[J.D. Wilson]

Medical Grand Rounds

12-7-78

Benign Prostatic Hypertrophy

Ten years ago (2-13-69) I reviewed the subject of benign prostatic hyperplasia (or hypertrophy) for these rounds and in particular the rationale for assuming that an underlying endocrinopathy may play a role in the etiology. We subsequently commenced a research effort devoted to the investigation of the pathophysiology, and in the interim several advances have been made in our laboratory and by others, largely summarized in a recent monograph (1). I propose today to provide a progress report on the problem. I want to acknowledge my indebtedness to various colleagues who have collaborated on this problem over the years - Robert Gloyna, P.K. Siiteri, Patrick Walsh, Gunther Jacobi, John Gazak and Ronald Moore.

1. Grayhack, J.T., J.D. Wilson, and M.J. Sherbenske. Benign Prostatic Hyperplasia. DHEW Publication No. (NIH) 76-1113, (February) 1975.

Natural History

Enlargement of the prostate to the point that it produces obstruction of the urethra and/or rectum is an almost universal finding in the aging man. Because of the refinements in prostatic surgery, it is not a leading cause of death but it continues to be a major cause of morbidity in men. The natural history of the disorder in man can be reconstructed from volume - age studies of the gland done by Swyer on 192 prostates at autopsy (2).

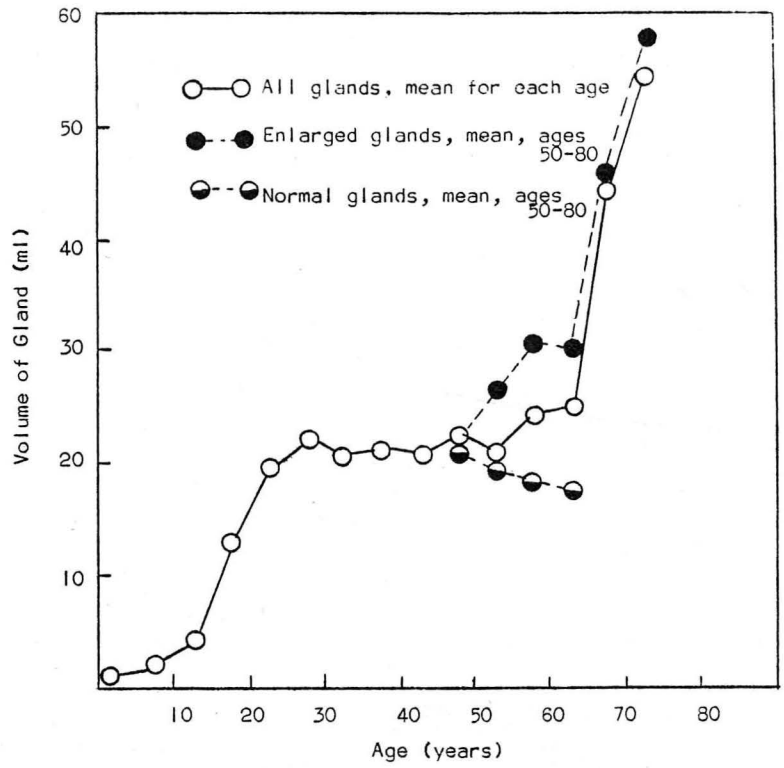

Fig. 1. Change in Mean Volumes of Prostate with Age

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

The gland weighs about 1.4g at birth, increases to about 4.2g prior to puberty, then grows to about 21 grams by age 20. On average there is no change until about 55 when a second growth spurt begins, reaching a mean weight of about 55g by age 70. There is no absolute correlation between weight and symptoms, and obstruction to the urethra can occur without an increase in total weight. However, it is unusual for symptoms to occur before the age of 55, at least in white men. In a small fraction of men the gland atrophies with age, presumably because of atherosclerosis of the arterioles that supply the gland.

3. Rotkin, I.D. Epidemiology of benign prostatic hypertrophy:review and speculations. In Benign Prostatic Hyperplasia. NIAMDD Workshop Proc., Feb., 1975, 105-116.

The disorder appears to be more common and to become manifest approximately 10 years earlier in blacks than whites (data are soft), whereas the Japanese have a lower incidence than do European or American men. The frequency of symptomatic prostatic hypertrophy in American men above the age of 50 varies from 50% to 75% in most series studied.

Histopathology

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

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

The discrepancy between weight and symptoms is due to the fact that benign prostatic hypertrophy begins in the periurethral area of the gland as a stromal proliferation into which invasion by ductular glandular epithelia occurs. The glandular tissue usually grows more rapidly than the fibromuscular elements so that in time the mass may appear wholly glandular. We do not know exactly when this process commences, probably not until after age 40. As the mass in the periurethral area enlarges it compresses the remainder of the gland and the urethra and may cause obstructive symptoms prior to enlargement beyond the limits of the old capsule.

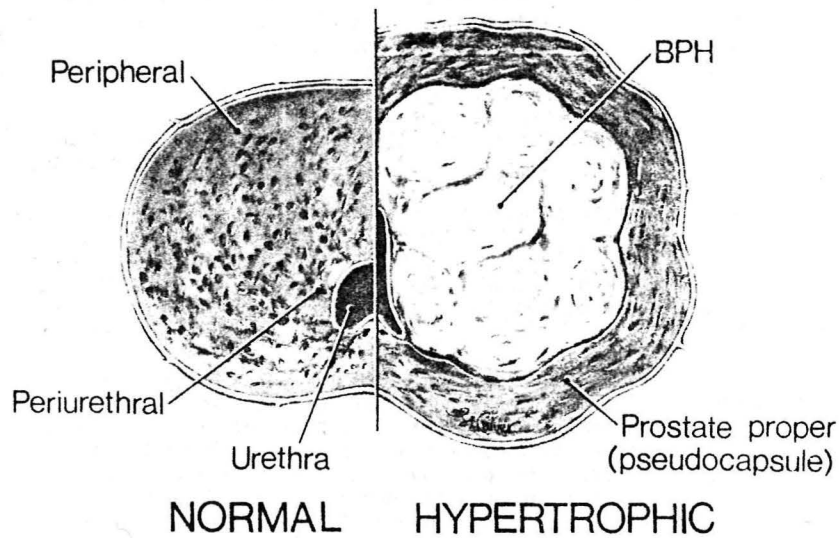

Fig. 2. Periurethral Origin of Benign Prostatic Hypertrophy

6. Fränks, L.M. Benign prostatic hyperplasia:gross and microscopic anatomy. In Benign Prostatic Hyperplasia. NIAMDD workshop proc., Feb., 1975, 63-89.

Thus, BPH nodules do not represent hyperplasia of a single, specific cell type, but instead there are at least four cells involved (smooth muscle fibers, myoepithelial cells, fibroblasts, and glandular epithelium). Consequently, the normal architecture between the various cell types is altered markedly, and the normal growth pattern which results in coordinated growth and division of neighboring epithelial and stromal cells within the tissue is disturbed so that cells may grow and divide independently of their neighbors to produce nodules whose cells are arranged with different architecture.

Embryology

7. 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.

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

It is likely that the periurethral origin of the disorder is of importance in the pathogenesis. Embryologically, all the glands that give rise to the prostate originate as independent groups of tubules which begin to grow in every direction from the urogenital sinus at about the twelfth week. From the last months of gestation and in post natal life these various groups of glands fuse, and most investigators have concluded that no division into functional lobes is possible. On cross section of the normal gland three general regions can be delineated - external, submucosal, and mucosal areas, and it is believed by most that there is no embryological distinction between the periurethral and outer glands.

9. McNeal, J.E. The prostrate and prostatic urethra:a morphologic synthesis. J. Urology. 107:1008, 1972.

10. McNeal, J.E. Developmental and comparative anatomy of the prostate. In Benign Prostatic Hyperplasia. NIAMDD Workshop Proc., Feb., 1975, 1-9.

However, McNeal has recently re-examined this issue and has concluded that prostatic hyperplasia always commences in the fourth of the glandular tissue that is in the middle of the urethra immediately around the ejaculation ducts. He has also concluded that these ducts have a different morphology and that this region of the prostate is actually derived from Wolffian duct rather than urogenital sinus. If true, this implies that benign prostatic hypertrophy in man is derived from a unique population of cells within the gland (and not present in the prostates of most species). This represents a novel view at present and has not been refuted or substantiated.

11. Cunha, G.R. Tissue interactions between epithelium and mesenchyme of urogenital and integumental origin. Anat. Rec. 172:529-542, 1972.

12. Cunha, G.R. The role of androgens in the epithelio-mesenchymal interactions involved in prostatic morphogenesis in embryonic-mice. Anat. Rec. 175:87-96, 1973.

Whatever the embryological origin of the region of prostate where the process commences, it is clear that the mesenchyme of the embryonic prostate is critical in mediating the epithelial response to androgen. Namely, any epithelium (snout for example) if mixed with urogenital mesenchyme is transformed to a glandular epithelium characteristic of the prostate. In contrast, when epithelium from the urogenital sinus is reconstituted with other mesenchyme, no glandular transformation takes place. This doubtedlessly explains why mesenchymal proliferation in early BPH usually results in secondary glandular proliferation.

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

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

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

16. 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 the histochemistry of the tissue and analysis by electron microscopy there is nothing distinctive about the cells themselves.

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

18. Huggins, C. The etiology of benign prostatic hypertrophy. Bull. N.Y. Aca. Med. 23:696, 1947.

19. 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.

20. 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.

However, the percentage of columnar (secretory) cells within glandular acini is decreased. Because of this and the increased stroma the prostatic secretion (and ejaculate) are decreased in volume in dog and man. Thus, Huggins defines prostatic hypertrophy as prostatic enlargement under conditions in which prostatic secretion is diminished.

Endocrine Control of the Prostate

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

22. Coffey, D.S. The biochemistry and physiology of the prostate and seminal vesicles. In Urology(Campbell's), J.H. Harrison, R.F. Gittes, A.D. Perlmutter, T.A. Stamey and P.C. Walsh (eds), W.B. Saunders, Philadelphia, 1:161-201, 1978.

The differentiation of the prostate during embryogenesis and the growth and secretion during post-embryonic life are under the control of testicular androgen. Therefore, since benign prostatic hypertrophy is thought to never develop in prepubertal castrates, it has been assumed widely that testicular secretions must play some role in its pathogenesis. The assumption has been that two factors are essential for its development - aging and an intact testis. Even if this assumption is true an endocrine abnormality may play a permissive role only and may not be the cause. However, the fact that hormones can be manipulated and measured has influenced the experimental work in the field.

Mechanism of Testosterone Action

23. 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.

24. 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.

25. Wilson, J.D. Metabolism of testicular androgens. In Handbook of Physiology, Section 7: Endocrinology, R.O. Greep, E.B. Astwood, (Eds), American Physiological Society, Washington, D.C., Vol. V, Male Reproductive System, Ch. 25, p. 491, 1975.

26. Wagner, R.K. and A. Hughes. I.current views on androgen receptors and mechanism of androgen action. In Androgens II and Antiandrogens, Springer-Verlag, Berlin.Heidelberg.New York, 1977.

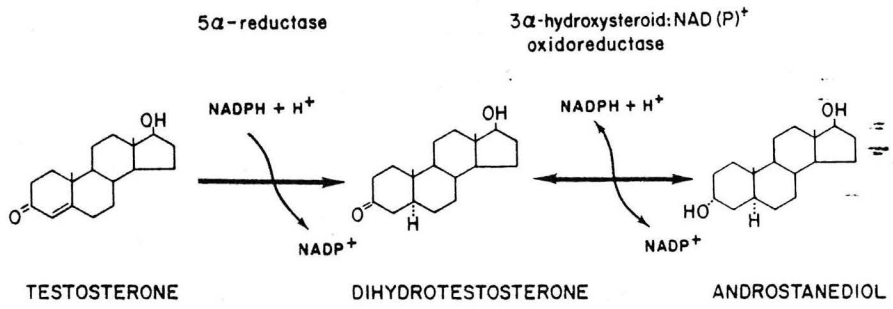

Fig. 3. Two principal enzymatic reactions involved in the 5α-androstane pathway in rat ventral prostate.

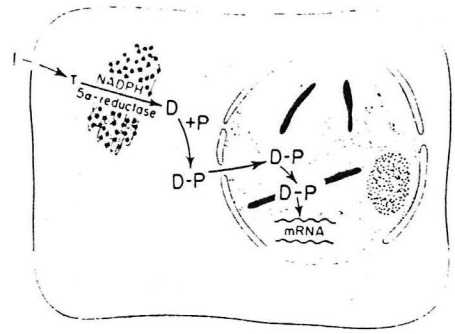

Fig. 4. Mechanism of action of testosterone in the cell of an androgen target tissue such as prostate. T, testosterone; D, dihydrotestosterone; P, dihydrotestosterone receptor protein; mRNA, messenger RNA.

27. Gloyna, R.E. and J.D. Wilson. A comparative study of the conversion of testosterone to 17β-hydroxy-5α-androstan-3-one (dihydrotestosterone) by prostate and epididymis. J. Clin. Endocr. 29:970-977, 1969.

28. Wilson, J.D. and R.E. Gloyna. Recent progress in hormone research. JCEM. relation between the capacity to form dihydrotestosterone and the capacity of the prostate in that species to grow.

When it became apparent that the active androgen that mediates many intracellular effects of testosterone is in fact dihydrotestosterone, Robert Gloyna performed a comparative study in eleven species of the relation between the capacity to form dihydrotestosterone and the capacity of the prostate in that species to grow.

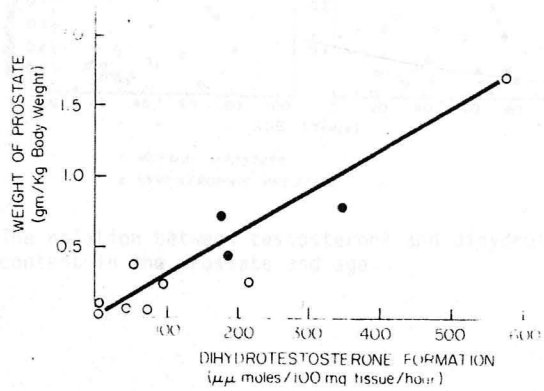

Fig. 5. The relation between the rate of dihydrotestosterone formation by prostate slices and the weight of the gland.

Studiesin Human Prostatic Hypertrophy.

29. Siiteri, P.K. and J.D. Wilson. Dihydrotestosterone in prostatic hypertrophy. I. The formation and content of dihydrotestosterone in the hypertrophic prostate of man. J. Clin. Invest. 49:1737, 1970.

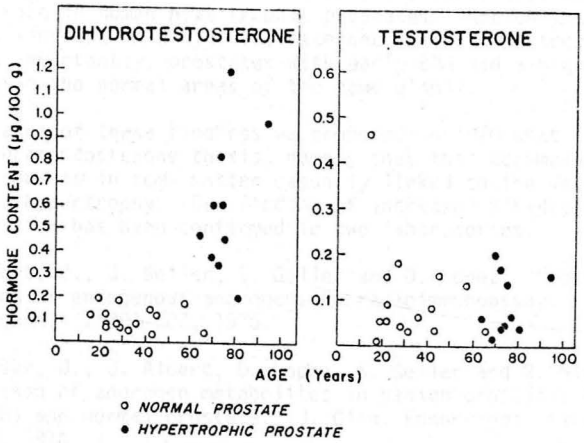

Fig. 6. The relation between testosterone and dihydrotestosterone content in the prostate and age.

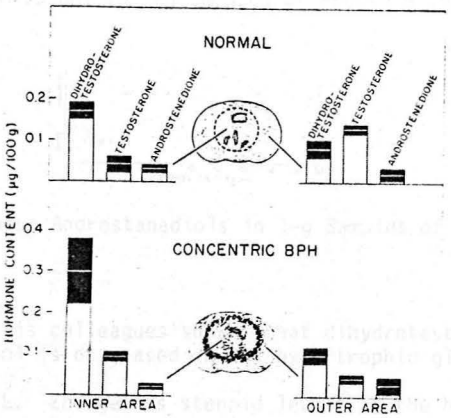

Fig. 7. Androgen content of the inner and outer regions of normal and early hypertrophic prostates. Three normal prostates and four prostates with concentric hypertrophy were dissected into inner and outer regions as indicated by the dotted lines. The bar graphs represent the mean content in each area of testosterone, dihydrotestosterone, and androstenedione (±SEM as a solid black portion of the bar above and below the mean values).

In view of the good correlation between growth and dihydrotestosterone formation, we decided to measure the concentration of dihydrotestosterone in human hypertrophic prostates. Not only was there a striking increase in dihydrotestosterone in the hypertrophic gland, but more importantly, prostates with early BPH had a higher content of DHT than the normal areas of the same glands.

Because of these findings we proposed in 1970 what can be termed the dihydrotestosterone thesis, namely that this accumulation of dihydrotestosterone is in some matter casually linked to the development of prostatic hypertrophy. Our finding of increased dihydrotestosterone concentration has been confirmed in two laboratories.

30. Albert, J., J. Geller, S. Geller and D. Lopez. Prostate concentrations of endogenous androgens by radioimmunoassay. J. Steroid Biochem. 7:301-307, 1976.

31. Geller, J., J. Albert, D. Lopez, S. Geller and G. Niwayama. Comparison of androgen metabolites in benign prostatic hypertrophy (BPH) and normal prostate. J. Clin. Endocrinol. Metab. 43: 686-688, 1976.

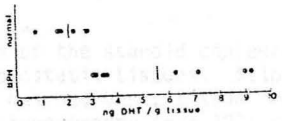

Fig. 8. Endogenous DHT in 1-g Samples of Prostate (bars indicate means)

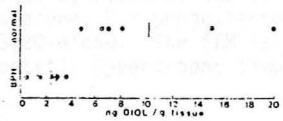

Fig. 9. Endogenous Androstanediols in 1-g Samples of Prostate

Geller and his colleagues showed that dihydrotestosterone is elevated and androstanediol is decreased in the hypertrophic gland.

32. Hammond, G.L. Endogenous steroid levels in the human prostate from birth to old age:a comparison of normal and diseased tissues. J. Endocr. 78:7-19, 1978.

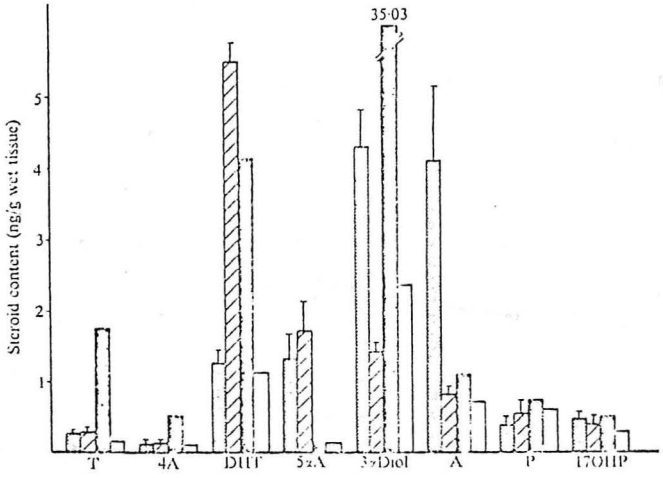

Fig. 10. Comparison of the steroid contents of normal adult and diseased prostatic tissues. Stippled bars, normal tissue (n = 18); hatched bars, tissue from patients with benign prostatic hypertrophy (n = 10); solid bars, untreated carcinomatous tissue (n = 1); open bars, oestrogen-treated carcinomatous tissue (n =3); T = testosterone; 4A = androstenedione; DHT = 17β-hydroxy-5α-androstan-3-one; 5αA = 5α-androstane-3,17-dione; 3αDiol = 5α-androstane-3α,17β-diol; A = androsterone; P = progesterone; 17OHP = 17α-hydroxy-4-pregnene-3,20-dione. The SEM is indicated for normal and benign prostatic hypertrophy samples.

Hammond has recently reported the same findings; of eight steroids measured the only one that is increased in benign prostatic hypertrophy is dihydrotestosterone.

Table 1. Concentrations (means with ranges in parentheses) of endogenous steroids in prostates from normal male subjects grouped according to age

Age group (years)	*n*	Steroid concentration (ng/g wet tissue)							
		T	4A	DHT	5αA	3αDiol	A	P	17OHP
Newborn, 6–10 days	3	0·23 (0·20–0·25)	0·19 (0·15–0·24)	3·94 (3·29–4·50)	2·57 (2·18–3·03)	2·42 (2·12–2·83)	4·12 (2·75–6·37)	1·87 (1·68–2·20)	1·00 (0·71–1·32)
Infants, 0·25–10	6	0·17 (0·13–0·22)	0·09 (0·00–0·16)	1·03 (0·50–1·60)	0·38 (0·22–0·52)	3·97 (2·65–6·39)	0·84 (0·50–1·31)	0·49 (0·30–0·82)	0·64 (0·18–1·14)
Pubertal, 13–14	4	0·15 (0·11–0·20)	0·07 (0·05–0·10)	1·14 (0·82–1·41)	0·27 (0·15–0·38)	3·30 (2·38–4·59)	1·94 (1·53–2·38)	0·31 (0·19–0·53)	0·22 (0·14–0·32)
Young adults, 20–49	10	0·24 (0·09–0·52)	0·15 (0·06–0·47)	1·26 (0·65–2·64)	1·11 (0·36–2·23)	5·15 (2·50–9·63)	3·34 (0·96–12·50)	0·43 (0·13–1·32)	0·41 (0·23–0·88)
Aged adults, 50–75	8	0·26 (0·06–0·51)	0·10 (0·05–0·24)	1·32 (0·52–2·23)	1·56 (0·32–5·65)	3·29 (2·35–4·30)	5·17 (0·63–16·06)	0·34 (0·11–0·73)	0·44 (0·17–1·01)

T, Testosterone; 4A, androstenedione; DHT, 17β-hydroxy-5α-androstan-3-one; 5αA, 5α-androstane-3,17-dione; 3αDiol, 5α-androstane-3α,17β-diol; A, androsterone; P, progesterone; 17OHP, 17α-hydroxy-4-pregnene-3,20-dione.

It is of interest that the dihydrotestosterone content of the newborn prostate is higher than in subsequent life and almost as high as that in BPH.

33. Vermeulen, A. Transport and distribution of androgens at different ages. In Androgens and Antiandrogens. L. Martin and M. Matta, eds. Raven press, New York, pp. 53-65, 1977.

34. Vermeulen, A., R. Rubens, and L. Verdonck. Testosterone secretion and metabolism in male senescence. J. Clin. Endocr. 34:730-735, 1972.

35. Vermeulen, A. and W. De Sy. Androgens in patients with benign prostatic hyperplasia before and after prostatectomy. J. Clin. Endocrinol. Metab. 43:1250-1254, 1976.

36. Hammond, G.L., M. Kontturi, P. Vihko and R. Vihko. Serum steroids in normal males and patients with prostatic diseases. Clinical Endocrinology 9:113121, 1978.

Furthermore, we now know a great deal about the background endocrinology of the aging man upon which prostatic hyperplasia develops.

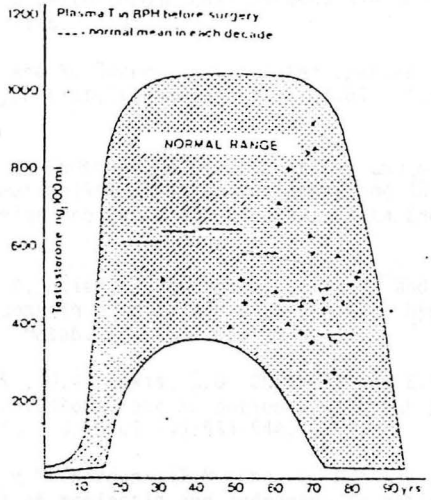

Fig. 11. Plasma T levels in patients with BPH with respect to the range of values in "normal" males.

Although the mean plasma testosterone falls in men past the age of 60, there is no difference in the levels of plasma testosterone in subjects with BPH and in age matched controls. Furthermore, the disorder commences before the plasma testosterone begins to fall.

37. Ito, T. and R. Horton. The source of plasma dihydrotestosterone in man. J. Clin. Invest. 50:1621-1627, 1971.

38. Mahoudeau, J.A., C.W. Bardin and M.B. Lipsett. The metabolic clearance rate and origin of plasma dihydrotestosterone in man and its conversion to the 5α-androstanediols. J. Clin. Invest. 50:1338-1344, 1971.

39. Tremblay, R.R., A. Kowarski, I.J. Park and C.J. Migeon. Blood production rate of dihydrotestosterone in the syndrome of male pseudohermaphroditism with testicular feminization. J. Clin. Endocrinol. Metab. 35:101-107, 1972.

While testosterone is primarily secreted by the testis into plasma, plasma dihydrotestosterone is largely derived from the peripheral conversion of circulating testosterone.

40. Lewis, J.G., R. Ghanadian and G.D. Chisholm. Serum 5α-dihydrotestosterone and testosterone changes with age in man. Acta Endocrinol. 82:444-448, 1976.

41. Pirke, K.M. and P. Doerr. Age related changes in free plasma testosterone, dihydrotestosterone and eostradiol. Acta Endocrinol. 80:171-178, 1975.

42. Becker, H., J. Kaufmann, H. Klosterhalfen and K.D. Voigt. In Vivo uptake and metabolism of ^{3}H-testosterone and ^{3}H-5α-dihydrotestosterone by human benign prostatic hypertrophy. Acta Endocrinol. 71:589-599, 1972.

43. Horton, R., P. Hsieh, J. Barberia, L. Pages and M. Cosgrove. Altered blood androgens in elderly men with prostate hyperplasia. J. Clin. Endocrinol. Metab. 41:793-796, 1975.

44. Ghanadian, R., J.G. Lewis, G.D. Chisholm and E.P.N. O'Donoghue. Serum dihydrotestosterone in patients with benign prostatic hypertrophy. Brit. J. Urol. 49:541-544, 1977.

45. Saroff, J., R.Y. Kirdani, T.M. Chu, Z. Wajsman and G.P. Murphy. Measurements of prolactin and androgens in patients with prostatic disease. Surg. Forum 28:568-569, 1977.

See also Ref. 35 and 36.

Four laboratories (Ref. 35 and 43-45) have reported slight elevations of plasma dihydrotestosterone in BPH patients whereas two laboratories (Ref. 36,42) observed no change in comparison with age matched controls.

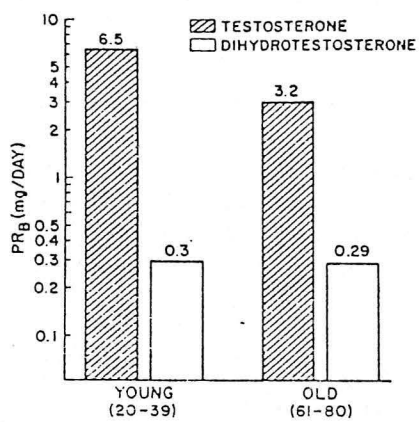

Fig. 12. Effect of age on the calculated blood production rate of testosterone and dihydrotestosterone in men.

46. Ishimaru, T., L. Pages and R. Horton. Altered metabolism of androgens in elderly men with benign prostatic hyperplasia. J. Clin. Endocrinol. Metab. 45:695-701, 1977.

However, the plasma production rate of dihydrotestosterone appears to be normal in patients with prostatic hypertrophy.

Thus, BPH commences when the plasma testosterone is normal and continues to develop in the face of decreases in the plasma level. The production of testosterone in aging men appears to be adequate to maintain normal levels of tissue testosterone and thus to support continued growth. The exact role of circulating dihydrotestosterone as a hormone is unknown, but at least it does not fall with age.

All these hormone studies are compatible with the thesis we originally proposed, namely that dihydrotestosterone accumulation (ultimately derived from plasma testosterone) is causally linked to the development of BPH. However, the weakness in this interpretation was that there was no way to disentangle cause from effect. It was equally likely that enhanced dihydrotestosterone was the consequence rather than the cause of the pathology. Therefore, it was essential to move to an experimental animal to document the role of dihydrotestosterone in prostatic hyperplasia.

The Problem of the Canine Model

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

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

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

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

Table 2. Prostatic Hyperplasia in Man and Dog

FEATURE		HUMAN	CANINE
NATURAL HISTORY	Age of Occurrence	> 40 years	> 5 years
	Incidence	50-75%	60-85%
CLINICAL PATHOLOGY	Local Anatomy	Nodular, Periurethral	Diffuse
	Histology	Epithelial + Stromal	Epithelial
	Obstructive Symptoms	Urethra > resection	Rectum > exertion
	Size	Variable	≥ 15 grams
ENDOCRINOLOGY	Dependence on Testicular Function	+	+

The only species other than man known to develop prostatic hyperplasia is the dog. For example, it does not occur in any other primate. The natural history of the processes in man and dog is similar - in both it is exceedingly common in the aging animal, and in both its development is dependent upon testicular function. In the dog it tends to enlarge posteriorally so that rectal obstruction is more common than urethral obstruction. At the histological level, however, there are distinct differences. The canine hyperplasia is predominantly glandular rather than stromal and involves the entire gland diffusely rather than commencing in the periurethral area. Therefore, it is not clear whether the processes have the same pathogenesis, but because it is the only animal model and because of the similarity in natural history, a considerable amount of investigation has been performed in the dog. The hope is that the pathogenesis will prove to be the same and that because of species differences the cellular reaction in the tissue is different.

Studies on Prostatic-Hyperplasia-in the Dog

51. Gloyna, R.E., P.K. Siiteri and J.D. Wilson. Dihydrotestosterone in prostatic hypertrophy. II. The formation and content of dihydrotestosterone in the hypertrophic canine prostate and the effect of dihydrotestosterone on prostate growth in the dog. J.. Clin. Invest. 49:1746-1753, 1970.

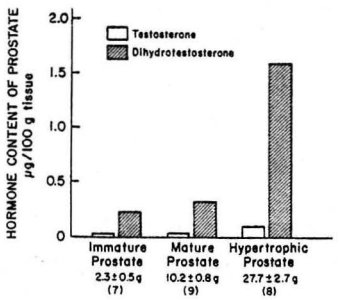

Fig. 13. Concentration of testosterone and dihydrotestosterone in immature, mature, and hypertrophic dog prostate. The average weight ±SEM for each pooled group is given, and the number of glands pooled is given in parentheses.

In our first study of the process in the dog, we showed that as in man the dihydrotestosterone content of the hypertrophic gland is elevated. We then set out to determine whether we could induce the development of prostatic hypertrophy in the castrate dog by the administration of pharmacological amounts of dihydrotestosterone.

52. Wilson, J.D., R.E. Gloyna and P.K. Siiteri. Androgen metabolism in the hypertrophic prostate. J. Steroid Biochem. 6:443-445, 1975.

Also 51.

We knew that the process requires a long time (≃ 5 years) to develop in the aging dog and assumed that we would have to perform long term studies to allow time for its development. Our negative studies and false starts can be summarized by saying that with either testosterone or dihydrotestosterone we were never able to induce the development of prostatic growth comparable to that in intact controls even in experiments lasting as long as two years.

Table 3. Effect of testosterone and dihydrotestosterone for two years on the dog prostate (52).

Group	Number	Treatment	Prostate Weight g
I Control	4	Triolein	14
II Castrate	4	Triolein	1.8
III Castrate	4	Dihydrotestosterone	6.6
IV Castrate	4	Testosterone	3.6

This failure to reproduce the condition appeared to be strong evidence against the "dihydrotestosterone thesis".

53. Kelch, R.P., M.R. Jenner, R. Weinstein, S.L. Kaplan, and M.M. Grumbach. Estradiol and testosterone secretion by human, simian, and canine testes, in males with hypogonadism and in male pseudohermaphrodites with the feminizing testis syndrome. J. Clin. Invest. 51:824-830, 1972.

54. Zuckerman, S., and J.R. Groome. The aetiology of benign enlargement of the prostate in the dog. J. Pathol. Bacteriol. 44:113-124, 1937.

55. Ewing, L., and B. Brown. Formation and secretion of 5α-androstan-17β-ol-3-one, 5α-androstan-3α,17β-diol and 5α-androstan-3α,17β-diol by the perfused rabbit testis epididymis. Endocrinology 96:479,1975.

Our interpretation of these negative results was that some hormone other than testosterone or dihydrotestosterone must be coming from the testis to promote prostatic growth. We then decided to examine the role of

other known testicular hormones that might play a role in the process, and in particular estradiol and 3α-androstanediol. Although estrogens alone (49) are known to cause atrophy of the dog prostate estradiol is secreted by the dog testis (53), and the possibility had been suggested as long ago as 1937 (54) that the combination of androgens and estrogen might play a role in the etiology. 3α-androstanediol was examined because it is a potent androgen in castrated animals and because in some species it is the second most important androgen secreted by the testis. (55).

56. Walsh, P.C. and J.D. Wilson. The induction of prostatic hypertrophy in the dog with androstanediol. J. Clin. Invest. 57:1093-1097, 1976.

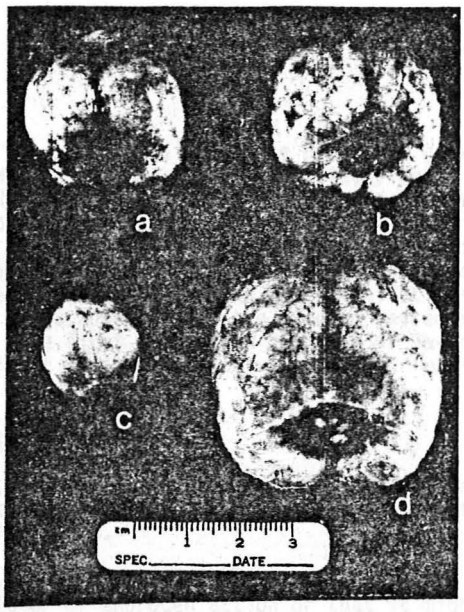

Fig. 14. Photographs of prostates from dogs treated with various hormonal regimens. a. Control, hypertrophic prostate, 16.2g (group I); b. castrate given androstanediol, 17.4g (group II); c. castrate given dihydrotestosterone plus estradiol, 4.0g (group III); d. castrate given androstanediol plus estradiol, 36.0g (group IV).

Table 4. Effect of Androstanediol and Androstanediol plus Estradiol on Prostate Weight in the Castrate Dog

Group	Preparation	Number	Average body wt	Treatment	Prostate wt			Number with prostates greater than 5 g at end
					Beginning	6 mo	12 mo	Average change	
			kg		g ± SEM	g ± SEM	g ± SEM	g	
I	Control	3	18	Triolein	5.6 ± 1.9	9.2 ± 1.3	12.5 ± 2.1	+6.9	1/3
II	Castrate	5	14	Androstanediol	4.6 ± 0.8	14.2 ± 4.3	14.7 ± 1.8	+10.1	2/5
III	Castrate	5	14	Dihydrotestosterone plus estradiol	4.5 ± 0.7	4.2 ± 0.9	3.6 ± 0.3	−0.9	0/5
IV	Castrate	5	15	Androstanediol plus estradiol	4.6 ± 0.9	29.5 ± 8.0	35.8 ± 1.4	+31.2	5/5
V	Castrate	3	22	Androstanediol plus estradiol	17.5 ± 3.0	56.2 ± 6.5	56.4 ± 6.4	+38.9	3/3

Not only did 3α-androstanediol induce prostatic growth equal to that of normal BPH, but perhaps more interestingly small amounts of estradiol enhanced the androstanediol-mediated growth rate considerably to result in the development of a profound hyperplasia. Thus, for the first time a true prostatic hyperplasia had been produced in the castrate dog by hormone treatment. [This phenomenon has been confirmed by two laboratories - Neumann in Berlin and Coffey at Johns Hopkins.] However, in terms of pathophysiology the finding raised more questions than it answered. The first relates to the role of 3α-androstanediol in this process; is it a direct or indirect cellular mediator of androgen induced growth in the tissues?

Role of 3α-Androstanediol

57. Jacobi, G.H., R.J. Moore and J.D. Wilson. Studies on the mechanism of 3α-androstanediol-induced growth of the dog prostate. Endocrinology 102: 1748-1755, 1978.

We originally assumed that 3α-androstanediol either acted as the intracellular mediator of androgen action or that it might circumvent the formation of some inhibitory metabolite of dihydrotestosterone. However, androstanediol does not bind to the receptor, and we were unable to demonstrate any inhibitory metabolites of dihydrotestosterone; furthermore, it was documented both in naturally occuring human (30-32) and canine prostatic hyperplasia (58) that 3α-androstanediol levels are not elevated in the hypertrophic gland. If anything, they appear to be low.

58. Moore, R.J., J.F. Quebbeman, and J.D. Wilson. Concentration of dihydrotestosterone and 3α-androstanediol in naturally occuring and androgen-induced prostatic hypertrophy in the dog. In preparation.

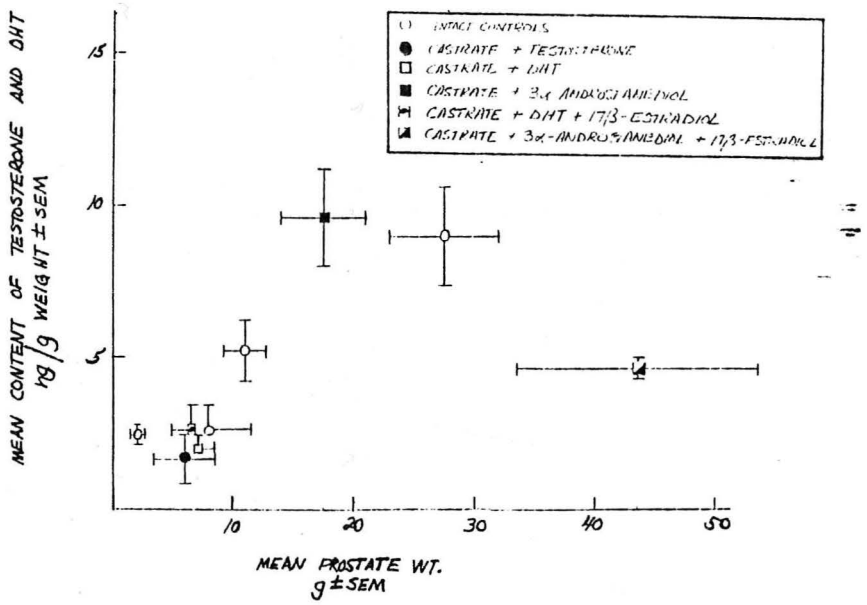

Fig. 15. Concentration of dihydrotestosterone and testosterone in prostates of dogs given various treatment

It was not until we examined the hormone content of the dog prostate under a variety of experimental conditions that the nature of the 3α-androstanediol effect became clear. The administration of 3α-androstanediol causes prostatic content of dihydrotestosterone to increase equal to that in the naturally occurring disorder and to a much higher level than in animals given equal amounts of dihydrotestosterone. If this fact is considered together with the demonstration by Bruchovsky that in the rat 3α-androstanediol must be converted to dihydrotestosterone prior to action as an androgen (59) and the fact that Bardin has reported that exogenously administered dihydrotestosterone is rapidly catabolized (unpublished) it seems reasonable to conclude that 3α-androstanediol exerts its peculiar effects on the dog prostate not because of a unique molecular effect but rather because of some pharmacological property that causes it to be a better precursor of intracellular dihydrotestosterone.

59. Bruchovsky, N. Comparison of the metabolites formed in rat prostate following in vivo administration of seven natural androgens. Endocrinology 89:1212, 1971.

We interpret this as strong support (indeed sufficient to cause a revival) of the original dihydrotestosterone thesis of prostatic hypertrophy. Since a hormonal treatment causes both prostatic growth and a simultaneous increase in dihydrotestosterone content equivalent to that in natural BPH we conclude that dihydrotestosterone probably causes prostatic hyperplasia in the dog. It follows that the administration of phenomenal levels of dihydrotestosterone should accomplish the same thing, a study which we are performing at present.

What is the Nature of the Synegistic Effect of Estradiol?

60. Siiteri,P.K. and P.C. MacDonald. Role of extraglandular estrogen in human endocrinology. In Handbook of Physiology, Section 7: Endocrinology, R.O. Greep and E.B. Astwood, Section Eds., American Physiological Society, Washington, D.C., 2:615-629, 1973.

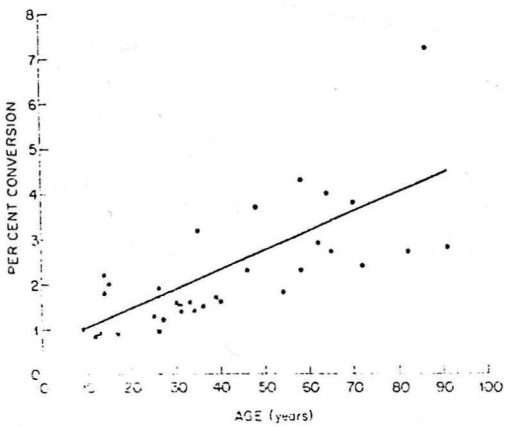

Fig. 16. Correlation of extent of conversion of androstenedione to estrone with age in males. Correlation coefficient equals 0.62.

The formation of estrone from circulating androstenedione actually increases with age in men.

61. Vermeulen, A. Testicular hormonal secretion and aging in males. In Benign Prostatic Hyperplasia, J.T. Grayhack, J.D. Wilson and M.J. Scherbenske, Eds. DHEW Publication No. (NIH) 76-1113, pp. 177-182, 1975.

Table 5. Plasma Testosterone and Estradiol as a Function of Age in 60 Normal Men (Ref. 61)

	<50 years	>65 years
TEBG Capacity, nM	35	89
Luteinizing Hormone, MIU/ml	13.0	22.5
Mean Plasma Testosterone, ng/dl	487	264
Mean Free Testosterone, ng/dl	10.6	3.6
Mean Plasma Estradiol, ng/dl	1.4	2.1
Mean Free Estradiol, ng/dl	0.026	0.028
Ratio Plasma $E_2/T(x10^3)$	2.9	7.9
Ratio Free $E_2/T(x10^3)$	2.4	7.8

Furthermore, plasma estradiol remains unchanged or increases slightly in the aging man so that the ratio of plasma estradiol to testosterone actually increases. Therefore, since estradiol acts synergistically to androgen in inducing prostatic hyperplasia in the dog it is attractive to postulate that the second burst of growth in the aging male is due to estrogen. To gain insight into the mechanism of this synergistic effect we first studied the effect of estradiol on the metabolism of androgen in the prostate and were unable to demonstrate an effect (57). In addition, estradiol does not seem to affect the concentration of dihydrotestosterone in the gland (58).

62. Moore, R.J., J.M. Gazak, and J.D. Wilson. Regulation of a cytoplasmic dihydrotestosterone - binding protein in dog prostate by 17β-estradiol. J. Clin. Invest. In press Feb. 1979.

Because estradiol is known to exert its synergistic effects with progesterone by regulating the amount of progesterone receptor protein, we decided to investigate the effect of estradiol on the androgen receptor of dog prostate. Treatment with estradiol increased the high affinity (approximate 8S) binding by about two fold. This increase is dose-dependent and appears to be specific for the dihydrotestosterone receptor.

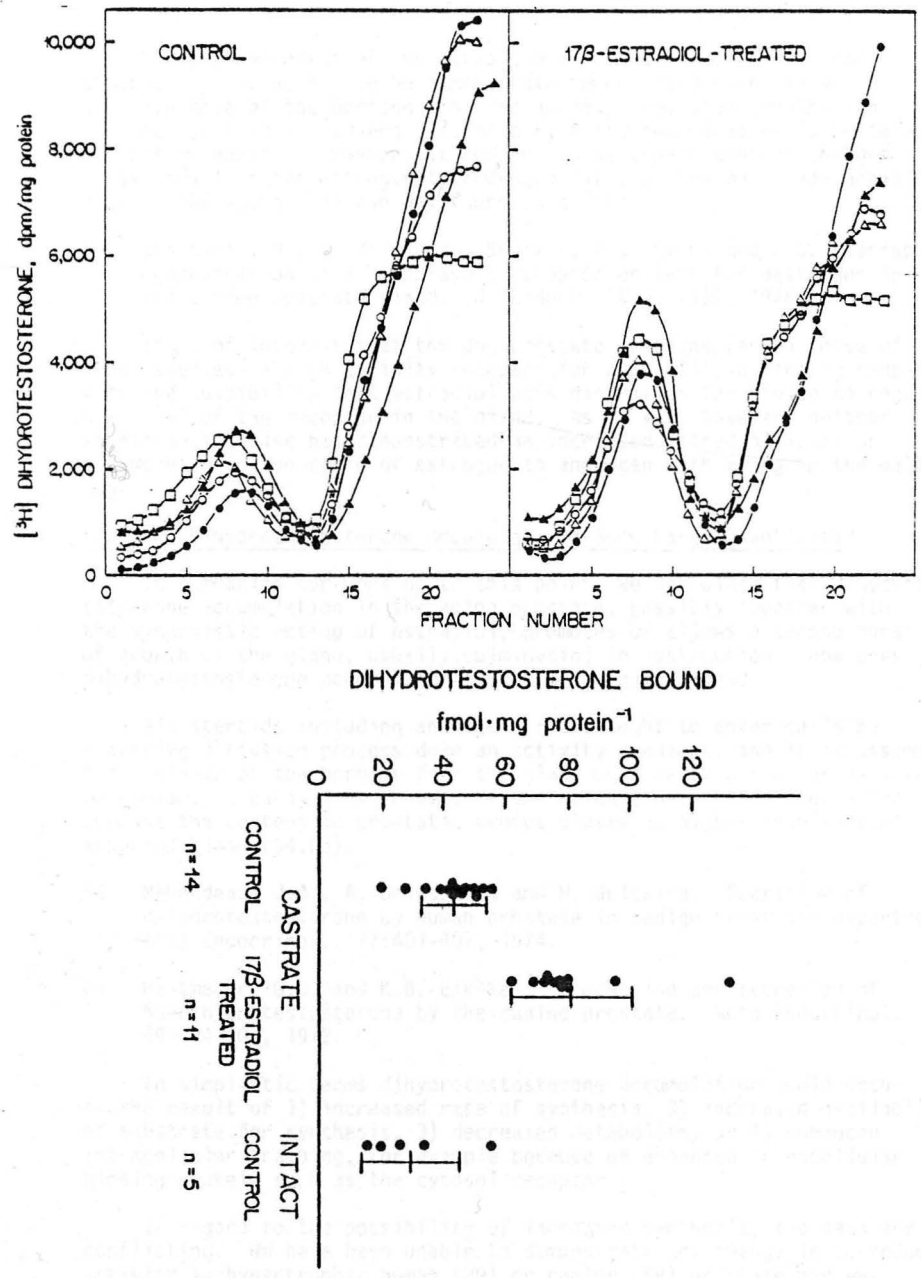

Fig. 17. Effect of 0.75 ng estradiol per week for three weeks on the androgen receptor of the dog prostate (ref. 62).

Thus, enhancement of the cytoplasmic androgen receptor in dog prostate by estradiol can be demonstrated under conditions in which the same dose of the hormone enhances androgen-mediated growth, and we conclude that the synergistic effect of the two hormones is mediated by this mechanism. However, it remains to be proven whether changes in estradiol or the estrogen to androgen ratio of the magnitude actually seen in the aging male can have such an effect.

63. Chaisiri , N., Y. Valotaire, Bronwen, A.J. Evans and C.G. Pierrepoint. Demonstration of a cytoplasmic receptor protein for oestrogen in the canine prostate gland. J. Endocr. 78:131-139, 1978.

It is of interest that the dog prostate contains (as do those of other species) a high affinity receptor for estradiol, a finding compatible with the possibility that estradiol acts direcly on the tissue to regulate the level of the receptor in the gland. As of yet, however, neither we nor anyone else has demonstrated an increased estradiol level or an increase in the ratio of estrogen to androgen with aging in the male dog.

How Does Dihydrotestosterone Accumulate in Such Large Quantities?

To summarize our work up to this point, we postulate that dihydrotestosterone accumulation in the aging prostate, possibly together with the synergistic action of estradiol, promotes or allows a second burst of growth of the gland, usually culminating in obstruction. How does dihydrotestosterone accumulate in such large quantities?

All steroids including androgens are thought to enter cells by a passive diffusion process down an activity gradient, and it is assumed that release of the hormone from the gland must be by a similar passive mechanism. Clearly dihydrotestosterone release occurs from the gland because the content in prostatic venous plasma is higher than that of arterial blood (64,65).

64. Mahoudeau, J.A., A. Delassalle and H. Bricaire. Secretion of dihydrotestosterone by human prostate in benign prostatic hypertrophy. Acta Endocrinol. 77:401-407, 1974.

65. Haltmeyer, G.C. and K.B. Eik-Nes. Production and secretion of 5α-dihydrotestosterone by the canine prostate. Acta Endocrinol. 69:394-402, 1972.

In simplistic terms dihydrotestosterone accumulation could occur as the result of 1) increased rate of synthesis, 2) increased availability of substrate for synthesis, 3) decreased metabolism, or 4) enhanced intracellular trapping, for example because of enhanced intracellular binding protein such as the cytosol receptor.

In regard to the possibility of increased synthesis, the data are conflicting. We have been unable to demonstrate any change in 5α-reductase activity in hypertrophic human (29) or canine (59) prostate nor was Prout et al. (68). However, two groups have reported slight increases

in 5α-reductase activity in the human disorder (66,67). We have repeated our studies (unpublished) in biopsy material and feel confident that the rate of formation of dihydrotestosterone is normal. In regard to the second possibility everyone who has measured the testosterone content is in agreement that it is unchanged.

66. Bruchovsky, N. and B. Lesser. Control of proliferative growth in androgen responsive organs and neoplasms. In Cellular Mechanisms Modulating Gonadal Hormone Action. R.L. Singhal and J.A. Thomas, Eds. University Park Press, Baltimore, pp. 1-55, 1976.

67. Krieg, M., W. Bartsch, S. Herzer, H. Becker and K.D. Voigt. Quantification of androgen binding globulin in prostate, muscle and plasma of patients with benign prostatic hypertrophy. Acta Endocrinol. 86:200-215, 1977.

68. Prout, G.R., Jr., B. Kliman, J.J. Daly, R.A. MacLaughlin and P.P.Griffin. In vitro uptake of ^{3}H testosterone and its conversion to dihydrotestosterone by prostatic carcinoma and other tissues. J. Urol. 116:603-610, 1976.

In regard to the possibility of decreased metabolism, the published data are in conflict. In three laboratories including ours (69-72) a clear cut increase in the 3α-hydroxysteroid dehydrogenase enzyme has been reported in hypertrophic human and canine glands. Whereas such a change was not shown in two other studies (66,67). Because our studies were performed under optimal conditions, my own belief is that there probably is an increase in the enzyme.

69. Geller, J. Endocrine pathogenesis of benign prostatic hypertrophy. Todays Clin. (March):56-61, 1978.

70. Shida, K., J. Shimazaki, Y. Ito, H. Yamanaka and H. Nagai-Yuasa. 3α-reduction of dihydrotestosterone in human normal and hypertrophic prostatic tissues. Invest. Urol. 13:241-245, 1975.

71. Jacobi, G.H. and J.D. Wilson. Formation of 5α-androstane-3α-17β-diol by normal and hypertrophic human prostate. J. Clin. Endocrinol. Metab. 44:107-115, 1977.

72. Jacobi, G.H. and J.D. Wilson. The formation of 5α-androstane-3α,17β-diol by dog prostate. Endocrinol. 99:602-610, 1976.

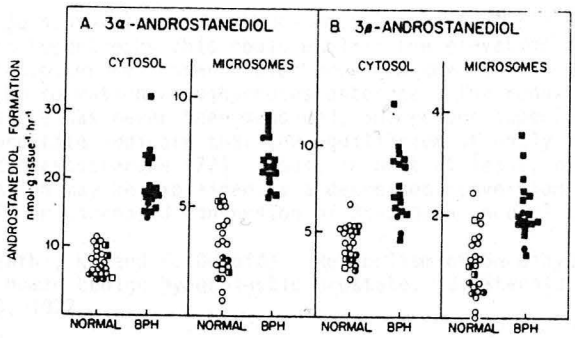

Fig. 18. NADPH-stimulated formation of 3α- and 3β-androstanediol by 40 human prostates (ref. 71).

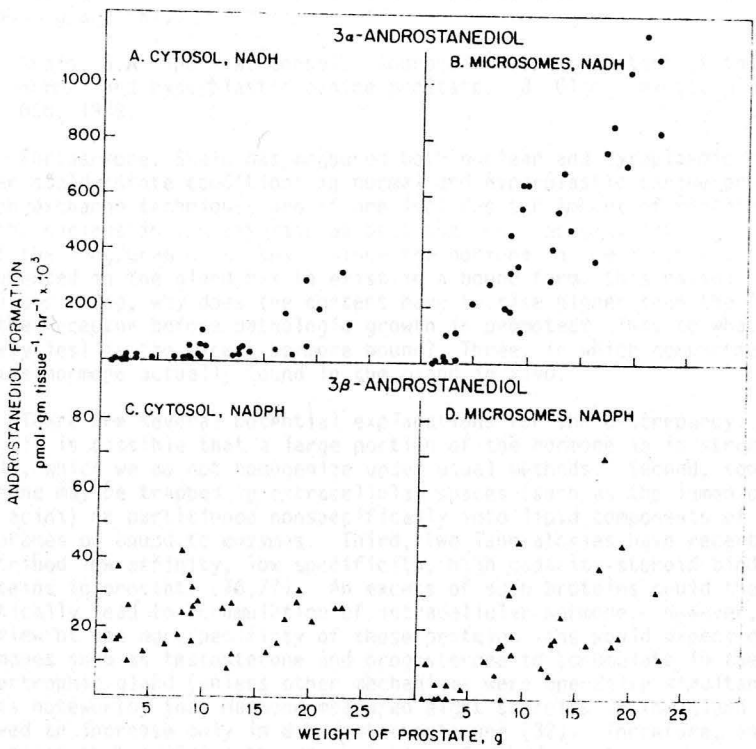

Fig. 19. Androstanediol formation per gram of tissue as a function of prostate weight.

If 3α-hydroxysteroid dehydrogenase is in fact elevated in benign prostatic hypertrophy this could explain the elevation in prostatic dihydrotestosterone concentration provided the equilibrium of the reaction favors the formation of dihydrotestosterone. The redox potential within the prostate has never been measured, but recent superfusion studies of the prostate indicate that the equilibrium strongly favors the formation of dihydrotestosterone (73). Thus, in part at least, dihydrotestosterone accumulation may be explained by a decreased conversion to 3α-androstanediol (or increased conversion of 3α-androstanediol to dihydrotestosterone.)

73. Malathi, K. and E. Gurpide. Metabolism of 5α-dihydrotestosterone in human benign hyperplastic prostate. J. Steroid Biochem. 8:141-145, 1977.

Increased intracellular binding remains an alternative possibility to explain this phenomenon. There is a discrepancy in the available data between hormone content and cytosol receptor concentration. Although we have demonstrated a doubling of the cytoplasmic androgen receptor under circumstances (androgen deprivation) (62) at best this amount of receptor could only account for approximately 1 ng dihydrotestosterone/gram of prostate or roughly a tenth of that known to accumulate in the hypertrophic gland (57).

74. Shain, S.A. and R.W. Boesel. Androgen receptor content of the normal and hyperplastic canine prostate. J. Clin. Invest. 61:654-660, 1978.

Furthermore, Shain has measured both nuclear and cytoplasmic receptors under steady state conditions in normal and hyperplastic canine prostates by an exchange technique, and if one includes the amount of receptor in the nucleus in the estimate at best one could account for only about 3 of the 10ng/gram of tissue. Since the hormone in the concentrations documented in the gland has to exist in a bound form, this raises several problems. One, why does the content have to rise higher than the level of the receptor before pathologic growth is promoted? Two, to what moiety(ies) is the excess hormone bound? Three, in which compartment(s) is the hormone actually found in the gland in vivo?

There are several potential explanations for the discrepancy. One, it is possible that a large portion of the hormone is in stromal cells, which we do not homogenize under usual methods. Second, some hormone may be trapped in extracellular spaces (such as the lumen of the acini) or partitioned nonspecifically into lipid components of membranes or bound to enzymes. Third, two laboratories have recently described low affinity, low specificity, high capacity-steroid binding proteins in prostate (76,77). An excess of such proteins could theoretically lead to accumulation of intracellular hormone. However, in view of the non-specificty of these proteins, one would expect other hormones such as testosterone and progesterone to accumulate in the hypertrophic gland (unless other mechanisms were operative simultaneously). It is noteworthy that Hammond measured eight steroids in the gland and showed an increase only in dihydrotestosterone (32). Therefore, any mechanism that explains the accumulation of dihydrotestosterone must provide an explanation for the specificity of the increase in dihydrotestosterone content.

It is my own belief that the accumulation of dihydrotestosterone in the hypertrophic prostate can be explained by an increase in 3α-hydroxysteroid dehydrogenase activity and a consequent decrease is the net conversion of dihydrotestosterone to 3α-androstanediol. Exactly how the increased content of dihydrotestosterone is stored in the gland is at present unclear. If the discrepancy between the cellular content and the amount of receptor protein is significant, then the nature of the discrepancy will have to be explained before we can understand the relation between growth and a given hormone level in the gland.

76. Wilson, E.M., O.A. Lea, and F.S. French. 95 binding protein for androgens and progesterone PNAS 74:1960, 1977.

77. Heyns, W. and P. De Moor. Prostatic binding protein - a steroid-binding protein secreted by rat prostate. Eur. J. Biochem. 78:221-230, 1977.

Again to summarize, 1) prostatic hypertrophy in the dog is accompanied by an increase in the dihydrotestosterone content of the gland, 2) the administration to the castrate male of a hormone that increases dihydrotestosterone content in the gland causes growth equivalent to that in naturally occurring hyperplasia, 3) the development of prostatic hypertrophy in the aging male might be due to an imbalance of estradiol/testosterone ratios with the result that an increased amount of hormone receptor results in a resumption of growth of the gland. 4) dihydrotestosterone may accumulate in the gland in part because of an increase in the receptor and/or because of a net decrease in the catabolism of dihydrotestosterone under conditions in which dihydrotestosterone formation is probably unchanged. 5) If there is a significant discrepancy between the amount of receptor bound hormone and the total cellular content then it will be necessary to explain it before we can understand the relation between hormone accumulation and growth of the gland.

Relation to the Problem in Man

It is clearly impossible to do similar studies in man, and it will be necessary to design appropriate clinical, epidemiologic and/or therapeutic studies that may provide information of pathophysiological import.

78. Walsh, P.C., M.G. McLoughlin, M. Menon and C. Tananis. Measurement of androgen receptors in human prostatic tissue: methodological consideration. In Prostatic Disease, Alan R. Liss, New York, pp. 159-168, 1976.

79. Menon, M., C.E. Tananis, L.L. Hicks, E.F. Hawkins, M.G. McLoughlin and P.C. Walsh. Characterization of the binding of a potent synthetic androgen, methyltrienolone, to human tissues. J. Clin. Invest., 61:150-162, 1978.

80. Shimazaki, J., T. Kodama, M. Wakisaka and T. Katayama. Dihydrotestosterone-binding protein in cytosols of normal and hypertrophic human prostates, and influence of estrogens and anti-androgens on the binding. Endocrinol. Japan, 24:9-14, 1977.

81. Sirett, D.A. and J.K. Grant. Androgen binding in cytosols and nuclei of human benign hyperplastic prostatic tissue. J. Endocr. 77:101-110, 1978.

A particular problem until recently has been the measurement of the androgen receptor in the human; the reason for the difficulty in man in contrast to the easy measurement in lower species is the presence in human plasma of a gross excess of testosterone binding globulin which contaminates the tissues. It has been necessary to utilize an artificial androgen (methltrieneolone) that binds to the receptor but not to the plasma binding protein to measure the receptor reliably. Even so, because of the problems inherent in interpreting the steady state levels it is unlikely that the measuring endogenous receptor levels will provide much information. (Admitedly, knowing whether stilbestrol increases the androgen receptor in the prostate might be of considerable interest, and this could probably be determined in men undergoing treatment for cancer.

82. Huggins, C. and R.A. Stevens. The effect of castration on benign hypertrophy of the prostate in man. J. Urol.43:705-714, 1940.

83. Wendel, E.F., G.E. Brannen, P.B. Putong and J.T. Grayhack. The effect of orchiectomy and estrogens on benign prostatic hyperplasia. J. Urol. 108:116-119, 1972.

84. Geller, J., R. Bora, T. Roberts, H. Newman, A. Lin and R. Silva. Treatment of benign prostatic hypertrophy with hydroxyprogesterone caproate - effect on clinical symptoms, morphology, and endocrine function. JAMA, 193:115128, 1965.

85. Geller, J., A. Angrist, K. Nakao, and H. Newman. Therapy with progestational agents in advanced benign prostatic hypertrophy. JAMA. 210:1421-1428, 1969.

86. Scott, W.W. and J.C. Wade. Medical treatment of benign nodular prostatic hyperplasia with cyproterone acetate. J. Urology. 101:81-85, 1969.

87. Hansson, V., and K.J. Tveter. Effect of anti-androgens on the uptake and binding of androgen by human benign nodular prostatic hyperplasia in vitro. Acta Endocr. 68:69-78, 1971.

88. Rangno, R.E., P.J.McLeod, J. Ruedy, and R.I. Ogilvie. Treatment of benign prostatic hypertrophy with medrogestone. Clin. Pharmacol. Ther. 12:658-665, 1971.

89. Caine, M., S. Perlberg and R. Gordon. The treatment of benign prostatic hypertrophy with flutamide (SCH 13521):a placebo-controlled study. J. Urology. 114:564-568, 1975.

Although significant functional improvement in the symptoms of prostatic hypertrophy can be induced by either surgical castration (82,83) or medical treatment with anti-androgenic drugs that causes functional castration (84-89) the resulting impotence is so devastating that such therapy has no role in treatment. However, no definite role of estrogen in male physiology is known for certian, and consequently it will be of interest to evaluate the effects of antiestrogens on the condition.

Even if such treatment were to prove of benefit, it will be necessary to determine the reason for the periurethral origin of the human disorder. The location itself suggests that some pathogenic factor from the semen or the urine might be absorbed into the periurethral region of the gland and initiate the development of hypertrophy.

Thus, in the past ten years we have gained considerable insight into the endocrine changes that accompany or cause benign prostatic hyperplasia in man and dog, and perhaps in another ten years we will be able to come up with a general theory as to its etiology and insight into its prevention.