BENIGN PROSTATIC HYPERPLASIA: THE QUEST FOR A MEDICAL THERAPY

Medical Grand Rounds

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Benign prostatic hyperplasia is a common affliction of aging. Although not a major contributor to mortality, the disorder has a significant impact on morbidity, quality of life, and health costs for elderly men. The standard (and generally successful) therapy is prostate surgery, but an effective medical therapy would be useful, if only for those men in whom surgery is contraindicated or impractical. As a by product of our interest in androgen physiology, BPH has been a focus of interest in my laboratory since 1968 and has been the subject of two of my previous grand rounds (2-13-69 and 12-7-78) and a review by me (1). For most of this 20+ years research on the problem was limited largely to studies in experimental animals. However, as the result of advances in imaging techniques and in the methods for dynamic assessment of urine flow and as the result of the development of candidate therapeutic agents by several pharmaceutical companies, BPH is now the subject of intense clinical and experimental study. [Indeed, the MESH computerized database lists some 2245 documents on this subject over the last 5 years.] Today's discussion should be viewed as a progress report that focuses on one approach to the problem, namely hormonal therapy. It is not designed to cover all approaches to the pathogenesis and therapy; for example, new surgical approaches such as balloon dilatation of the urethra and simple incision of the urethra will be mentioned only in a cursory way.

Natural History and Epidemiology

The natural history of the disorder is still poorly understood. Its development was originally examined by Swyer who measured prostate volume at autopsy as a function of age (2).

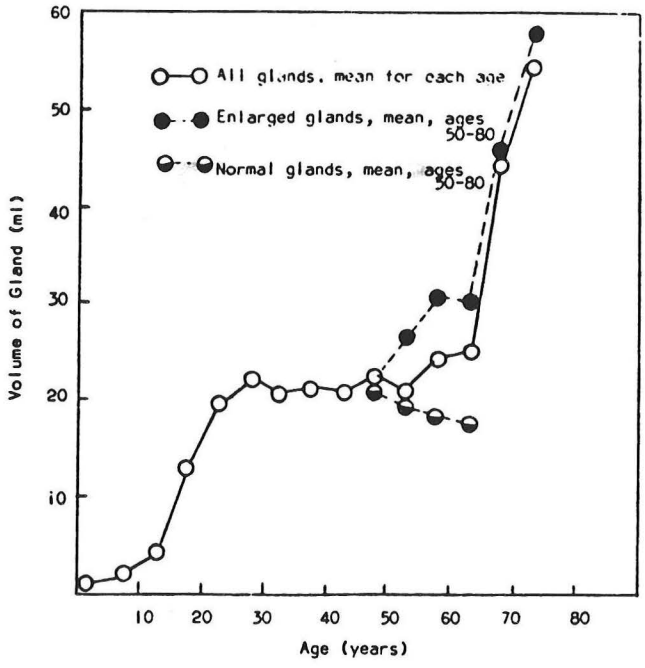


Fig. 1. Change in Mean Volumes of Prostate with Age

The gland weighs about 1.4 g at birth, increases to about 4.2 g prior to puberty, and then grows to about 15-20 g by age 20. On average there is no change until about age 55 when a second growth spurt begins so that the mean weight is about 55 g by age 70. In a small fraction of men the gland atrophies with age, presumably because of vascular insufficiency.

This volume/age curve requires qualification for two reasons. First, histological changes of BPH may be present prior to age 30 (3) (Figure 2).

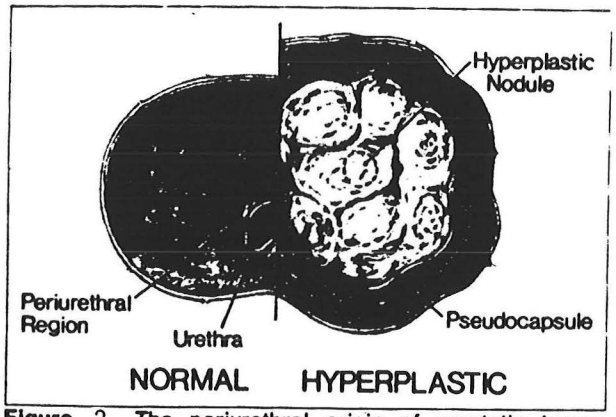


Figure 2 The periurethral origin of prostatic hyperplasia.

The discrepancy between weight and histology is due in part to the fact that BPH begins in the periurethral area as a mixed hyperplasia of stromal and epithelial elements. As the mass in the periurethral area enlarges it compresses the remainder of the gland to form a pseudocapsule, and the volume (weight) of the gland does not increase until the limits of the old capsule are exceeded, possibly requiring 25 years (4, 5) (Fig. 3, 4).

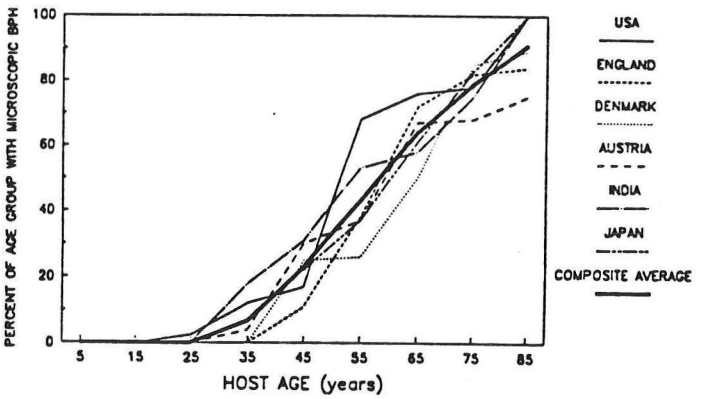


Fig. 3 Age-specific prevalence of microscopic BPH in various geographic male populations. Data were obtained from the following sources—USA: Baron and Angrist, 1941 [2]; England: combined data from Swyer, 1944 [4] and Franks, 1954 [5]; Denmark: Holund, 1980 [8]; Austria: Moore, 1943 [3]; India: Pradhan and Chandra, 1975 [7]; and Japan: Karube, 1961 [6]. The composite average was obtained by averaging all six studies.

Figure 3

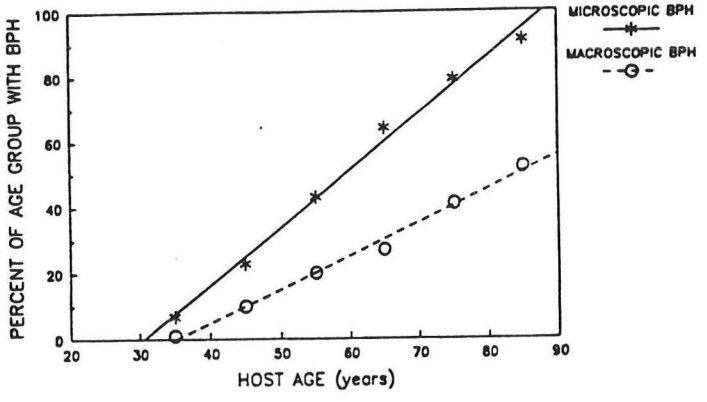


Fig. 4 Age-specific prevalence of microscopic vs. macroscopic pathological BPH. The line for microscopic BPH is obtained by a linear regression analysis of the composite data presented in Figure 1. The line for the macroscopic BPH is obtained by a linear regression analysis of the average data presented in Table I.

Figure 4

Second, there is no clear relation between prostate weight and symptomology. On the one hand, obstruction to urine outflow can occur in normal sized prostates with periurethal pathology; on the other hand, only a fraction of men with true prostatic enlargement become symptomatic (3). The term "prostatism" is nonspecific in that it can also occur with other disorders. Nevertheless, it is common to categorize the obstruction symptoms into stages.

Table 1

TABLE 1 Function: Symptoms and Stages in the Development of Prostatism

Prostatism: all symptoms related to prostatic enlargement through BPH
Stage I: slow stream, frequency, urgency, hesitancy, residual urine < 50 ml
Stage II: same as stage I, but residual urine > 50 ml
Stage III: chronic retention, upper tract dilatation with or without uremia
Other symptoms: urge incontinence, paradox incontinence, acute urinary retention; symptoms may not be specifically related to BPH

Stage 1 is associated with a slow urine stream, urgency, frequency, hesitancy, and a residual urine volume <50 ml. Stage II is characterized by large volume of residual urine. Stage III is associated with chronic retention that causes upper urinary tract damage and may or may not cause uremia.

On average about 10% of men with Stage I disease show severe enough progression over 5 years to warrant prostate surgery (3). As a consequence of the fact that some men never develop symptoms and because of the slow rate of progression in those who do develop symptoms, only about 10-25% of men eventually undergo surgery despite the fact that 70-80% of men have BPH at autopsy. Furthermore, when surgery is performed it is usually in men who are in Stage I of the disease.

The epidemiology is also incompletely understood. The disorder seems to be most common in Blacks, Caucasians, and Jews and less common in Asia, and the average course of disease in Blacks appears to be accelerated. Increasing age and intact androgen supply appear to be the only prerequisites for its development. No other risk factors have been identified (6).

Pathogenesis

The etiology is completely unknown, and the various theories as to pathogenesis were reviewed in the previous protocols for these rounds and have recently been updated by Isaacs and Coffey (7) and by Geller (8, 9). The disorder in some manner causes a disorganization of the basic relation between the epithelial elements, the smooth muscle, and the stromal fibroblasts. Since the embryonic prostate stroma controls the androgen-mediated differentiation of the prostatic epithelium (10, 11), in some sense the condition is due to disordered relationship between the components of the tissue as a result of

which the prostatic epithelium is induced to renewed growth. This process in turn is assumed to involve paracrine/apocrine growth factors within the tissue such as fibroblast growth factor or TGF-α (12). The net consequence is hyperplastic growth of disorganized tissue so that prostatic secretion decreases in volume as prostatic size increases.

In the absence of insight into etiology, most attention in to pathophysiology has focused on the normal control of prostatic growth and on the androgen dependence of prostatic hyperplasia, the major features of which are summarized in Table 2 (13).

Table 2

ANDROGEN DEPENDENCE OF BPH

Pre-Pubertal Castration Prevents BPH
Surgical or Medical Castration in Adults Leads to Some Degree of Prostatic Involution
Prostatic Levels of DHT and Androgen Receptor Remain High with Aging
Roles for Androgen (and Estrogen) have been Established in Canine BPH

Although the role of androgen in this process is almost certainly permissive rather than causal, the quest for experimental therapy has been largely based on this relation. For this reason it is appropriate to review briefly the role of androgen in prostate physiology.

Androgen and the Prostate

The differentiation of the prostate during embryogenesis, the growth of the gland at the time of sexual maturation, and the formation of the prostatic secretion in the mature adult are all under the control of androgen, and prostatic hyperplasia occurs rarely, if at all, in prepubertal castrates (1). In view of the critical role of androgen in the differentiation and growth of the gland, it is not surprising, furthermore, that mutations that impair androgen synthesis or androgen action inhibit prostatic growth at all stages. More importantly, it has been believed since the 19th century that the condition is ameliorated by surgical castration (1). It was believed for many years, however, that prostate hyperplasia occurs on a background of a slight decrease in circulating androgen levels and a slight increase in estrogen levels (1). As more careful studies are done in this regard it is now clear that any changes with age in androgen or estrogen levels, total or bioavailable, occur only in the very elderly, many years after the initiation of prostatic hyperplasia (15, 16). Hence, any effects of circulating gonadal steroids in the initiation of this condition must be mediated at normal adult male plasma levels. Continued growth of the hyperplastic gland during the fifth to seventh decades, however, may be enhanced to by changes in the ratios of estrogen to androgen.

If androgen is involved in the pathogenesis, it follows that the mechanism lies in the prostate itself. Plasma testosterone serves as a precursor for formation in extraglandular tissues of two other types of active steroid hormones - 5α-reduced androgens and estradiol (Fig. 5).

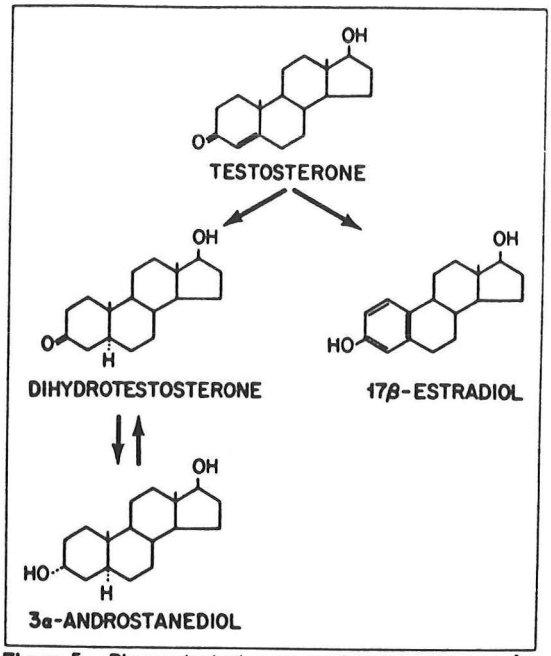


Figure 5. Plasma testosterone serves as a precursor for two other types of steroid hormones—5α-reduced androgens (dihydrotestosterone and 3α-androstanediol) and 17β-estradiol.

Current concepts of the mechanism of action of androgen are summarized in Fig. 6

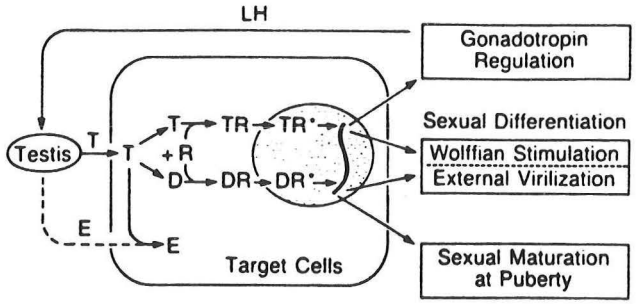


Fig. 6 Schematic diagram of normal androgen physiology. LH, luteinizing hormone; T, testosterone; D, dihydrotestosterone; E, estradiol; R, receptor, R*, transformed receptor.

Testosterone (T), the major plasma androgen, enters cells by what is probably a passive diffusion process. Inside the cell, T is 5α-reduced to dihydrotestosterone (D). D is bound to a specific, high affinity receptor protein (R) in the nucleus and cytoplasm. The hormone receptor complex is then transformed to the DNA binding state and binds to steroid regulatory elements in the DNA 5' to genes. The consequence is altered transcription of genes containing such elements.

The recognition in this laboratory in 1968 that dihydrotestosterone is the prostatic androgen in the rat (17, 18) stimulated us to investigate the pathogenesis of human prostatic hyperplasia and in the only animal model of prostatic hyperplasia, the dog. That work which was described previously in these rounds (1) can be summarized as follows:

1. *Dihydrotestosterone is the major androgen in the prostates of all species including those of men and dog (18).*

2. *The concentration of dihydrotestosterone in the hyperplastic human prostate is increased in most (19-23) but not all studies (24). The critical point is that dihydrotestosterone not testosterone - is the nuclear androgen in the normal prostate and in BPH.*

3. *Administration to the castrated dog of any androgen that causes an increase in the concentration of dihydrotestosterone in the prostate to approximately 5 ng/g causes development of prostatic growth equivalent to that in spontaneous hyperplasia in the dog (25, 26) (Figs. 7, 8)*

4. *The administration to dogs of estradiol along with androgen profoundly accelerates prostatic growth (25), almost certainly by enhancing the amount of androgen receptor in the tissue (27) (Fig. 9).*

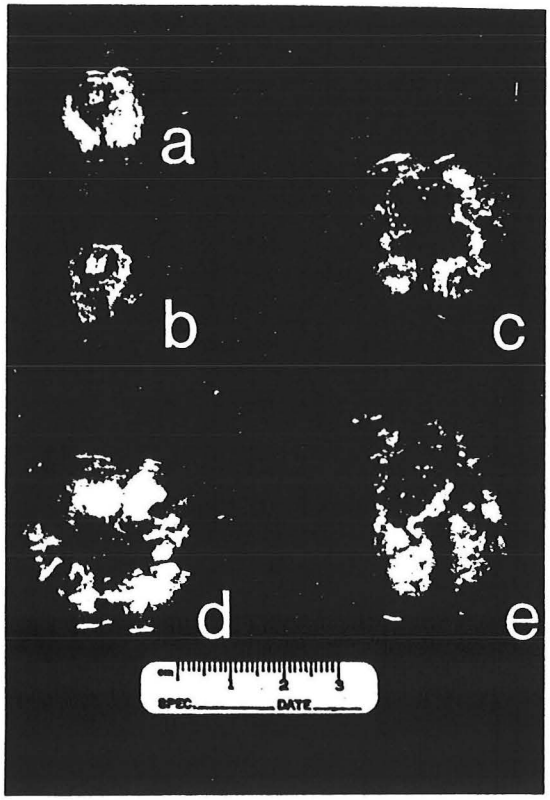


FIGURE 7 Photographs of prostates of castrated and control dogs and of dogs treated with supraphysiological doses of dihydrotestosterone and 3α-androstanediol. (*a*) Control, immature prostate, 3.2 g; (*b*) castrate prostate after 12 wk, 3.3 g; (*c*) spontaneous canine prostatic hyperplasia, 18.8 g; (*d*) castrated dog given fivefold doses of 3α-androstanediol (375 mg/wk) for 12 wk, 19.1 g; (*e*) castrate given fivefold doses of dihydrotestosterone (375 mg/wk) for 12 wk, 25 g.

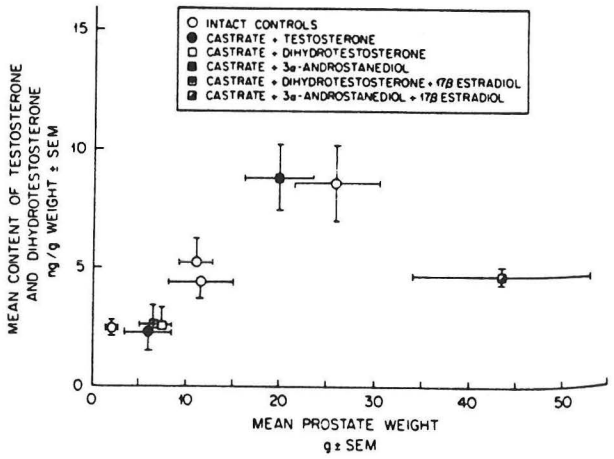


FIGURE 8 The relation between prostate weight and the mean concentration of testosterone plus dihydrotestosterone in the prostate. The intact control groups in Tables I and II are shown by the open circles, and the various treatment groups in Table II are designated by individual symbols.

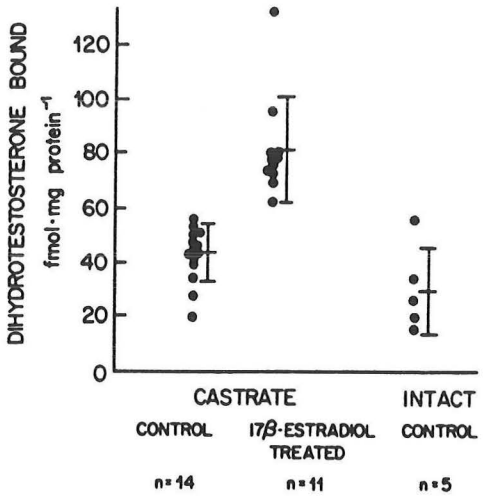


FIGURE 9 8S binding of [^{3}H]dihydrotestosterone by prostate cytosol from castrate control, 17β-estradiol-treated castrate, and intact control dogs. Cytosol preparations from each treatment group were incubated with 3 nM [^{3}H]dihydrotestosterone and subjected to density gradient sedimentation. Binding was calculated from the radioactivity in the 8S region as described in the text. Values (±SD) for each treatment mean, respectively, were 43.7±10.4, 81.9±19.5, and 29.1 ±15.6 fmol dihydrotestosterone bound per milligram cytosol protein.

As the result of these various studies we proposed in 1980 a true hormone model to explain the role of the testes in the pathogenesis of canine prostatic hyperplasia (7) (Table 3).

Table 3

TWO HORMONE MODELS FOR PROSTATIC HYPERPLASIA IN THE DOG

Hormone	*Role*
Dihydrotestosterone	*Cellular Mediator of Hyperplasia*
Estradiol	*Enhances Action of Dihydrotestosterone*

Namely, dihydrotestosterone is the cellular mediation of prostatic growth - normal and hyperplasic - in the dog, and estradiol plays a secondary role in the process to enhance dihydrotestosterone action. This dog model has been confirmed in several laboratories, but it was not clear whether the model applied to the human disorder and, if so, it was not clear why the process occurs only in two species - man and dog. It was at this point around 1980 that the studies in this area reached a stand still. One obviously can not do cause and affect relationship studies in man, and the only way that the pathogenesis could be studied in human was by experimental therapy. Even if the dog model were applicable to the human disorder, however, it did not necessarily follow that therapeutic intervention would be successful because the human gland becomes so fibrotic that the hyperplasia might be irreversible once it occurs (1).

Several potential strategies could be invisioned to test the two hormone thesis in man (Table 4).

Table 4

POTENTIAL STRATEGIES TO TEST THE BIHORMONAL THESIS IN MAN

ANDROGEN ABLATION	*Side Effects*
Surgical Castration	*Impotence*
LHRH Agonists	*Impotence, Hot Flashes*
ANTIANDROGENS	
Flutamide	*Gynecomastia*
Progestogens	*Impotence*
Cyproterone Acetate	*Imptoence*
ESTROGEN INHIBITORS	
Antiestrogens	*?*
Aromatase Inhibitors	*?*
5α-REDUCTASE INHIBITION	*?*

The development of potent drugs to block specific phases of androgen synthesis, metabolism, and action has stimulated a great deal of interest in this arena - and in particular the development of LHRH agonists that cause a reversible medical castration, antiandrogens such as flutamide, which are potent competitive inhibitors of the binding of dihydrotestosterone to the androgen receptor, 5α-reductase inhibitors (finasteride) that block the conversion of testosterone to dihydrotestosterone, and inhibitors of estrogen such as aromatase inhibitors that prevent the conversion of testosterone to estradiol and antiestrogens.

Assessment of Therapy

The assessment of the effectiveness of therapy in this condition is difficult for several reasons (28, 29):

1. *There is no constant relation between prostate size and either symptomatology or outflow obstruction.*

2. *Reliable means of quantifying changes in prostate size, urine flow, and pressure-flow relationships have only recently been developed and are still in the refinement stage.*

3. *As described above, the natural history is incompletely understood so that early intervention studies are difficult to design.*

4. *The outcomes of conservative management and surgical therapy are still incompletely understood.*

It is for these reasons that attempts to document whether surgical castration is effective gave such equivocal results before it become possible to quantify changes in prostate size by MRI/ultrasound techniques and to assess changes in urine by dynamic flow measurements (30, 31). The surgical castration studies did establish that the operation caused histological changes of epithelial atrophy but, as expected, that enlarged fibrotic glands do not return to normal size (30, 31). It is beyond the scope of this discussion to review the assessment of prostatic function in detail except to say that prostate size and urine flow can now be quantified with a reasonable degree of precision and reproductibility. Symptomatology is still difficult to assess.

Androgen Deprivation Therapy for Benign Prostatic Hyperplasia

Medical Castration

Testosterone synthesis can be blocked with potent luteinizing hormone releasing hormone (LHRH) agonists that block the pituitary release of gonadotropin, thus preventing the production of testicular androgen. Peters and Walsh treated nine men who had bladder outlet obstruction secondary to BPH with nafrelin acetate for 6 months (32). Serum testosterone fell to castrate levels, and there was concomitant decrease in libido and/or impotence. The prostate decreased 24% on average in size after 4 months and returned to pretreatment size after 6 months of stopping therapy. Three patients had significant clinical improvement, as measured by maximum urine flow rate and symptoms. Gabrilove and coworkers in a similar study observed a 46% decrease in prostate volume after 6 months of such therapy (33, 34), and Bosch et al reported that after 3 months of therapy there was a 30% decrease in prostatic size but no concomitant urodynamic improvement (35). Bianchi et al reported that such regimen produced a significant improvement in symptoms and in prostate size (36). Finally Schlegel and Brendler reported that occasional dramatic improvement can occur, as in the case of one man with urinary retention who was a poor candidate for surgery but had a decrease in prostate size from 132 to 42 grams and spontaneous onset of micturition (37). This therapy causes a profound decrease in prostatic dihydrotestosterone (38, 39), a decrease in prostate 5α-reductase activity (38), and a decrease in serum prostate specific antigen levels to castrate levels (40). LHRH agonists are available but are approved therapy only for treatment of prostatic carcinoma.

This therapy is associated with the expected consequences of castration in all men including impotence and particularly severe hot flashes and is a legitimate therapeutic option only in these few patients with lower urinary tract obstruction who are not candidates for surgery.

The importance of the LHRH agonist studies was to document that the testis does play a continuing role in the maintenance of the hyperplastic prostate gland and to suggest that endocrine factors play similar roles in the pathogenesis of the disorder in dogs and human (41). The implication is that more selective therapeutic agents might be devised to block the action of androgens selectively within the prostate. A second implication was that the maximal benefit one would predict in men with advanced disease would be improvement in 30%.

Antiandrogens

Antiandrogens that have been tried for prostatic hyperplasia (see McConnell (14) for review) include flutamide (which in the form of its metabolite hydroxy-flutamide blocks the binding of dihydrotestosterone to the androgen receptor) and cyproterone acetate and other progestational drugs that inhibit gonadotropin and block androgen binding to a variable degree. Of these flutamide is by far the most potent and the only one available in the U.S. Early studies on 30 men given flutamide or placebo did not document significant improvement in urinary flow rate, residual urine, a prostate size (42), but the Paulsens group at Duke has reported in abstract form that flutamide causes a 40% decrease in prostate volume over 6 months and an improvement in urine flow rate and urinary symptomatic scores (43, 44). Half of patients develop gynecomastia/breast pain, and half have gastrointestinal side effects. Only one patient experienced erectile dysfunction. Additional work will have to be done to determine the true effectiveness of antiandrogens such as flutamide in prostatic hyperplasia, but the side effects will likely limit their usefulness.

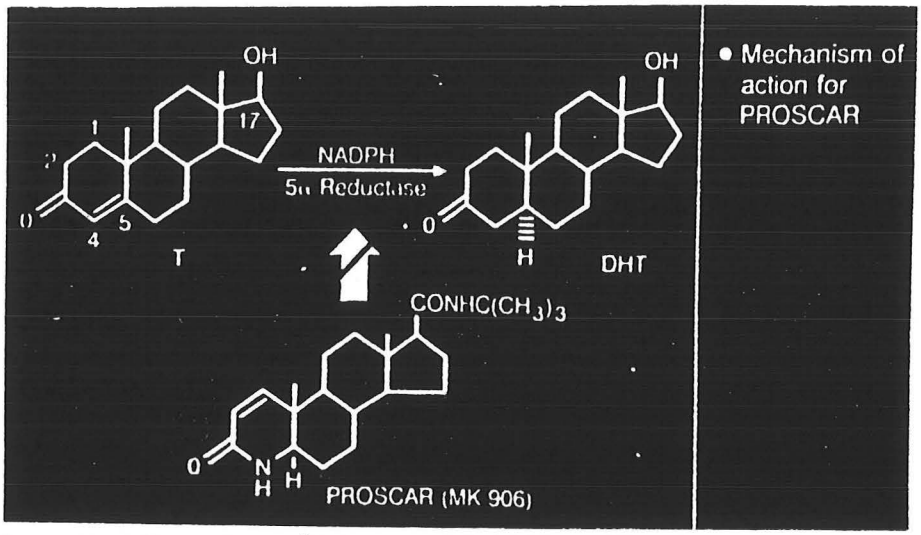
Aromatase Inhibitors and Anti-Estrogens

The clinical use of antiestrogens and aromatase inhibitors has received little study in men in large part because most available agents were either non specific (tamoxifen is both an antiestrogen and a weak estrogen agonist) or ineffective (testolactone works in vitro but not very well in vivo). Tamoxifen in men with BPH enhances the level of luteinizing hormone in plasma and consequently causes a secondary rise in androgen levels (45). Consequently, it would probably be beneficial only in combination with other agents. Aromatase inhibitors offer more promise (46). In one uncontrolled study of 13 men with complete urinary obstruction treatment with testolactone caused a 26% decrease in average prostate volume and a return to spontaneous micturition in 7 of the 13 (47); whether these effects were due to inhibition of aromatase or to other effects of testosterone was not established. More specific aromatase inhibitors are being tested in benign prostatic hyperplasia (48). Some of these agents have been studied in the dog model with equivocable success (49-53). The most promising of these agents 1-methyl-androsta-1,4-diene-3,17-dione specifically inhibits proliferation of the stroma in the dog prostate and is now being evaluated in human trials. It is too early to say whether such agents will have a role either as sole therapy or as a part of combination therapy with other agents.

5α-Reductase Inhibition

The concept of using an inhibitor of the enzyme 5α-reductase to cause regression of BPH arose from studies indicating that dihydrotestosterone is the active androgen in the normal prostate, documentation that dihydrotestosterone plays a role in canine prostatic hyperplasia, and recognition that men with inherited deficiency of the enzyme do not develop a prostate gland. It was therefore reasoned that an inhibitor of the enzyme might induce one phenotypic feature of 5α-reductase deficiency, impairment of prostatic growth, without producing all the side effects of antiandrogen therapy. Several pharmaceutical companies have developed candidate drugs, of which the most promising are a series of azasteroids developed at the Merck, Sharp and Dohme Research Laboratories in which the 4 carbon of the steroid molecule is replaced by a

nitrogen. Several agents of this class have been studied; the effects virtually identical differing only in the frequency of side effects, and consequently they will be discussed as a class. The agent that is now being humans in humans is finasteride shown in Figure 10 (54-56).



Finasteride (MK-906; Proscar™) is a reversible inhibitor of 5α-reductase in the prostate, liver, and other tissues. By inhibiting the 5α-reductase enzyme, it effectively blocks the conversion of testosterone (T) to dihydrotestosterone (DHT). Despite the structural similarity of MK-906 to steroid molecules, it has no known steroid-like toxicities. (Courtesy of Dr. Elizabeth Stoner, Merck Research Laboratories)

Figure 10

These agents are extraordinary potent competitive inhibitors of the enzyme within apparent Ki about 5-10 times as potent as the best endogenous substrate of the enzyme (57). They are effective by mouth (58), and when administered to pregnant animals the agent crosses the placenta and impairs virilization of the external genitalia but not the wolffian ducts of male embryos (59), thus causing a phenocopy of 5α-reductase deficiency (Figs. 11, 12). When administered to newborn animals, in contrast, they inhibit all dihydrotestosterone mediated growth phenomena - including growth of structures of derived from wolffian ducts (epididymis, seminal vesicles) and the urogenital sinus (prostate) as well as the external genitalia (penis and scrotum) (60) (Fig. 13). After sexual maturation and growth of the external genitalia are complete, however, the major effect seems to be at the level of the prostate (Figure 11) (60).

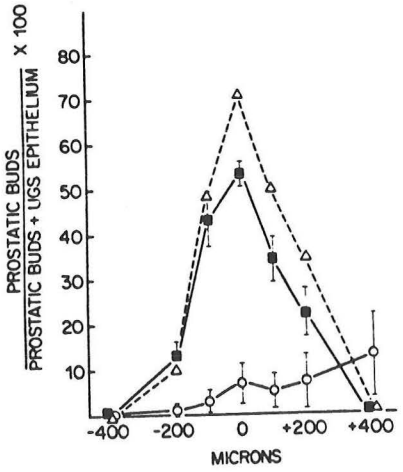


FIG. 11 Inhibition of prostate development in the fetal rat treated with L652,931. Pregnant rats were treated daily with 50 mg L632,931/kg BW from days 14–22 of gestation. Control rats were injected with vehicle (90% triolein oil-10% ethanol) only or with L652,931 plus 50 mg/kg·day DHT. Urogenital sinuses (UGS) were dissected from male fetuses on day 22 of gestation, fixed, embedded, and sectioned at 5 μm. Prostate development was assessed by determining the percentage of urogenital sinus-derived epithelium that was prostatic buds in representative sections proximal or distal to the point at which the Wolffian ducts enter the urogenital sinus (designated 0 μm). Each *point* represents the mean percentage of prostatic epithelium ± SE in four control (■) or six L652,931-treated (○) male urogenital sinuses. Prostate formation was quantitated in only one urogenital sinus from the L652,931- plus DHT-treated group (△).

Figure 11

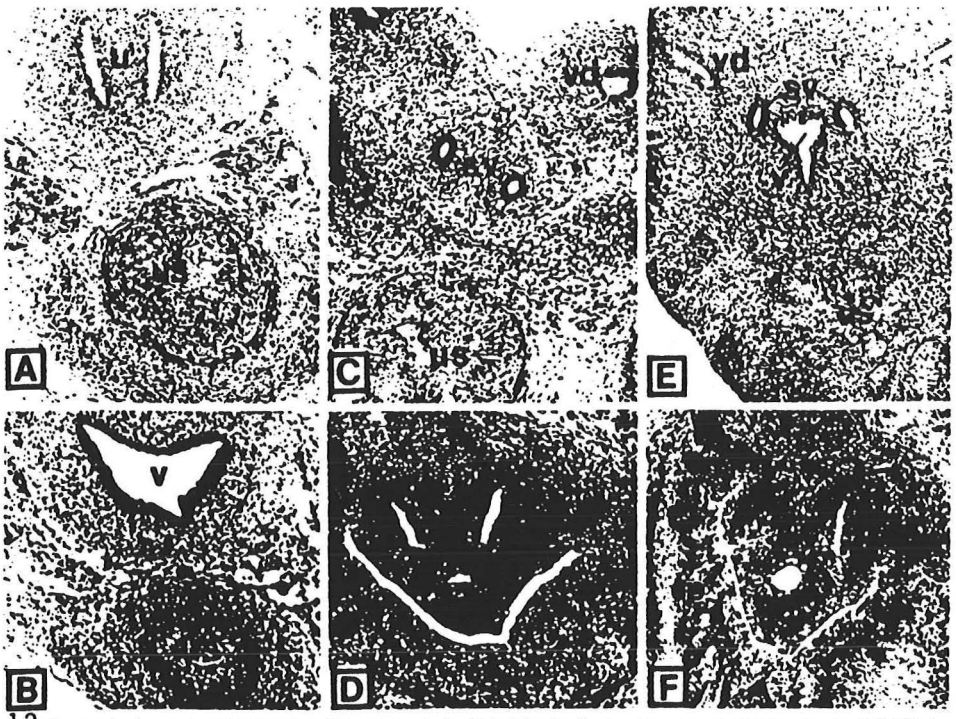


Fig 12 Prostate development and Wolffian duct differentiation in day 22 fetal female offspring of rats treated with 50 mg/kg·day L652,931 plus 50 mg/kg·day DHT from days 14-22 of gestation. A and B, Control females; C and D, control male; E and F, female treated with 5α-reductase inhibitor plus DHT. Sections depicted in B and E are at similar levels through female urogenital tracts. Sections D and F are at similar levels through female urogenital tracts. Sections D and F are at similar levels of male and female urogenital sinuses, respectively. u, uterus; us, urogenital sinus; v, vagina; sv, seminal vesicle; vd, vas deferens; p, prostate.

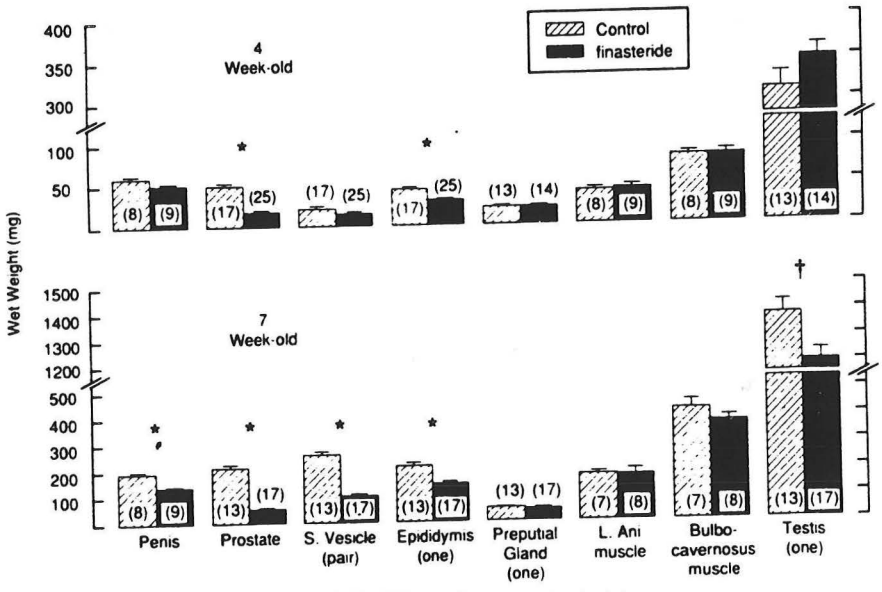


Fig. 13 Effect of postnatal administration of a 5α-reductase inhibitor (finasteride) on the weights of accessory sex glands, penis, sexually dimorphic muscles, and testis in male rats. Newborn rats were treated from the third postnatal day with the 5α-reductase inhibitor as described in the text. Each *bar* represents a mean ± SEM for the number of independent observations indicated in *parentheses*. ★, $P < 0.001$; †, $P = 0.01$ (significant difference between control and 5α-reductase inhibitor-treated groups).

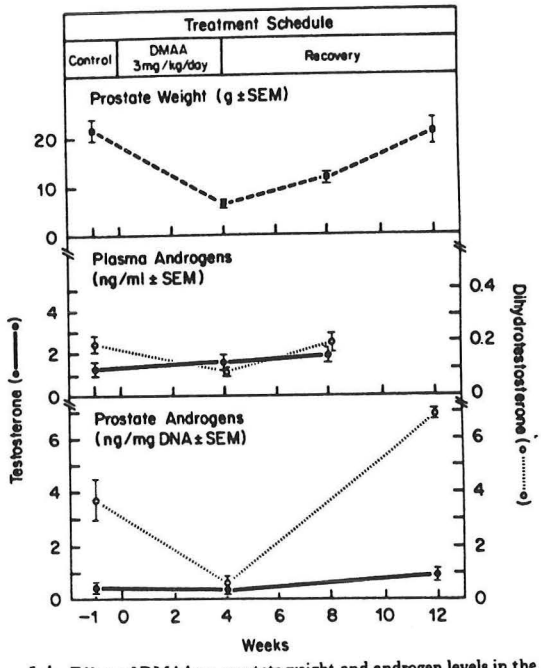


Fig. 14 Effect of DMAA on prostate weight and androgen levels in the plasma and prostate of dogs with intact testes. Each value represents the mean ± SEM for five dogs. In this study, the prostates were biopsied before the commencement of treatment as well as after 4 weeks treatment with DMAA and after 8 weeks of recovery.

In the dog with prostatic hyperplasia the agent caused a profound decrease in plasma and prostate dihydrotestosterone levels and in prostatic weight (61) and also has the capacity of blocking the action of testosterone on the growth of the gland (61) (Table 5)

Table 5

TABLE 5 Effect of testosterone cypionate (0.4 mg/kg BW·day) with or without DMAA (3 mg/kg BW·day) on prostate weight and androgen concentrations in prostate and plasma of castrate dogs

	Castrate + testosterone cypionate			Castrate + testosterone cypionate + DMAA		
	Precastrate control	2 Weeks	4 Weeks	Precastrate control	2 Weeks	4 Weeks
Prostate wt (g ± SEM)	11.4 ± 0.9		21.4 ± 2.4	11.2 ± 1.2		5.6 ± 0.7
Prostatic testosterone (ng/mg DNA ± SEM)			3.1 ± 0.6			4.1 ± 1.3
Prostatic dihydrotestosterone (ng/mg DNA ± SEM)			15.1 ± 1.8			4.0 ± 1.8
Plasma testosterone (ng/ml ± SEM)	1.7 ± 0.9	6.1 ± 0.7	8.6 ± 1.0	2.3 ± 0.7	6.4 ± 0.7	8.4 ± 0.9
Plasma dihydrotestosterone (ng/ml ± SEM)	0.2 ± 0.1	0.5 ± 0.1	0.9 ± 0.3	0.2 ± 0.1	0.4 ± 0.1	0.5 ± 0.1

Dogs with normal prostates were castrated and divided into two groups; one group of four dogs was given 0.4 mg testosterone cypionate/kg BW·day, and the other group of five dogs was given the same dose of testosterone cypionate plus 3 mg DMAA/kg BW·day. After 4 weeks, the dogs were killed, and plasma and prostates were assessed as described.

In the dog, furthermore, the drug does not seem to influence sex drive or potency or have other side effects.

The mechanism of action of the drug is complex. Under in vitro conditions the agent appears to act purely as a competitive and reversible inhibitor (57). In intact animals however, the agent causes a decrease in the amount as well as the activity of the enzyme in prostate (62). [Castration is also known to cause a decrease in the amount of prostatic 5α-reductase (63), implying that dihydrotestosterone may play a specific role in the induction of enzyme action.] (Fig. 15).

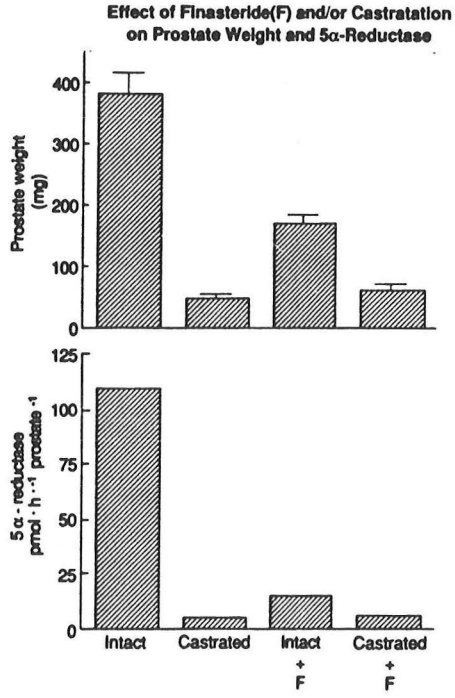


Figure 15

The mechanism by which finasteride lowers enzyme activity involves a decrease in the amount of mRNA for the enzyme (62) (Table 6).

Table 6

EFFECT OF FINASTERIDE or 5α-REDUCTASE mRNA IN ANDROGEN TREATED RATS

Group	Treatment	Average Prostate Weight mg	5α-reductase pmol/h/prostate	5α-Reductase MRNA DA/prostate
Control	Triolein	333	349	8.2
Castrate	Triolein	24	11	0.2
Castrate	Testosterone	110	487	4.1
Castrate	Dihydrotestosterone	78	168	2.4
Castrate	Testosterone + F	52	46	0.5
Castrate	Dihydrotestosterone + F	101		

By whatever mechanism the agent is extraordinary potent in man. It causes both a profound decrease in circulating dihydrotestosterone levels (58) and, more importantly, an equally profound decrease in prostatic dihydrotestosterone levels (64) (Fig. 16).

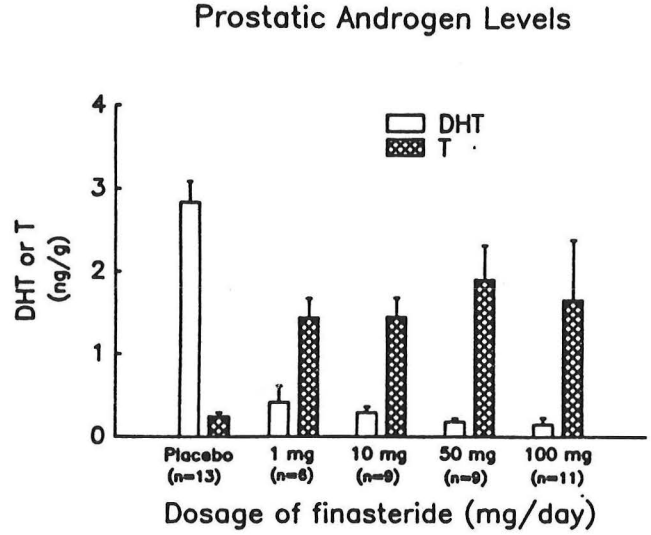


Figure 16

The above data were obtained in a collaborative study between Geller's laboratory and our laboratory (64) and almost certainly represent an underestimate of effectiveness because the condition of the experiment do not approximate the steady state. Even so, the inhibitor causes castrate levels of dihydrotestosterone in prostate without effecting plasma testosterone which is critical for normal libido and sexual function. This agent furthermore, causes a minimum of non mechanism based side effects and appears to be safe.

Extensive clinical trials have been undertaken to determine the efficiency and long-term safety of finasteride in BPH. I am going to describe the phase 2 studies - a comparative, double blind 6 month safety efficacy study in 190 subjects done in 6 institutions including ours (65). [Twelve month phase three studies involving more than 800 subjects have now been completed; I do not have slides from that study, but in general the results of the two studies are comparable.]

Prostate size was estimated by MRI and/or ultrasonography; urine flow rates were determined from graphic recordings under standardized conditions, and a questionnaire was utilized to assess the effects of the drug on the symptoms of urinary obstruction. To be accepted into the study maximal urine flow had to be equal to or less than 15 ml/sec. The results of this study are summarized on the next three figures (Figs. 17, 18).

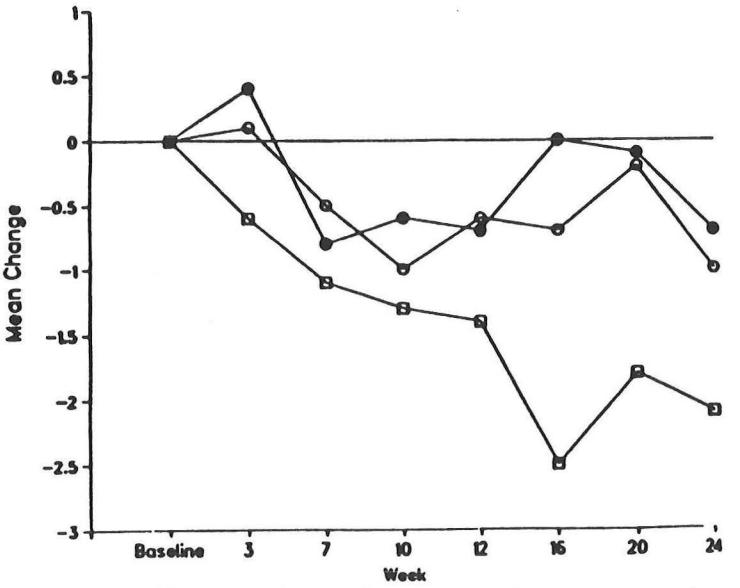


Fig. 17 Mean change in obstructive symptoms in men on Finasteride for 6 months.

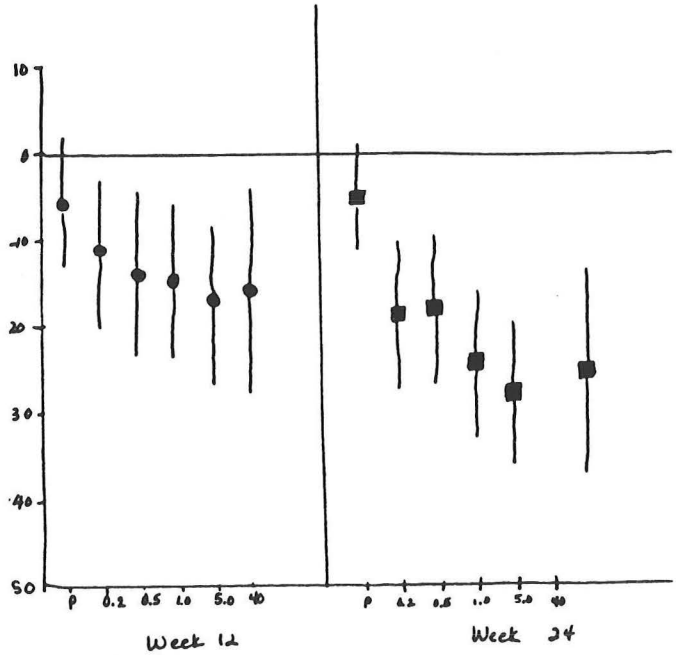


Fig. 18 Mean change in prostate volume measured by MRI after 12 or 24 weeks on Finasteride (95% Confidence Intervals)

In summary, finasteride causes results that are virtually identical to those of surgical/medical castration, namely a 25% decrease in prostatic size, significant urodynamic improvement in about a third of patients, and a disappointing effect on symptoms (in part because of a placebo effect on symptoms). Thus, while we appear to have achieved a selective tissue castration, the therapeutic effectiveness can either be interpreted as promising or disappointing. This is not a miracle drug. However, it was not reasonable to expect that the drug would be more effective than castration, and the fact that some patients improve is encouraging. What is needed at this stage are additional trials to include early intervention studies and combination therapy with finasteride and with an aromatase inhibitor or an alpha blocker.

Other Potential Medical Therapys

α-Adrenergic Blockade

Randomized, placebo-controlled, multiinstitutional clinical trials of alpha-blockers are now underway in the United States. The rationale for such a study is that the base of the bladder and the prostate are rich in α 1 receptors and that alpha adrenergic mechanisms are believed to play a role in urinary tract obstruction. In preliminary studies orally effective α 1 adrenergic blockers are reported to cause increases in maximal urine flow rates and improvement in symptoms (66-70). Such agents presumably would not influence the natural history of BPH but might have a major role to play in combination with an agent that shrinks the prostate.

Summary

We now have considerable insight into the role of androgens - and specifically the role of dihydrotestosterone - in controlling the growth of the prostate, but it is not clear at present whether this insight will be of major therapeutic benefit. It now appears that inhibition of 5α-reductase produces an effect that is virtually identical to medical/surgical castration - a 25% decrease in prostate size, a modest increase in maximal urine flow, and an even more modest improvement in symptoms. It is unlikely that any form of androgen deprivation alone will produce a more significant improvement, given the nature of the histological changes in the hyperplastic prostate. Therefore, future therapeutic study will have to be directed either to early intervention studies in which the therapeutic aim is to prevent worsening of pathology and/or symptoms or to combination therapy in which the aim is either to improve symptoms (α-adrenergic blockade or prostate incisional surgery) or to reduce size by an additional mechanism (aromatase inhibitor). In brief, despite 20 plus years of work there is much additional work to be done to achieve the ideal medical therapy.

REFERENCES

1. *Wilson JD. The pathogenesis of benign prostatic hyperplasia. Amer J Med 68:745-756, 1980.*

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

3. *Schröder FH, Blom JHM. Natural history of benign prostatic hyperplasia (BPH). The Prostate Supplement 2:17-22, 1989.*

4. *Deming CL, Wolf JS. The anatomic origin of benign prostatic enlargement. J Urol 42:566, 1939.*

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

6. *Ekman P. BPH epidemiology and risk factors. The Prostate Supplement 2:23-31, 1989.*

7. *Isaacs JT, Coffey DS. Etiology and disease process of benign prostatic hyperplasia. The Prostate Supplement 2:33-50, 1989.*

8. *Geller J. Overview of benign prostatic hypertrophy. Supplement to Urology 34:57-63, 1989.*

9. *Geller J. Pathogenesis and medical treatment of benign prostatic hyperplasia. The Prostate Supplement 2:95-104, 1989.*

10. *Cunha GR, Chung LWK, Shannon JM, Fujji H. Hormonal induced morphogenesis and growth: role of the mesenchymal-epithelial interactions. Recent Prog Horm Res 39:559-598, 1983.*

11. *Cunha GR, Chung LWK, Shannon JM. Stromal-epithelial interactions in sex differentiation. Biol Reprod 22:19-42, 1980.*

12. *Begun FP, Story MT, Jacobs SC, Lawson RK. Distribution of basic fibroblast growth factor within the prostate. J Urol (Abstract) 141:307a, 1989.*

13. *McConnell JD. Medical management of benign prostatic hyperplasia with androgen suppression. The Prostate Supplement 3:49-59, 1990.*

14. *McConnell JD. Androgen ablation and blockade in the treatment of benign prostatic hyperplasia. Urol Clin North Am 17:661-670, 1990.*

15. *Harman SM, Tsitouras PD. Reproductive hormones in aging men. I. Measurements of sex steroids, basal luteinizing hormone, and Leydig cell response to human chorionic gonadotropin. J Clin Endocrinol Metab 51:35-40, 1980.*

16. *Tsitouras PD. Effects of age on testicular function. Endocrinol Metab Clin North Am 16:1045-1059, 1987.*

17. *Bruchovsky N, Wilson JD. The conversion of testosterone to 5α-androstan-17β-ol-3-one by rat prostate in vivo and in vitro. J Biol Chem 243:2012-2021, 1968.*

18. Gloyna RE, Wilson JD. A comparative study of the conversion of testosterone to 17β-hydroxy-5α-androstan-3-one (dihydrotestosterone) by prostate and epididymis. J Clin Endocrinol 29:970-977, 1969.

19. Siiteri PK, Wilson JD. Dihydrotestosterone in prostatic hyprtrophy. I. The formation and content of dihydrotestosterone in the hypertrophic prostate of man. J Clin Invest 49:1737-1745, 1970.

20. Hammond GL. Endogenous steroid levels in human prostate from birth to old age: a comparison of normal and diseased tissue. J Endocrinol 78:7-19, 1978.

21. Meikle AW, et al: Subnormal tissue 3 alpha-androstanediol and androsterone in prostatic hyperplasia. J Clin Endocrinol Metab 47:909-913, 1978.

22. Bolton NJ, Lukkarinen O, Vihko R. Concentrations of androgens in human benign prosatic hypertophic tissues incubated for up to three days. Prostate 9:159-167, 1986.

23. Belis JA. Methodologic basis for the radioimmunoassay of endogenous steroids in human prostate tissue. Invest Urol 17:332-336, 1980.

24. Walsh PC, Hutchins GM. Tissue content of dihydrotestosterone in human prostatic hyperplasia is not suprandormal. J Clin Invest 72:172-177, 1983.

25. Walsh PC, Wilson JD. The induction of prostatic hypertrophy in the dog with androstanediol. J Clin Invest 57:1093-1097, 1976.

26. Moore RJ, Gazak JM, Quebbeman JF, Wilson JD. Concentration of dihydrotestosterone and 3α-androstanediol in naturally occurring and androgen-induced prostatic hyperplasia in the dog. J Clin Invest 64:1003-1010, 1979.

27. Moore RJ, Gazak JM, Wilson JD. Regulation of cytoplasmic dihydrotestosterone binding in dog prostate by 17β-estradiol. J Clin Invest 63:351-357, 1979.

28. Wein AJ. Evaluation of treatment response to drugs in benign prostatic hyperplasia. Urol Clin North Am 17:631-640, 1990.

29. Barry MJ. Medical outcomes research and benign prostatic hyperplasia. The Prostate Supplement 3:61-74, 1990.

30. Huggins C, Stevens RA. The effect of castration on benign prostatic hypertrophy in men. J Urol 43:705, 1940.

31. Wendel EF, Brannen GE, Putong PB, Grayback JT. The effect of orchiectomy and estrogens on benign prostatic hyperplasia. J Urol 108:116, 1972.

32. Peters CA, Walsh PC. The effect of nafarelin acetate, a luteinizing-hormone-releasing hormone agonist, on benign prostatic hyperplasia. N Engl J Med 317:599-604, 1987.

33. Gabrilove JL, Levine AC, Kirschenbaum A, Droller M. Effect of a GNRH analogue (Leuprolide) on benign prostatic hypertrophy. J Clin Endocrinol Metab 64:1331-1333, 1987.

34. Gabrilove JL, Levine AC, Kirschenbaum A, Droller M. Effect of long-acting gonadotropin-releasing hormone analog (Leuprolide) therapy on prostatic size and symptoms in 15 men with benign prostatic hypertrophy. J Clin Endocrinol Metab 69:629-632, 1989.

35. Bosch RJLH, Derek J, Griffiths JHMB, Schroeder FH. Treatment of benign prostatic hyperplasia by androgen deprivation: effects on prostate size and urodynamic parameters. J Urol 141:68-72, 1989.

36. Bianchi S, Gravina G, Podesta A, Barletta D, Franchi F, Kicovic P, Luisi M. Treatment of complicated benign prosatic hyperplasia with LHRH-analogues in aged patients. Intl J Androl 12:104-109, 1989.

37. Schlegel PN, Brendler CB. Management of urinary retention due to benign prostatic hyperplasia using luteinizing hormone-releasing hormone agonist. Urol 34:69-72, 1989.

38. Fonti G, Salerno R, Moneti G, Zoppi S, Fiorelli G, Marinoni T, Natali A. Constantini A, Serio M, Martin L, Motta M. Three month treatment with a long-acting gonadotropin-releasing hormone agonist of patients with benign prostatic hyperplasia: effects on tissue and androgen concentration. 5 alpha-reductase activity and androgen receptor content. J Clin Endocrinol Metab 68:461-468, 1989.

39. Salerno R, Moneti G, Forti G, Magini A, Natali A, Saltutti C, DiCello V, Costantini A, Serio M. Simultaneous determination of testosterone, dihydrotestosterone and 5α-androstan-3α,-17β-diol by isotopic dilution mass spectrometry in plasma and prostatic tissue of patients affected by benign prostatic hyperplasia effects of 3-month treatment with GnRH analog. J Androl 9:234-240, 1988.

40. Weber JP, Oesterling JE, Peters CA, Partin AW, Chan DW, Walsh PC. The influence of reversible androgen deprivation on serum prostate-specific antigen levels in men with benign prostatic hyperplasia. J Urol 141:987-992, 1989.

41. Wilson JD. The testes and the prostate: A continuing relationship. N Engl J Med 317:628-629, 1987.

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

43. Stone NN, Clejan S, Ray PS, Smith JA, Scardino PT, Smith RB, Khanna OP, Paulson DF. A double-blind randomized controlled study of the effect of flutamide on benign prostatic hypertrophy: Side effects and hormonal changes (abstr.) J Urol 141:307A. 1989.

44. Stone N, Ray PS, Smith JA, Scardino PT, Smith RB, Khanna OP, Paulson DF, Spiegel RJ, Neri RO, Cullen DA. A double-blind randomized controlled study of the effect of flutamide on benign prostatic hyperplaisa: Clinical efficacy (abstr.) J Urol 141:240A, 1989.

45. Stahl F, Schnorr D, Rohde W, Poppe I, Geier TH, Dörner G. Effects of tamoxifen on the levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), 17β-oestradiol (E_2), total and free testosterone (T) and total and free dihydrotestosterone (DHT) in blood of patients with benign prostatic hyperplasia. Exp Clin Endocrinol 28:82:21-28, 1983.

46. Henderson D, Habenicht U-F, Nishino Y, El Etreby MF. Estrogens and benign prostatic hyperplaisa: The basis for aromatase inhibitor therapy. Steroids 50:219-233, 1987.

47. Schweikert HU, Tunn UW. Effects of the aromatase inhibitor testolactone on human benign prostatic hyperplaisa. Steroids 50:191-200, 1987.

48. Schweikert HU. Personal Communication.

49. Habenicht UF, Schwarz K, Schweikert HU, Neumann F,NEl Etreby MF. Development of a model for the induction of estrogen-related prostatic hyperplasia in the dog and its response to the aromatase inhibitor 4-hydroxy-4-androstene-3, 17-dione: Preliminary results. The Prostate 8:181-914, 1986.

50. Habenicht UF, El Etreby MF. Synergic inhibitory effects of the aromatase inhibitor 1-methyl-androstan-1, 4-diene-3, 17-dione and the antiandrogen cyproterone acetate on androstenedione-induced hyperplastic effects in the prostates of castrated dogs. The Prostate 11:133-143, 1987.

51. Habenicht UF, El Etreby MF. Selective inhibition of androstenedione-induced prostate growth in intact beagle dogs by a combined treatment with the antiandrogen cyproterone acetate and the aromatase inhibitor 1-methyl-androsta-1,4-diene-3,17-dione. The Prostate 14:309-322, 1989.

52. Juniewicz PE, Oesterling JE, Walters JR, SDteele RE, Niswender GD, Coffey DS, Ewing LL. Aromatase inhibition in the dog. I. Effect on serum LH, serum testosterone concentrations, testicular secretions and spermatogenesis. J Urol 139:827-831, 1988.

53. Oesterling JE, Juniewicz PE, Walters JR, Strandberg JD, Steele RE, Ewing LL, Coffey DS. Aromatase inhibition in the dog. II. Effect on growth, function, and pathology of the prostate. J Urol 139:832-839, 1988.

54. Brooks Jr, Berman C, Garnes D, et al: Prostatic effects induced in dogs by chronic acute oral administration of 5α-reductase inhibitors. Prostate 9:65, 1986.

55. Brooks Jr, Berman C, Glitzer MS, et al: Effect of a new 5α-reductase inhibitor on size, histological characteristics, and androgen concentrations of the canine prostate. Prostate 3:35, 1982.

56. Brooks JR, Berman C, Primka RL, et al: 5α-reductase inhibitory and anti-androgenic activities of some 4-azasteroids in the rat. Steroids 14:1, 1986.

57. Leshin M, Wilson JD. Inhibition of steroid 5α-reductase from human skin fibroblasts by 17 -N,N-diethylcarbamoyl-4-methyl-4-aza-5α androstan-3-one. J Steroid Biochem 17:245-250, 1982.

58. Vermeulen A, Giaguli VA, De Schepper P, Buntinx A, Stoner E. Hormonal effects of an orally active 4-azasteroid inhibitor of 5α-reductase in humans. The Prostate 14:45-53, 1989.

59. George, F.W., and K.G. Peterson. 5α-Dihydrotestosterone formation is necessary for embryogenesis of the rat prostate. Endocrinology 122:1159-1164, 1988.

60. George FW, Johnson L, Wilson JD. The effect of a 5α-reductase inhibitor on androgen physiology in the immature male rat. Endocrinology 125:2434-2438, 1989.

61. Wenderoth UK, George FW, Wilson JD. The effect of a 5α-reductase inhibitor on androgen-mediated growth of the dog prostate. Endocrinology 113:59-573, 1983.

62. George FW, Russell DW, Wilson JD. The 5α-reductase inhibitor, finasteride, prevents androgen-stimulated synthesis of 5α-reductase enzyme in rat prostate. In preparation.

63. Moore RJ, Wilson JD. The effect of androgenic hormones on the reduced nicotinamide adenine dinucleotide phosphate: Δ3-ketosteroid 5α-oxidoreductase of rat ventral prostate. Endocrinology 93:581-592, 1973.

64. McConnell JD, Wilson JD, George FW, Geller J, Walsh PC, Ewing LL, Isaacs J, Stoner E. An inhibitor of 5α-reductase, MK-906, suppresses prostatic dihydrotestosterone in men with benign prostatic hyperplasia. J Urol 141:231A, 1989.

65. Stoner E et al. The clinical effects of a 5α-reductase inhibitor, finasteride, on benign prostatic hyperplasia. Submitted for Publication.

66. Lepor H. Alpha adrenergic antagonists for the treatment of symptomatic BPH. Internatl J Clin Pharmacol Ther Toxicol 27:151-155, 1989.

67. Lepor H. Role of alpha-adrenergic blockers in the treatment of benign prostatic hyperplaisa. The Prostate Supplement 3:75-84, 1990.

68. Fabricius PG, Weizert P, Dunzendorfer U, Hannaford JM, Maurath C. Efficacy of once-a-day terazosin in benign prostatic hyperplasia: A randomized, double-blind placebo-controlled clinical trial. The Prostate Supplement 3:85-93, 1990.

69. Caine M. Alpha-adrenergic blockers for the treatment of benign prostatic hyperplasia. Urol Clin North Am 17:641-649, 1990.

70. Lepor H. Role of long-acting selective alpha-1 blockers in the treatment of benign prostatic hyperplasia. Urol Clin North Am 17:651-659, 1990.