrogen therapy alone or in combination with androgens. When given in significant dosages, however, estrogens do inhibit testosterone secretion and produce a temporary functional castration.

BENIGN PROSTATIC HYPERTROPHY IN ANIMALS

34. Huggins, C. Endocrine control of prostatic cancer. Science 97:541, 1943.

35. Schlotthauer, C. F. Observations on the prostate gland of the dog. T. Am. Vet. Med. Ass. 81:645, 1932.

36. Berg, O. A. The normal prostate gland of the dog. Acta Endocrinol. 27:129, 1958.

37. Berg, O. A. Parenchymatous hypertrophy of the canine prostate gland. Acta Endocrinol. 27:140, 1958.

38. Berg, O. A. Effect of stilboesterol on the prostate gland in normal puppies and adult dogs. Acta Endocrinol. 27:155, 1958.

With the possible exception of the lion, the only species which develops a benign prostatic hypertrophy is the dog. Indeed, the frequency of benign prostatic hypertrophy in non-castrated dogs above the age of 8 approaches that of man (60-80%). And, while this prostatic enlargement resembles that of man in size (40-100 grams) and function (a diminished rate of secretion), it does have two distinctive features: the histological picture is of an almost exclusive hyperplasia of the glandular elements with virtually no fibrosis and the major symptom is constipation rather than urinary tract obstruction.

RESULTS OF ATTEMPTS OF NON-EXTIRPATIVE THERAPY

39. Clarke, R. The prostate and the endocrines. Brit. J. Urol. 9:254, 1937.

Of ninety-three patients treated neither by prostatectomy nor by any other treatment except relief of obstruction when it occurred, a large number (57-62%) showed sustained improvement over a four year period following a single instrumentation. This illustrates the need for a careful control series in evaluating any therapy.

40. Domnaic, F. Benign prostatic hypertrophy: amino acid therapy for symptomatic relief. J. Am. Geriatrics Soc. 10:426, 1962.

41. Geller, J., R. Bora, T. Roberts, H. Newman, A. Lin, and R. Silva. Treatment of benign prostatic hypertrophy with hydroxyprogesterone caproate. JAMA 193:121, 1965.

42. Geller, J., B. Fruchtman, C. Meyer, and H. Newman. Effect of progestational agents on gonadal and adrenal cortical function in patients with benign prostatic hypertrophy and carcinoma of the prostate. J. Clin. Endocrinol. Met. 27:556, 1967.

43. Gordon, H. W. and C. P. Schaffner. The effect of polyene macrolides on the prostate gland and canine prostatic hyperplasia. PNAS 60:1201, 1968.

(Also Ref. 4)

Nevertheless, uncontrolled series of patients treated with various agents do continue to be published from time to time. While none of these therapeutic regimens have been more than a passing vogue to date, there has been a recent report (43) of a dramatic shrinkage of canine prostates following administration of polyene antibiotics, a regimen yet untried in man.

In summary, any etiological theory as to the underlying cause of benign prostatic hypertrophy should account for the following features of the problem:

1. The androgen dependent growth of the gland
2. A sudden growth spurt after the age of 40 and after 20 years of stable size
3. Maximum growth when the testicular function is probably less than maximal
4. Decreased secretion of the enlarged gland
5. The remarkable segregation of the problem within the animal kingdom to man, the dog, and (possibly apocryphally) the lion.
6. Possible infrequency of the problem in Asiatic races.

METABOLISM OF TESTOSTERONE BY THE PROSTATE

44. Wilson, J. D., and P. M. Loeb. Estrogen and androgen control of cell biosynthesis in target organs, in Developmental and Metabolic Control Mechanisms and Neoplasia. 19th Annual Sympos. on Fundamental Cancer Research, Williams and Wilkins, Baltimore, Md., 1965, p. 375-391.

45. Wilson, J. D., N. Bruchovsky, and J. N. Chatfield. Intranuclear localization of testosterone-1,2-^{3}H in rat prostate. Proc. III International Congress of Endocrinology. In Press.

Following the administration of testosterone-1,2-^{3}H to rats, the major fraction which is taken up by target tissues is bound to a protein in the nucleus, the presumed site of action of the hormone.

46. Farnsworth, W. E. and J. R. Brown. Metabolism of testosterone by the human prostate. JAMA 183:140, 1963.

47. Farnsworth, W. E. and J. R. Brown. Testosterone metabolism in the prostate. National Cancer Institute Monograph 12:323, 1963.

48. Shimazaki, J., H. Kurihara, Y. Ito, and K. Shida. Testosterone metabolism in prostate. Gunma J. Med. Sci. 14:313, 1965.

It was observed by these two groups of investigators that following the incubation of slices of human and rat prostate with testosterone-^{3}H, one of the metabolites was the 5α reduced derivative, dihydrotestosterone. Since it was only one of several metabolites in these whole cell preparations, however, these results were generally ignored.

49. Bruchovsky, N. and J. D. Wilson. The conversion of testosterone to 5α-androstan-17β-ol-3-one by rat prostate in vivo and in vitro. J. Biol. Chem. 243:2012, 1968.

50. Bruchovsky, N. and J. D. Wilson. The intranuclear binding of testosterone and 5α-androstan-17β-ol-3-one by rat prostate. J. Biol. Chem. 243:5953, 1968.

These papers clearly demonstrate that dihydrotestosterone is the only nuclear metabolite of testosterone in rat prostate and that it is the principal molecular species actually bound to the nucleoprotein.

51. Dorfman, R. I. and R. A. Shipley. Androgens. New York: John Wiley and Sons, Inc. 1956.

52. Saunders, F. J. Some aspects of relation of structure of steroids to their prostate-stimulating effects. National Cancer Inst. Monograph 12:139, 1963.

These observations, plus the reports that dihydrotestosterone was a more potent androgen than testosterone itself suggested that this substance might be the active form of testosterone.

53. Wilson, J. D., and J. D. Walker. The conversion of testosterone to 5α-androstan-17β-ol-3-one (dihydrotestosterone) by skin slices of man. J. Clin. Invest. In Press.

However, in studies of the conversion of testosterone to dihydrotestosterone by explants of skin in man, this reduction correlated best with growth rather than with other testosterone actions.

54. Baulieu, E. E., Ilse Lasnitzki, and P. Robel. Metabolism of testosterone and action of metabolites on prostate glands grown in organ culture. Nature 219:1155, 1968.

55. Baulieu, E. E., Ilse Lasnitzki, and P. Robel. Testosterone, prostate gland, and hormone action. Biochem. and Biophys. Res. Com. 32:575, 1968.

Furthermore, in testing the effects of several testosterone analogues on prostatic growth in organ culture, Baulieu and Lasnitzski have reported that it promotes growth but not the secretory function of the prostate.

56. Gloyna, R. E. and J. D. Wilson. A comparative study of the conversion of testosterone to dihydrotestosterone by the prostate. Clin. Res. 17:23, 1969.

From this comparative study of the reductase level in the prostates of nine species several generalizations can be drawn:

1.) Conversion of testosterone to dihydrotestosterone occurs during the immature growth phase in all prostates.

2.) In those prostates in which growth is limited, the ability to form dihydrotestosterone drops out completely (bull) or remains low (cat, mouse, guinea pig, bobcat).

3.) Continued growth of the prostate (man, dog, lion, rat) is associated with continued high rates of conversion.

4.) Administration of dihydrotestosterone to castrated rats for long periods of time (4 months) produces a histological picture closely resembling that of BPH in man, e.g. increased size, marked increase in fibrous tissue, decreased secretion, and a diminished height of the columnar cells.

Together these studies suggest the possibility that the conversion of testosterone to dihydrotestosterone may be involved in the evolution of benign prostatic hypertrophy.